ARENA PHARMACEUTICALS INC
Form 424B5
January 17, 2006

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This filing is made pursuant to Rule 424(b)(5)
under the Securities Act of 1933
in connection with Registration No. 333-129519

The information contained in this preliminary prospectus supplement is not complete and may be changed. The registration statement filed with the Securities and Exchange Commission relating to these securities has been declared effective. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities and are not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

Subject to Completion, Dated January 17, 2006

8,500,000 Shares

Common Stock

We are offering 8,500,000 shares of our common stock.

Our common stock is quoted on the Nasdaq National Market under the symbol "ARNA." On January 13, 2006, the last reported sale price of our common stock was $15.74 per share.

Investing in our common stock involves risks. See "Risk Factors" beginning on page S-7 of this prospectus supplement.

	Per Share	Total
Public offering price	$	$
Underwriting discount	$	$
Proceeds, before expenses, to Arena	$	$

The underwriters may also purchase up to an additional 1,275,000 shares from us at the public offering price, less the underwriting discount, within 30 days from the date of this prospectus supplement to cover over-allotments.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved 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.

The underwriters expect to deliver the shares against payment in New York, New York on , 2006.

Joint Book-Running Managers

CIBC World Markets **UBS Investment Bank**

Co-Managers

Needham & Company, LLC

Piper Jaffray

SG Cowen & Co.

Morgan Joseph **Montgomery & Co., LLC**

The date of this prospectus supplement (to the prospectus dated November 16, 2005) is , 2006

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Prospectus Supplement

Prospectus

ABOUT THIS PROSPECTUS SUPPLEMENT

We provide information to you about this offering of shares of our common stock in two separate documents that are bound together: (1) this prospectus supplement, which describes the specific details regarding this offering; and (2) the accompanying prospectus, which provides general information, some of which may not apply to this offering. Generally, when we refer to this "prospectus," we are referring to both documents combined. If information in this prospectus supplement is inconsistent with the accompanying prospectus, you should rely on this prospectus supplement.

You should rely only on information contained in or incorporated by reference into 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. We are offering to sell and seeking offers to buy shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein are accurate only as of their respective dates, regardless of the time of delivery of this prospectus supplement or of any sale of our common stock.

Arena Pharmaceuticals®, Arena® and our corporate logo are registered service marks of Arena. CART is an unregistered service mark of Arena. All other brand names or trademarks appearing in this prospectus supplement and the accompanying prospectus are the property of their respective holders.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information contained in other parts of this prospectus supplement and the accompanying prospectus. Because it is a summary, it does not contain all of the information that you should consider before investing in our shares. You should read the entire prospectus supplement and accompanying prospectus and the documents incorporated by reference herein and therein carefully.

Arena Pharmaceuticals, Inc.

We are a clinical-stage biopharmaceutical company focusing on the discovery, development and commercialization of small molecule drugs targeting G protein-coupled receptors, or GPCRs, in four major therapeutic areas: metabolic, central nervous system, cardiovascular and inflammatory diseases. Our drug candidates act on or through known and orphan GPCRs, and were discovered using our GPCR-focused drug discovery technologies and capabilities.

We have three internally discovered, clinical-stage drug candidates. The most advanced is APD356, a selective 5-HT_{2C} serotonin receptor agonist under investigation for the treatment of obesity. We recently completed a 469 patient, 12 week Phase 2b clinical trial of APD356 in obese patients, which demonstrated highly statistically significant and clinically meaningful weight loss versus placebo at all three doses studied. We expect to begin Phase 3 clinical development in the second half of 2006. Our lead drug candidate for the treatment of insomnia is APD125, a compound with a novel mechanism of action (a selective 5-HT_{2A} serotonin receptor inverse agonist). We expect to begin a Phase 2 clinical trial of APD125 by the end of the first quarter of 2006. As part of our collaboration with Merck & Co., Inc., our partner began a Phase 1 clinical trial of an Arena-discovered compound for the treatment of atherosclerosis and related disorders in the third quarter of 2005. We also have an active collaboration with Ortho-McNeil, Inc., a Johnson & Johnson company, for the treatment of type 2 diabetes. Two drug candidates in this collaboration are currently in preclinical development.

Our goal is to discover, develop and commercialize novel, orally bio-available drugs that address major unmet medical needs by targeting GPCRs. GPCRs are a class of receptors that mediate the majority of cell-to-cell communication in humans and a high percentage of today's prescription drugs target one or more GPCRs. We believe that approved GPCR-based drugs target about 60, or 30%, of the approximately 190 known GPCRs, predominantly in the biogenic amine family, a sub-family of Class 1 GPCRs. GPCRs are categorized as "known" when their naturally occurring, or native, ligands have been identified. Scientists have used molecular cloning in combination with the sequencing of the human genome to identify both additional receptor subtypes of known GPCRs as well as hundreds of novel GPCRs. These novel GPCRs are categorized as "orphan" GPCRs because their native ligands have not been identified. We believe orphan GPCRs offer significant promise for the development of novel GPCR-based therapeutics, and, therefore, are an important focus of our discovery research. We believe our GPCR-focused technologies and integrated discovery and development capabilities will allow us to continue to build our pipeline of unique and selective drug candidates.

We intend to commercialize our drug candidates independently and with partners. We have retained marketing rights to our development programs, except for those relating to our cardiovascular collaboration with Merck and our diabetes partnership with Ortho-McNeil. We have not received regulatory approval for, or generated commercial revenues from, marketing or selling drugs.

Our Research & Development Programs

We have a diverse product pipeline that targets large and attractive market opportunities in several therapeutic areas. The following table summarizes our current independent and partnered development programs and selected research programs:

Program/Indication	Development Status	Next Potential Milestone	Marketing Rights
Metabolic			
APD356 (obesity)	Phase 2 complete	Initiate Phase 3 (2H06)	Arena
19AJ/1 (diabetes)	Preclinical	Initiate Phase 1	Ortho-McNeil
19AJ/2 (diabetes)	Preclinical	Initiate Phase 1	Ortho-McNeil
Diabetes	Research		Arena
CNS			
APD125 (insomnia)	Phase 1 complete	Initiate Phase 2 (1Q06)	Arena
Wakefulness promoter	Research		Arena
Cardiovascular			
Niacin (raise HDL/atherosclerosis)	Phase 1	Initiate Phase 2	Merck
APD791 (arterial thrombosis)	Preclinical	Initiate Phase 1 (around end of 2006)	Arena
Cardioprotection	Research		Arena
Inflammation			
Cytokine modulators	Research		Arena
T and B cell modulators	Research		Arena

Recent Clinical Developments

ADP356

In June 2005, we began a randomized, double-blinded, multiple-dose, 12-week Phase 2b clinical trial of APD356 in obese patients comparing doses of 10 mg and 15 mg once daily and 10 mg twice daily of APD356 to placebo. The primary endpoint of the trial was weight loss after administration of APD356 for 12 weeks. In December 2005, we announced that over the 12-week treatment period, there was a highly statistically significant ($p<0.001$) average weight loss of 4.0, 5.7 and 7.9 pounds at daily doses of 10 mg, 15 mg and 20 mg (10 mg dosed twice daily), respectively, in patients taking APD356, compared to 0.7 pounds for the placebo group. As in the Phase 2a clinical trial, weight loss was progressive. APD356 was generally well tolerated at all doses investigated in the trial and there were no apparent effects on heart valves or pulmonary artery pressures, as assessed by echocardiograms taken at baseline and at the end of the treatment period.

APD125

In June 2005, we announced results from the Phase 1 clinical trial program of APD125. APD125 was well tolerated at all doses investigated in the Phase 1 program. The announced top-line data demonstrated that APD125 caused a robust and highly statistically significant ($p=0.0002$) increase in the amount of deep, or slow wave, sleep in volunteers with normal sleep/wake patterns. In addition, other statistically significant signals indicative of improved sleep maintenance were seen, including statistically significant increases in stage 3 and stage 4 sleep, reductions in stage 1 sleep, reductions in the number of awakenings and an increase in delta power during slow wave sleep.

Financial Update

As of December 31, 2005, our cash, cash equivalents and short-term investments available for sale totaled $127.9 million.

Corporate Information

We were incorporated in Delaware in April 1997, and our principal executive offices are located at 6166 Nancy Ridge Drive, San Diego, California 92121. Our telephone number is (858) 453-7200 and website address is http://www.arenapharm.com. Information contained in, or accessible through, our website does not constitute a part of this prospectus supplement or the accompanying prospectus.

The Offering

Common stock to be offered	8,500,000 shares
Common stock to be outstanding after this offering	43,990,571 shares
Use of proceeds	We intend to use the net proceeds from this offering for the clinical and preclinical development of our internally discovered product candidates, for discovery research for new product candidates and for general corporate purposes, including working capital.
Nasdaq National Market symbol	ARNA

The number of shares of common stock to be outstanding after this offering as reflected in the table above is based on the actual number of shares outstanding as of December 31, 2005, which was 35,490,571, and does not include, as of that date:

- 5,060,306 shares of common stock issuable upon conversion of our Series B-1 Preferred at a conversion price of $7.50 per share;
- 1,689,226 shares of common stock issuable upon conversion of our Series B-2 Preferred at a conversion price of $7.00 per share;
- 1,936,200 shares of common stock issuable upon the exercise of outstanding warrants at an exercise price of $10.00 per share;
- 3,652,831 shares of common stock issuable upon exercise of outstanding options at a weighted average exercise price of $8.07 per share;
- 583,661 shares of common stock available for future issuance under our equity compensation plans;
- 492,406 shares of common stock available for future issuance under our 2001 Employee Stock Purchase Plan; and
- 134,169 shares of common stock available for future issuance under our Deferred Compensation Plan.

Except as otherwise indicated, all information in the prospectus supplement assumes no exercise by the underwriters of their over-allotment option.

Summary Consolidated Financial Data

The following table sets forth our summary consolidated financial data. This data has been derived from our audited consolidated financial statements for the years ended December 31, 2002, 2003 and 2004, and our unaudited consolidated financial statements for the nine month periods ended September 30, 2004 and 2005, and as of September 30, 2005, all of which are incorporated by reference into this prospectus supplement. You should read this information in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our financial statements and the related notes, which are incorporated by reference into this prospectus supplement. The results of operations for interim periods are not necessarily indicative of operating results for the full year.

	Years Ended December 31,			Nine Months Ended September 30,	
	2002	2003	2004	2004	2005
				(Unaudited)	
Consolidated Statements of Operations Data:					
Revenues:					
Total revenues	$ 19,421,765	$ 12,834,279	$ 13,685,822	$ 11,565,000	$ 17,356,879
Operating Expenses:					
Research and development	44,399,136	50,885,417	57,729,138	42,055,010	58,760,870
General and administrative	7,499,011	8,553,910	10,449,281	7,610,225	8,210,171
Amortization of deferred compensation	2,264,934	3,236,087	1,466,245	1,167,378	350,824
Amortization of acquired technology	1,586,127	1,621,220	1,824,761	1,215,915	1,152,747
Total operating expenses	55,749,208	64,296,634	71,469,425	52,048,528	68,474,612
Interest income (expense) and other, net	3,497,505	4,402,916	(208,167)	(143,808)	2,287,016
Net loss	(32,829,938)	(47,059,439)	(57,991,770)	(40,627,336)	(48,830,717)
Dividends on redeemable convertible preferred stock		(26,858)	(1,437,384)	(1,071,612)	(1,313,328)
Accretion of discount related to redeemable convertible preferred stock		(35,516)	(1,851,883)	(1,388,912)	(7,372,014)
Net loss allocable to common stockholders	$ (32,829,938)	$ (47,121,813)	$ (61,281,037)	$ (43,087,860)	$ (57,516,059)
Net loss per share allocable to common stockholders, basic and diluted	$ (1.19)	$ (1.74)	$ (2.40)	$ (1.70)	$ (1.69)
Shares used in calculating net loss per share allocable to common stockholders, basic and diluted	27,487,537	27,159,234	25,527,617	25,313,716	34,064,695

	September 30, 2005	
	Actual	As Adjusted(1)
Consolidated Balance Sheet Data (unaudited):		
Cash, cash equivalents and short-term investments available for sale	$ 148,118,473	$ 273,908,460
Working capital	91,258,777	217,048,764
Total assets	218,432,811	344,222,798
Financing obligation, including deferred interest	13,428,944	13,428,944
Accumulated deficit	(226,322,574)	(226,322,574)
Stockholders' equity	118,503,001	244,292,988

(1) A $1.00 increase (decrease) in the assumed public offering price of $15.74 per share would increase (decrease) the amounts representing cash, cash equivalents and short-term investments available for sale, total assets and stockholders' equity by $8.0 million.

The as adjusted consolidated balance sheet data gives effect to the sale of 8,500,000 shares of common stock offered by us in this offering at an assumed public offering price of $15.74 per share, after deducting the underwriting discount and our estimated offering expenses.

The actual and as adjusted consolidated balance sheet data does not give effect to any redemption of our outstanding Series B-1 Preferred. The holders of our Series B-1 Preferred can require us at any time to redeem all or some of their outstanding shares of Series B-1 Preferred. The aggregate redemption price at September 30, 2005, was approximately $37.6 million, and accrues interest at 4.0% annually. We may be able to satisfy a portion of this amount with shares of our common stock if certain criteria are met.

RISK FACTORS

You should consider carefully the risks described below, together with other information in this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein, before you make a decision to invest in our common stock. If any of the following events actually occur, our business, operating results, prospects or financial condition could be materially and adversely affected. This could cause the trading price of our common stock to decline and you may lose all or part of your investment. The risks described below are not the only ones that we face. Additional risks not presently known to us or that we currently deem immaterial may also affect our business operations.

Risks Relating to Our Business

We will need additional funds to conduct our planned research and development efforts, and we may not be able to obtain such funds.

We had losses of $57.5 million for the nine months ended September 30, 2005, and we had an accumulated deficit of $226.3 million from our inception in April 1997 through September 30, 2005. Our losses have resulted in large part from the significant research and development expenditures we have made in seeking to identify and validate new drug targets and develop compounds that could become marketed drugs.

We expect that our operating expenses over the next several years will be significant and that we will continue to have significant operating losses in the near term, even if we or our collaborators are successful in advancing our compounds or partnered compounds.

We do not have any commercial products. It takes many years and potentially hundreds of millions of dollars to successfully develop a preclinical or early clinical compound into a marketed drug. Even with the anticipated proceeds from this offering, we will have substantially less money than we would need to successfully develop a compound into a marketed drug. Additional funding may not be available to us or may not be available on terms that you or we believe are favorable. If additional funding is not available, we may have to delay, reduce the scope of or eliminate one or more of our research or development programs.

Our stock price could decline significantly based on the results and timing of our clinical trials.

We expect to announce results from our Phase 2 clinical trial of APD125 for insomnia by around the middle of 2006 and to announce the commencement of a Phase 3 clinical trial of APD356 for obesity in the second half of 2006. Results of the Phase 2 clinical trial of APD125 may not be viewed favorably by us or third parties, including investors, analysts and potential collaborators. In addition, we may not be successful in commencing the Phase 2 clinical trial of APD125 or Phase 3 clinical trial of APD356 on our projected timetable, if at all. Biotechnology company stock prices have declined significantly when clinical results were unfavorable or perceived negatively or when clinical trials were delayed or otherwise did not meet expectations. Failure to initiate or delays in our clinical trials of APD356, APD125 or any of our other product candidates, or unfavorable results or negative perceptions regarding any of such trials, could cause our stock price to decline significantly.

Clinical trials for our product candidates are expensive and time consuming, and their progress may be interrupted and their outcome is uncertain.

Clinical trials are very expensive, difficult to design and implement, and can be more expensive than originally anticipated. The clinical trial process is also time consuming. Assuming favorable results, we estimate that the clinical trials of our most advanced product candidates will continue for several years and may take significantly longer to complete. Before we can obtain regulatory approval for the commercial sale of any product candidate that we wish to develop, we are required to complete

extensive clinical trials in humans to demonstrate its safety and efficacy for treatment of specific indications and monitor safety throughout the clinical development process. All of our product candidates are prone to the risks of failure inherent in drug development. Even if we believe the data collected from clinical trials of our drug candidates are promising, such data may not be sufficient to support approval by the FDA or any other U.S. or foreign regulatory approval. Administering any of our product candidates to humans may produce undesirable side effects. These side effects could interrupt, delay or halt clinical trials of our product for any or all of the targeted indications. The FDA, other regulatory authorities, our collaborators, or we may suspend or terminate clinical trials at any time. Any failure or significant delay in completing clinical trials for our product candidates, or in receiving regulatory approval for the sale of any drugs resulting from our product candidates, may severely harm our business and reputation. The timing of the commencement, continuation and completion of clinical trials may be subject to significant delays relating to various causes, including:

lack of effectiveness during the clinical trials;

side effects experienced by study participants or other safety issues;

slower than expected rates of patient recruitment and enrollment;

delays or inability to manufacture or obtain sufficient quantities of materials for use in clinical trials;

delays in obtaining regulatory approvals to commence a study or "clinical holds" or delays requiring suspension or termination of a study by a regulatory agency such as the FDA after a study is commenced;

delays in identifying and reaching agreement on acceptable terms with prospective clinical trial sites;

uncertainty regarding proper dosing;

unfavorable results from on-going clinical trials and preclinical studies;

failure of our clinical research organizations to comply with all regulatory and contractual requirements or otherwise fail to perform their services in a timely or acceptable manner;

scheduling conflicts with participating clinicians and clinical institutions;

inability or unwillingness of medical investigators to follow our clinical protocols; or

difficulty in maintaining contact with subjects during or after treatment, which may result in incomplete data.

Our product candidates are subject to extensive regulation, which can be costly and time consuming, cause unanticipated delays, or prevent the receipt of the required approvals to develop or commercialize products.

The clinical development, manufacturing, labeling, packaging, storage, record-keeping, advertising, promotion, export, marketing and distribution of our product candidates are subject to extensive regulation by the FDA and other regulatory agencies in the United States and by comparable governmental authorities in foreign markets. Neither our collaborators nor we are permitted to market our potential products in the United States until we receive regulatory approval from the FDA. Neither our collaborators nor we have received marketing approval for any of our product candidates. The process of obtaining regulatory approval is expensive, often takes many years, and can vary substantially based upon the type, complexity and novelty of the product involved. Specific preclinical data, chemical data, a proposed clinical study protocol and other information must be submitted to the FDA as part of an IND application. Clinical trials may commence only after the IND application becomes effective. A New Drug Application, or NDA, must be supported by extensive clinical and preclinical data

regarding manufacturing, process and controls to demonstrate the safety and effectiveness of the product candidate. Approval policies or regulations may change. Moreover, failure to comply with the FDA and other applicable foreign and United States regulatory requirements may subject us to administrative or judicially imposed sanctions. These include warning letters, civil and criminal penalties, injunctions, product seizure and detention, product recalls, total or partial suspension of production, and refusal to approve pending NDAs, or supplements to approved NDAs.

We submitted an IND application to the FDA to permit us to commence a Phase 2 trial of APD125 in the United States. The FDA has subsequently requested additional and reformatted information, and the initiation of our Phase 2 trial is pending their review and allowance. Based on our communications with the FDA, we expect to initiate our Phase 2 trial on APD125 by the end of the first quarter of 2006, and to have results of this trial around the middle of this year. However, we cannot be sure that the FDA will not raise additional issues or that our proposed Phase 2 trial will be allowed to proceed in a timely manner or at all.

We have not previously filed NDAs with the FDA, nor have we previously conducted large scale Phase 3 trials, which are significantly larger and more complex than earlier stage trials. This lack of experience may impede our ability to successfully complete these trials and obtain FDA approval in a timely manner, if at all, for our product candidates for which development and commercialization is our responsibility. Despite the time and expense invested, regulatory approval is very uncertain and never guaranteed and we could encounter problems that cause us to abandon clinical trials or to repeat or perform additional preclinical testing and clinical trials. The FDA has substantial discretion in the drug approval process. The number of preclinical studies and clinical trials that will be required for FDA approval varies depending on the product candidate, the disease or condition that the product candidate is designed to address, and the regulations applicable to any particular product candidate. The FDA can delay, limit or deny approval of a product candidate for many reasons, including:

not finding a product candidate sufficiently safe and/or effective;

not finding the data from preclinical testing and clinical trials sufficient to prove safety or efficacy;

not approving of our or a third-party manufacturers' processes or facilities; or

changes in its approval policies or the adoption of new regulations.

Because, in part, of the early stage of our product candidate research and development process, we cannot predict whether or not regulatory approval will be obtained for any product we develop. We are conducting clinical trials on only two of our product candidates, APD356 and APD125, and only one of our product candidates is undergoing clinical trials by a partner, Merck. Compounds developed by us, alone or with other parties, may not prove to be safe and effective in clinical trials and may not meet all of the applicable regulatory requirements needed to receive marketing approval. Administering any of our product candidates to humans may produce undesirable side effects. These side effects could interrupt, delay or halt clinical trials of our product candidates and could result in the FDA or other regulatory authorities denying approval of our product candidates for any or all of the targeted indications. If regulatory approval of a product is granted, the approval will be limited to those disease states and conditions for which the product is demonstrated through clinical trials to be sufficiently safe and effective. Failure to obtain regulatory approval will delay or prevent us from commercializing products. These risks also apply to the development activities of our collaborators, and we do not expect any drugs resulting from our collaborators' research and development efforts to be commercially available for many years, if ever. The FDA, other regulatory authorities, our collaborators or we may suspend or terminate clinical trials at any time. Any failure or significant delay in completing clinical trials for our product candidates, or in receiving regulatory approval for the sale of any drugs resulting from our product candidates, may severely harm our business and reputation.

The results of preclinical studies and completed clinical trials are not necessarily predictive of future results, and our current product candidates may not have favorable results in later studies or trials.

Preclinical studies and Phase 1 and Phase 2 clinical trials are not primarily designed to test the efficacy of a product candidate, but rather to test safety, to study pharmacokinetics and pharmacodynamics, and to understand the product candidate's side effects at various doses and schedules. Success in preclinical studies or completed clinical trials does not ensure that later studies or trials, including continuing preclinical studies and large-scale clinical trials, will be successful nor does it necessarily predict future results. Favorable results in early studies or trials may not be repeated in later studies or trials, and product candidates in later stage trials may fail to show desired safety and efficacy despite having progressed through initial-stage trials. Unfavorable results from ongoing preclinical studies or clinical trials could result in delays, modifications or abandonment of ongoing or future clinical trials. In addition, we may report top-line data from time to time. Top-line data is based on preliminary analysis of key efficacy and safety data, and is subject to change.

A number of companies in the biotechnology industry have suffered significant setbacks in advanced clinical trials, even after promising results in earlier trials. Clinical results are frequently susceptible to varying interpretations that may delay, limit or prevent regulatory approvals. Negative or inconclusive results or adverse medical events during a clinical trial could cause a clinical trial to be delayed, repeated or terminated. In addition, failure to construct appropriate clinical trial protocols could result in the test or control group experiencing a disproportionate number of adverse events and could cause a clinical trial to be delayed, repeated or terminated.

Our most advanced product candidates, APD356 and APD125, have not completed the large, pivotal Phase 3 trials for efficacy and safety that are required for FDA approval. Preclinical data and the limited clinical results that we have obtained for APD356 and APD125 may not predict results from studies in larger numbers of subjects drawn from more diverse populations treated for longer periods of time or, in the case with APD125, when patients with insomnia are studied rather than normal volunteers. They also may not predict the ability of APD356 or APD125 to achieve or sustain the desired effects in the intended population or to do so safely.

We have developed APD356 to more selectively stimulate the 5-HT_{2C} serotonin receptor because we believe this selectivity may avoid the cardiovascular side effects associated with fenfluramine and dexfenfluramine, two serotonin-releasing agents and non-selective serotonin receptor agonists, both of which were withdrawn from the market in 1997 after reported incidences of heart valve disease and pulmonary hypertension associated with their usage. We may not be correct in this belief, however, and APD356's selectivity profile may not avoid the undesired side effects. Moreover, the potential relationship between the activity of APD356 and the activity of fenfluramine and dexfenfluramine may result in increased FDA regulatory scrutiny of the safety of APD356 and may raise potential adverse publicity in the marketplace, which could affect clinical enrollment or ultimately sales if APD356 is approved for sale. In response to our Investigational New Drug, or IND, submission for APD356, the FDA recommended we assess the abuse potential and requested that we provide our plans for cardiac valve monitoring during Phase 2 and Phase 3 clinical trials. We expect our communication with the FDA on these issues to be ongoing.

We have developed APD125 to selectively inhibit the 5-HT_{2A} serotonin receptor because we believe this mechanism may be better tolerated and improve sleep quality and maintenance as compared to existing sleep therapies. Preclinical data and the results from our Phase 1 clinical trial in subjects with normal sleep patterns may not predict APD125's effects on sleep quality, sleep maintenance or sleep onset latency in patients with insomnia.

We will be required to demonstrate through larger-scale clinical trials that these product candidates are safe and effective for use in a diverse population before we can seek regulatory approvals for their commercial sale. There is typically a high rate of attrition from the failure of

product candidates proceeding through clinical trials. To date, long-term safety and efficacy have not yet been demonstrated in clinical trials for any of our product candidates. If APD356 or APD125 fails to demonstrate sufficient safety and efficacy in any clinical trial, we will experience potentially significant delays in, or decide to abandon development of, that product candidate. If we abandon or are delayed in our development efforts related to APD356 or APD125, or any other product candidate, we may not be able to generate sufficient revenues to continue our operations at the current level or become profitable, our reputation in the industry and in the investment community would likely be significantly damaged, it may not be possible to complete financings, and our stock price would likely decrease significantly.

Many of our research and development programs are in early stages of development, and may not result in the commencement of clinical trials.

