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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-115362

The information in this prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been filed with the Securities and Exchange Commission and has been declared effective. This prospectus supplement and the accompanying prospectus are not an offer to sell these securities and we are not soliciting an offer to buy these securities in any state where the offer or sale is not permitted or would be unlawful prior to registration or qualification under the securities laws of any such state.

Subject to completion. Dated September 22, 2004

PRELIMINARY PROSPECTUS SUPPLEMENT
(to prospectus dated May 7, 2004)

8,000,000 Shares

Pain Therapeutics, Inc.

Common Stock

$ per share

We are selling 8,000,000 shares of our common stock.

Our common stock is quoted on the Nasdaq National Market under the symbol "PTIE." On September 20, 2004, the last sale price for the common stock as reported on the Nasdaq National Market was $7.84 per share.

Investing in our common stock involves risks. See " Risk Factors" beginning on page S-6.

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.

	Per Share	Total
Public offering price	$	$
Underwriting discount	$	$
Proceeds to Pain Therapeutics, Inc. (before expenses)	$	$

The underwriters may also purchase up to an additional 1,200,000 shares of common stock at the public offering price, less the underwriting discount and commissions, within 30 days of the date of this prospectus supplement. The underwriters may exercise this option to cover over-allotments, if any. If the underwriters exercise the option in full, the total underwriting discount and commissions will be $.

The underwriters expect to deliver shares to purchasers on or about , 2004

Joint Book-Running Managers

Citigroup **UBS Investment Bank**

CIBC World Markets **Rodman & Renshaw**

, 2004

You should rely only on the information contained in or incorporated by reference in this prospectus. We have not authorized anyone to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information contained in this prospectus is accurate as of any date other than the date on the front of this prospectus.

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Prospectus Supplement

Prospectus

The BUTTERFLY DESIGN/LOGO is registered as a trademark of Pain Therapeutics, Inc. This prospectus supplement and the accompanying prospectus also include product names, trade names and trademarks of other companies. All other product names, trade names and trademarks appearing in this prospectus are the property of their respective holders.

ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus are part of a registration statement that we filed with the SEC using a shelf registration process. Under the shelf registration process, we may offer up to 15,000,000 shares of our common stock, of which this offering is a part. In the accompanying prospectus, we provide you with a general description of the common stock we may offer under our shelf registration statement. In this prospectus supplement, we provide you with specific information about the shares of our common stock that we are selling in this offering. Both this prospectus supplement and the accompanying prospectus include important information about us, our common stock and other information you should know before investing. This prospectus supplement also adds, updates and changes information contained in the accompanying prospectus. You should read both this prospectus supplement and the accompanying prospectus as well as additional information described under “Where You Can Find More Information” and “Incorporation By Reference” on page S-30 of this prospectus supplement before investing in our common stock.

You should rely only on the information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. We have not authorized anyone to provide you with different information. We are not making an offer to sell these securities in any state where the offer is not permitted. You should not assume that the information contained in this prospectus supplement or the accompanying prospectus is accurate as of any date other than the dates on the front covers of these documents.

Unless specifically stated, information in this prospectus supplement assumes the underwriters will not exercise their over-allotment option and no other person will exercise any other outstanding options or warrants.

SUMMARY

This summary highlights information contained elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus. This is not intended to be a complete description of the matters covered in this prospectus supplement and the accompanying prospectus and is subject to and qualified in its entirety by reference to the more detailed information and financial statements (including the notes thereto) included or incorporated by reference in this prospectus supplement and the accompanying prospectus. When we refer to "we," "us," "our" or "the Company," we mean Pain Therapeutics, Inc., unless the context indicates otherwise.

Pain Therapeutics, Inc.

We are a biopharmaceutical company dedicated to the development of innovative drugs. Our Company specializes in developing safer or more efficacious drugs for use in pain management, particularly in the area of opioid painkillers, which are sometimes referred to as narcotic painkillers. According to IMS Health, U.S. sales for opioid painkillers exceeded $4.5 billion in 2002, representing a 35% compound annual growth rate since 1998. We own worldwide commercial rights to all of our drug candidates.