Many of our research and development programs are in the discovery or preclinical stage of development. The process of discovering compounds with therapeutic potential is expensive, time consuming and unpredictable. Similarly, the process of conducting preclinical studies of compounds that we discover requires the commitment of a substantial amount of our technical and financial resources and personnel. We may not discover additional compounds with therapeutic potential, and any of the compounds for which we are conducting preclinical studies may not result in the commencement of clinical trials. If we are unable to identify and develop new product candidates, we may not be able to maintain a clinical development pipeline or generate revenues.

The technologies on which we rely may not result in the discovery or development of commercially viable products.

Our GPCR technologies include technologies that allow us to discover drug-like compounds that act on receptor subtypes of known GPCRs and novel GPCRs where the native ligands have not been identified. These methods of identifying, prioritizing and screening molecular targets are unproven, and may not result in the regulatory approval and commercialization of any therapeutic products. We do not believe that there are any drugs on the market that have been discovered or developed using our proprietary technologies. If we are unable to identify additional product candidates using our proprietary drug discovery technologies, we may not be able to maintain a clinical development pipeline or generate revenues.

Another company, organization or individual could have, or could develop, a technology targeting GPCRs to discover and develop compounds into drugs more effectively or efficiently than our screening and other technologies. Such a technology could render our technologies, in particular our constitutively activated receptor technology, or CART, and Melanophore technology, obsolete or noncompetitive.

If we are not successful in advancing our lead programs, we may have to curtail some of our activities.

If we are not successful in achieving additional milestones under our cardiovascular collaboration with Merck or our diabetes collaboration with Ortho-McNeil, or developing or partnering APD356 or APD125 or any of our other lead programs, we may not be able to raise additional capital or generate significant partnering revenues in the short term. If we do not receive additional capital or partnering revenues, we may need to license some or all of our programs on financial terms that are unfavorable to us. Also, without additional capital or partnering revenues, we would need to re-evaluate our strategy of moving multiple drug discovery and development programs forward while at the same time maintaining our research and discovery capabilities. Based on such evaluation, we may need to significantly curtail some of our current and planned programs and expenditures. We do not know what programs, if any, we would need to curtail, but we believe narrowing our pipeline would reduce our opportunities for success.

Our revenues depend upon the actions of our existing and potential collaborators.

Our revenues were $13.7 million and $12.8 million for the years ended December 31, 2004 and 2003, respectively, and were $17.4 million for the nine months ended September 30, 2005. Our revenues depend upon the success of our existing collaborations and on our ability to enter into new collaborations. We will receive little additional revenues from our existing collaborators if our own or our collaborators' research, development or, ultimately, marketing efforts are unsuccessful, or if our agreements are terminated early. Typically, our collaborators (and not us) control the development of compounds into drugs after we have met early preclinical scientific milestones. In addition, we may not have complete access to information about the results and status of our collaborators' clinical trials and regulatory programs and strategies. We are not entitled to the more significant milestone payments under our agreements until our collaborators have advanced compounds in clinical testing. Our partners may not devote adequate resources to the development of our compounds and may not develop or implement a successful clinical or regulatory strategy. Only one of our partners, Merck, has advanced one of our compounds into clinical testing and paid us the applicable milestone. We cannot guarantee that any of the other development, approval or sales milestones in our existing or future collaborations will be satisfied, or that we will receive any payments for the achievement of those other milestones.

For the year ended December 31, 2004, revenues recognized under our collaboration with Merck represented approximately 95% of our total revenues. For the nine months ended September 30, 2005, 100% of our revenues were from our collaborations with Merck and Ortho-McNeil. We expect substantially all of our revenues for the remaining three months of 2005 will have been derived from our collaborations with Merck and Ortho-McNeil. Our revenues will be materially impacted if:

- our agreement with either Merck or Ortho-McNeil is terminated;
- our collaborators do not devote their time and financial resources to develop compounds under our collaborations;
- our collaborators dispute whether we have achieved a milestone, rights to a particular receptor or compound, or other terms of our agreements;
- our collaborators use alternative technologies to our technologies and compete with us in developing products; or
- our collaborators experience failures in the discovery or development of compounds identified with our technologies or in the clinic or marketplace with other products that cause them to discontinue or slow down our collaboration.

Our ability to enter into new collaborations depends on the outcomes of our preclinical and clinical testing. We do not control these outcomes. In addition, even if our testing is successful, pharmaceutical companies may not partner with us on terms that we believe are acceptable until we have advanced our product candidates into the clinic and, possibly, through later-stage clinical trials, if at all.

Our collaboration agreements with Merck and Ortho-McNeil may be terminated in certain circumstances.

The term of our amended collaborative research program with Merck is three years from October 21, 2004. Merck can terminate this program: (i) for "Technical Grounds," by giving 30 days prior notice, if both Merck and we agree that Technical Grounds have occurred; or (ii) in the event of our change in control (as defined in the agreement), by giving 30 days prior notice. Technical Grounds include circumstances where: (1) our joint research committee (a committee of an equal number of Merck and our representatives) concludes that (a) a significant adverse event affecting all the targets, all program compounds and all active compounds under the program has arisen during the conduct of

the program, or (b) continuation of the program is no longer scientifically promising because the role of all the targets proves incorrect, or none of the targets are valid as a suitable target for development of a pharmaceutical product; or (2) Merck's patent department, upon consultation with our patent attorneys, makes a reasonable determination that valid third-party patent rights block the achievement of significant program goals.

In addition, either party can terminate the agreement if the other party breaches its material obligations under the agreement by causes and reasons within its control, has not cured such breach within 90 days of receiving a letter requesting such cure, and there is no dispute as to whether such breach has occurred. In lieu of terminating the agreement, however, Merck can terminate the research program and certain other aspects of the agreement after giving 90 days prior notice if we materially breach our obligations during the course of the program and fail to cure such breach, if such default cannot be cured within such 90-day period, or if we do not commence and diligently continue good faith efforts to cure such default during such period.

The initial term of the research program under our agreement with Ortho-McNeil is until December 20, 2006, unless extended for an additional year by Ortho-McNeil or as we may otherwise agree. We and Ortho-McNeil each have the right to terminate the agreement early if the other party commits an uncured material breach of its obligations. Further, Ortho-McNeil may terminate the agreement without cause during the term of the research program, provided that in such event it pays us the balance of its research funding obligation for the initial term of the research program in a lump sum, unless the termination is due to a change of control of Arena (as defined in the agreement), in which case Ortho-McNeil may terminate either the agreement or the research program under the agreement, without the payment of additional research funding to us. At any time after the end of the research program, Ortho-McNeil may terminate the agreement by providing us at least 60 days prior written notice. Upon termination of the agreement, all rights to the compounds developed under the collaboration will revert to us.

We may have conflicts with our prospective, current or past collaborators that could delay or prevent the development or commercialization of our product candidates.

We may have conflicts with our prospective, current or past collaborators, such as conflicts concerning the interpretation of preclinical or clinical data, the achievement of milestones, or the ownership of intellectual property. If any conflicts arise with Ortho-McNeil, Merck or any other prospective, current or past collaborator, such collaborator may act in a manner that is adverse to our best interests. Any such disagreement could result in one or more of the following, each of which could delay or prevent the development or commercialization of our product candidates, and in turn prevent us from generating revenues:

- unwillingness on the part of a collaborator to pay us research funding, milestone payments or royalties that we believe are due to us under a collaboration;
- uncertainty regarding ownership of intellectual property rights arising from our collaborative activities, which could prevent us from entering into additional collaborations;
- unwillingness on the part of a collaborator to keep us informed regarding the progress of its development and commercialization activities or to permit public disclosure of the results of those activities; or
- slowing or cessation of a collaborator's development or commercialization efforts with respect to our product candidates.

Drug discovery and development is intensely competitive in the therapeutic areas on which we focus. If our competitors develop treatments that are approved faster, marketed better or demonstrated to be more effective or safer than our product candidates, our commercial opportunities will be reduced or eliminated.

We focus our efforts on GPCRs. Because GPCRs are an important target class for drug discovery efforts, we believe that many pharmaceutical and biotechnology companies and other organizations have internal drug discovery programs focused on GPCRs. Many of the drugs that our collaborators or we are attempting to discover and develop would compete with existing therapies. In addition, many companies are pursuing the development of new drugs that target the same diseases and conditions that we target. Many of our competitors, particularly large pharmaceutical companies, have substantially greater research and development capabilities and greater financial, scientific and human resources than we do. Companies that complete clinical trials, obtain required regulatory agency approvals and commence commercial sale of their drugs before we do for the same indication may achieve a significant competitive advantage, including certain patent and FDA marketing exclusivity rights. In addition, our competitors may develop drugs with fewer side effects, more desirable characteristics (such as route of administration or frequency of dosing) or greater efficacy than our drugs, if any, for the same indication. Any results from our research and development efforts, or from our joint efforts with our existing or any future collaborators, may not compete successfully with existing or newly discovered products or therapies.

Setbacks and consolidation in the pharmaceutical and biotechnology industries, and our or our collaborators' inability to obtain third-party coverage and adequate reimbursement, could make partnering more difficult and diminish our revenues.

Setbacks in the pharmaceutical and biotechnology industries, such as those caused by safety concerns relating to high-profile drugs like Vioxx and Celebrex, competition from generic drugs and litigation, and industry consolidation may have an adverse effect on us. For example, pharmaceutical companies may be less willing to enter into new collaborations or continue existing collaborations if they are integrating a new operation as a result of a merger or acquisition or if their therapeutic areas of focus change following a merger. Moreover, our and our collaborators' ability to commercialize future drugs will depend in part on government regulation and the availability of coverage and adequate reimbursement from third-party payers, including government payers, such as the Medicaid and Medicare programs. Government and third-party payers are increasingly attempting to contain healthcare costs by limiting coverage and reimbursement levels for new drugs. These efforts may limit our commercial opportunities by reducing the amount a potential collaborator is willing to pay to license our programs or product candidates in the future due to a reduction in the potential revenues from drug sales.

We rely on third parties to conduct our clinical trials. If those parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to advance our product candidates in a timely manner or at all.

In the course of our discovery, preclinical testing and clinical trials, we have relied and continue to rely on third parties, including laboratories, investigators, clinical research organizations and manufacturers, to perform critical services for us. For example, we are relying on contract clinical sites to conduct our clinical trials for APD356 and APD125. Clinical research organizations are and will continue to be responsible for many aspects of the trials, including finding and enrolling subjects for testing and administering the trials. These third parties may not be available when we need them or, if they are available, may not comply with all regulatory and contractual requirements or may not otherwise perform their services in a timely or acceptable manner. These independent third parties may also have relationships with other commercial entities, some of which may compete with us. As a result of our dependence on third parties, we may face delays or failures outside of our direct control. These

risks also apply to the development activities of our collaborators, and we do not control our collaborators' research and development, clinical trials or regulatory activities. We do not expect any drugs resulting from our collaborators' research and development efforts to be commercially available for many years, if ever.

We or a third-party manufacturer may encounter a manufacturing failure that could delay the clinical development or regulatory approval of our product candidates, or their ultimate commercial production if approved.

Any performance failure on the part of us or a third-party manufacturer could delay clinical development or regulatory approval of our product candidates. Manufacturers often encounter difficulties involving production yields, regulatory compliance, quality control and quality assurance, as well as shortages of qualified personnel. We or a third-party manufacturer may encounter such difficulties. The manufacturers are subject to ongoing periodic unannounced inspection by the FDA, the Drug Enforcement Administration of the U.S. Department of Justice and corresponding state agencies to ensure strict compliance with current good manufacturing practices and other applicable government regulations and corresponding foreign standards. We do not have control over a third-party manufacturer's compliance with these regulations and standards. If one of our manufacturers fails to maintain compliance, the production of our product candidates could be interrupted, resulting in delays, additional costs and potentially lost revenues.

We may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.

From time to time we consider strategic transactions, such as acquisitions of companies, asset purchases and out-licensing or in-licensing of compounds or technologies. Additional potential transactions we may consider include a variety of different business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any such transaction may require us to incur non-recurring or other charges, may increase our near and long-term expenditures and may pose significant integration challenges or disrupt our management or business, which could harm our operations and financial results.

Our efforts will be seriously jeopardized if we are unable to retain and attract key employees.

Our success depends on the continued contributions of our principal management, development and scientific personnel, and the ability to hire and retain key personnel, particularly in the clinical development area as we transition more of our programs from research into drug development. We face intense competition for such personnel. The loss of services of any principal member of our management or scientific staff, particularly Jack Lief, our President and Chief Executive Officer, and Dominic P. Behan, Ph.D., our Senior Vice President and Chief Scientific Officer, could adversely impact our operations and ability to raise additional capital. To our knowledge, neither Mr. Lief nor Dr. Behan plans to leave, retire or otherwise disassociate with us in the near future.

We may encounter significant delays or problems with our chemical development facility.

We have a chemical development facility for process research, the scale-up and production of intermediates and other compounds for research and development purposes, and the production of active pharmaceutical ingredients for use in clinical trials. We may encounter delays and problems in operating our chemical development facility due to:

- governmental approvals, permits and regulation of the facility;
- accidents during operation of the facility;
- failure of equipment for the facility;

delays in receiving raw materials from suppliers;

natural or other disasters; or

other factors inherent in operating a complex manufacturing facility.

We may not be able to operate our chemical development facility in a cost-effective manner or in a time frame that is consistent with our expected future manufacturing needs. If this were the case, we would need to seek alternative means to fulfill our manufacturing needs, which could delay progress on our programs.

We use biological materials, hazardous materials, chemicals and radioactive compounds.

Our research and development activities involve the use of potentially harmful biological materials as well as hazardous materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. These materials and various wastes resulting from their use are stored at our facility pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

an interruption of our research and development efforts;

injury to our employees and others;

environmental damage resulting in costly clean up; and

liabilities under federal, state and local laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products.

In such an event, we may be held liable for any resulting damages, and any such liability could exceed our resources. Although we carry insurance in amounts and type that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research and development efforts caused by contamination, and we cannot be certain that the coverage or coverage limits of our insurance policies will be adequate.

We may incur substantial liabilities from any product liability claims if our insurance coverage for those claims is inadequate.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials, and will face an even greater risk if we sell our product candidates commercially. An individual may bring a liability claim against us if one of our product candidates causes, or merely appears to have caused, an injury. If we cannot successfully defend ourselves against a product liability claim, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

decreased demand for our product candidates;

injury to our reputation;

withdrawal of clinical trial subjects;

costs of related litigation;

substantial monetary awards to subjects or other claimants;

loss of revenues; and

the inability to commercialize our product candidates.

We have limited product liability insurance that covers our clinical trials. We intend to expand our insurance coverage to include the sale of commercial products if marketing approval is obtained for any

of our product candidates. However, insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost, and we may not have insurance coverage that will be adequate to satisfy any liability that may arise.

We may incur increased costs as a result of recently enacted changes in laws and regulations relating to corporate governance matters.

Changes in the laws and regulations affecting public companies, including the provisions of the Sarbanes-Oxley Act of 2002 and rules adopted by the Securities and Exchange Commission and by the Nasdaq National Market, may result in increased costs to us. These laws, rules and regulations could make it more difficult or costly for us to obtain certain types of insurance, including director and officer liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to their requirements.

Our operations might be interrupted by the occurrence of a natural disaster or other catastrophic event.

All of our laboratories and offices are in a single location in San Diego. We depend on our laboratories and other facilities and on our collaborators, contractors and vendors for the continued operation of our business. Natural disasters or other catastrophic events, including terrorist attacks, power interruptions, wildfires and other fires, actions of animal rights activists, earthquakes and wars could disrupt our operations or those of our collaborators, contractors and vendors. Even though we believe we carry commercially reasonable business interruption and liability insurance, and our contractors may carry liability insurance, that protect us in certain events, we might suffer losses as a result of business interruptions that exceed the coverage available under our and our contractors' insurance policies or for which we or our contractors do not have coverage. For example, we are not insured against a terrorist attack. Any natural disaster or catastrophic event could have a significant negative impact on our operations and financial results. Moreover, any such event could delay our research and development programs.

Even if any of our product candidates receives regulatory approval, our product candidates will still be subject to extensive post-market regulation.

If we or our collaborators receive regulatory approval for our product candidates, we will also be subject to ongoing FDA obligations and continued regulatory review, such as continued safety reporting requirements, and we may also be subject to additional FDA post-marketing obligations, all of which may result in significant expense and limit our ability to commercialize our products.

If any of our product candidates receive United States regulatory approval, the FDA may still impose significant restrictions on the indicated uses for which such products may be marketed or impose ongoing requirements for potentially costly post-approval studies. In addition, regulatory agencies subject a product, its manufacturer and the manufacturer's facilities to continual review and inspections. The subsequent discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, may result in restrictions on the marketing of that product, and could include withdrawal of the product from the market. Failure to comply with applicable regulatory requirements may result in:

- issuance of warning letters by the FDA;
- fines and other civil penalties;

criminal prosecutions;

injunctions, suspensions or revocations of marketing licenses;

suspension of any ongoing clinical trials;

suspension of manufacturing;

delays in commercialization;

refusal by the FDA to approve pending applications or supplements to approved applications filed by us or our collaborators;

refusals to permit products to be imported or exported to or from the United States;

restrictions on operations, including costly new manufacturing requirements; and

product recalls or seizures.

The FDA's policies may change and additional government regulations may be enacted that could prevent or delay regulatory approval of our product candidates or further restrict or regulate post-approval activities. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are not able to maintain regulatory compliance, we might not be permitted to market our drugs and our business could suffer.

In order to market any products outside of the United States, we and our collaborators must establish and comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy. Approval procedures vary among countries and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks associated with FDA approval as well as additional presently unanticipated risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others. Failure to obtain regulatory approval in other countries or any delay or setback in obtaining such approval could have the same adverse effects associated with regulatory approval in the United States, including the risk that our product candidates may not be approved for all indications requested and that such approval may be subject to limitations on the indicated uses for which the product may be marketed.

New accounting pronouncements may impact our future results of operations.

In December 2004, the Financial Accounting Standards Board, or FASB, issued Statement of Financial Accounting Standards, or SFAS, No. 123R, "Share-Based Payment." This statement, which will be effective in our first quarter of 2006, will change how we account for share-based compensation, and may have an adverse or negative impact on our results of operations or our stock price.

We currently account for share-based payments to employees and directors using the intrinsic value method. Under this method, we generally do not recognize any compensation related to stock option grants we issue under our stock option plans or the discounts we provide under our employee stock purchase plan.

SFAS No. 123R requires us to recognize share-based compensation as compensation expense in the statement of operations based on the fair values of such equity on the date of the grant, with the compensation expense recognized over the period in which the recipient is required to provide service in exchange for the equity award. This statement also requires us to adopt a fair value-based method for measuring the compensation expense related to share-based compensation. The impact of adoption

of SFAS No. 123R cannot be predicted at this time because it will depend on levels of share-based payments granted in the future. However, had we adopted SFAS No. 123R in prior periods, the impact of that standard would have approximated the impact of SFAS No. 123 as described in the notes to our consolidated financial statements. SFAS No. 123R also requires the benefits of tax deductions in excess of recognized compensation cost to be reported as a financing cash flow, rather than as an operating cash flow. This requirement will reduce our net operating cash flows and increase our net financing cash flows in periods after adoption. SFAS No. 123R may also delay when we may become profitable.

Future changes in generally accepted accounting principles, including pronouncements relating to revenue recognition, might have a significant effect on our reported results, including reporting of transactions completed before the effective date of such pronouncements, if ever.

Risks Relating to Our Intellectual Property

Our success is dependent on intellectual property rights held by us and third parties and our interest in these rights is complex and uncertain.

Our success will depend on our own and on our collaborators' abilities to obtain, secure and defend patents. In particular, the patents directed to our most advanced product candidates and other compounds discovered using our technologies are important to commercializing drugs. We have numerous U.S. and foreign patent applications pending for our technologies, including patent applications on drug lead discovery techniques using CART, genetically altered GPCRs, GPCRs that we have discovered, new uses for previously discovered GPCRs, and compounds discovered using CART and Melanophore and other technologies.

The procedures for obtaining a patent in the U.S. and in most foreign countries are complex. These procedures require an analysis of the scientific technology related to the invention and many legal issues. Consequently, the analysis of our patent applications will be complex and time consuming. Our patent position is very uncertain and we do not know when, or if, we will obtain additional patents for our technologies.

In addition, other entities may challenge the validity or enforceability of our patents and patent applications in litigation or administrative proceedings. Even the issuance of a patent is not conclusive as to its validity or enforceability. We cannot make assurances as to how much protection, if any, will be given to our patents if we attempt to enforce them and they are challenged. It is possible that a competitor or a generic pharmaceutical provider may successfully challenge our patents and those challenges may result in reduction in our patents' coverage.

As of December 31, 2005, we owned, in part or in whole, or had exclusively licensed the following patents: 17 in the United States, 95 in European countries, eight in New Zealand, five in Australia, four in Lebanon, one in Japan, one in Singapore, one in Hong Kong and one in Israel. In addition, as of December 31, 2005, we had approximately 457 patent applications before the United States Patent and Trademark Office, foreign patent offices and international patent authorities. These patents and patent applications are divided into 78 distinct families of related patents that are directed to CART, Melanophore technology, other novel screening methods, chemical compositions of matter, methods of treatment using chemical compositions, or GPCR genes. One of our patent families was exclusively in-licensed and contains a single issued patent. Seven of our patent families containing a total of eight patents and 70 patent applications were the subject of joint inventions by our employees and the employees of other entities. The remaining 70 patent families containing a total of 124 patents and 387 patent applications were invented solely by our employees. There is no assurance that any of these patent applications will issue, or that any of the patents will be enforceable or will cover a drug product or other commercially significant product or method.

In 2000, the United States Patent and Trademark Office began issuing broad patent claims that could allow patent holders to control the use of all drug products that modulate a particular drug target or GPCR, regardless of whether the infringing drug product bears any structural resemblance to a chemical compound known to the patent holder at the time of patent filing. The question of whether these new patent claims are valid is highly controversial and the subject of litigation. Whether we or our competitors are able to obtain and enforce such patent claims, particularly as they apply to the GPCRs that are the subject of our drug development activities, may have a significant impact on our potential revenues from any drugs that we are able to develop.

We also rely on confidentiality agreements and trade secrets to protect our technologies. However, such information is difficult to protect. We require our employees to contractually agree not to improperly use our confidential information or disclose it to others, but we may be unable to determine if our employees have conformed or will conform to their legal obligations under these agreements. We also enter into confidentiality agreements with prospective collaborators, collaborators, service providers and consultants, but we may not be able to adequately protect our trade secrets or other proprietary information in the event of any unauthorized use or disclosure or the lawful development by others of this information. Many of our employees and consultants were, and many of them may currently be, parties to confidentiality agreements with other pharmaceutical and biotechnology companies, and the use of our technologies could violate these agreements. In addition, third parties may independently discover our trade secrets or proprietary information.

Some of our academic institution licensors, research collaborators and scientific advisors have rights to publish data and information to which we have rights. We generally seek to prevent our partners from disclosing scientific discoveries before we have the opportunity to file patent applications on such discoveries. In some of our collaborations we do not have control over our partners' ability to disclose their own discoveries under the collaboration and in some of our academic collaborations we are limited to relatively short periods to review a proposed publication and file a patent application. If we cannot maintain the confidentiality of our technologies and other confidential information in connection with our collaborations, our ability to receive patent protection or protect our proprietary information will be impaired.

A dispute regarding the infringement or misappropriation of our proprietary rights or the proprietary rights of others could be costly and result in delays in our research and development activities.

Our commercial success also depends upon our ability to develop, manufacture, market and sell our product candidates and conduct our research and development activities without infringing or misappropriating the proprietary rights of other entities. There are many patents and patent applications filed, and that may be filed, by others relating to drug discovery and development programs that could be determined to be similar, identical or superior to ours or our licensors or collaborators. We may be exposed to future litigation by other entities based on claims that our product candidates, technologies or activities infringe the intellectual property rights of others. Numerous U.S. and foreign issued patents and pending patent applications owned by others exist in the area of GPCRs, including some which purport to allow the patent holder to control the use of all drug products that modulate a particular drug target or GPCR, regardless of whether the infringing drug product bears any structural resemblance to a chemical compound known to the patent holder at the time of patent filing. Numerous U.S. and foreign issued patents and pending patent applications owned by others also exist in the therapeutic areas in which we are developing products. These could materially affect our ability to develop our product candidates or sell our products, and our activities, or those of our licensors or collaborators, could be determined to infringe these patents. Because patent applications can take many years to issue, there may be currently pending applications, unknown to us, which may later result in issued patents that our product candidates or technologies may infringe. There also may be existing patents, of which we are not aware, that our product candidates or

technologies may inadvertently infringe. Further, there may be issued patents and pending patent applications in fields relevant to our business, of which we are or may become aware, that we believe we do not infringe or that we believe are invalid or relate to immaterial portions of our overall drug discovery and development efforts. We cannot assure you that other entities holding any of these patents or patent applications will not assert infringement claims against us for damages or seeking to enjoin our activities. We also cannot assure you that, in the event of litigation, we will be able to successfully assert any belief we may have as to non-infringement, invalidity or immateriality, or that any infringement claims will be resolved in our favor.

In addition, other entities may infringe or misappropriate our proprietary rights, and we may have to institute costly legal action to protect our intellectual property rights. We may not be able to afford the costs of enforcing or defending our intellectual property rights against other entities.

Other organizations, companies and individuals are seeking proprietary positions on genomics information that overlap with the government-sponsored project to sequence the human genome. Our activities, or those of our licensors or collaborators, could be affected by conflicting positions that may exist between any overlapping genomics information made available publicly as a result of the government sponsored project and genomics information that other organizations, companies or individuals consider to be proprietary.

There could also be significant litigation and other administrative proceedings in our industry that affect us regarding patent and other intellectual property rights. Any legal action or administrative action against us, or our collaborators, claiming damages or seeking to enjoin commercial activities relating to our drug discovery and development programs could:

require us, or our collaborators, to obtain a license to continue to use, manufacture or market the affected products, methods or processes, which may not be available on commercially reasonable terms, if at all;

prevent us from importing, making, using, selling or offering to sell the subject matter claimed in patents held by others and subject us to potential liability for damages;

consume a substantial portion of our managerial, scientific and financial resources; or

be costly, regardless of the outcome.

Furthermore, because of the substantial amount of pre-trial document and witness discovery required in connection with intellectual property litigation, there is risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, during the course of this kind of litigation, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the trading price of our common stock.

We have been contacted from time to time by third parties regarding their intellectual property rights, sometimes asserting that we may need a license to use their technologies. If we fail to obtain any required licenses or make any necessary changes to our technologies, we may be unable to develop or commercialize some or all of our product candidates.

We cannot protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on all of our drug discovery technologies throughout the world would be prohibitively expensive. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own drug products. These products may compete with our products and may not be covered by any of our patent claims or other intellectual property rights.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States, and many companies have encountered significant problems in protecting and defending such rights in foreign jurisdictions. Many countries, including certain countries in Europe, have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties (for example, the patent owner has failed to "work" the invention in that country or the third party has patented improvements). In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of the patent. Compulsory licensing of life saving drugs is also becoming increasingly popular in developing countries either through direct legislation or international initiatives. Such compulsory licenses could be extended to include some of our product candidates, which could limit our potential revenue opportunities. Moreover, the legal systems of certain countries, particularly certain developing countries, do not favor the aggressive enforcement of patents and other intellectual property protection, particularly those relating to biotechnology and/or pharmaceuticals, which makes it difficult for us to stop the infringement of our patents. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

Risks Relating to Our Securities

Our stock price will likely be volatile, and your investment in our stock could decline in value.

Our stock price has fluctuated historically. From January 1, 2004, to January 13, 2006, the market price of our stock was as low as $3.48 per share and as high as $17.58 per share.

Very few biotechnology products being tested will ultimately receive FDA approval, and a biotechnology company may experience a significant drop in its stock price based on an adverse clinical trial result or regulatory action. Our stock price may fluctuate significantly, depending on a variety of factors, including:

- our success or failure in clinical trials;
- the timing of the discovery of drug leads and the development of our product candidates;
- entering into a new collaboration or modifying or terminating an existing collaboration;
- the timing and receipt by us of milestone and royalty payments or failing to achieve and receive the same;
- changes in the research and development budgets of our existing or potential collaborators;
- others introducing new drug discovery techniques or introducing or withdrawing drugs that target the same diseases and conditions that we or our collaborators target;
- regulatory actions;
- expenses related to, and the results of, litigation and other proceedings relating to intellectual property rights or other matters; and
- accounting changes, including the expense impact of SFAS No. 123R.

We are not able to control all of these factors. Period-to-period comparisons of our financial results are not necessarily indicative of our future performance. In addition, if our revenues or results of operations in a particular period do not meet stockholders' or analysts' expectations, our stock price may decline and such decline could be significant.

Holders of our Series B Preferred can require us to redeem their Series B Preferred.

On December 24, 2003, we completed the private placement to two institutional investors of (i) an aggregate of 3,500 shares of our Series B-1 Preferred, (ii) seven-year Warrants to purchase up to an aggregate of 1,486,200 shares of our common stock at an exercise price of $10.00 per share (subject to weighted-average adjustment in certain circumstances) and (iii) Unit Warrants to purchase for a period of approximately 16 months from December 24, 2003, up to $11.5 million of our Series B-2 Preferred and additional seven-year Warrants to purchase up to 450,000 shares of our common stock at an exercise price of $10.00 per share (subject to weighted-average adjustment in certain circumstances). On April 22, 2005, the investors exercised their Unit Warrants in full.

The holders of our Series B-1 Preferred can require us at any time to redeem all or some of their shares of Series B-1 Preferred at such shares' stated value, plus accrued but unpaid dividends thereon to the date of payment and any applicable penalties. The stated value is the original holder's investment plus any dividends settled by increasing the stated value at the time the dividend is payable. The aggregate redemption price of our Series B-1 Preferred at December 31, 2005, was approximately $38.0 million, and accrues interest at 4.0% annually.

The holders of our Series B-2 Preferred will be entitled to require us to redeem their shares of Series B-2 Preferred at such shares' stated value, plus accrued but unpaid dividends thereon to the date of payment and any applicable penalties if, following the 21st month anniversary of the original issue date of the Series B-2 Preferred, the average of the closing prices of our common stock for any 30 consecutive trading days is below $7.00, which is the conversion price for the Series B-2 Preferred. The aggregate redemption price of our Series B-2 Preferred at December 31, 2005, was approximately $11.8 million, and accrues interest at 4.0% annually.

Also, the holders of the Series B-2 Preferred may require us to redeem their shares if we issue common stock or common stock equivalents for an effective net price to us per share less than approximately $5.33 (excluding, among other things, certain common stock and common stock equivalents issued or issuable (i) to our officers, directors, employees or consultants, (ii) in connection with certain strategic partnerships or joint ventures, and (iii) in connection with certain mergers and acquisitions). "Effective net price" is not defined in the Certificate of Designations governing our Series B-2 Preferred. The holders of our Series B-2 Preferred may assert that effective net price should be calculated as the amount we receive after paying any discounts and other expenses related to any such issuance.

In addition to the foregoing redemption rights, at any time following the occurrence of a "Triggering Event," a holder of the Series B Preferred may require us to repurchase all or any portion of the Series B Preferred then held by such holder at a price per share equal to the greater of 115.0% of the stated value or the market value (as calculated under the Certificate of Designations for the Series B-1 Preferred and the Series B-2 Preferred) of such shares of Series B Preferred plus all accrued but unpaid dividends thereon to the date of payment. "Triggering Event" is specifically defined in the Certificate of Designations for the Series B-1 Preferred and the Series B-2 Preferred, and includes any of the following events: (i) immediately prior to a bankruptcy event; (ii) we fail for any reason to timely deliver a certificate evidencing any securities to a purchaser or the exercise or conversion rights of the holders are otherwise suspended for other than a permissible reason; (iii) any of certain events of default (as set forth in the Registration Rights Agreement with the Series B Preferred holders) occur and remain uncured for 60 days; (iv) we fail to make any cash payment required under the Series B Preferred transaction documents and such failure is not timely cured; (v) the issuance of a going concern opinion by our independent registered public accounting firm that is not timely cured; (vi) we breach a section of the Series B Preferred purchase agreement relating to indebtedness and subordination; or (vii) we default in the timely performance of any other obligation under the Series B Preferred transaction documents and such default is not timely cured.

We will also be required to redeem any shares of the Series B Preferred that remain outstanding on the fifth anniversary of their issuance at a price equal to the amount of the original holder's original investment, plus all accrued but unpaid dividends thereon to the date of such payment.

If we are required to redeem all or some of the currently outstanding shares of our Series B Preferred, we may be able to pay a portion of the redemption price using shares of our common stock if certain other enumerated conditions are satisfied, including:

- we have sufficient number of shares of common stock available for issuance;
- the shares of common stock to be issued are registered under an effective registration statement or are otherwise available for sale under Rule 144(k) under the Securities Act;
- our common stock is listed on the Nasdaq National Market or other eligible market;
- the shares to be issued can be issued without violating the rules of the Nasdaq National Market or any applicable trading market or a provision of our certificate of designations; and
- no bankruptcy event has occurred.

If we are permitted to satisfy a portion of a redemption by using shares of our common stock, and if we elect to do so, the number of shares to be issued to holders of Series B Preferred will be determined by dividing their cash redemption price by the lesser of the conversion price or 95.0% of the average of the volume weighted average price of our common stock for either 10 or 15 trading days.

There can be no assurance that if we have to redeem our Series B Preferred, that we will be able to pay a portion of the redemption price using shares of our common stock. If we use common stock to redeem a portion of the Series B Preferred, your ownership interest may be significantly diluted. If we are required or elect to redeem shares of the Series B Preferred using cash, we may not have sufficient cash to redeem these shares or to continue our planned research and discovery activities. In such event we may try to raise additional capital by issuing new stock, but there can be no assurance that capital will be available on acceptable terms or at all.

There are a substantial number of shares of our common stock eligible for future sale in the public market, and the sale of these shares could cause the market price of our common stock to fall.

There were 35,490,571 shares of our common stock outstanding as of December 31, 2005. The outstanding shares of our Series B-1 Preferred are convertible into up to 5,060,306 shares of common stock at $7.50 per share of common stock. The outstanding shares of our Series B-2 Preferred are convertible into up to 1,689,226 shares of common stock at $7.00 per share of common stock. Holders of Series B Preferred are entitled to receive a 4.0% annual dividend that is payable by issuing common stock or by increasing the amount of common stock that is issuable upon conversion of the Series B Preferred. In addition, holders of our Series B Preferred own Warrants to acquire common stock, which, if exercised and converted, would obligate us to issue up to 1,936,200 additional shares of common stock at an exercise price of $10.00 per share. If the closing price of our common stock is equal to or above $14 for 30 consecutive trading days, upon 10 trading days' prior written notice, we will have the right to, and the Warrant holders will have the right to require us to, call and cancel any unexercised portion of the Warrants (subject to certain conditions). Upon exercise of a Warrant following such call notice and prior to the Warrant cancellation date, we will be obligated to issue to the Warrant holder an exchange warrant entitling the holder to purchase shares of our common stock equal to the amount of the holder's Warrant that was called. This exchange warrant will contain the same terms and conditions as the original Warrant, except that the maturity date will be seven years from the date of issuance of such exchange warrant and the exercise price will be equal to 130% of the average of the volume weighted average prices of our common stock for the five trading days preceding

the original Warrant cancellation date. In addition, as of December 31, 2005, there were 3,652,831 common stock options issued and outstanding under our equity compensation plans at a weighted average exercise price of $8.07, 583,661 additional shares of common stock issuable under our equity compensation plans, 492,406 shares of common stock reserved for issuance under our 2001 Employee Stock Purchase Plan and 134,169 shares issuable under our Deferred Compensation Plan. A substantial number of the shares described above, when issued upon exercise, will be available for immediate resale in the public market. The market price of our common stock could decline as a result of such resales due to the increased number of shares available for sale in the market.

Any future equity or debt issuances by us may have dilutive or adverse effects on our existing stockholders.

We have financed our operations, and we expect to continue to finance our operations, primarily by issuing and selling our common stock or securities convertible into or exercisable for shares of our common stock. In light of our need for additional financing, we may issue additional shares of common stock or additional convertible securities that could dilute your ownership in our company and may include terms that give new investors rights that are superior to yours. Moreover, any issuances by us of equity securities may be at or below the prevailing market price of our common stock and in any event may have a dilutive impact on your ownership interest, which could cause the market price of our common stock to decline. The terms of our Series B Preferred limit our ability to engage in certain equity issuances.

We may also raise additional funds through the incurrence of debt, and the holders of any debt we may issue would have rights superior to your rights in the event we are not successful and are forced to seek the protection of the bankruptcy laws. The terms of our Series B Preferred limits our ability to incur debt.

Our largest stockholders may take actions that are contrary to your interests, including selling their stock.

A small number of our stockholders hold a significant amount of our outstanding stock. These stockholders may support competing transactions and have interests that are different from yours. In addition, the average number of shares of our stock that trade each day is generally low. As a result, sales of a large number of shares of our stock by these large stockholders or other stockholders within a short period of time could adversely affect our stock price.

Provisions of our Series B Preferred may prevent or make it more difficult for us to raise funds or take certain other actions.

Provisions of our Series B Preferred require us to obtain approval of the preferred stockholders, or otherwise trigger rights of first refusal or payment provisions, to (i) offer or sell new securities, other than in specified underwritten offerings or strategic partnerships or joint venture and certain other exceptions, (ii) sell or issue common stock or securities issuable into common stock below certain prices, (iii) incur debt or allow liens on our property, other than certain permitted debt and liens, (iv) amend our certificate of incorporation so as to affect adversely any rights of the preferred stockholders, (v) authorize or create a new class of stock that will be senior or equal to the Series B Preferred in terms of dividends, redemption or distribution of assets, (vi) use more than $25.0 million in cash for acquisitions, or (vii) take certain other actions. These provisions may make it more difficult for us to take certain corporate actions and could delay, discourage or prevent future financings.

Our rights agreement and certain provisions in our charter documents and Delaware law could delay or prevent a change in management or a takeover attempt that you may consider to be in your best interest.

We have adopted certain anti-takeover provisions, including a stockholders' rights plan, dated as of October 30, 2002, between us and Computershare Trust Company, Inc., as Rights Agent, as amended

on December 24, 2003. The rights plan will cause substantial dilution to any person who attempts to acquire us in a manner or on terms not approved by our board of directors.

The rights agreement and Certificate of Designations for the Series B Preferred, as well as other provisions in our certificate of incorporation and by-laws and under Delaware law, could delay or prevent the removal of directors and other management and could make more difficult a merger, tender offer or proxy contest involving us that you may consider to be in your best interest. For example, these provisions:

- allow our board of directors to issue preferred stock without stockholder approval;
- limit who can call a special meeting of stockholders;
- eliminate stockholder action by written consent; and
- establish advance notice requirements for nomination for election to the board of directors or for proposing matters to be acted upon at stockholders meetings.

We may allocate the net proceeds from this offering in ways that you and other stockholders may not approve.

We intend to use the net proceeds from this offering:

- for the clinical and preclinical development of our internally discovered product candidates;
- for discovery research for new product candidates; and
- for general corporate purposes, including working capital.

Our management will, however, have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not necessarily improve our operating results or enhance the value of our common stock. The proceeds may be used to pay the redemption price for some or all of the outstanding Series B-1 Preferred, if the holders elect to have their preferred stock redeemed.

FORWARD-LOOKING STATEMENTS

This prospectus supplement and the accompanying prospectus, including the documents that we incorporate by reference herein and therein, contain "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These forward-looking statements can generally be identified as such because the context of the statement will include words such as "may," "will," "intends," "plans," "believes," "anticipates," "expects," "estimates," "predicts," "potential," "continue," "likely," "unlikely" or "opportunity," the negative of these words or words of similar import. Similarly, statements that describe our future plans, strategies, intentions, expectations, objectives, goals or prospects are also forward-looking statements. Discussions containing these forward-looking statements may be found, among other places, in the "Business" section of this prospectus supplement and the "Business" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections incorporated by reference from our most recent Annual Report on Form 10-K and our Quarterly Reports on Form 10-Q for the quarters ended subsequent to our filing of such Annual Report on Form 10-K with the SEC, as well as any amendments thereto reflected in subsequent filings with the SEC. These forward-looking statements are based largely on our expectations and projections about future events and future trends affecting our business, and are subject to risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. The risks and uncertainties include, among others, those noted in "Risk Factors" above.

In addition, past financial and/or operating performance is not necessarily a reliable indicator of future performance and you should not use our historical performance to anticipate results or future period trends. We can give no assurances that any of the events anticipated by the forward-looking statements will occur or, if any of them do, what impact they will have on our results of operations and financial condition. Except as required by law, we undertake no obligation to publicly revise our forward-looking statements to reflect events or circumstances that arise after the filing of this prospectus supplement or the filing of the accompanying prospectus or documents incorporated by reference herein and therein that include forward-looking statements.

USE OF PROCEEDS

We estimate that the net proceeds from the sale of the shares of common stock we are offering will be approximately $125.8 million. If the underwriters exercise the over-allotment option in full, the net proceeds of the shares we sell will be approximately $144.7 million. "Net proceeds" is what we expect to receive after paying the underwriting discounts and commissions and other expenses of this offering. For the purpose of estimating net proceeds, we are assuming that the public offering price will be $15.74 per share. A $1.00 increase (decrease) in the assumed public offering price of $15.74 per share would increase (decrease) the net proceeds to us from this offering by $8.0 million.

We intend to use the net proceeds from this offering for the clinical and preclinical development of our internally discovered product candidates, for discovery research for new product candidates, and for general corporate purposes, including working capital.

The timing and amount of our actual expenditures will be based on many factors, including the timing and success of our clinical trials, whether we partner any of our internal programs and whether we choose to curtail some of our research activities. As a result, we will retain broad discretion in determining how we will allocate the net proceeds from this offering.

Until we use the net proceeds of this offering, we intend to invest the funds in short-term, investment grade, interest-bearing securities.

DIVIDEND POLICY

We have never paid any cash dividends on our capital stock. We anticipate that we will retain earnings, if any, to support operations and to finance the growth and development of our business. Therefore, we do not expect to pay cash dividends in the foreseeable future. In addition, we are prohibited from paying cash dividends on any of our capital stock other than our Series B Preferred, which accrues interest at 4.0% annually, without the approval of the holders of the Series B Preferred.

CAPITALIZATION

The following table shows:

- our capitalization on September 30, 2005; and
- our capitalization on September 30, 2005, assuming the completion of this offering at an assumed public offering price of $15.74 per share, less the underwriting discount and estimated offering expenses payable by us.

	September 30, 2005	
	Actual	As Adjusted(1)
	(Unaudited)	
Financing obligation, including deferred interest	$ 13,428,944	$ 13,428,944
Redeemable convertible preferred stock	11,705,976	11,705,976
Common stock, $.0001 par value; 67,500,000 shares authorized, 35,383,425 issued and outstanding, actual; 67,500,000 shares authorized, 43,883,425 shares issued and outstanding, as adjusted	3,851	4,701
Additional paid-in capital	368,391,848	494,180,985
Treasury stock	(23,070,000)	(23,070,000)
Accumulated other comprehensive loss	(16,735)	(16,735)
Deferred compensation	(483,389)	(483,389)
Accumulated deficit	(226,322,574)	(226,322,574)
Total stockholders' equity	118,503,001	244,292,988
Total capitalization	$ 143,637,921	$ 269,427,908

(1) A $1.00 increase (decrease) in the assumed public offering price of $15.74 per share would increase (decrease) each of additional paid-in capital, stockholders' equity and total capitalization by $8.0 million.

The number of shares of common stock as reflected in the actual and as adjusted columns above is based on the actual number of shares outstanding as of September 30, 2005, and does not include, as of that date:

- 5,009,546 shares of common stock issuable upon conversion of our Series B-1 Preferred at a conversion price of $7.50 per share;
- 1,672,282 shares of common stock issuable upon conversion of our Series B-2 Preferred at a conversion price of $7.00 per share;
- 1,936,200 shares of common stock issuable upon the exercise of outstanding warrants at an exercise price of $10.00 per share;

3,624,707 shares of common stock issuable upon exercise of outstanding options at a weighted average exercise price of $8.04 per share;

656,361 shares of common stock available for future issuance under our equity compensation plans;

554,976 shares of common stock available for future issuance under our 2001 Employee Stock Purchase Plan; and

134,169 shares of common stock available for future issuance under our Deferred Compensation Plan.

The actual and as adjusted column data does not give effect to any redemption of our outstanding Series B-1 Preferred. The holders of our Series B-1 Preferred can require us at any time to redeem all or some of their outstanding shares of Series B-1 Preferred. The aggregate redemption price at September 30, 2005, was approximately $37.6 million, and accrues interest at 4.0% annually. We may be able to satisfy a portion of this amount with shares of our common stock if certain criteria are met.

DILUTION

Our unaudited net tangible book value on September 30, 2005 was approximately $110.2 million, or $3.11 per share of common stock. "Net tangible book value" is total assets minus the sum of liabilities and intangible assets. "Net tangible book value per share" is net tangible book value divided by the total number of common stock shares outstanding.

After giving effect of the sale of 8,500,000 shares of common stock offered by us in this offering, our pro forma net tangible book value on September 30, 2005 would have been $236.0 million, or $5.38 per share of common stock. The adjustments made to determine pro forma net tangible book value per share are the following:

- an increase in total assets to reflect the net proceeds of the offering as described under "Use of Proceeds" (assuming that the public offering price will be $15.74 per share); and
- the addition of the number of shares offered by this prospectus supplement to the number of shares outstanding.

The following table illustrates the pro forma increase in net tangible book value of $2.27 per share and the dilution (the difference between the offering price per share and net tangible book value per share) to new investors:

Assumed public offering price per share	$	15.74
Net tangible book value per share as of September 30, 2005	$	3.11
Increase in net tangible book value per share attributable to offering	$	2.27
Pro forma net tangible book value per share as of September 30, 2005, after giving effect to the offering	$	5.38
Dilution per share to new investors in the offering	$	10.36

A $1.00 increase (decrease) in the assumed public offering price of $15.74 per share would increase (decrease) our pro forma net tangible book value after giving effect to the offering by $8.0 million, the pro forma net tangible book value per share after giving effect to the offering by approximately $0.19 per share and the dilution per share to new investors in the offering by approximately $0.82 per share.

The following table shows the difference between existing stockholders and new investors with respect to the number of shares purchased from us, the total consideration paid and the average price paid per share. The table assumes that the public offering price will be $15.74 per share.

	Shares Purchased		Total Consideration		
	Number	Percent	Amount	Percent	Average Price Per Share
Existing stockholders	35,383,425	80.6%	$ 349,566,329	72.3%	$ 9.88
New investors	8,500,000	19.4%	$ 133,790,000	27.7%	$ 15.74
Total	43,883,425	100.0%	$ 483,356,329	100.0%	$ 11.02

A $1.00 increase (decrease) in the assumed public offering price of $15.74 per share would increase (decrease) both the total consideration by new investors and the total consideration by all stockholders by $8.5 million and increase (decrease) the average price per share by all stockholders by approximately $0.19 per share.

The above discussion and tables are based on 35,383,425 shares of common stock outstanding as of September 30, 2005, and does not include, as of that date:

- 5,009,546 shares of common stock issuable upon conversion of our Series B-1 Preferred at a conversion price of $7.50 per share;

1,672,282 shares of common stock issuable upon conversion of our Series B-2 Preferred at a conversion price of $7.00 per share;

1,936,200 shares of common stock issuable upon the exercise of outstanding warrants at an exercise price of $10.00 per share;

3,624,707 shares of common stock issuable upon exercise of outstanding options at a weighted average exercise price of $8.04 per share;

656,361 shares of common stock available for future issuance under our equity compensation plans;

554,976 shares of common stock available for future issuance under our 2001 Employee Stock Purchase Plan; and

134,169 shares of common stock available for future issuance under our Deferred Compensation Plan.

BUSINESS

We are a clinical-stage biopharmaceutical company focusing on the discovery, development and commercialization of small molecule drugs targeting G protein-coupled receptors, or GPCRs, in four major therapeutic areas: metabolic, central nervous system, cardiovascular and inflammatory diseases. Our drug candidates act on or through known and orphan GPCRs, and were discovered using our GPCR-focused drug discovery technologies and capabilities.

We have three internally discovered, clinical-stage drug candidates. The most advanced is APD356, a selective 5-HT_{2C} serotonin receptor agonist under investigation for the treatment of obesity. We recently completed a 469 patient, 12 week Phase 2b clinical trial of APD356 in obese patients, which demonstrated highly statistically significant and clinically meaningful weight loss versus placebo at all three doses studied. We expect to begin Phase 3 clinical development in the second half of 2006. Our lead drug candidate for the treatment of insomnia is APD125, a compound with a novel mechanism of action (a selective 5-HT_{2A} serotonin receptor inverse agonist). We expect to begin a Phase 2 clinical trial of APD125 by the end of the first quarter of 2006. As part of our collaboration with Merck & Co., Inc., our partner began a Phase 1 clinical trial of an Arena-discovered compound for the treatment of atherosclerosis and related disorders in the third quarter of 2005. We also have an active collaboration with Ortho-McNeil, Inc., a Johnson & Johnson company, for the treatment of type 2 diabetes. Two drug candidates in this collaboration are currently in preclinical development.

Our goal is to discover, develop and commercialize novel, orally bio-available drugs that address major unmet medical needs by targeting GPCRs. GPCRs are a class of receptors that mediate the majority of cell-to-cell communication in humans and a high percentage of today's prescription drugs target one or more GPCRs. We believe that approved GPCR-based drugs target about 60, or 30%, of the approximately 190 known GPCRs, predominantly in the biogenic amine family, a sub-family of Class 1 GPCRs. GPCRs are categorized as "known" when their naturally occurring, or native, ligands have been identified. Scientists have used molecular cloning in combination with the sequencing of the human genome to identify both additional receptor subtypes of known GPCRs as well as hundreds of novel GPCRs. These novel GPCRs are categorized as "orphan" GPCRs because their native ligands have not been identified. We believe orphan GPCRs offer significant promise for the development of novel GPCR-based therapeutics, and, therefore, are an important focus of our discovery research. We believe our GPCR-focused technologies and integrated discovery and development capabilities will allow us to continue to build our pipeline of unique and selective drug candidates.

We intend to commercialize our drug candidates independently and with partners. We have retained marketing rights to our development programs, except for those relating to our cardiovascular collaboration with Merck and our diabetes partnership with Ortho-McNeil. We have not received regulatory approval for, or generated commercial revenues from, marketing or selling drugs.