Our Pipeline

Our clinical pipeline consists of three proprietary drug candidates. We are developing these three oral, small molecule drugs to treat patients who suffer from severe chronic pain, such as pain associated with advanced osteoarthritis, low-back pain or irritable bowel syndrome, or IBS.

Two of our novel drug candidates are in multiple Phase III clinical trials. We expect our third drug candidate to enter a Phase III clinical program by the end of 2004. Our drug candidates are:

- Oxytrex™, a new oral opioid painkiller that is currently in two Phase III clinical trials for the treatment of severe chronic pain;
- PTI-901, a drug candidate to treat men and women with IBS that is currently in two Phase III clinical trials; and
- Remoxy™, an anti-abuse version of long-acting oxycodone that is expected to enter a Phase III clinical program in December 2004.

Oxytrex

Oxytrex is an oral opioid painkiller with a novel mechanism of action. We believe Oxytrex could be an effective substitute for oxycodone, a narcotic painkiller widely used today to treat severe chronic pain. Sales of oxycodone exceeded $1.9 billion in 2003. We own worldwide commercial rights to Oxytrex.

Our clinical results to date have shown that Oxytrex provides superior and prolonged pain relief compared to oxycodone. In June 2003, we announced results from a Phase II study of over 350 patients suffering from severe osteoarthritic pain. In that study, Oxytrex reduced patients' pain scores by about 40% ($p<0.001$ vs. placebo and $p=0.006$ vs. oxycodone) over the study's 21-day treatment period. By comparison, an equivalent daily dose of oxycodone reduced patients' pain scores by 24%. Published pre-clinical results also demonstrate that the technology used in Oxytrex results in a lack of opioid addiction, tolerance or physical dependence in animals. However, for ethical reasons we have not tested these properties in humans and we are not evaluating these properties in our Phase III clinical trials.

We are conducting two large, randomized, double-blinded, placebo-controlled Phase III studies with Oxytrex in patients who suffer from severe chronic pain. Both Phase III studies are being conducted to compare the analgesic efficacy of Oxytrex relative to oxycodone or placebo during a three-month treatment period. The primary endpoint is analgesic efficacy as measured by clinically accepted criteria. In June 2003, we initiated the first study to assess the analgesic efficacy of Oxytrex in over 700 patients with severe low-back pain in over 40 U.S. clinical sites. In September 2004, we successfully completed patient enrollment in this study. This study remains blinded. We expect to unblind this study and to announce clinical results in the first quarter of 2005. In March 2004, we initiated a second Phase III study and we are continuing to enroll patients in over 40 U.S. clinical sites. We plan to enroll over 700 patients with severe osteoarthritic pain in this study. We expect to complete patient enrollment in the first quarter of 2005 and to announce clinical results of this study in the second quarter of 2005.

PTI-901

PTI-901 is intended to treat men or women who suffer from chronic IBS. If approved by the U.S. Food and Drug Administration, or FDA, for this indication, we believe PTI-901 will target a market in excess of $1 billion per year. We own worldwide commercial rights to PTI-901.

Chronic IBS is a painful abdominal disorder that leads to major changes in bowel habits. Published presentations estimate that IBS afflicts over 10% of the U.S. population and accounts for about 20% to 50% of referrals to gastroenterology clinics. The causes of IBS are not known and currently there is no cure. For unknown reasons, IBS predominantly affects women.

There are no FDA-approved drugs to treat men with IBS. There are two FDA-approved drugs to treat women with IBS. Both of these drugs impact gut motility. These motility drugs slow down or speed up the gut, thereby relieving diarrhea or constipation, respectively. In contrast, we view IBS as a nervous system disorder with gut-related syndromes. We believe an appropriate dose of PTI-901 modulates aberrant neuronal communication within the gut, thus restoring proper bowel function and relieving abdominal pain. In this regard, we believe PTI-901 represents a novel mechanism of action.

We announced results from a 50-patient pilot study with PTI-901 in men and women in May 2003, and we presented these results at the American College of Gastroenterology meeting in October 2003. In this open-label study, patients with IBS reported a 76% response rate to PTI-901. This response rate was observed in men and women and occurred without drug-related safety issues.