Our Research & Development Programs

We have a diverse product pipeline that targets large and attractive market opportunities in several therapeutic areas. The following table summarizes our current independent and partnered development programs and selected research programs:

Program/Indication	Development Status	Next Potential Milestone	Marketing Rights
Metabolic			
APD356 (obesity)	Phase 2 complete	Initiate Phase 3 (2H06)	Arena
19AJ/1 (diabetes)	Preclinical	Initiate Phase 1	Ortho-McNeil
19AJ/2 (diabetes)	Preclinical	Initiate Phase 1	Ortho-McNeil
Diabetes	Research		Arena
CNS			
APD125 (insomnia)	Phase 1 complete	Initiate Phase 2 (1Q06)	Arena
Wakefulness promoter	Research		Arena
Cardiovascular			
Niacin (raise HDL/atherosclerosis)	Phase 1	Initiate Phase 2	Merck
APD791 (arterial thrombosis)	Preclinical	Initiate Phase 1 (around end of 2006)	Arena
Cardioprotection	Research		Arena
Inflammation			
Cytokine modulators	Research		Arena
T and B cell modulators	Research		Arena

APD356

Our most advanced drug candidate, APD356, is a novel and selective 5-HT_{2C} receptor agonist for the treatment of obesity that is expected to enter Phase 3 clinical development in the second half of 2006. Obesity and a related condition known as metabolic syndrome affect tens of millions of adults and children in the United States and pose serious long-term threats to their health and welfare. Studies have shown that modest weight loss of as little as five percent of initial body weight can result in a meaningful reduction in the risks of other diseases associated with obesity, such as diabetes and cardiovascular disease. Currently, medical treatment options for obesity and metabolic syndrome are very limited.

Two non-selective, serotonin-acting drugs widely used for weight loss, fenfluramine and dexfenfluramine (often used in combination with phentermine, the combination of which was commonly referred to as "fen-phen"), though efficacious as appetite suppressants and for treatment of obesity, were withdrawn from the market in 1997 after reported incidences of heart valve disease and pulmonary hypertension associated with their usage. Based on our preclinical studies and clinical trial data to date, we believe that APD356 stimulates the 5-HT_{2C} serotonin receptor more selectively than, and is therefore unlikely to cause the cardiovascular side effects associated with, fenfluramine and dexfenfluramine.

Mechanism of Action. APD356 selectively stimulates the 5-HT_{2C} serotonin receptor, a GPCR located in the hypothalamus. Stimulation of this hypothalamic receptor is strongly associated with feeding behavior and satiety. We conducted preclinical studies examining the activity and 5-HT receptor subtype specificity of APD356. In these studies, APD356 demonstrated a high affinity and specificity for the 5-HT_{2C} receptor, with approximately 15-fold and 100-fold selectivity over the 5-HT_{2A} and 5-HT_{2B} receptors, respectively, and no pharmacologic activity at other serotonin receptors. The fenfluramines release serotonin, and their primary metabolite, norfenfluramine, also has activity at the 5-HT_{2B} receptor, stimulation of which has been implicated in the heart valve abnormalities associated with these drugs. Because of its selectivity, we believe that APD356 is unlikely to cause the cardiovascular side effects associated with fenfluramine and dexfenfluramine. This belief has been recently supported in our clinical studies of four and 12 weeks duration in which no apparent effects of the drug were seen on heart valves or pulmonary arterial pressures. However, additional studies will be required to confirm these results.

Clinical Development. We have completed multiple Phase 1 and Phase 2 studies of APD356. The first Phase 2 study included 352 obese patients dosed for 28 days, and the second included 469 obese patients dosed for 12 weeks. Highly statistically significant and clinically meaningful weight loss was observed for the term of both studies, without evidence of any apparent drug effect on heart valves or pulmonary artery pressures, as assessed by serial echocardiograms. APD356 was generally well tolerated in both Phase 2 studies.

In July 2004, we announced results from a three-part Phase 1a clinical trial of APD356 that established a maximum tolerated dose for the drug candidate. In November 2004, we announced results from a Phase 1b clinical trial of APD356 in obese volunteers. APD356 was well tolerated; there were no severe or serious adverse events reported and no withdrawals due to an adverse event. Based on a comparison of echocardiograms taken at screening with those taken at the end of treatment and two and three months thereafter, there was no apparent drug effect on heart valves or pulmonary artery pressures.

In May 2005, we announced Phase 2a clinical trial results of a randomized, double-blinded, multiple-dose, 28-day study in obese patients comparing doses of 1 mg, 5 mg and 15 mg of APD356 to placebo. Over the 28-day treatment period, there was a highly statistically significant ($p=0.0002$) average weight loss of 2.9 pounds in patients taking the 15 mg dose of APD356 versus 0.9 pounds for the placebo group. APD356 was generally well tolerated at all doses investigated in the trial. An assessment of follow-up echocardiograms taken at the end of dosing and approximately 90 days after patients received their first doses of APD356 in the Phase 2a clinical trial indicated no apparent drug effect on heart valves or pulmonary artery pressures.

In June 2005, we began a randomized, double-blinded, multiple-dose, 12-week Phase 2b clinical trial of APD356 in obese patients comparing doses of 10 mg and 15 mg once daily and 10 mg twice daily of APD356 to placebo. The primary endpoint of the trial was weight loss after administration of APD356 for 12 weeks. In December 2005, we announced that over the 12-week treatment period, there was a highly statistically significant ($p<0.001$) average weight loss of 4.0, 5.7 and 7.9 pounds at daily doses of 10 mg, 15 mg and 20 mg (10 mg dosed twice daily), respectively, in patients taking APD356, compared to 0.7 pounds for the placebo group. As in the Phase 2a clinical trial, weight loss was progressive. APD356 was generally well tolerated at all doses investigated in the trial and there were no apparent effects on heart valves or pulmonary artery pressures, as assessed by echocardiograms taken at baseline and at the end of the treatment period.

Development Plan. Following discussions with the FDA, we plan to begin our first pivotal Phase 3 clinical trial in the second half of 2006. We anticipate that the primary endpoint for this trial will be weight loss over a one-year period versus placebo. We expect to plan our Phase 3 program to meet or

exceed the relevant FDA guidelines which, for this type of indication, typically require the enrollment of thousands of patients and multiple years to execute.

Intellectual Property. As of December 31, 2005, we had issued patents covering compositions of matter for APD356 and related compounds, and related methods of treatment, in the United States, Hong Kong, and 30 countries within Europe (including Germany, France, the United Kingdom, Italy and Spain), and applications pending in about 24 other countries including Japan, Canada and China.

APD125

Our lead drug candidate for insomnia, APD125, is a novel and selective 5-HT_{2A} receptor inverse agonist that we expect to enter a Phase 2 clinical trial by the end of the first quarter of 2006. The National Institutes of Health estimated in 2003 that between 30 to 40 percent of U.S. adults report some level of insomnia and insomnia is a chronic problem for about 10 percent of the population. In these cases, the lack of restful sleep impairs the person's ability to carry out their daily responsibilities because they are too tired or have trouble concentrating. However, the great majority of insomnia patients do not seek treatment. Currently marketed therapies for insomnia include Ambien® and Ambien® CR, marketed by Sanofi-Aventis, Lunesta®, marketed by Sepracor, Sonata®, marketed by King Pharmaceuticals, Inc., Rozerem®, a melatonin MT1 and MT2 agonist marketed by Takeda Pharmaceuticals North America, Inc., and various benzodiazepines, including Valium®. With the exception of Rozerem, these therapies generally work by activating the GABA-A receptor in the brain, causing a general CNS-suppressive effect. While the GABA-A drugs may be effective at initiating sleep, they have side effects including the risk of developing tolerance to the drug and the potential for causing a sensation of dullness and lethargy upon awakening, often referred to as the "hangover effect." In addition, GABA-A drugs are DEA-scheduled, controlled substances due to their potential for abuse. Despite these limitations, current worldwide sales estimates for medications for insomnia are in excess of $5 billion for 2006.

Mechanism of Action. Preclinical data demonstrate that by selectively targeting the 5-HT_{2A} receptor, APD125 acts through a different mechanism than currently marketed insomnia drugs, blocking a general CNS-activating effect, rather than initiating a general CNS-suppressive effect. Because of the different mechanism of action, APD125 may not have the side effects generally associated with currently marketed GABA-A drugs. Through this novel mechanism, APD125 has the potential to reduce insomnia symptoms and improve sleep maintenance by decreasing the number of awakenings during the night, decreasing the amount of wake time after initial sleep onset and increasing the amount of time spent in deep sleep, or slow wave sleep (stage 3 and stage 4 sleep), the most restorative type of sleep.

Our preclinical studies have shown that, in animals, APD125 increases both the quality and total time of non-REM sleep, the most restorative phase of the sleep cycle in humans, while having no effect on REM (rapid eye movement or dream) sleep. The total increase in non-REM sleep time was manifested by fewer bouts of longer duration, indicating an increase in sleep consolidation. In addition, animals treated with APD125 showed an increase in delta power during non-REM sleep, a brain wave activity associated with increased sleep intensity. The improvements in non-REM duration and quality observed with APD125 administration were at least as robust as those observed with a prototypic GABA-A hypnotic control drug, Ambien. However, unlike Ambien, APD125 did not adversely affect REM sleep in these studies. We believe these animal data suggest that APD125 has the potential to improve the treatment of insomnia over GABA-A hypnotics.

Clinical Development. In December 2004, we initiated our Phase 1 clinical trial program of APD125 in healthy volunteers. The Phase 1 program consisted of three clinical trials designed to evaluate the single and multiple dose safety and pharmacokinetics of APD125 in normal volunteers.

Additionally, it evaluated the pharmacodynamics of nighttime dosing by assessing effects on sleep patterns in normal volunteers using polysomnography.

In June 2005, we announced results from the Phase 1 clinical trial program of APD125. APD125 was well tolerated at all doses investigated in the Phase 1 program. The announced top-line data demonstrated that APD125 caused a robust and highly statistically significant (p=0.0002) increase in the amount of deep, or slow wave, sleep in volunteers with normal sleep/wake patterns. In addition, other statistically significant signals indicative of improved sleep maintenance were seen, including statistically significant increases in stage 3 and stage 4 sleep, reductions in stage 1 sleep, reductions in the number of awakenings and an increase in delta power, the deepest form of slow wave sleep.

Development Plan. Following allowance by the FDA, we plan to begin a Phase 2 clinical trial by the end of the first quarter of 2006. In this three-way crossover, dose-ranging trial, we expect to enroll approximately 125 patients with insomnia, and measure a number of parameters, including primarily measures of sleep maintenance but also time to sleep onset. We expect results from that trial around the middle of 2006.

Intellectual Property. As of December 31, 2005, we had issued patents covering compositions of matter for APD125 and related compounds, and related methods of treatment, in the United States, Lebanon, and 33 countries within Europe (including Germany, France, the United Kingdom, Italy and Spain), and applications pending in about 14 other jurisdictions and before the WIPO, designating all contracting states.

APD791

APD791 is a novel, orally bio-available and selective inverse agonist of the 5-HT_{2A} serotonin receptor, that we advanced into preclinical development as our lead anti-thrombotic drug candidate. Thrombosis is the formation of a clot, or thrombus, inside a blood vessel that restricts the flow of blood. The formation of a thrombus is often caused by an injury to the wall of the blood vessel. The injury to the blood vessel activates platelets, which then aggregate and adhere to one another as they start to release certain factors, including serotonin, that facilitate thrombosis. Thrombi that form in diseased atherosclerotic arteries of the heart may cause acute coronary syndrome or myocardial infarction, and thrombi that form in the vessels of the brain may cause stroke. The American Heart Association estimates that in the United States alone over 12 million people alive in 2003 had survived either a myocardial infarction or a stroke. To reduce the risk of future events, many subjects receive daily anti-thrombotic therapy. Worldwide sales of Plavix, a leading anti-thrombotic marketed by Bristol-Myers Squibb and Sanofi-Aventis, has been estimated to exceed $6 billion in 2005.

Mechanism and Preclinical Data. Preclinical data suggest that APD791 is a novel, orally bio-available and selective inverse agonist of the 5-HT_{2A} serotonin receptor. Serotonin activation of the 5-HT_{2A} receptor on platelets and vascular smooth muscle is thought to play an important role in the events leading to thrombosis. Consequently, elevated serotonin levels are associated with increased cardiovascular risk. Normally, when a platelet is activated by one of a number of factors such as thrombin or collagen, the platelet releases serotonin, which promotes platelet aggregation, vasoconstriction and intimal hyperplasia, or thickening of the vessel wall. By blocking activation of the 5-HT_{2A} receptor on platelets and in other cardiovascular tissues, based on our preclinical studies, APD791 inhibits activation of the receptor and is thought to curb platelet aggregation, vasoconstriction and intimal hyperplasia, thereby reducing the risk of thrombosis. We believe APD791 represents a new approach to reducing the risk of arterial thrombo-embolic disease.

In animal models, APD791 demonstrated a better therapeutic index than certain other approved anti-thrombotic agents we tested due to a separation of anti-thrombotic activity from the increased bleeding that may be seen with these agents, which are members of other classes of drugs.

Development Plan. We advanced APD791 into preclinical development in December 2005 and plan to initiate clinical development around the end of 2006.

Intellectual Property. As of December 31, 2005, we had patent applications covering compositions of matter for APD791, and related methods of treatment, pending before the WIPO (designating all contracting states), and in additional jurisdictions that are not contracting states of the WIPO.

19AJ / Ortho-McNeil Collaboration

Our lead drug candidates for diabetes target an orphan GPCR, which we call 19AJ, which is expressed in the pancreas. Our two lead compounds for this target are currently in preclinical development in partnership with Ortho-McNeil. Diabetes is a major worldwide disease. Based on 2003 data, the International Diabetes Foundation estimated that in 2005, there were 194 million adults with diabetes worldwide, an increase of over 40% since 1995. The 2003 figures included approximately 16 million in the United States and approximately 48 million in the European region. Approximately 90%, or 175 million, of diabetics suffer from type 2 diabetes, the adult-onset form of the disease. Type 2 diabetes is characterized by inadequate response to insulin and/or inadequate secretion of insulin as blood glucose levels rise. Therapies for type 2 diabetes are directed toward correcting the body's inadequate response with oral medications, or directly modifying insulin levels through direct injection of insulin or insulin analogs.

Oral medications for type 2 diabetes include insulin releasers such as glyburide, insulin sensitizers such as Actos and Avandia and agents that slow the uptake of glucose into the bloodstream such as Precose and Glyset. The worldwide market for diabetes medications exceeded $10 billion and oral anti-diabetes drugs exceeded $6 billion in 2004. However, a significant portion of type 2 diabetics fail oral medication and require injected insulin therapy. Current oral medications for type 2 diabetes have a number of side effects, including hypoglycemia, weight gain and edema. Numerous pharmaceutical and biotechnology companies are seeking to develop insulin sensitizers, novel insulin formulations and other therapeutics to improve the treatment of diabetes.

Mechanism and Preclinical Data. 19AJ is a receptor that we have found to be expressed in beta cells, the cells in the pancreas responsible for producing insulin in response to increases in blood glucose. We believe 19AJ represents a novel mechanism for generating a new class of drugs for diabetes that may offer advantages over current approaches. Our preclinical results indicate that stimulating the 19AJ receptor allows beta cells to produce insulin more efficiently in response to changes in blood glucose levels. In addition, we have found in these studies that stimulation of the 19AJ receptor leads to increased levels and activity of intracellular factors thought to be involved in the preservation of beta cells. Unlike the GLP-1 receptor, the 19AJ receptor appears amenable to small molecule drug development. We have discovered potent, selective and orally available small molecule agonists of the receptor that improve glucose tolerance and lower blood glucose levels in animal models of diabetes. The 19AJ mechanism is glucose dependent, so that in our animal studies our compounds only lowered blood glucose when it rose above normal levels, such as after a meal. Our preclinical results indicate these compounds do not lower normal fasting baseline glucose levels in animal models and, therefore, do not cause hypoglycemia, unlike the glucose-insensitive sulphonylureas.

Development Plans and Partnership Status. In December 2004, we entered into a collaboration and license agreement with Ortho-McNeil to further develop compounds for the potential treatment of type 2 diabetes and other disorders. Our two lead compounds are currently in preclinical development with Ortho-McNeil. In January 2005, we received a $17.5 million upfront payment and two milestones payments of $2.5 million each. We are eligible to receive up to $295 million in milestone payments for each compound, as well as royalty payments associated with Ortho-McNeil's commercialization of any drugs discovered under the agreement. These milestone payments include development and approval milestone payments of up to $132.5 million for the first indication and $62.5 million for the second

indication for each compound, and up to $100.0 million in sales milestone payments for each product resulting from the collaboration.

Intellectual Property. As of December 31, 2005, we had issued patents related to the 19AJ receptor target that is the subject of our diabetes collaboration with Ortho-McNeil in Australia, New Zealand, and 18 European countries (including Germany, France, the United Kingdom, Italy, Switzerland, Sweden and Spain), and applications pending in eight additional jurisdictions including the United States and Japan.

Merck Cardiovascular Collaboration

There are very successful drugs available for lowering LDL cholesterol. However, development of novel, effective therapies to increase HDL cholesterol remains a major focus of research. We believe that such therapies may reduce the risk of atherosclerotic heart disease and compete in the large anti-hyperlipidemic market.

In October 2002, we entered into a research and licensing agreement with Merck to collaborate on three GPCRs to develop therapeutics for atherosclerosis and related disorders. We believe one or more of these GPCRs plays a role in regulating plasma lipid profiles, including HDL cholesterol, the so-called "good cholesterol," and is responsible for the HDL-raising activity of niacin. In October 2004, we extended and expanded our collaboration with Merck and Merck selected one of our compounds for preclinical development. In July 2005, we announced the achievement of a $2.0 million milestone related to the initiation by Merck of a Phase 1 clinical trial of an Arena-discovered compound.

As of December 31, 2005, we had received $21.5 million from Merck in upfront and milestone payments and an equity investment. We may receive additional milestone payments of up to $32.0 million for Merck's clinical and marketing achievements, as well as royalty payments associated with Merck's commercialization of any drugs discovered under the agreement. In addition, we have received research funding from Merck since the inception of our collaboration, and, under our agreement, Merck will pay us $5.7 million per year for collaboration research through October 19, 2007.

Intellectual Property. We have an issued patent in the United States related to the niacin receptor target that is the subject of our cardiovascular disease collaboration with Merck.

Other Research and Development Programs

Cardiovascular. Acute myocardial infarction, which is commonly known as a heart attack, is often followed by heart failure in survivors. Myocardial infarction and often heart failure are direct consequences of atherosclerosis, and both remain major causes of death. We have identified certain GPCRs that we believe play a role in these processes and are seeking to identify small molecules directed at these GPCR targets that we believe could provide cardio-protection following myocardial infarction.

CNS Disorders. Many GPCRs are found predominately in the brain or the CNS, and, therefore, we believe targeting GPCRs provides an opportunity to selectively treat various CNS diseases. Many approved drugs for indications ranging from insomnia and narcolepsy to depression, schizophrenia and Parkinson's disease, target GPCRs. Our discovery efforts in CNS disorders are focused on indications with large market opportunities where current therapies have significant limitations.

Inflammatory Disorders. We are developing small molecule therapeutics that target GPCRs involved in the inflammatory process. We have identified GPCRs that are found in specific immune cell types. We believe these GPCRs modulate the inflammatory process, and we are applying our screening technologies to these targets to identify small molecules that could activate or inhibit these GPCRs.

Some of the GPCRs we are targeting are expressed on T and B cells and macrophages, and could be important in the modulation of key cytokines that mediate inflammatory processes such as TNF-alpha.

Other Diabetes Programs. For metabolic diseases, we are working on a series of orphan GPCR targets in addition to 19AJ in order to develop orally available therapies to treat type 1 and type 2 diabetes. For example, we are conducting research with receptors that may act to regulate glucose uptake, glucose absorption, insulin sensitivity, insulin secretion, lipid levels and production of glucose in the liver. In order to treat general metabolic disease, we have prioritized GPCRs that have the potential to modulate blood glucose and lipid levels.

Other Obesity Programs. In addition to APD356 and other compounds that act on the 5-HT_{2C} serotonin receptor, we have discovery programs focused on several different GPCRs implicated in obesity. Our drug discovery efforts are directed at identifying novel drug candidates that target GPCRs in the CNS and peripheral tissues to reduce fat mass in humans. We have identified both known and orphan GPCRs expressed in the hypothalamus, an area of the brain known to be critical for regulating satiety and metabolism, that we believe regulate food intake and weight. We have also identified targets in fat cells that may represent targets for obesity. We have identified early lead compounds for obesity targets other than the 5-HT_{2C} serotonin receptor, and are currently evaluating these compounds for their ability to reduce food intake and body weight.

Our Proprietary GPCR Technologies and Programs

Our drug candidates have resulted from our GPCR-focused drug discovery technologies and capabilities, including Constitutively Activated Receptor Technology, or CART, and our Melanophore technology, and our approach to drug discovery and development. Our integrated drug discovery platform allows us to determine GPCR function, tissue and cell distribution, and potential relation to disease.

Traditional ligand-based drug screening methods require the time-consuming identification and use of the receptor's native ligand to discover small molecule compounds that will bind at, or close to, the native ligand's binding site on the receptor. In contrast, we have developed technologies that do not require the use of the native ligand. Instead, we are able to activate a GPCR so that the G protein signals without the presence of the native ligand, by using our Constitutively Activated Receptor Technology, or CART, and other technologies. Applying our technologies to constitutively activate GPCRs assists in discovering drug-like compounds by stimulating the GPCR to mimic the biological response that occurs when the native ligand binds to the receptor. These technologies help avoid a major bottleneck in drug discovery efforts at orphan receptors by eliminating the step of first identifying the native ligand. We have found that our constitutive activation technologies can be applied broadly to GPCRs.

Our constitutive activation technologies allow us to simultaneously identify drug leads that act as receptor activators, or agonists, which increase the detected biological response, or act as receptor inhibitors, which decrease the detected response. We can also identify inverse agonists, which inhibit ligand-independent, as well as ligand-dependent, receptor activity.

We believe that our constitutive activation technologies offer several key advantages for drug discovery over traditional screening techniques that require the use of the native ligand including:

- not requiring prior identification of the native ligand for an orphan receptor;
- enhancing the detection of, and allowing us to simultaneously identify, both receptor inhibitor and receptor activator drug leads;
- allowing for the identification of drug leads that inhibit both ligand-independent and ligand-dependent activity; and

providing the ability to discover novel and improved therapeutics directed at known receptors.

We use our constitutive activation technologies in combination with our patented Melanophore technology. Our Melanophore technology is a broadly applicable high-throughput screen for GPCRs. When a GPCR is activated (either by a ligand or independent of a ligand through constitutive activation), the GPCR couples to one or more G proteins, including those belonging to the Gs, Gq, and Gi/o classes. Melanophore technology can detect GPCRs that couple to major G protein classes. We believe our Melanophore technology is, therefore, also well-suited for studies of orphan receptors whose coupling parameters are unknown. We believe Melanophore technology provides us with a robust, reproducible, high-throughput and low-cost means for identifying and optimizing GPCR agonists, antagonists, and inverse agonists, and is sensitive enough to detect the constitutive activity of many GPCRs.

Our Strategy

The key elements of our scientific and business strategy are to:

Advance our lead programs. We intend to continue to advance our current drug candidates, with a partner or independently, through clinical development and, if successful, to commercialization.

Discover and develop additional small molecule drug candidates targeting GPCRs. We intend to continue to discover and develop orally bio-available, small-molecule compounds for GPCRs identified or validated through our research efforts.

Focus on attractive market opportunities. Obesity, insomnia, diabetes, atherosclerosis and arterial thrombosis each represent multi-billion dollar market opportunities. We intend to continue to focus on these and other markets with attractive commercial potential.

Retain significant commercial rights and/or economic value for our drug candidates. We intend to maximize the value of our drug candidates through both independent development and partnerships with pharmaceutical and larger biotechnology companies with commercial infrastructures.

Continue to build our development capabilities. To capitalize on our discoveries, we plan to continue to expand our clinical development capabilities as our drug candidates enter into, and move through, clinical trials.

Maintain strong discovery research capabilities. Our proprietary technologies, our drug discovery infrastructure and the integrated approach to research used by our scientists, have allowed us to identify a number of GPCR targets and novel compounds. We believe these and other discoveries will continue to fuel our pipeline.

Intellectual Property

Our success depends in large part on our ability to protect our proprietary technology, compounds and information, and to operate without infringing the proprietary rights of third parties. We rely on a combination of patent, trade secret, copyright, and trademark laws, as well as confidentiality agreements, licensing agreements, and other agreements, to establish and protect our proprietary rights.

As of December 31, 2005, we owned, in part or in whole, or had exclusively licensed the following patents: 17 in the United States, 95 in European countries, eight in New Zealand, five in Australia, four in Lebanon, one in Japan, one in Singapore, one in Hong Kong and one in Israel. In addition, as of December 31, 2005, we had approximately 457 patent applications before the United States Patent and Trademark Office, foreign patent offices and international patent authorities. These patents and patent applications are divided into 78 distinct families of related patents that are directed to CART,

Melanophore technology, other novel screening methods, chemical compositions of matter, methods of treatment using chemical compositions, or GPCR genes. One of our patent families was exclusively in-licensed and contains a single issued patent. Seven of our patent families containing a total of eight patents and 70 patent applications were the subject of joint inventions by our employees and the employees of other entities. The remaining 70 patent families containing a total of 124 patents and 387 patent applications were invented solely by our employees. There is no assurance that any of these patent applications will issue, or that any of the patents will be enforceable or will cover a drug product or other commercially significant product or method. Except for the U.S. patents relating to our Melanophore technology, the term of most of our other current patents commenced, and most of our future patents, if any, will commence, on the date of issuance and terminate 20 years from the earliest effective filing date of the patent application. Since our U.S. Melanophore patents were issued under now superseded rules that provided a patent term of 17 years from the date of issuance, the term of these patents are scheduled to end in 2012. Because the time from filing to issuance of biotechnology patent applications is often more than three years, the resulting term of our pending patent applications, if any, on our products and technologies may be substantially less than 20 years. In the United States, Europe and some other jurisdictions, patent term extensions are available for certain delays in either patent office proceedings or marketing and regulatory approval processes. However, due to the specific requirements for obtaining these extensions, there is no assurance that our patents will be afforded extensions even if we encounter significant delays in patent office proceedings or marketing and regulatory approval.

We seek patent protection for our key inventions, including clinical candidates and drug candidates we identify, routes for chemical synthesis, CART, new receptors that we discover, and genetically altered receptors. It has generally been possible to obtain broad composition of matter patents on novel chemical compounds. It has also generally been possible to obtain broad method patents for techniques and procedures for screening and drug-identification technologies. It has generally been more difficult to obtain broad composition of matter patents for nucleic acid and amino acid sequences. However, it has been possible to obtain patents that protect specific sequences and functional equivalents of those sequences. Furthermore, intellectual property law allows for separate and distinct patents for novel, altered genetic sequences that have improved properties over previously disclosed sequences. We believe that we can obtain patents on certain of our CART-activated receptor sequences because they are not functional equivalents of the natural version of the receptor.

In addition to patent protection, we rely on trade secrets, proprietary know-how, and continuing technological advances to develop and maintain our competitive position. To maintain the confidentiality of our trade secrets and proprietary information, all of our employees are required to enter into and adhere to an employee confidentiality and invention assignment agreement, laboratory notebook policy, and invention disclosure protocol, as a condition of employment. Additionally, our employee confidentiality and invention assignment agreement requires that our employees not bring to us, or use without proper authorization, any third-party proprietary technology. We also require our consultants and collaborators that have access to proprietary property and information to execute confidentiality and invention rights agreements in our favor before beginning their relationship with us. While such arrangements are intended to enable us to better control the use and disclosure of our proprietary property and provide for our ownership of proprietary technology developed on our behalf, they may not provide us with meaningful protection for such property and technology in the event of unauthorized use or disclosure.

Competition

The biotechnology and pharmaceutical industries are highly competitive and are subject to rapid and significant change. We face significant competition from organizations that are pursuing the same or similar technologies. We also face significant competition from organizations that are pursuing drugs

that would compete with the drug candidates we are developing. We may not be able to compete successfully against these organizations, which include many large, well-financed and experienced pharmaceutical and biotechnology companies, as well as academic and research institutions and government agencies.

The focus of our scientific and business strategy is on GPCRs. We believe that many pharmaceutical and biotechnology companies and other organizations have internal drug discovery programs focused on GPCRs. In addition, other companies have attempted to overcome the problems associated with traditional drug screening by embarking on a variety of alternative strategies. Developments by others may render our drug candidates or technologies obsolete or noncompetitive.

Our present competitors with respect to APD356 include Abbott Laboratories, which markets Meridia, and Hoffman-La Roche, the U.S. prescription drug unit of the Roche Group, which markets Xenical. A potential future competitor is Sanofi-Aventis, which is developing rimonabant, a cannabinoid-1 blocker. In addition, we believe that there are potentially competing 5-HT_{2C} programs at Roche and GlaxoSmithKline, Inc.

In addition to the marketed compounds described above under the APD125 discussion, Pfizer/Neurocrine have submitted an NDA for indiplon. We believe Sanofi-Aventis and Eli Lilly, and possibly other companies, are developing potentially competing 5-HT_{2A} programs for insomnia.

Many of our existing and potential competitors have substantially greater drug development capabilities and financial, scientific and marketing resources than we do. Additional consolidation in the pharmaceutical industry may result in even more resources being concentrated with our competitors. As a result, our competitors may be able to devote greater resources than we can to the research, development, marketing and promotion of drug discovery techniques or therapeutic products, or to adapt more readily to technological advances than we can. Accordingly, our competitors may succeed in obtaining patent protection, receiving FDA approval, or commercializing products before we do.

We expect to encounter significant competition for the principal drug candidates we are developing. Companies that complete clinical trials, obtain regulatory approvals and commence commercial sales of their products before us may achieve a significant competitive advantage. Furthermore, we will be competing against companies with substantially greater manufacturing, marketing, distribution and selling capabilities, and any drug candidate that we successfully develop may compete with existing therapies that have long histories of safe and effective use.

We rely on our collaborators for support of development programs and for the manufacturing and marketing of drug candidates. Our collaborators may be conducting multiple drug development efforts within the same disease areas that are the subject of their agreements with us, which may negatively impact the development of drugs that they discover that are subject to our agreements. Generally, our agreements with our collaborators do not preclude them from pursuing development efforts in one or more therapeutic areas of interest in which we have internal development efforts ongoing. In addition, we face and will continue to face intense competition from other companies for such collaborative arrangements, and technological and other developments by others may make it more difficult for us to establish such relationships.

Employees

As of December 31, 2005, we had 314 employees, including 266 in research and development and 48 employees in administration, which includes finance, legal, facilities and other general support areas. None of our employees is covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

UNDERWRITING

We have entered into an underwriting agreement with the underwriters named below. CIBC World Markets Corp. and UBS Securities LLC are acting as representative of the underwriters.

The underwriting agreement provides for the purchase of a specific number of shares of common stock by each of the underwriters. The underwriters' obligations are several, which means that each underwriter is required to purchase a specified number of shares, but is not responsible for the commitment of any other underwriter to purchase shares. Subject to the terms and conditions of the underwriting agreement, each underwriter has severally agreed to purchase the number of shares of common stock set forth opposite its name below:

Underwriter	Number of Shares
CIBC World Markets Corp.	
UBS Securities LLC	
Needham & Company, LLC	
Piper Jaffray & Co.	
SG Cowen & Co., LLC	
Morgan Joseph & Co. Inc.	
Montgomery & Co., LLC	
Total	8,500,000

The underwriters have agreed to purchase all of the shares offered by this prospectus supplement (other than those covered by the over-allotment option described below) if any are purchased. Under the underwriting agreement, if an underwriter defaults in its commitment to purchase shares, the commitments of non-defaulting underwriters may be increased or the underwriting agreement may be terminated, depending on the circumstances.

The shares should be ready for delivery on or about , 2006 against payment in immediately available funds. The underwriters are offering the shares subject to various conditions and may reject all or part of any order. The representative had advised us that the underwriters propose to offer the shares directly to the public at the public offering price that appears on the cover page of this prospectus supplement. In addition, the representative may offer some of the shares to other securities dealers at such price less a concession of $ per share. The underwriters may also allow, and such dealers may reallow, a concession not in excess of $ per share to other dealers. After the shares are released for sale to the public, the representative may change the offering price and other selling terms at various times.

We have granted the underwriters an over-allotment option. This option, which is exercisable for up to 30 days after the date of this prospectus supplement, permits the underwriters to purchase a maximum of 1,275,000 additional shares from us to cover over-allotments. If the underwriters exercise all or part of this option, they will purchase shares covered by the option at the public offering price that appears on the cover page of this prospectus supplement, less the underwriting discount. If this option is exercised in full, the total price to public will be $ and the total proceeds to us will be $. The underwriters have severally agreed that, to the extent the over-allotment option is exercised, they will each purchase a number of additional shares proportionate to the underwriter's initial amount reflected in the foregoing table.

The following table provides information regarding the amount of the discount to be paid to the underwriters by us:

	Per Share	Total Without Exercise of Over-Allotment Option	Total with Full Exercise of Over-Allotment Option
Arena Pharmaceuticals, Inc.	$	$	$

A $1.00 increase (decrease) in the assumed public offering price of $15.74 per share would increase (decrease) the underwriting commission by $0.0575 per share and the total without the exercise of the over-allotment option by approximately $0.5 million and the total with the full exercise of the over-allotment option by approximately $0.6 million.

We estimate that our total expenses of this offering, excluding the underwriting discount, will be approximately $307,000.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act of 1933.

We, our executive officers and directors have agreed to a 90-day "lock up" with respect to shares of common that they beneficially own, including securities that are convertible into shares of common stock and securities that are exchangeable or exercisable for shares of common stock. This means that, subject to certain exceptions, for a period of 90 days following the date of this prospectus supplement, we and such persons may not offer, sell, pledge or otherwise dispose of these securities without the prior written consent of CIBC World Markets Corp. and UBS Securities LLC.

The representatives have informed us that they do not expect discretionary sales by the underwriters to exceed five percent of the shares offered by this prospectus supplement.

Rules of the Securities and Exchange Commission may limit the ability of the underwriters to bid for or purchase shares before the distribution of the shares is completed. However, the underwriters may engage in the following activities in accordance with the rules:

Stabilizing transactions The representative may make bids or purchases for the purpose of pegging, fixing or maintaining the price of the shares, so long as stabilizing bids do not exceed a specified maximum.

Over-allotments and syndicate covering transactions The underwriters may sell more shares of our common stock in connection with this offering than the number of shares than they have committed to purchase. This over-allotment creates a short position for the underwriters. This short sales position may involve either "covered" short sales or "naked" short sales. Covered short sales are short sales made in an amount not greater than the underwriters' over-allotment option to purchase additional shares in this offering described above. The underwriters may close out any covered short position either by exercising their over-allotment option or by purchasing shares in the open market. To determine how they will close the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market, as compared to the price at which they may purchase shares through the over-allotment option. Naked short sales are short sales in excess of the over-allotment option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that, in the open market after pricing, there may be downward pressure on the price of the shares that could adversely affect investors who purchase shares in this offering.

Penalty bids If the representative purchases shares in the open market in a stabilizing transaction or syndicate covering transaction, they may reclaim a selling concession from the underwriters and selling group members who sold those shares as part of this offering.

Passive market making Market makers in the shares who are underwriters or prospective underwriters may make bids for or purchases of shares, subject to limitations, until the time, if ever, at which a stabilizing bid is made.

Similar to other purchase transactions, the underwriters' purchases to cover the syndicate short sales or to stabilize the market price of our common stock may have the effect of raising or maintaining the market price of our common stock or preventing or mitigating a decline in the market price of our common stock. As a result, the price of the shares of our common stock may be higher than the price that might otherwise exist in the open market. The imposition of a penalty bid might also have an effect on the price of the shares if it discourages resales of the shares.

Neither we nor the underwriters makes any representation or prediction as to the effect that the transactions described above may have on the price of the shares. These transactions may occur on the Nasdaq National Market or otherwise. If such transactions are commenced, they may be discontinued without notice at any time.

Notice to Non-U.S. Investors

The offering is exclusively conducted under applicable private placement exemptions and therefore it has not been and will not be notified to, and this document or any other offering material relating to the shares has not been and will not be approved by, the Belgian Banking, Finance and Insurance Commission ("Commission bancaire, financière et des assurances/Commissie voor het Bank, Financie en Assurantiewezen"). Any representation to the contrary is unlawful.

Each underwriter has undertaken not to offer sell, resell, transfer or deliver, or to take any steps thereto, directly or indirectly, any shares, and not to distribute or publish this document or any other material relating to the shares or to the offering in a manner which would be construed as: (a) a public offering under the Belgian Royal Decree of 7 July 1999 on the public character of financial transactions; or (b) an offering of securities to the public under Directive 2003/71/EC which triggers an obligation to publish a prospectus in Belgium. Any action contrary to these restrictions will cause the recipient and us to be in violation of the Belgian securities laws.

No regulatory consent or approval has been sought in respect of the offering in Jersey and it must be distinctly understood that the Jersey Financial Services Commission is not responsible for our financial soundness or the correctness of any statements made or opinions expressed in connection with us. The offer of shares is personal to the person to whom this prospectus is being delivered, and an application for the shares will only be accepted from such person. This prospectus is being issued to persons in Jersey in reliance on the Financial Services (Investment Business (Overseas Persons Exemption)) (Jersey) Order 2001 and accordingly the provisions of the Financial Services (Jersey) Law 1998 do not apply to CIBC World Markets Corp. or UBS Securities LLC, or their respective affiliates, or any other persons who, in connection with this offer, are dealing with or carrying on other specified investment business with persons in Jersey.

This prospectus relates to a private placement and does not constitute an offer to the public in Guernsey to subscribe for the shares offered hereby. No regulatory consent or approval has been sought in respect of the offering in Guernsey and it must be distinctly understood that the Guernsey Financial Services Commission is not responsible for our financial soundness or the correctness of any statements made or opinions expressed in connection with us. The offer of shares is personal to the person to whom this prospectus is being delivered, and an application for the shares will only be accepted from such person. The offering is only being promoted in or from within Guernsey to persons licensed under the Protection of Investors (Bailiwick of Guernsey) Law, 1987 (as amended), the Insurance Business (Guernsey) Law, 1986 (as amended), the Banking Supervision (Bailiwick of

Guernsey) Law, 1994 or the Regulation of Fiduciaries, Administration Businesses and Company Directors, etc. (Bailiwick of Guernsey) Law, 2000.

Neither this prospectus nor any other offering material relating to the shares has been submitted to the clearance procedures of the *Autorité des marchés financiers* in France. The shares have not been offered or sold and will not be offered or sold, directly or indirectly, to the public in France. Neither this prospectus nor any other offering material relating to the shares has been or will be: (a) released, issued, distributed or caused to be released, issued or distributed to the public in France; or (b) used in connection with any offer for subscription or sale of the shares to the public in France. Such offers, sales and distributions will be made in France only: (i) to qualified investors, or *investisseurs qualifies*, and/or to a restricted circle of investors, or *cercle restreint d'investisseurs*, in each case investing for their own account, all as defined in and in accordance with Articles L.411-2, D.411-1, D.411-2, D.734-1, D.744-1, D.754-1 and D.764-1 of the French *Code monétaire et financier*; (ii) to investment services providers authorised to engage in portfolio management on behalf of third parties; or (iii) in a transaction that, in accordance with article L.411-2-II-1°-or-2°-or 3° of the French *Code monétaire et financier* and article 211-2 of the General Regulations, or *Règlement Général* of the *Autorité des marchés financiers*, does not constitute a public offer, or *appel public à l'épargne*. Such shares may be resold only in compliance with Articles L.411-1, L.411-2, L.412-1 and L.621-8 through L.621-8-3 of the French *Code monétaire et financier*.

In relation to each member state of the European Economic Area which has implemented the Prospectus Directive, which we refer to each as a relevant member state, each underwriter has represented and agreed that with effect from and including the date on which the Prospectus Directive is implemented in that member state, which we refer to as the relevant implementation date, it has not made and will not make an offer of shares to the public in that relevant member state, except that it may, with effect from and including the relevant implementation date, make an offer of shares to the public in that relevant member state:

(a) in (or in Germany, where the offer starts within) the period beginning on the date of publication of a prospectus in relation to the shares, which has been approved by the competent authority in that relevant member state or, where appropriate, approved in another relevant member state and notified to the competent authority in that relevant member state, all in accordance with the Prospectus Directive and ending on the date which is 12 months after the date of such publication;

(b) at any time to legal entities which are authorised or regulated to operate in the financial markets or, if not so authorised or regulated, whose corporate purpose is solely to invest in shares;

(c) at any time to any legal entity which has two or more of (1) an average of at least 250 employees during the last financial year; (2) a total balance sheet of more than €43,000,000; and (3) an annual net turnover of more than €50,000,000, as shown in its last annual or consolidated accounts; or

(d) at any time in any other circumstances which do not require the publication by the Company of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an "offer of shares to the public" in relation to any shares in any relevant member state means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe for the shares, as the same may be varied in that member state by any measure implementing the Prospectus Directive in that member state and the expression Prospectus Directive means Directive 2003/71/EC and includes any relevant implementing measure in each relevant member state.

Each underwriter has represented, warranted and agreed that:

(a) it has only communicated or caused to be communicated and will only communicate or cause to be communicated any invitation or inducement to engage in investment activity (within the meaning of section 21 of the Financial Services and Markets Act 2000, or FSMA) received by it in connection with the issue or sale of any shares in circumstances in which section 21(1) of the FSMA does not apply to us; and

(b) it has complied with and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the shares in, from or otherwise involving the United Kingdom.

In the State of Israel, the shares offered hereby may not be offered to any person or entity other than the following:

(a) a fund for joint investments in trust (i.e., mutual fund), as such term is defined in the Law for Joint Investments in Trust, 5754-1994, or a management company of such a fund;

(b) a provident fund as defined in Section 47(a)(2) of the Income Tax Ordinance of the State of Israel, or a management company of such a fund;

(c) an insurer, as defined in the Law for Oversight of Insurance Transactions, 5741-1981, (d) a banking entity or satellite entity, as such terms are defined in the Banking Law (Licensing), 5741-1981, other than a joint services company, acting for their own account or fro the account of investors of the type listed in Section 15A(b) of the Securities Law 1968;

(d) a company that is licensed as a portfolio manager, as such term is defined in Section 8(b) of the Law for the Regulation of Investment Advisors and Portfolio Managers, 5755-1995, acting on its own account or for the account of investors of the type listed in Section 15A(b) of the Securities Law 1968;

(e) a company that is licensed as an investment advisor, as such term is defined in Section 7(c) of the Law for the Regulation of Investment Advisors and Portfolio Managers, 5755-1995, acting on its own account;

(f) a company that is a member of the Tel Aviv Stock Exchange, acting on its own account or for the account of investors of the type listed in Section 15A(b) of the Securities Law 1968;

(g) an underwriter fulfilling the conditions of Section 56(c) of the Securities Law, 5728-1968;

(h) a venture capital fund (defined as an entity primarily involved in investments in companies which, at the time of investment, (i) are primarily engaged in research and development or manufacture of new technological products or processes and (ii) involve above-average risk);

(i) an entity primarily engaged in capital markets activities in which all of the equity owners meet one or more of the above criteria; and

(j) an entity, other than an entity formed for the purpose of purchasing shares in this offering, in which the shareholders equity (including pursuant to foreign accounting rules, international accounting regulations and U.S. generally accepted accounting rules, as defined in the Securities Law Regulations (Preparation of Annual Financial Statements), 1993) is in excess of NIS 250 million.

Any offeree of the shares offered hereby in the State of Israel shall be required to submit written confirmation that it falls within the scope of one of the above criteria. This prospectus will not be distributed or directed to investors in the State of Israel who do not fall within one of the above criteria.

The offering of the shares offered hereby in Italy has not been registered with the Commissione Nazionale per la Società e la Borsa, or CONSOB, pursuant to Italian securities legislation and, accordingly, the shares offered hereby cannot be offered, sold or delivered in the Republic of Italy, or Italy, nor may any copy of this prospectus or any other document relating to the shares offered hereby be distributed in Italy other than to professional investors (*operatori qualificati*) as defined in Article 31, second paragraph, of CONSOB Regulation No. 11522 of 1 July, 1998 as subsequently amended. Any offer, sale or delivery of the shares offered hereby or distribution of copies of this prospectus or any other document relating to the shares offered hereby in Italy must be made:

(a) by an investment firm, bank or intermediary permitted to conduct such activities in Italy in accordance with Legislative Decree No. 58 of 24 February 1998 and Legislative Decree No. 385 of 1 September 1993, which we refer to as the Banking Act;

(b) in compliance with Article 129 of the Banking Act and the implementing guidelines of the Bank of Italy; and

(c) in compliance with any other applicable laws and regulations and other possible requirements or limitations which may be imposed by Italian authorities.

This prospectus has not been approved by or registered with the Norwegian Stock Exchange or the Norwegian register of Business Enterprises under Chapter 5 of the Norwegian Securities Trading Act 1997. No shares have been offered or sold, and may not be offered or sold, to any persons in Norway in any way that would constitute an offer to the public other than to persons who invest in securities as part of their professional activity and who are registered with the Oslo Stock Exchange in this capacity, or otherwise only in circumstances where an exemption from the duty to publish a prospectus under the Norwegian Securities Trading Act 1997 is applicable.

The shares offered pursuant to this will not be offered, directly or indirectly, to the public in Switzerland and this prospectus does not constitute a public offering prospectus as that term is understood pursuant to art. 652a or art. 1156 of the Swiss Federal Code of Obligations. We have not applied for a listing of the shares being offered pursuant to this prospectus on the SWX Swiss Exchange or on any other regulated securities market, and consequently, the information presented in this prospectus does not necessarily comply with the information standards set out in the relevant listing rules. The shares being offered pursuant to this prospectus have not been registered with the Swiss Federal Banking Commission as foreign investment funds, and the investor protection afforded to acquirers of investment fund certificates does not extend to acquirers of securities.

Investors are advised to contact their legal, financial or tax advisers to obtain an independent assessment of the financial and tax consequences of an investment in the shares.

No marketing of any financial products or services has been or will be made from within the United Arab Emirates and no subscription to any securities, financial products or financial services may or will be consummated within the United Arab Emirates. Neither CIBC World Markets Corp. nor UBS Securities LLC are licensed brokers or dealers or investment advisors under the laws applicable in the United Arab Emirates and do not advise individuals resident in the United Arab Emirates as to the appropriateness of investing in or purchasing or selling securities or other financial products. Nothing contained in this document is intended to constitute investment, legal, tax, accounting or other professional advice. This document is for your information only and nothing in this document is intended to endorse or recommend a particular course of action. You should consult with an appropriate professional for specific advice rendered on the basis of your situation.

LEGAL MATTERS

Selected legal matters with respect to the validity of common stock offered by this prospectus supplement will be passed upon for us by Cooley Godward LLP, San Diego, California. Certain legal matters in connection with the common stock offered in this prospectus supplement will be passed upon for the underwriters by Latham & Watkins LLP, Menlo Park, California.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2004, and management's assessment of the effectiveness of our internal control over financial reporting as of December 31, 2004, as set forth in their reports, which are incorporated by reference in this prospectus supplement and elsewhere in the registration statement. Our financial statements and management's assessment are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We have filed with the SEC a registration statement on Form S-3 under the Securities Act with respect to the shares of common stock we are offering under this prospectus supplement. This prospectus supplement and the accompanying prospectus do not contain all of the information set forth in the registration statement and the exhibits to the registration statement. For further information with respect to us and the securities we are offering under this prospectus supplement, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement. We also file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy the registration statement, as well as any other material we file with the SEC, at the SEC's Public Reference Room at 450 Fifth Street, N.W., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for more information on the Public Reference Room. The SEC maintains an Internet site that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC, including Arena. The SEC's Internet site can be found at http://www.sec.gov.

IMPORTANT INFORMATION INCORPORATED BY REFERENCE

The SEC allows us to "incorporate by reference" into this prospectus supplement the information we file with it, which means that we can disclose important information to you by referring you to those documents. Information incorporated by reference is part of this prospectus supplement. Later information filed with the SEC will update and supersede this information. The SEC's Internet site can be found at http://www.sec.gov.

We incorporate by reference the documents listed below and any future filings made with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act until this offering is completed:

- our Annual Report on Form 10-K for the year ended December 31, 2004;
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2005, June 30, 2005 and September 30, 2005;
- our Current Reports on Form 8-K (other than information furnished rather than filed), filed with the SEC on January 13, 2005, January 21, 2005, February 1, 2005, February 9, 2005, April 25, 2005, May 5, 2005, May 11, 2005, June 7, 2005, June 30, 2005, August 26, 2005, October 11, 2005, December 13, 2005, December 21, 2005 and December 30, 2005.
- the description of our Stockholders Rights Plan contained in our registration statement on Form 8-A filed on November 15, 2002, as amended on December 30, 2003, including any amendments or reports filed for the purposes of updating this description; and
- the description of our common stock contained in our registration statement on Form 8-A filed on July 26, 2000, including any amendments or reports filed for the purposes of updating this description.

You may request a copy of these filings, at no cost, by contacting us at:

Arena Pharmaceuticals, Inc.
Attention: Investor Relations
6166 Nancy Ridge Drive
San Diego, CA 92121
Telephone number: (858) 453-7200

In accordance with Section 412 of the Exchange Act, any statement contained in a document incorporated by reference herein shall be deemed modified or superseded to the extent that a statement contained herein or in any other subsequently filed document which also is or is deemed to be incorporated by reference herein modifies or supersedes such statement.

PROSPECTUS

Arena Pharmaceuticals, Inc.

Common Stock

Our common stock is listed on the Nasdaq National Market under the symbol "ARNA." On November 1, 2005, the last reported sale price of our common stock on the Nasdaq National Market was $10.21 per share.

This prospectus and the accompanying prospectus supplement will allow us to sell up to 10,000,000 shares of our common stock over time in one or more offerings. Each time we offer shares, we will provide you with a supplement to this prospectus. You should read this prospectus, the information incorporated by reference in this prospectus and any prospectus supplement carefully before you invest.

Investing in our common stock involves a high degree of risk. See "Risk Factors" beginning on page 2 of this prospectus and as updated in our future filings made with the Securities and Exchange Commission, which are incorporated by reference in this prospectus.

This prospectus may not be used to offer or sell any securities unless accompanied by a prospectus supplement.

The securities may be sold by us to or through underwriters or dealers, directly to purchasers or through agents designated from time to time. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus. If any underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such underwriters and any applicable discounts or commissions and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds we expect to receive from such sale will also be set forth in a prospectus supplement. This prospectus may not be used to sell any of the common stock unless accompanied by a 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 is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is November 16, 2005.

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We are not making an offer to sell or seeking an offer to buy shares of our common stock under this prospectus or any applicable prospectus supplement in any jurisdiction where the offer or sale is not permitted. The information contained in this prospectus, any applicable prospectus supplement and the documents incorporated by reference herein and therein are accurate only as of their respective dates, regardless of the time of delivery of this prospectus or any sale of a security.

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, using a "shelf" registration process. Under this shelf registration statement, we may sell up to 10,000,000 shares of our common stock in one or more offerings. Each time we sell any of our common stock under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of that offering. We may also add, update or change in a prospectus supplement any of the information contained in this prospectus or in documents we have incorporated by reference into this prospectus. This prospectus, together with any applicable prospectus supplement and the documents incorporated by reference into this prospectus, include all material information relating to this offering. You should carefully read both this prospectus and any applicable prospectus supplement together with the additional information described under "Where You Can Find More Information" before buying common stock in this offering.

SUMMARY

Arena Pharmaceuticals, Inc.

We are a clinical-stage biopharmaceutical company focusing on the discovery, development and commercialization of small molecule drugs in four major therapeutic areas: metabolic, cardiovascular, inflammatory and central nervous system diseases. We are developing a broad pipeline of compounds that act on an important class of drug targets called G protein-coupled receptors, or GPCRs, using our knowledge of GPCRs and our technologies, including CART (Constitutively Activated Receptor Technology) and Melanophore. We have three internally discovered, clinical-stage product candidates. Our most advanced clinical compound, APD356, a selective 5-HT2C serotonin receptor agonist for the treatment of obesity, is in a Phase 2b clinical trial. Our lead product candidate for the treatment of insomnia, APD125, a compound with a novel mechanism of action (a selective 5-HT2A receptor inverse agonist), is scheduled to begin a Phase 2 clinical trial by the end of 2005. As part of our collaboration with Merck & Co., Inc., our product candidate for the treatment of atherosclerosis and related disorders is in a Phase 1 clinical trial. We also have an active collaboration with Ortho-McNeil, Inc., a Johnson & Johnson company, for the treatment of type 2 diabetes.

The pharmaceutical marketplace in which we operate includes many large, well-established companies competing with us to develop treatments for the same diseases and disorders. See "Risk Factors."

Arena Pharmaceuticals® and Arena® are registered service marks of Arena. CART is an unregistered service mark of Arena. Our corporate offices are located at 6166 Nancy Ridge Drive, San Diego, California 92121. Our telephone number is (858) 453-7200. Our website address is www.arenapharm.com. Information contained in our website does not constitute part of this prospectus.

Unless otherwise specified or required by context, references in this prospectus to "we," "us," "our" and "Arena" refer to Arena Pharmaceuticals, Inc. and its subsidiary on a consolidated basis.

RISK FACTORS

An investment in our common stock involves a high degree of risk. You should consider carefully the risks described below, together with other information in this prospectus, any applicable prospectus supplement and the information incorporated by reference herein and therein, before you make a decision to invest in our common stock. If any of the risks described below actually occur, our business, operating results, prospects or financial condition could be materially and adversely affected. This could cause the trading price of our common stock to decline and you may lose all or part of your investment. Moreover, the risks described below are not the only ones that we face. Additional risks not currently known to us or that we currently deem immaterial may also affect our business, operating results, prospects or financial condition.

Risks Relating to Our Business

We will need additional funds to conduct our planned research and development efforts, and we may not be able to obtain such funds.

We had losses of $57.5 million for the nine months ended September 30, 2005, and we had an accumulated deficit of $226.3 million from our inception in April 1997 through September 30, 2005. Our losses have resulted in large part from the significant research and development expenditures we have made in seeking to identify and validate new drug targets and develop compounds that could become marketed drugs.

We expect that our operating expenses over the next several years will be significant and that we will continue to have significant operating losses in the near term, even if we or our collaborators are successful in advancing our compounds or partnered compounds.

We do not have any commercial products. It takes many years and potentially hundreds of millions of dollars to successfully develop a preclinical or early clinical compound into a marketed drug. We have substantially less money than we will need to successfully develop a compound into a marketed drug. Additional funding may not be available to us or may not be available on terms that you or we believe are favorable. If additional funding is not available, we may have to delay, reduce the scope of or eliminate one or more of our research or development programs.

Our stock price could decline significantly based on the results and timing of our clinical trials.

We expect to announce results from our Phase 2b clinical trial of our most advanced product candidate, APD356 for obesity, around the end of the year. In addition, we also expect to announce additional safety results from our recent Phase 1 clinical trial for our second most advanced product candidate, APD125 for insomnia. These results may not be favorable or viewed favorably by us or third parties, including investors, analysts and potential collaborators. Biotechnology company stock prices have declined significantly where clinical results were not favorable, were perceived negatively or otherwise did not meet expectations. Failure to initiate or delays in our clinical trials of APD356, APD125 or of any of our other product candidates, or unfavorable results or negative perceptions regarding any of such trials, could cause our stock price to decline significantly.

Clinical trials for our product candidates are expensive, time consuming, may be interrupted and their outcome is uncertain.

Clinical trials are very expensive and difficult to design and implement. The clinical trial process is also time consuming. Assuming favorable results, we estimate that the clinical trials of our most advanced product candidates will continue for several years. Before we can obtain regulatory approval for the commercial sale of any product candidate that we wish to develop, we are required to complete extensive clinical trials in humans to demonstrate its safety and efficacy. The timing of the

commencement, continuation and completion of clinical trials may be subject to significant delays relating to various causes, including:

- lack of effectiveness during the clinical trials;
- unforeseen or serious side effects experienced by study participants or other safety issues;
- slower than expected rates of patient recruitment and enrollment;
- delays or inability to manufacture or obtain sufficient quantities of materials for use in clinical trials;
- delays in obtaining regulatory approvals to commence a study or "clinical holds" or other delays requiring suspension or termination of a study by a regulatory agency such as the FDA after a study is commenced;
- delays in identifying and reaching agreement on acceptable terms with prospective clinical trial sites;
- uncertainty regarding proper dosing;
- scheduling conflicts with participating clinicians and clinical institutions;
- inability or unwillingness of medical investigators to follow our clinical protocols; or
- difficulty in maintaining contact with subjects during or after treatment, which may result in incomplete data.

The results of preclinical studies and completed clinical trials are not necessarily predictive of future results, and our current product candidates may not have favorable results in later studies or trials.

Preclinical studies and Phase 1 and Phase 2 clinical trials are not primarily designed to test the efficacy of a product candidate, but rather to test safety, to study pharmacokinetics and pharmacodynamics, and to understand the product candidate's side effects at various doses and schedules. Success in preclinical or completed clinical trials does not ensure that later large-scale trials will be successful nor does it necessarily predict future results. Favorable results in early trials may not be repeated in later trials.

A number of companies in the biotechnology industry have suffered significant setbacks in advanced clinical trials, even after promising results in earlier trials. Clinical results are frequently susceptible to varying interpretations that may delay, limit or prevent regulatory approvals. Negative or inconclusive results or adverse medical events during a clinical trial could cause a clinical trial to be delayed, repeated or terminated. In addition, failure to construct appropriate clinical trial protocols could result in the test or control group experiencing a disproportionate number of adverse events and could cause a clinical trial to be delayed, repeated or terminated.

Clinical trials of our most advanced product candidates, APD356 and ADP125, have been conducted only in small numbers of subjects. Preclinical data and the limited clinical results we have obtained for APD356 and APD125 may not predict results from studies in larger numbers of subjects drawn from more diverse populations treated for longer periods of time or, in the case with APD125, when patients with insomnia are studied rather than normal volunteers, and also may not predict the ability of APD356 or APD125 to achieve or sustain the desired effects in the intended population or to do so safely.

We have developed APD356 to more selectively stimulate the 5-HT2C serotonin receptor because we believe this selectivity may avoid the cardiovascular side effects associated with fenfluramine and dexfenfluramine, two serotonin-releasing agents and non-selective serotonin receptor agonists, both of which were withdrawn from the market in 1997 after reported incidences of heart valve disease and

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pulmonary hypertension associated with their usage. We may not be correct in this belief, however, and APD356's selectivity profile may not avoid the undesired side effects. Moreover, the potential relationship between the activity of APD356 and fenfluramine and dexfenfluramine may result in increased FDA regulatory scrutiny of the safety of APD356 and may raise potential adverse publicity in the marketplace. In response to our Investigational New Drug submission for APD356, the FDA recommended we assess the abuse potential and requested that we provide our plans for cardiac valve monitoring during Phase 2 and Phase 3 clinical trials. We have submitted to the FDA our plan for cardiac valve monitoring and our communication with the FDA on these issues is expected to be on-going.

We have developed APD125 to selectively inhibit the 5-HT2A serotonin receptor because we believe this mechanism may be better tolerated and improve sleep quality and maintenance as compared to existing sleep therapies. Preclinical data and the results from our Phase 1 clinical trial in subjects with normal sleep patterns may not predict APD125's effects on sleep quality, sleep maintenance or sleep onset latency in patients with insomnia.

We will be required to demonstrate through larger-scale clinical trials that these product candidates are safe and effective for use in a diverse population before we can seek regulatory approvals for their commercial sale. There is typically an extremely high rate of attrition from the failure of product candidates proceeding through clinical trials. To date, long-term safety and efficacy have not yet been demonstrated in clinical trials for any of our product candidates. If APD356 or APD125 fails to demonstrate sufficient safety and efficacy in any clinical trial, we will experience potentially significant delays in, or decide to abandon development of, that product candidate. If we abandon or are delayed in our development efforts related to APD356 or APD125, or any other product candidate, we may not be able to generate sufficient revenues to continue our operations at the current level or become profitable, our reputation in the industry and in the investment community would likely be significantly damaged, it may not be possible to complete financings, and our stock price would likely decrease significantly.

Our research and development programs are in early stages of development, and may not result in the commencement of clinical trials.

Our research and development programs are in the discovery or preclinical stage of development. The process of discovering compounds with therapeutic potential is expensive, time consuming and unpredictable. Similarly, the process of conducting preclinical studies of compounds that we discover requires the commitment of a substantial amount of our technical and financial resources andpersonnel. We may not discover additional compounds with therapeutic potential, and any of the compounds for which we are conducting preclinical studies may not result in the commencement of clinical trials. If we are unable to identify and develop new product candidates, we may not be able to maintain a clinical development pipeline or generate revenues.

The technologies on which we rely may not result in the discovery or development of commercially viable products.

Our GPCR technologies include technologies that allow us to discover drug-like compounds that act on receptor subtypes of known GPCRs and novel GPCRs where the native ligands have not been identified. These methods of identifying, prioritizing and screening molecular targets are unproven approaches that may not result in the regulatory approval and commercialization of any therapeutic products. We do not believe that there are any drugs on the market that have been discovered or developed using our proprietary technologies. If we are unable to identify additional product candidates using our proprietary drug discovery technologies, we may not be able to maintain a clinical development pipeline or generate revenues.

Another company, organization or individual could have, or could develop, a technology targeting GPCRs to discover and develop compounds into drugs more effectively or efficiently than our screening and other technologies. Such a technology could render our technologies, in particular our constitutively activated receptor technology, or CART, and Melanophore technology, obsolete or noncompetitive.

Our product candidates are subject to extensive regulation, which can be costly and time consuming, cause unanticipated delays, or prevent the receipt of the required approvals to commercialize products.

The clinical development, manufacturing, labeling, packaging, storage, record-keeping, advertising, promotion, export, marketing, and distribution of our product candidates are subject to extensive regulation by the FDA and other regulatory agencies in the United States and by comparable governmental authorities in foreign markets. Neither we nor our collaborators are permitted to market our potential products in the United States until we receive regulatory approval from the FDA. Neither we nor our collaborators have received marketing approval for any of our product candidates. The process of obtaining regulatory approval is expensive, often takes many years, and can vary substantially based upon the type, complexity and novelty of the product involved. A New Drug Application, or NDA, must be supported by extensive clinical and preclinical data regarding manufacturing, process and controls to demonstrate the safety and effectiveness of the product candidate. Approval policies or regulations may change. Moreover, failure to comply with the FDA and other applicable foreign and United States regulatory requirements may subject us to administrative or judicially imposed sanctions. These include warning letters, civil and criminal penalties, injunctions, product seizure and detention, product recalls, total or partial suspension of production, and refusal to approve pending NDAs, or supplements to approved NDAs.

In addition, we have not previously filed NDAs with the FDA. This lack of experience may impede our ability to obtain FDA approval in a timely manner, if at all, for our product candidates for which development and commercialization is our responsibility. Despite the time and expense invested, regulatory approval is very uncertain and never guaranteed and we could encounter problems that cause us to abandon clinical trials or to repeat or perform additional preclinical testing and clinical trials. The FDA has substantial discretion in the drug approval process. The number of preclinical studies and clinical trials that will be required for FDA approval varies depending on the product candidate, the disease or condition that the product candidate is designed to address, and the regulations applicable to any particular product candidate. The FDA can delay, limit or deny approval of a product candidate for many reasons, including:

not finding a product candidate sufficiently safe and/or effective;

not finding the data from preclinical testing and clinical trials sufficient;

not approving of our or a third-party manufacturers' processes or facilities; or

changes in its approval policies or the adoption of new regulations.

Because, in part, of the early stage of our product candidate research and development process, we cannot predict whether or not regulatory approval will be obtained for any product we develop. Only two of our product candidates, APD356 and APD125, are undergoing clinical trials by us, and only one of our product candidates is undergoing clinical trials by a partner, Merck. Compounds developed by us, alone or with other parties, may not prove to be safe and effective in clinical trials and may not meet all of the applicable regulatory requirements needed to receive marketing approval. Administering any of our product candidates to humans may produce undesirable side effects. These side effects could interrupt, delay or halt clinical trials of our product candidates and could result in the FDA or other regulatory authorities denying approval of our product candidates for any or all of the targeted indications. If regulatory approval of a product is granted, the approval will be limited to those disease

states and conditions for which the product is demonstrated through clinical trials to be sufficiently safe and effective. Failure to obtain regulatory approval will delayor prevent us from commercializing products. These risks also apply to the development activities of our collaborators, and we do not expect any drugs resulting from our collaborators' research and development efforts to be commercially available for many years, if ever. The FDA, other regulatory authorities, our collaborators or we may suspend or terminate clinical trials at any time. Any failure or significant delay in completing clinical trials for our product candidates, or in receiving regulatory approval for the sale of any drugs resulting from our product candidates, may severely harm our business and reputation.

If we are not successful in advancing our lead programs, we may have to curtail some of our activities.

If we are not successful in achieving additional milestones under our cardiovascular collaboration with Merck or our diabetes collaboration with Ortho-McNeil, or developing or partnering APD356 or APD125 or any of our other lead programs, we may not be able to raise additional capital or generate significant partnering revenues in the short term. If we do not receive additional capital or partnering revenues, we may need to license some or all of our programs on financial terms that are unfavorable to us. Also, without additional capital or partnering revenues, we would need to re-evaluate our strategy of moving multiple drug discovery and development programs forward while at the same time maintaining our research and discovery capabilities. Based on such evaluation, we may need to significantly curtail some of our current and planned programs and expenditures. We do not know what programs, if any, we would need to curtail, but we believe narrowing our pipeline would reduce our opportunity for success.

Our revenues depend upon the actions of our existing and potential collaborators.

Our revenues were $13.7 million and $12.8 million for the years ended December 31, 2004 and 2003, respectively, and were $17.4 million for the nine months ended September 30, 2005. Our revenues depend upon the success of our existing collaborations and on our ability to enter into new collaborations. We will receive little additional revenues from our existing collaborators if our own or our collaborators' research, development or, ultimately, marketing efforts are unsuccessful, or if our agreements are terminated early. Typically, our collaborators (and not us) control the development of compounds into drugs after we have met early preclinical scientific milestones, and we are not entitled to the more significant milestone payments under our agreements until our collaborators have advanced compounds in clinical testing. Only one of our partners, Merck, has advanced one of our compounds into clinical testing and paid us the applicable milestone. We cannot guarantee that any of the other development, approval or sales milestones in our existing or future collaborations will be satisfied, or that we will receive any payments for the achievement of those other milestones.

For the year ended December 31, 2004, revenues recognized under our collaboration with Merck represented approximately 95% of our total revenues. For the nine months ended September 30, 2005, 100% of our revenues were from our collaborations with Merck and Ortho-McNeil. We expect substantially all of our revenues for the remaining three months of 2005 will be derived from our collaborations with Merck and Ortho-McNeil. Our revenues will be materially impacted if:

- our agreement with either Merck or Ortho-McNeil is terminated;
- our collaborators do not devote their time and financial resources to develop compounds under our collaborations;
- our collaborators dispute whether we have achieved a milestone, rights to a particular receptor or compound, or other terms of our agreements;
- our collaborators use alternative technologies to our technologies and compete with us in developing products; or

our collaborators experience failures in the discovery or development of compounds identified with our technologies or in the clinic or marketplace with other products that cause them to discontinue or slow down our collaboration.

Our ability to enter into new collaborations depends on the outcomes of our preclinical and clinical testing. We do not control these outcomes. In addition, even if our testing is successful, pharmaceutical companies may not partner with us on terms that we believe are acceptable until we have advanced our product candidates into the clinic and, possibly, through later-stage clinical trials, if at all.

Our collaboration agreements with Merck and Ortho-McNeil may be terminated in certain circumstances.

The term of our amended collaborative research program with Merck is three years from October 21, 2004. Merck can terminate this program: (i) for "Technical Grounds," by giving 30 days prior notice, if both Merck and we agree that Technical Grounds have occurred; or (ii) in the event of our change in control (as defined in the agreement), by giving 30 days prior notice. Technical Grounds include circumstances where: (1) our joint research committee (a committee of an equal number of Merck and our representatives) concludes that (a) a significant adverse event affecting all the targets, all program compounds and all active compounds under the program has arisen during the conduct of the program, or (b) continuation of the program is no longerscientifically promising because the role of all the targets proves incorrect, or none of the targets are valid as a suitable target for development of a pharmaceutical product; or (2) Merck's patent department, upon consultation with our patent attorneys, makes a reasonable determination that valid third-party patent rights block the achievement of significant program goals.

In addition, either party can terminate the agreement if the other party breaches its material obligations under the agreement by causes and reasons within its control, has not cured such breach within 90 days of receiving a letter requesting such cure, and there is no dispute as to whether such breach has occurred. In lieu of terminating the agreement, however, Merck can terminate the research program and certain other aspects of the agreement after giving 90 days prior notice if we materially breach our obligations during the course of the program and fail to cure such breach, if such default cannot be cured within such 90-day period, or if we do not commence and diligently continue good faith efforts to cure such default during such period.

Our agreement with Ortho-McNeil will continue until the expiration of Ortho-McNeil's payment obligations for research funding, milestone payments and royalties, unless the agreement is terminated earlier by either party. We and Ortho-McNeil each have the right to terminate the agreement early if the other party commits an uncured material breach of its obligations. Further, Ortho-McNeil may terminate the agreement without cause during the term of the research program, provided that in such event it pays us the balance of its research funding obligation in a lump sum, unless the termination is due to a change of control of Arena (as defined in the agreement), in which case Ortho-McNeil may terminate either the agreement or the research program under the agreement, without the payment of additional research funding to us. At any time after the end of the research program, Ortho-McNeil may terminate the agreement by providing us at least 60 days prior written notice. Upon termination of the agreement, all rights to the compounds developed under the collaboration will revert to us.

We may have conflicts with our collaborators that could delay or prevent the development or commercialization of our product candidates.

We may have conflicts with our collaborators, such as conflicts concerning the interpretation of preclinical or clinical data, the achievement of milestones, or the ownership of intellectual property developed during the collaboration. If any conflicts arise with Ortho-McNeil, Merck or any other collaborator, such collaborator may act in a manner that is adverse to our best interests. Any such

disagreement could result in one or more of the following, each of which could delay or prevent the development or commercialization of our product candidates, and in turn prevent us from generating revenues:

- unwillingness on the part of a collaborator to pay us research funding, milestone payments or royalties we believe are due to us under a collaboration;
- uncertainty regarding ownership of intellectual property rights arising from our collaborative activities, which could prevent us from entering into additional collaborations;
- unwillingness on the part of a collaborator to keep us informed regarding the progress of its development and commercialization activities or to permit public disclosure of the results of those activities; or
- slowing or cessation of a collaborator's development or commercialization efforts with respect to our product candidates.

Drug discovery and development is intensely competitive in the therapeutic areas on which we focus. If our competitors develop treatments that are approved faster, marketed better or demonstrated to be more effective or safer than our product candidates, our commercial opportunity will be reduced or eliminated.

We focus our efforts on GPCRs. Because GPCRs are an important target class for drug discovery efforts, we believe that many pharmaceutical and biotechnology companies and other organizations have internal drug discovery programs focused on GPCRs. Many of the drugs that we or our collaborators are attempting to discover and develop would compete with existing therapies. In addition, many companies are pursuing the development of new drugs that target the same diseases and conditions that we target. Many of our competitors, particularly large pharmaceutical companies, have substantially greater research and development capabilities and greater financial, scientific and human resources than we do. Companies that complete clinical trials, obtain required regulatory agency approvals and commence commercial sale of their drugs before we do for the same indication may achieve a significant competitive advantage, including certain patent and FDA marketing exclusivity rights. In addition, our competitors may develop drugs with fewer side effects, more desirable characteristics (such as route of administration or frequency of dosing) or greater efficacy than our drugs, if any, for the same indication. Any results from our research and development efforts, or from our joint efforts with our existing or any future collaborators, may not compete successfully with existing or newly discovered products or therapies.

Consolidation and setbacks in our industry and our or our collaborator's inability to obtain acceptable prices for drugs could make partnering more difficult and diminish our revenues.

Consolidation in the pharmaceutical and biotechnology industry, setbacks caused by safety concerns relating to high-profile drugs like Vioxx and Celebrex, competition from generic drugs and litigation may have an adverse effect on us. In addition, pharmaceutical companies may be less willing to enter into new collaborations or continue existing collaborations if they are integrating a new operation as a result of a merger or acquisition, if their therapeutic areas of focus change following a merger, or if they have reduced research budgets as a result of some financial setback.

Our and our collaborators' ability to commercialize future drugs will depend in part on government regulation and the reimbursement policies of government authorities, private health insurers and other third-party payers. Government and third-party payers are increasingly attempting to contain healthcare costs by limiting coverage and reimbursement levels for new drugs. These efforts may limit our commercial opportunities by reducing the amount a potential collaborator is willing to pay to license our programs or product candidates in the future by reducing the potential revenues that we and our collaborators could generate from drug sales.

We rely on third parties to conduct our clinical trials. If those parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to advance our product candidates in a timely manner or at all.

In the course of our discovery, preclinical testing and clinical trials, we have relied and continue to rely on third parties, including laboratories, investigators, clinical research organizations and manufacturers, to perform critical services for us. For example, we are relying on contract clinical sites to conduct our clinical trials for APD356 and APD125. Clinical research organizations will be responsible for many aspects of the trials, including finding and enrolling subjects for testing and administering the trials. These third parties may not be available when we need them or, if they are available, may not comply with all regulatory and contractual requirements or may not otherwise perform their services in a timely or acceptable manner. These independent third parties may also have relationships with other commercial entities, some of which may compete with us. As a result of our dependence on third parties, we may face delays or failures outside of our direct control. These risks also apply to the development activities of our collaborators, and we do not expect any drugs resulting from our collaborators' research and development efforts to be commercially available for many years, if ever.

Any performance failure on the part of a third-party manufacturer could delay clinical development or regulatory approval of our product candidates. Third-party manufacturers often encounter difficulties involving production yields, quality control and quality assurance, as well as shortages of qualified personnel. The manufacturers are subject to ongoing periodic unannounced inspection by the FDA, the Drug Enforcement Administration of the U.S. Department of Justice and corresponding state agencies to ensure strict compliance with current good manufacturing practices and other applicable government regulations and corresponding foreign standards. We do not have control over third-party manufacturers' compliance with these regulations and standards. If one of our manufacturers fails to maintain compliance, the production of our product candidates could be interrupted, resulting in delays, additional costs and potentially lost revenues.

We may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.

From time to time we consider strategic transactions, such as acquisitions of companies, asset purchases and out-licensing or in-licensing of compounds or technologies. Additional potential transactions we may consider include a variety of different business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any such transaction may require us to incur non-recurring or other charges, may increase our near and long-term expenditures and may pose significant integration challenges or disrupt our management or business, which could harm our operations and financial results.

Our efforts will be seriously jeopardized if we are unable to retain and attract key employees.

Our success depends on the continued contributions of our principal management, development and scientific personnel, and the ability to hire and retain key personnel, particularly in the clinical development area as we transition more of our programs from research into drug development. We face intense competition for such personnel. The loss of services of any principal member of our management or scientific staff, particularly Jack Lief, our President and Chief Executive Officer, and Dominic P. Behan, Ph.D., our Senior Vice President and Chief Scientific Officer, could adversely impact our operations and ability to raise additional capital. To our knowledge, neither Mr. Lief nor Dr. Behan plans to leave, retire or otherwise disassociate with us in the near future.

We may encounter significant delays or problems with our chemical development facility.

We have a chemical development facility for process research, the scale-up and production of intermediates and other compounds for research and development purposes, and the production of active pharmaceutical ingredients for use in clinical trials.

We may encounter delays and problems in operating our chemical development facility due to:

- governmental approvals, permits and regulation of the facility;
- accidents during operation of the facility;
- failure of equipment for the facility;
- delays in receiving raw materials from suppliers;
- natural or other disasters; or
- other factors inherent in operating a complex manufacturing facility.

We may not be able to operate our chemical development facility in a cost-effective manner or in a time frame that is consistent with our expected future manufacturing needs. If this were the case, we would need to seek alternative means to fulfill our manufacturing needs, which could delay progress on our programs.

We use biological materials, hazardous materials, chemicals and radioactive compounds.

Our research and development activities involve the use of potentially harmful biological materials as well as hazardous materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. These materials and various wastes resulting from their use are stored at our facility pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- an interruption of our research and development efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products.

In such an event, we could be held liable for any resulting damages, and any such liability could exceed our resources. Although we carry insurance in amounts and type that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research and development efforts caused by contamination, and we cannot be certain that the coverage or coverage limits of our insurance policies will be adequate.

We may incur substantial liabilities from any product liability claims if our insurance coverage for those claims is inadequate.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials, and will face an even greater risk if we sell our product candidates commercially. An individual may bring a liability claim against us if one of our product candidates causes, or merely appears to have caused, an injury. If we cannot successfully defend ourselves against a product liability claim, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

decreased demand for our product candidates;

injury to our reputation;

withdrawal of clinical trial subjects;

costs of related litigation;

substantial monetary awards to subjects or other claimants;

loss of revenues; and

the inability to commercialize our product candidates.

We have limited product liability insurance that covers our clinical trials. We intend to expand our insurance coverage to include the sale of commercial products if marketing approval is obtained for any of our product candidates. However, insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost, and we may not have insurance coverage that will be adequate to satisfy any liability that may arise.

We may incur increased costs as a result of recently enacted changes in laws and regulations relating to corporate governance matters.

Changes in the laws and regulations affecting public companies, including the provisions of the Sarbanes-Oxley Act of 2002 and rules adopted by the Securities and Exchange Commission and by the Nasdaq National Market, may result in increased costs to us. These laws, rules and regulations could make it more difficult or costly for us to obtain certain types of insurance, including director and officer liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to their requirements.

Our operations might be interrupted by the occurrence of a natural disaster or other catastrophic event.

All of our laboratories and offices are in a single location in San Diego. We depend on our laboratories and other facilities and on our collaborators, contractors and vendors for the continued operation of our business. Natural disasters or other catastrophic events, including terrorist attacks, power interruptions, wildfires and other fires, actions of animal rights activists, earthquakes and wars could disrupt our operations or those of our collaborators, contractors and vendors. Even though we believe we carry commercially reasonable business interruption and liability insurance, and our contractors may carry liability insurance, that protect us in certain events, we might suffer losses as a result of business interruptions that exceed the coverage available under our and our contractors' insurance policies or for which we or our contractors do not have coverage. For example, we are not insured against a terrorist attack. Any natural disaster or catastrophic event could have a significant negative impact on our operations and financial results. Moreover, any such event could delay our research and development programs.

Even if any of our product candidates receives regulatory approval, our product candidates will still be subject to extensive post-market regulation.

If we or our collaborators receive regulatory approval for our product candidates, we will also be subject to ongoing FDA obligations and continued regulatory review, such as continued safety reporting requirements, and we may also be subject to additional FDA post-marketing obligations, all of which may result in significant expense and limit our ability to commercialize our products.

If any of our product candidates receive United States regulatory approval, the FDA may still impose significant restrictions on the indicated uses for which such products may be marketed or impose ongoing requirements for potentially costly post-approval studies. In addition, regulatory agencies subject a product, its manufacturer and the manufacturer's facilities to continual review and inspections. The subsequent discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, may result in restrictions on the marketing of that product, and could include withdrawal of the product from the market. Failure to comply with applicable regulatory requirements may result in:

issuance of warning letters by the FDA;

fines and other civil penalties;

criminal prosecutions;

injunctions, suspensions or revocations of marketing licenses;

suspension of any ongoing clinical trials;

suspension of manufacturing;

delays in commercialization;

refusal by the FDA to approve pending applications or supplements to approved applications filed by us or our collaborators;

refusals to permit products to be imported or exported to or from the United States;

restrictions on operations, including costly new manufacturing requirements; and

product recalls or seizures.

The FDA's policies may change and additional government regulations may be enacted that could prevent or delay regulatory approval of our product candidates or further restrict or regulate post-approval activities. We cannot predict the likelihood, nature or extent of adverse government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are not able to maintain regulatory compliance, we might not be permitted to market our drugs and our business could suffer.

In order to market any products outside of the United States, we and our collaborators must establish and comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy. Approval procedures vary among countries and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks associated with FDA approval as well as additional presently unanticipated risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others. Failure to obtain regulatory approval in other countries or any delay or setback in obtaining such approval could have the same adverse effects associated with regulatory approval in the United States, including the risk that our product candidates may not be approved for all indications requested and that such approval may be subject to limitations on the indicated uses for which the product may be marketed.

New accounting pronouncements may impact our future results of operations.

In December 2004, the Financial Accounting Standards Board, or FASB, issued Statement of Financial Accounting Standards, or SFAS, No. 123R, "Share-Based Payment." This statement, which

will be effective in our first quarter of 2006, will change how we account for share-based compensation, and may have a significant impact on our future results of operations.

We currently account for share-based payments to employees and directors using the intrinsic value method. Under this method, we generally do not recognize any compensation related to stock option grants we issue under our stock option plans or the discounts we provide under our employee stock purchase plan.

SFAS No. 123R will require us to recognize share-based compensation as compensation expense in the statement of operations based on the fair values of such equity on the date of the grant, with the compensation expense recognized over the period in which the recipient is required to provide service in exchange for the equity award. This statement will also require us to adopt a fair value-based method for measuring the compensation expense related to share-based compensation. We have begun, but have not completed, evaluating the impact of the adoption of SFAS 123R on our results of operations. Historically, we have used the Black-Scholes option pricing model, which is widely used to estimate the value of traded options that have no vesting restrictions and are fully transferable, which are significantly different characteristics from our employee stock options. In connection with evaluating the impact of SFAS 123R, we are considering the potential implementation of different valuation methods to determine the fair value of share-based compensation. We believe the adoption of SFAS 123R will have a material impact on our results of operations, regardless of the valuation method used. SFAS 123R also requires the benefits of tax deductions in excess of recognized compensation cost to be reported as a financing cash flow, rather than as an operating cash flow. This requirement will reduce our net operating cash flows and increase our net financing cash flows in periods after adoption. SFAS 123R may also delay when we may become profitable.

Future changes in generally accepted accounting principles, including pronouncements relating to revenue recognition, may have a significant effect on our reported results, including reporting of transactions completed before the effective date of such pronouncements.

Risks Relating to Our Intellectual Property

Our success is dependent on intellectual property rights held by us and third parties and our interest in these rights is complex and uncertain.

Our success will depend on our own and on our collaborators' abilities to obtain, secure and defend patents. In particular, the patents directed to our most advanced product candidates and other compounds discovered using our technologies are important to commercializing drugs. We have numerous U.S. and foreign patent applications pending for our technologies, including patent applications on drug lead discovery techniques using CART, genetically altered GPCRs, GPCRs that we have discovered, new uses for previously discovered GPCRs, and compounds discovered using CART and Melanophore and other technologies.

The procedures for obtaining a patent in the U.S. and in most foreign countries are complex. These procedures require an analysis of the scientific technology related to the invention and many legal issues. Consequently, the analysis of our patent applications will be complex and time consuming. Our patent position is very uncertain and we do not know when, or if, we will obtain additional patents for our technologies.

In addition, other entities may challenge the validity or enforceability of our patents and patent applications in litigation or administrative proceedings. Even the issuance of a patent is not conclusive as to its validity or enforceability. We cannot make assurances as to how much protection, if any, will be given to our patents if we attempt to enforce them and they are challenged. It is possible that a competitor or a generic pharmaceutical provider may successfully challenge our patents and those challenges may result in reduction in our patents' coverage.

As of October 31, 2005, we owned, in part or in whole, or had exclusively licensed the following patents: 17 in the United States, 63 in European countries, eight in New Zealand, six in Australia, four in Lebanon, one in Japan, one in Singapore, one in Hong Kong and one in Israel. In addition, as of October 31, 2005, we had approximately 344 patent applications before the United States Patent and Trademark Office, foreign patent offices and international patent authorities. These patents and patent applications are divided into 80 distinct families of related patents that are directed to CART, Melanophore technology, other novel screening methods, chemical compositions of matter, methods of treatment using chemical compositions, or GPCR genes. One of our patent families was exclusively in-licensed and contains a single issued patent. Seven of our patent families containing a total of nine patents and 57 patent applications were the subject of joint inventions by our employees and the employees of other entities. The remaining 72 patent families containing a total of 92 patents and 287 patent applications were invented solely by our employees. There is no assurance that any of these patent applications will issue, or that any of the patents will be enforceable or will cover a drug product or other commercially significant product or method.

In 2000, the United States Patent and Trademark Office began issuing broad patent claims that could allow patent holders to control the use of all drug products that modulate a particular drug target or GPCR, regardless of whether the infringing drug product bears any structural resemblance to a chemical compound known to the patent holder at the time of patent filing. The question of whether these new patent claims are valid is highly controversial and the subject of intense litigation. Whether we or our competitors are able to obtain and enforce such patent claims, particularly as they apply to the GPCRs that are the subject of our drug development activities, may have a significant impact on our potential revenues from any drugs that we are able to develop.

We also rely on trade secrets to protect our technologies. However, trade secrets are difficult to protect. We require our employees to contractually agree not to improperly use our trade secrets or disclose them to others, but we may be unable to determine if our employees have conformed or will conform to their legal obligations under these agreements. We also require collaborators, service providers and consultants to enter into confidentiality agreements, but we may not be able to adequately protect our trade secrets or other proprietary information in the event of any unauthorized use or disclosure or the lawful development by others of this information. Many of our employees and consultants were, and many of them may currently be, parties to confidentiality agreements with other pharmaceutical and biotechnology companies, and the use of our technologies could violate these agreements. In addition, third parties may independently discover our trade secrets or proprietary information.

Some of our academic institution licensors, research collaborators and scientific advisors have rights to publish data and information to which we have rights. We generally seek to prevent our partners from disclosing scientific discoveries before we have the opportunity to file patent applications on such discoveries. In some of our collaborations we do not have control over our partners' ability to disclose their own discoveries under the collaboration and in some of our academic collaborations we are limited to relatively short periods to review a proposed publication and file a patent application. If we cannot maintain the confidentiality of our technologies and other confidential information in connection with our collaborations, our ability to receive patent protection or protect our proprietary information will be impaired.

A dispute regarding the infringement or misappropriation of our proprietary rights or the proprietary rights of others could be costly and result in delays in our research and development activities.

Our commercial success also depends upon our ability to develop, manufacture, market and sell our product candidates and conduct our research and development activities without infringing or misappropriating the proprietary rights of other entities. There are many patents and patent applications filed, and that may be filed, by others relating to drug discovery and development

programs that could be determined to be similar, identical or superior to ours or our licensors or collaborators. We may be exposed to future litigation by other entities based on claims that our product candidates, technologies or activities infringe the intellectual property rights of others. Numerous U.S. and foreign issued patents and pending patent applications owned by others exist in the area of GPCRs, some of which purport to allow the patent holder to control the use of all drug products that modulate a particular drug target or GPCR, regardless of whether the infringing drug product bears any structural resemblance to a chemical compound known to the patent holder at the time of patent filing. Numerous U.S. and foreign issued patents and pending patent applications owned by others also exist in the therapeutic areas in which we are developing products. These could materially affect our ability to develop our product candidates or sell our products, and our activities, or those of our licensors or collaborators, could be determined to infringe these patents. Because patent applications can take many years to issue, there may be currently pending applications, unknown to us, which may later result in issued patents that our product candidates or technologies may infringe. There also may be existing patents, of which we are not aware, that our product candidates or technologies may inadvertently infringe. Further, there may be issued patents and pending patent applications in fields relevant to our business, of which we are or may become aware, that we believe we do not infringe or that we believe are invalid or relate to immaterial portions of our overall drug discovery and development efforts. We cannot assure you that other entities holding any of these patents or patent applications will not assert infringement claims against us for damages or seeking to enjoin our activities. We also cannot assure you that, in the event of litigation, we will be able to successfully assert any belief we may have as to non-infringement, invalidity or immateriality, or that any infringement claims will be resolved in our favor.

In addition, other entities may infringe or misappropriate our proprietary rights, and we may have to institute costly legal action to protect our intellectual property rights. We may not be able to afford the costs of enforcing or defending our intellectual property rights against other entities.

Other organizations, companies and individuals are seeking proprietary positions on genomics information that overlap with the government sponsored project to sequence the human genome. Our activities, or those of our licensors or collaborators, could be affected by conflicting positions that may exist between any overlapping genomics information made available publicly as a result of the government sponsored project and genomics information that other organizations, companies or individuals consider to be proprietary.

There could be significant litigation and other administrative proceedings in our industry that affect us regarding patent and other intellectual property rights. Any legal action or administrative action against us, or our collaborators, claiming damages or seeking to enjoin commercial activities relating to our drug discovery and development programs could:

- require us, or our collaborators, to obtain a license to continue to use, manufacture or market the affected products, methods or processes, which may not be available on commercially reasonable terms, if at all;
- prevent us from importing, making, using, selling or offering to sell the subject matter claimed in patents held by others and subject us to potential liability for damages;
- consume a substantial portion of our managerial, scientific and financial resources; or
- be costly, regardless of the outcome.

Furthermore, because of the substantial amount of pre-trial document and witness discovery required in connection with intellectual property litigation, there is risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, during the course of this kind of litigation, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these

results to be negative, it could have a substantial adverse effect on the trading price of our common stock.

We have been contacted from time to time by third parties regarding their intellectual property rights, sometimes asserting that we may need a license to use their technologies. If we fail to obtain any required licenses or make any necessary changes to our technologies, we may be unable to develop or commercialize some or all of our product candidates.

We cannot protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on all of our drug discovery technologies throughout the world would be prohibitively expensive. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own drug products. These products may compete with our products and may not be covered by any of our patent claims or other intellectual property rights.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States, and many companies have encountered significant problems in protecting and defending such rights in foreign jurisdictions. Many countries, including certain countries in Europe, have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties (for example, the patent owner has failed to "work" the invention in that country or the third party has patented improvements). In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of the patent. Compulsory licensing of life saving drugs is also becoming increasingly popular in developing countries either through direct legislation or international initiatives. Such compulsory licenses could be extended to include some of our product candidates, which could limit our potential revenue opportunities. Moreover, the legal systems of certain countries, particularly certain developing countries, do not favor the aggressive enforcement of patents and other intellectual property protection, particularly those relating to biotechnology and/or pharmaceuticals, which makes it difficult for us to stop the infringement of our patents. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

Risks Relating to Our Securities

Our stock price will likely be volatile, and your investment in our stock could decline in value.

Our stock price has fluctuated historically. From January 1, 2003, to October 31, 2005, the market price of our stock was as low as $3.48 per share and as high as $10.54 per share.

Very few biotechnology products being tested will ultimately receive FDA approval, and a biotechnology company may experience a significant drop in its stock price based on an adverse clinical trial result or regulatory action. Our stock price may fluctuate significantly, depending on a variety of factors, including:

- our success or failure in clinical trials;
- the timing of the discovery of drug leads and the development of our product candidates;
- entering into a new collaboration or modifying or terminating an existing collaboration;
- the timing and receipt by us of milestone and royalty payments or failing to achieve and receive the same;
- changes in the research and development budgets of our existing or potential collaborators;

others introducing new drug discovery techniques or introducing or withdrawing drugs that target the same diseases and conditions that we or our collaborators target;

regulatory actions; and

expenses related to, and the results of, litigation and other proceedings relating to intellectual property rights or other matters.

We are not able to control all of these factors. Period-to-period comparisons of our financial results are not necessarily indicative of our future performance. In addition, if our revenues or results of operations in a particular period do not meet stockholders' or analysts' expectations, our stock price may decline and such decline could be significant.

Holders of our Series B Preferred can require us to redeem their Series B Preferred.

On December 24, 2003, we completed the private placement to two institutional investors of (i) an aggregate of 3,500 shares of our Series B-1 Preferred, (ii) seven-year Warrants to purchase up to an aggregate of 1,486,200 shares of our common stock at an exercise price of $10.00 per share (subject to weighted-average adjustment in certain circumstances) and (iii) Unit Warrants to purchase for a period of approximately 16 months from December 24, 2003, up to $11.5 million of our Series B-2 Preferred and additional seven-year Warrants to purchase up to 450,000 shares of our common stock at an exercise price of $10.00 per share (subject to weighted-average adjustment in certain circumstances). On April 22, 2005, the investors exercised their Unit Warrants in full.

The holders of our Series B-1 Preferred can require us to redeem all or some of their shares of Series B-1 Preferred at such shares' stated value, plus accrued but unpaid dividends thereon to the date of payment and any applicable penalties. The stated value is the original holder's investment plus any dividends settled by increasing the stated value at the time the dividend is payable. The aggregate redemption price of our Series B-1 Preferred at September 30, 2005, was approximately $37.6 million, and accrues interest at 4.0% annually.

The holders of our Series B-2 Preferred will be entitled to require us to redeem their shares of Series B-2 Preferred at such shares' stated value, plus accrued but unpaid dividends thereon to the date of payment and any applicable penalties, if, following the 21st month anniversary of the original issue date of the Series B-2 Preferred, the average of the closing prices of our common stock for any 30 consecutive trading days is below $7.00, which is the conversion price for the Series B-2 Preferred.

Also, the holders of the Series B-2 Preferred may require us to redeem their shares if we issue common stock or common stock equivalents for an effective net price to us per share less than approximately $5.33 (excluding, among other things, certain common stock and common stock equivalents issued or issuable (i) to our officers, directors, employees or consultants, (ii) in connection with certain strategic partnerships or joint ventures, and (iii) in connection with certain mergers and acquisitions). "Effective net price" is not defined in the Certificate of Designations governing our Series B-2 Preferred. The holders of our Series B-2 Preferred may assert that effective net price should be calculated as the amount we receive after paying any discounts and other expenses related to any such issuance.

In addition to the foregoing redemption rights, at any time following the occurrence of a "Triggering Event," a holder of the Series B Preferred may require us to repurchase all or any portion of the Series B Preferred then held by such holder at a price per share equal to the greater of 115.0% of the stated value or the market value (as calculated under the Certificate of Designations for the Series B-1 Preferred and the Series B-2 Preferred) of such shares of Series B Preferred plus all accrued but unpaid dividends thereon to the date of payment. "Triggering Events" include any of the following events: (i) immediately prior to a bankruptcy event; (ii) we fail for any reason to timely deliver a certificate evidencing any securities to a purchaser or the exercise or conversion rights of the holders

are otherwise suspended for other than a permissible reason; (iii) any Event (as defined in the Registration Rights Agreement with the Series B Preferred holders) occurs and remains uncured for 60 days; (iv) we fail to make any cash payment required under the Series B Preferred transaction documents and such failure is not timely cured; (v) the issuance of a going concern opinion by our independent registered public accounting firm that is not timely cured; (vi) we breach a section of the Series B Preferred purchase agreement relating to indebtedness and subordination; or (vii) we default in the timely performance of any other obligation under the Series B Preferred transaction documents and such default is not timely cured.

We will also be required to redeem any shares of the Series B Preferred that remain outstanding on the fifth anniversary of their issuance at a price equal to the amount of the original holder's original investment, plus all accrued but unpaid dividends thereon to the date of such payment. "Triggering Event" is specifically defined in the Certificate of Designations for the Series B-1 Preferred and the Series B-2 Preferred.

If we are required to redeem all or some of the currently outstanding shares of our Series B Preferred, we may be able to pay a portion of the redemption price using shares of our common stock if certain other enumerated conditions are satisfied, including:

- we have sufficient number of shares of common stock available for issuance;
- the shares of common stock to be issued are registered under an effective registration statement or are otherwise available for sale under Rule 144(k) under the Securities Act;
- our common stock is listed on the Nasdaq National Market or other eligible market;
- the shares to be issued can be issued without violating the rules of the Nasdaq National Market or any applicable trading market or a provision of our certificate of designations; and
- no bankruptcy event has occurred.

If we are permitted to satisfy a portion of a redemption by using shares of our common stock, and if we elect to do so, the number of shares to be issued to holders of Series B Preferred will be determined by dividing their cash redemption price by the lesser of the conversion price or 95.0% of the average of the volume weighted average price of our common stock for either 10 or 15 trading days.

There can be no assurance that if we have to redeem our Series B Preferred, that we will be able to pay a portion of the redemption price using shares of our common stock. If we use common stock to redeem a portion of the Series B Preferred, your ownership interest may be significantly diluted. If we are required or elect to redeem shares of the Series B Preferred using cash, we may not have sufficient cash to redeem these shares or to continue our planned research and discovery activities. In such event we may try to raise additional capital by issuing new stock, but there can be no assurance that capital will be available on acceptable terms or at all.

There are a substantial number of shares of our common stock eligible for future sale in the public market, and the sale of these shares could cause the market price of our common stock to fall.

There were 35,387,800 shares of our common stock outstanding as of October 31, 2005. The outstanding shares of our Series B-1 Preferred are convertible into up to 5,009,546 shares of common stock at $7.50 per share of common stock. The outstanding shares of our Series B-2 Preferred are convertible into up to 1,672,282 shares of common stock at $7.00 per share of common stock. Holders of Series B Preferred are entitled to receive a 4.0% annual dividend that is payable by issuing common stock or by increasing the amount of common stock that is issuable upon conversion of the Series B Preferred. In addition, holders of our Series B Preferred own Warrants to acquire common stock, which, if exercised and converted, would obligate us to issue up to 1,936,200 additional shares of

common stock at an exercise price of $10.00 per share. In addition, as of October 31, 2005, there were 3,639,732 common stock options issued and outstanding under our equity compensation plans at a weighted average exercise price of $8.00, 636,961 additional shares of common stock issuable under our equity compensation plans, 554,976 shares of common stock reserved for issuance under our 2001 Employee Stock Purchase Plan and 134,169 shares issuable under our Deferred Compensation Plan. A substantial number of the shares described above, when issued upon exercise, will be available for immediate resale in the public market. The market price of our common stock could decline as a result of such resales due to the increased number of shares available for sale in the market.

Any future equity or debt issuances by us may have dilutive or adverse effects on our existing stockholders.

We have financed our operations, and we expect to continue to finance our operations, primarily by issuing and selling our common stock or securities convertible into or exercisable for shares of our common stock. In light of our need for additional financing, we may issue additional shares of common stock or additional convertible securities that could dilute your ownership in our company and may include terms that give new investors rights that are superior to yours. Moreover, any issuances by us of equity securities may be at or below the prevailing market price of our common stock and in any event may have a dilutive impact on your ownership interest, which could cause the market price of our common stock to decline. The terms of our Series B Preferred limit our ability to engage in certain equity issuances.

We may also raise additional funds through the incurrence of debt, and the holders of any debt we may issue would have rights superior to your rights in the event we are not successful and are forced to seek the protection of the bankruptcy laws. The terms of our Series B Preferred limits our ability to incur debt.

Our largest stockholders may take actions that are contrary to your interests, including selling their stock.

A small number of our stockholders hold a significant amount of our outstanding stock. These stockholders may support competing transactions and have interests that are different from yours. In addition, the average number of shares of our stock that trade each day is generally low. As a result, sales of a large number of shares of our stock by these large stockholders or other stockholders within a short period of time could adversely affect our stock price.

Provisions of our Series B Preferred may prevent or make it more difficult for us to raise funds or take certain other actions.

Provisions of our Series B Preferred require us to obtain approval of the preferred stockholders, or otherwise trigger rights of first refusal or payment provisions, to (i) offer or sell new securities, other than in specified underwritten offerings or strategic partnerships or joint venture and certain other exceptions, (ii) sell or issue common stock or securities issuable into common stock below certain prices, (iii) incur debt or allow liens on our property, other than certain permitted debt and liens, (iv) amend our certificate of incorporation so as to affect adversely any rights of the preferred stockholders, (v) authorize or create a new class of stock that will be senior or equal to the Series B Preferred in terms of dividends, redemption or distribution of assets, (vi) use more than $25.0 million in cash for acquisitions, or (vii) take certain other actions. These provisions may make it more difficult for us to take certain corporate actions and could delay, discourage or prevent future financings.

Our rights agreement and certain provisions in our charter documents and Delaware law could delay or prevent a change in management or a takeover attempt that you may consider to be in your best interest.

We have adopted certain anti-takeover provisions, including a stockholders' rights plan, dated as of October 30, 2002, between us and Computershare Trust Company, Inc., as Rights Agent, as amended

on December 24, 2003. The rights plan will cause substantial dilution to any person who attempts to acquire us in a manner or on terms not approved by our board of directors.

The rights agreement and Certificate of Designations for the Series B Preferred, as well as other provisions in our certificate of incorporation and by-laws and under Delaware law, could delay or prevent the removal of directors and other management and could make more difficult a merger, tender offer or proxy contest involving us that you may consider to be in your best interest. For example, these provisions:

- allow our board of directors to issue preferred stock without stockholder approval;
- limit who can call a special meeting of stockholders;
- eliminate stockholder action by written consent; and
- establish advance notice requirements for nomination for election to the board of directors or for proposing matters to be acted upon at stockholders meetings.

We may allocate the net proceeds from this offering in ways that you and other stockholders may not approve.

We intend to use the net proceeds from this offering:

- for the clinical and preclinical development of our internally discovered product candidates;
- for discovery research for new product candidates; and
- for general corporate purposes, including working capital.

Our management will, however, have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not necessarily improve our operating results or enhance the value of our common stock. The proceeds may be used to pay the redemption price for some or all of the outstanding Series B-1 Convertible Preferred Stock, if the holders elect to have their preferred stock redeemed.

FORWARD-LOOKING STATEMENTS

This prospectus including the documents that we incorporate by reference herein contains, and any applicable prospectus supplement including the documents we incorporate by reference therein may contain, "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These forward-looking statements can generally be identified as such because the context of the statement will include words such as "may," "will," "intends," "plans," "believes," "anticipates," "expects," "estimates," "predicts," "potential," "continue," or "opportunity," the negative of these words or words of similar import. Similarly, statements that describe our future plans, strategies, intentions, expectations, objectives, goals or prospects are also forward-looking statements. Discussions containing these forward-looking statements may be found, among other places, in "Business" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" incorporated by reference from our most recent Annual Report on Form 10-K and our Quarterly Reports on Form 10-Q for the quarters ended subsequent to our filing of such Annual Report on Form 10-K with the SEC, as well as any amendments thereto reflected in subsequent filings with the SEC. These forward-looking statements are or will be, as applicable, based largely on our expectations and projections about future events and future trends affecting our business, and so are or will be, as applicable, subject to risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. The risks and uncertainties include, among others, those noted in "Risk Factors" above and in any applicable prospectus supplement and any documents incorporated by reference herein or therein.

In addition, past financial or operating performance is not necessarily a reliable indicator of future performance and you should not use our historical performance to anticipate results or future period trends. We can give no assurances that any of the events anticipated by the forward-looking statements will occur or, if any of them do, what impact they will have on our results of operations and financial condition. Except as required by law, we undertake no obligation to publicly revise our forward-looking statements to reflect events or circumstances that arise after the date of this prospectus or the prospectus supplement or the date of documents incorporated by reference in this prospectus that include forward-looking statements.

USE OF PROCEEDS

Except as described in any prospectus supplement, we currently intend to use the net proceeds from the sale of our common stock under this prospectus for the clinical and preclinical development of our internally discovered product candidates, for discovery research for new product candidates, and for general corporate purposes, including working capital.

DESCRIPTION OF CAPITAL STOCK

As of the date of this prospectus, our amended and restated certificate of incorporation authorizes us to issue 67,500,000 shares of common stock, par value $.0001 per share, and 7,500,000 shares of preferred stock, par value $.0001 per share. As of October 31, 2005, approximately 35.4 million shares of common stock were outstanding. To date, our board of directors has designated 350,000 of the authorized shares of preferred stock as Series A Junior Participating Preferred Stock (the "Series A Preferred Stock"), which series is described in greater detail below under "Share Purchase Rights Plan," and 4,650 of the authorized shares of preferred stock as Series B Convertible Preferred Stock as described in greater detail below under "Series B Preferred Stock." As of October 31, 2005, 4,650 shares of Series B Preferred Stock were outstanding.

The following summary describes the material terms of our capital stock and stockholder rights plan. The description of capital stock and stockholder rights plan is qualified by reference to our amended and restated certificate of incorporation, our bylaws, the certificate of designation for our Series A Preferred Stock and our Series B Convertible Preferred Stock, and our stockholder rights plan, which are incorporated by reference as exhibits into the registration statement of which this prospectus is a part.

Common Stock

Voting. Common stockholders are entitled to one vote per share for the election of directors and on all other matters that require stockholder approval.

Dividends and Other Distributions. Holders of our common stock are entitled to share in an equal amount per share in any dividends declared by our board of directors on the common stock and paid out of legally available assets.

Distribution on Dissolution. Subject to any preferential rights of any outstanding preferred stock, in the event of our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in the assets remaining after payment of liabilities and the liquidation preferences of any outstanding preferred stock.

Other Rights. Our common stock does not carry any preemptive rights enabling a holder to subscribe for, or receive shares of, any class of our common stock or any other securities convertible into shares of any class of our common stock, or any redemption rights.

Preferred Stock

Under our amended and restated certificate of incorporation, our board of directors has the authority, without further action by stockholders, to designate up to 7,500,000 shares of preferred stock in one or more series and to fix the rights, preferences, privileges, qualifications and restrictions granted to or imposed upon the preferred stock, including dividend rights, conversion rights, voting rights, rights and terms of redemption, liquidation preference and sinking fund terms, any or all of which may be greater than the rights of the common stock. To date, our board of directors has designated 350,000 of the authorized shares of preferred stock as the Series A Preferred Stock, which series is described in greater detail below under "Share Purchase Rights Plan," and 4,650 of the authorized shares of preferred stock as Series B Convertible Preferred Stock as described in greater detail below under "Series B Preferred Stock."

The issuance of additional preferred stock could adversely affect the voting power of holders of common stock and reduce the likelihood that common stockholders will receive dividend payments and payments upon liquidation. The issuance could have the effect of decreasing the market price of the

common stock. The issuance of preferred stock also could have the effect of delaying, deterring or preventing a change in control of us.

Share Purchase Rights Plan. Each outstanding share of our common stock has attached to it one preferred share purchase right, which we refer to as a Right. Each Right entitles the registered holder to purchase from us one one-hundredth of a share of Series A Preferred Stock at a price of $36 (the "Purchase Price"), subject to adjustment. The description and terms of the Rights are set forth in a Rights Agreement dated as of October 30, 2002, between us and Computershare Trust Company, Inc. as Rights Agent, which is incorporated by reference as an exhibit into the registration statement of which this prospectus is a part.

Until the earlier to occur of (i) 10 days following a public announcement that a person or group of affiliated or associated persons (an "Acquiring Person") have acquired beneficial ownership of 10% or more of our outstanding common stock or (ii) 10 business days (or such later date as may be determined by action of our board of directors prior to such time as any person or group of affiliated persons becomes an Acquiring Person) following the commencement of, or announcement of an intention to make, a tender offer or exchange offer the consummation of which would result in the beneficial ownership by a person or group of 10% or more of our outstanding common stock (the earlier of such dates being called the "Distribution Date"), the Rights will be evidenced, with respect to any of our common stock certificates outstanding as of November 13, 2002, by such common stock certificate with a copy of the Summary of Rights in the form attached as Exhibit C to the Rights Agreement.

The Rights Agreement provides that none of our directors or officers shall be deemed to beneficially own any of our common stock owned by any other director or officer by virtue of such persons acting in their capacities as such, including, without limitation, in connection with any formulation and publication of our board of director's recommendation of its position, and any actions taken in furtherance thereof, with respect to any acquisition proposal relating to Arena, a tender or exchange offer for any of our common stock or any solicitation of proxies with respect to any of our common stock.

The Rights Agreement provides that, until the Distribution Date (or earlier redemption or expiration of the Rights), the Rights will be transferred with and only with our common stock. Until the Distribution Date (or earlier redemption or expiration of the Rights), new common stock certificates issued after November 13, 2002, upon transfer or new issuance of our common stock will contain a notation incorporating the Rights Agreement by reference. Until the Distribution Date (or earlier redemption or expiration of the Rights), the surrender for transfer of any certificates for our common stock outstanding as of November 13, 2002, even without such notation or a copy of the Summary of Rights attached thereto, will also constitute the transfer of the Rights associated with our common stock represented by such certificate. As soon as practicable following the Distribution Date, separate certificates evidencing the Rights ("Right Certificates") will be mailed to holders of record of our common stock as of the close of business on the Distribution Date and such separate Right Certificates alone will evidence the Rights.

The Rights are not exercisable until the Distribution Date. The Rights will expire on October 30, 2012, (the "Final Expiration Date"), unless the Final Expiration Date is extended or the Rights are earlier redeemed or exchanged by us, in each case, as described below.

The Purchase Price payable, and the number of shares of the Series A Preferred Stock or other securities or property issuable, upon exercise of the Rights are subject to adjustment from time to time to prevent dilution (i) in the event of a stock dividend on, or a subdivision, combination or reclassification of, the Series A Preferred Stock, (ii) upon the grant to holders of the Series A Preferred Stock of certain rights or warrants to subscribe for or purchase Series A Preferred Stock at a price, or securities convertible into Series A Preferred Stock with a conversion price, less than the

then-current market price of the Series A Preferred Stock or (iii) upon the distribution to holders of the Series A Preferred Stock of evidences of indebtedness or assets (excluding regular periodic cash dividends paid out of earnings or retained earnings or dividends payable in Series A Preferred Stock) or of subscription rights or warrants (other than those referred to above).

The number of outstanding Rights and the number of one one-hundredths of a share of Series A Preferred Stock issuable upon exercise of each Right are also subject to adjustment in the event of a stock split of our common stock or a stock dividend on our common stock payable in our common stock or subdivisions, consolidations or combinations of our common stock occurring, in any such case, prior to the Distribution Date.

Series A Preferred Stock purchasable upon exercise of the Rights will not be redeemable. Once issued upon exercise of Rights, each share of Series A Preferred Stock will be entitled to a minimum preferential quarterly dividend payment of $1 per share but will be entitled to an aggregate dividend of 100 times the dividend declared per share of our common stock. In the event of liquidation, the holders of outstanding shares of Series A Preferred Stock will be entitled to a minimum preferential liquidation payment of $100 per share but will be entitled to an aggregate payment of 100 times the payment made per share of our common stock. Each outstanding share of Series A Preferred Stock will have 100 votes, voting together with our common stock. Finally, in the event of any merger, consolidation or other transaction in which our common stock is exchanged, each outstanding share of Series A Preferred Stock will be entitled to receive 100 times the amount received per share of our common stock. These rights are protected by customary antidilution provisions.

Because of the nature of the Series A Preferred Stock's dividend, liquidation and voting rights, the value of the one one-hundredth interest in a share of Series A Preferred Stock purchasable upon exercise of each Right should approximate the value of one share of our common stock.

In the event that any person or group of affiliated or associated persons becomes an Acquiring Person, the Rights Agreement provides that proper provision shall be made so that each holder of a Right, other than Rights beneficially owned by the Acquiring Person (which will thereafter be void), will thereafter have the right to receive (subject to adjustment) upon exercise thereof at the then current Purchase Price, that number of shares of our common stock having a market value of two times the Purchase Price. At any time after any person or group becomes an Acquiring Person and prior to the acquisition by such person or group of 50% or more of our outstanding common stock, our board of directors may exchange the Rights (other than Rights owned by such person or group, which will have become void), in whole or in part, at an exchange ratio of one share of our common stock, or one one-hundredth of a share of Series A Preferred Stock (or of a share of a class or series of our preferred stock having equivalent rights, preferences and privileges), per Right (subject to adjustment).

In the event that we are acquired in a merger or other business combination transaction or 50% or more of our consolidated assets or earning power are sold after a person or group has become an Acquiring Person, proper provision will be made so that each holder of a Right will thereafter have the right to receive, upon the exercise thereof at the then current Purchase Price, that number of shares of common stock of the acquiring company which at the time of such transaction will have a market value of two times the Purchase Price.

With certain exceptions, no adjustment in the Purchase Price will be required until cumulative adjustments require an adjustment of at least 1% in the Purchase Price. No fractional shares of Series A Preferred Stock will be issued (other than fractions which are integral multiples of one one-hundredth of a share of Series A Preferred Stock, which may, at our election, be evidenced by depositary receipts) and in lieu thereof, an adjustment in cash will be made based on the market price of the Series A Preferred Stock on the last trading day prior to the date of exercise.

At any time prior to the acquisition by a person or group of affiliated or associated persons of beneficial ownership of 10% or more of our outstanding common stock, our board of directors may redeem the Rights in whole, but not in part, at a price of $.01 per Right (the "Redemption Price"). The redemption of the Rights may be made effective at such time on such basis with such conditions as our board of directors in its sole discretion may establish.

The terms of the Rights may be amended by our board of directors without the consent of the holders of the Rights, including an amendment to (i) fix a Final Expiration Date later than October 30, 2012, (ii) reduce the Redemption Price or (iii) increase the Purchase Price, except that from and after such time as any person or group of affiliated or associated persons becomes an Acquiring Person no such amendment may adversely affect the interests of the holders of the Rights (other than the Acquiring Person and its affiliates and associates).

Until a Right is exercised, the holder thereof, as such, will have no rights as a stockholder of Arena, including, without limitation, the right to vote or to receive dividends.

Series B Preferred Stock. On December 24, 2003, we completed the private placement of $35 million of Series B-1 Convertible Preferred Stock to two institutional investors (the "Investors") pursuant to a Securities Purchase Agreement (the "Securities Purchase Agreement").

The Series B-1 Convertible Preferred Stock is convertible into our common stock at a fixed conversion price of $7.50 per share. If not previously converted, we must redeem the Series B-1 Convertible Preferred Stock five years from the original issue date or earlier under certain circumstances. We may make any such redemption in cash or, if certain conditions have been met, in shares of our common stock. Dividends on the Series B-1 Convertible Preferred Stock are payable at a rate of 4% per annum either in kind or in shares of our common stock.

In connection with the sale of the Series B-1 Convertible Preferred Stock, we issued to the Investors seven-year Warrants to purchase up to 1,486,200 shares of our common stock at an exercise price of $10.00 per share. We also issued to the Investors Unit Warrants giving such Investors the right to purchase from us for a period of approximately 16 months, at their option, up to $11.5 million of Series B-2 Convertible Preferred Stock and additional seven-year Warrants to purchase shares of our common stock. On April 22, 2005, the Investors exercised their Unit Warrants in full and received (i) an aggregate of 1,150 shares of the Company's Series B-2 Convertible Preferred Stock and (ii) seven-year Warrants to purchase an aggregate of 450,000 shares of common stock at an exercise price of $10.00 per share (subject to weighted-average adjustment in certain circumstances).

If not previously converted, the Company must redeem the Series B-2 Convertible Preferred Stock in five years from April 22, 2005, or earlier under certain circumstances, at such shares' stated value, plus accrued but unpaid dividends thereon to the date of payment and any applicable penalties. Any such redemption may be made by the Company in cash or, subject to certain conditions, in shares of common stock. The Series B-2 Convertible Preferred Stock is convertible into common stock at a fixed conversion price of $7.00 per share. Otherwise, the Series B-2 Convertible Preferred Stock has substantially identical terms as the Series B-1 Convertible Preferred Stock, as more fully described in the Certificate of Designations relating to the Series B Convertible Preferred Stock (the "Certificate of Designations").

So long any shares of Series B Convertible Preferred Stock are outstanding, we cannot, directly or indirectly, incur or guarantee, assume or suffer to exist any debt other than permitted debt, as more fully described in the Securities Purchase Agreement. In addition, so long as shares of Series B Convertible Preferred Stock are outstanding, we cannot, directly or indirectly, allow or suffer to exist any lien other than permitted liens, as more fully described in the Securities Purchase Agreement.

From the end of the Blockout Period (as defined in the Securities Purchase Agreement) and for so long as an Investor holds 20% of the shares of Series B Convertible Preferred Stock originally

purchased by such Investor, the Company will not, directly or indirectly, effect any Subsequent Placement (as defined in the Securities Purchase Agreement), unless, among other things, we have delivered to each Investor a written notice of any proposed or intended issuance or sale or exchange of the securities being offered in such Subsequent Placement offering to issue and sell to or exchange with each Investor a pro rata portion of fifty percent (50%) of the offered securities, based on such Investor's pro rata portion of the aggregate purchase price paid by the Investors for all of the shares of Series B Convertible Preferred Stock purchased under the Securities Purchase Agreement.

Each Investor agrees that for so long as it holds Series B Convertible Preferred Stock, it shall vote its shares of Series B Convertible Preferred Stock and our common stock on all matters in which such Investor is entitled to vote and on which holders of common stock have the right to vote, in the manner recommended by our board of directors to all of our shareholders unless our board of directors elects to permit the Investors to vote such shares in their own discretion.

If a Change of Control (as defined in the Certificate of Designations) occurs before the two-year anniversary of the original issue date of the Series B Convertible Preferred Stock, we can repurchase the Series B Convertible Preferred Stock at a price equal to the greater of 125% of the stated value or the market value (as calculated in the Certificate of Designations) of such shares of Series B Convertible Preferred Stock plus all accrued but unpaid dividends thereon to the date of payment. If such Change of Control occurs following the two-year anniversary of the original issue date of the Series B Convertible Preferred Stock, we can repurchase the Series B Convertible Preferred Stock at a price equal to the greater of 115% of the stated value or the market value (as calculated in the Certificate of Designations) of such shares of Series B Convertible Preferred Stock plus all accrued but unpaid dividends thereon to the date of payment. We can elect to pay any such redemption in shares of our common stock, if certain conditions have been met.

The holders of our Series B-1 Preferred can require us to redeem all or some of their shares of Series B-1 Preferred at such shares' stated value, plus accrued but unpaid dividends thereon to the date of payment and any applicable penalties. The stated value is the original holder's investment plus any dividends settled by increasing the stated value at the time the dividend is payable. The holders of our Series B-2 Preferred will be entitled to require us to redeem their shares of Series B-2 Preferred at such shares' stated value, plus accrued but unpaid dividends thereon to the date of payment and any applicable penalties, if, following the 21st month anniversary of the original issue date of the Series B-2 Preferred, the average of the closing prices of our common stock for any 30 consecutive trading days is below $7.00, which is the conversion price for the Series B-2 Preferred. Also, the holders of the Series B-2 Preferred may require us to redeem their shares if we issue common stock or common stock equivalents for an effective net price to us per share less than approximately $5.33 (excluding, among other things, certain common stock and common stock equivalents issued or issuable (i) to our officers, directors, employees or consultants, (ii) in connection with certain strategic partnerships or joint ventures, and (iii) in connection with certain mergers and acquisitions). We can elect to pay any such redemption in shares of our common stock, if certain conditions have been met.

At any time following the occurrence of a Triggering Event (as defined in the Certificate of Designations), a holder of the Series B Convertible Preferred Stock may require us to repurchase all or any portion of the Series B Convertible Preferred Stock then held by such holder at a price per share equal to the greater of 115% of the stated value or the market value (as calculated in the Certificate of Designations) of such shares of Series B Convertible Preferred Stock plus all accrued but unpaid dividends thereon to the date of payment. We can elect to pay such redemption price in shares of our common stock under certain circumstances.

Our Stockholders Rights Plan has been amended to provide, among other things, that the Investors will not become "Acquiring Persons" solely by virtue of such purchases and issuances of our common stock in connection therewith.

Anti-Takeover Provisions

Delaware Law. We are governed by the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a publicly held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a period of three years after the date of the transaction in which the person became an interested stockholder, unless before the date that the person became an "interested stockholder," our board of directors approved either the "business combination" or the transaction which makes the person an "interested stockholder," or after the date that the person became an "interested stockholder," the business combination is approved by our board of directors and the vote of at least 66$^{2}/_{3}$% of our outstanding voting stock that is not owned by the "interested stockholder." Generally, a "business combination" includes a merger, asset sale or other transaction resulting in a financial benefit to the stockholder. An "interested stockholder" is a person who either owns 15% or more of our outstanding voting stock or, together with affiliates and associates, owns or, within three prior years, did own, 15% or more of our outstanding voting stock. The statute could have the effect of delaying, deferring or preventing a change in our control.

Bylaw and Certificate of Incorporation Provisions. Our bylaws provide that special meetings of our stockholders may be called only by the Chairman of the board of directors, our Chief Executive Officer, our President, or by the board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors. Our amended and restated certificate of incorporation also specifies that the authorized number of directors may be changed only by resolution of the board of directors and does not include a provision for cumulative voting for directors. Under cumulative voting, a minority stockholder holding a sufficient percentage of a class of shares may be able to ensure the election of one or more directors. These and other provisions contained in our amended and restated certificate of incorporation and bylaws could delay or discourage transactions involving an actual or potential change in control of us or our management, including transactions in which stockholders might otherwise receive a premium for their shares over then current prices. Such provisions could also limit the ability of stockholders to remove current management or approve transactions that stockholders may deem to be in their best interests and could adversely affect the price of our common stock.

Transfer Agent And Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, Inc.

Listing on the Nasdaq National Market

Our common stock is listed on the Nasdaq National Market under the symbol "ARNA."

PLAN OF DISTRIBUTION

We may sell our common stock covered by this prospectus in any of three ways (or in any combination):

- to or through underwriters or dealers;
- directly to one or more purchasers; or
- through agents.

We may distribute the common stock:

- from time to time in one or more transactions at a fixed price or prices, which may be changed from time to time;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

The prospectus supplement or supplements will describe the method of distribution and set forth the terms of the offering of our common stock covered by this prospectus, including:

- the name or names of any underwriters, dealers or agents;
- the amounts of securities underwritten or purchased by each of them;
- the purchase price of the common stock and the proceeds we will receive from the sale;
- any over-allotment options under which underwriters may purchase additional common stock from us;
- any underwriting discounts or commissions or agency fees and other items constituting underwriters' or agents' compensation;
- the public offering price of the common stock;
- any discounts, commissions or concessions allowed or reallowed or paid to dealers; and
- any securities exchange or market on which the common stock may be listed.

Any initial public offering price and any discounts or concessions allowed or reallowed or paid to dealers may be changed from time to time. We may determine the price or other terms of the common stock offered under this prospectus by use of an electronic auction. We will

describe how any auction will determine the price or any other terms, how potential investors may participate in the auction and the nature of the obligations of the underwriter, dealer or agent in the applicable prospectus supplement.

Underwriters may offer and sell the offered common stock from time to time in one or more transactions, including negotiated transactions, at a fixed public offering price or at varying prices determined at the time of sale. If underwriters are used in the sale of any common stock, the common stock will be acquired by the underwriters for their own account and may be resold from time to time in one or more transactions described above. The common stock may be either offered to the public through underwriting syndicates represented by managing underwriters, or directly by underwriters. Generally, the underwriters' obligations to purchase the common stock will be subject to certain conditions precedent. The underwriters will be obligated to purchase all of the common stock if they purchase any of the common stock. We may use underwriters with whom we have a material relationship. We will describe in the prospectus supplement, naming the underwriter, the nature of any such relationship.

We may sell the common stock through agents from time to time. The prospectus supplement will name any agent involved in the offer or sale of the common stock and any commissions we pay to them. Generally, any agent will be acting on a best efforts basis for the period of its appointment. We may authorize underwriters, dealers or agents to solicit offers by certain purchasers to purchase the common stock from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. The contracts will be subject only to those conditions set forth in the prospectus supplement, and the prospectus supplement will set forth any commissions we pay for solicitation of these contracts.

Agents and underwriters may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution with respect to payments which the agents or underwriters may be required to make in respect thereof. Agents and underwriters may be customers of, engage in transactions with, or perform services for us in the ordinary course of business.

Any underwriter may engage in overallotment, stabilizing transactions, short covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Overallotment involves sales in excess of the offering size, which create a short position. This short sales position may involve either "covered" short sales or "naked" short sales. Covered short sales are short sales made in an amount not greater than the underwriters' over-allotment option to purchase additional shares in this offering described above. The underwriters may close out any covered short position either by exercising their over-allotment option or by purchasing shares in the open market. To determine how they will close the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market, as compared to the price at which they may purchase shares through the over-allotment option. Naked short sales are short sales in excess of the over-allotment option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that, in the open market after pricing, there may be downward pressure on the price of the shares that could adversely affect investors who purchase shares in this offering. Stabilizing transactions permit bids to purchase the underlying security for the purpose of fixing the price of the security so long as the stabilizing bids do not exceed a specified maximum. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a covering transaction to cover short positions.

Similar to other purchase transactions, an underwriter's purchase to cover the syndicate short sales or to stabilize the market price of our common stock may have the effect of raising or maintaining the market price of our common stock or preventing or mitigating a decline in the market price of our common stock. As a result, the price of the shares of our common stock may be higher than the price that might otherwise exist in the open market. The imposition of a penalty bid might also have an effect on the price of the shares if it discourages resales of the shares.

Neither we nor the underwriters makes any representation or prediction as to the effect that the transactions described above may have on the price of the shares. If such transactions are commenced, they may be discontinued without notice at any time.

LEGAL MATTERS

The validity of the securities being offered hereby will be passed upon by Cooley Godward LLP, San Diego, California.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2004, and management's assessment of the effectiveness of our internal control over financial reporting

as of December 31, 2004, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements and management's assessment are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and special reports, proxy statements and other information with the SEC. You may read and copy any document we file at the SEC's public reference room at 450 Fifth Street, N.W., Washington, D.C., 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the public reference room. Our SEC filings are also available to the public at the SEC's website at *http://www.sec.gov*.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" the information we file with them, which means that we can disclose important information to you by referring you to those documents instead of having to repeat the information in this prospectus. The information incorporated by reference is considered to be part of this prospectus, and later information that we file with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings we will make with the SEC under Sections 13(a), 13(c), 14, or 15(d) of the Securities Exchange Act of 1934 after the date of this prospectus until the termination of the offering of the shares covered by this prospectus (other than information furnished under Items 2.02 or Item 7.01 of Form 8-K):

our annual report on Form 10-K for the fiscal year ended December 31, 2004 (filed on March 2, 2005);

our quarterly reports on Form 10-Q for the quarterly periods ended March 31, 2005 (filed on May 5, 2005), June 30, 2005 (filed on August 4, 2005) and September 30, 2005 (filed on November 7, 2005);

our proxy for our annual meeting of stockholders on June 13, 2005 (filed on April 22, 2005);

our current reports on Form 8-K filed on January 13, 2005, January 21, 2005, February 1, 2005, February 9, 2005, April 25, 2005, May 5, 2005, May 11, 2005, June 7, 2005, June 30, 2005, August 26, 2005 and October 11, 2005;

a description of the amendment to our Stockholders Rights Plan on Form 8-A/A filed on December 30, 2003;

the description of our common stock contained in our registration statement on Form 8-A, filed on July 26, 2000, including any amendment or reports filed for the purpose of updating such description; and

all filings we make with the SEC pursuant to the Securities Exchange Act of 1934 after the date of the initial registration statement, of which this prospectus is a part, and prior to the effectiveness of the registration statement.

You can request a copy of these filings, at no cost, by writing or telephoning us at the following address or telephone number:

Arena Pharmaceuticals, Inc.
6166 Nancy Ridge Drive
San Diego, California 92121
(858) 453-7200
Attn: Investor Relations

This prospectus is part of a registration statement we filed with the SEC. That registration statement and the exhibits filed along with the registration statement contain more information about us and the shares in this offering. Because information about documents referred to in this prospectus is not always complete, you should read the full documents which are filed as exhibits to the registration statement. You may read and copy the full registration statement and its exhibits at the SEC's public reference rooms or their website.

8,500,000 Shares

Common Stock

PROSPECTUS SUPPLEMENT

, 2006

Joint Book-Running Managers

CIBC World Markets **UBS Investment Bank**

Co-Managers

Needham & Company, LLC

Piper Jaffray

SG Cowen & Co.

Morgan Joseph **Montgomery & Co., LLC**

You should rely only on the information contained or incorporated by reference in this prospectus supplement. No dealer, salesperson or other person is authorized to give information that is not contained or incorporated by reference in this prospectus supplement. This prospectus supplement is not an offer to sell nor is it seeking an offer to buy these securities in any jurisdiction where the offer or sale is not permitted. The information contained in this prospectus supplement is correct only as of the date of this prospectus supplement, regardless of the time of the delivery of this prospectus supplement or any sale of these securities.

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