Based on these results and our discussions with the FDA, we initiated a Phase III program with PTI-901 in November 2003. This program consists of two clinical studies that are designed to be identical in all respects, except for gender. The first Phase III study plans to enroll 600 women, while the second study plans to enroll 600 men. Each Phase III study is randomized double-blinded and placebo-controlled and will assess the clinical effects of a once-daily dose of PTI-901 during a three-month treatment period. The primary endpoint is relief of IBS symptoms as measured by clinically accepted criteria. We expect to complete patient enrollment for the Phase III study in women in the second quarter of 2005 and patient enrollment for the Phase III study in men in the second half of 2005.

Remoxy

In November 2003, we announced a novel drug candidate which we named Remoxy. Remoxy is being developed as an anti-abuse version of long-acting oral oxycodone. Sales of long-acting oxycodone were approximately $1.9 billion in 2003. We own worldwide commercial rights to Remoxy.

The active drug ingredient in Remoxy is oxycodone. Oxycodone is a strong narcotic painkiller that was developed around 1920 as a substitute for morphine. When used as prescribed, oxycodone can relieve severe chronic pain. However, oxycodone has an abuse potential similar to morphine. In addition, the U.S. Drug Enforcement Administration, or the DEA, and the national media have linked illicit oxycodone use to widespread patterns of drug abuse, addiction, diversion and drug overdose. In the United States, drug-abuse related emergency room visits are reported by the Department of Health and Human Service's Drug Abuse Warning Network, or DAWN. DAWN reports 22,000 oxycodone mentions in emergency room visits in 2002, a 450% increase from 4,000 oxycodone mentions in emergency room visits in 1994.

Remoxy's novel formulation is specifically designed to foil abusers who attempt to tamper with the drug in order to induce a powerful euphoric high. In June 2004, we announced clinical results from human volunteers in the United Kingdom. These data demonstrate Remoxy is significantly less abusable than Oxycontin®, a brand leader in long-acting oxycodone. In a clinical comparison of the two drugs, Oxycontin released over twice as much active ingredient than Remoxy in two abuse studies involving high-proof alcohol ($p=0.03$) and chewing ($p=0.02$) in the first hour of the studies (when abusers presumably expect to get high). We plan to announce new anti-abuse data in human volunteers with Remoxy in the fourth quarter of 2004. In September 2004, we received regulatory clearance from the FDA to initiate clinical studies with Remoxy in the United States. We also plan to initiate a Phase III clinical program with Remoxy in the United States in December 2004.

We believe the anti-abuse technology used in Remoxy is applicable to different oral opioid painkillers. Using this platform technology, we will seek to develop anti-abuse versions of one or more additional opioid painkillers.

Our Strategy

Our commercial goal is to build a drug franchise in pain management. Our clinical goal is to continue to develop novel drugs that are more effective or safer than drugs used in the clinic today. Our strategy includes the following elements:

Focus on Clinical Development and Late Stage Products. We believe this focus will enable us to generate product revenues earlier than if we were focused on early-stage research and discovery activities.

Retain Significant Rights to Our Drugs. We currently retain worldwide commercialization rights to all of our technology and drug candidates in all markets and indications. In general, we intend to independently develop our drug candidates through late-stage clinical trials. In market segments that require large or specialized sales forces, such as the market for oxycodone products, we may seek sales and marketing alliances with third parties.

Outsource Key Functions. We intend to continue to outsource pre-clinical studies, clinical trials and formulation and manufacturing activities. We believe outsourcing permits significant time savings and allows for more efficient deployment of our resources.

Pursue In-licensing or Acquisition Opportunities. We intend to evaluate promising drug candidates or technologies to further expand our product pipeline. Our in-licensing strategy consists of evaluating clinical or pre-clinical stage opportunities in therapeutic areas that are related to our core expertise in drug development. We believe this strategy could diversify some of the risks inherent in focusing on a single therapeutic area and could also increase our probability of commercial success.

Recent Developments

Completion of Patient Enrollment For Phase III Study With Oxytrex

In September 2004, we successfully completed enrollment in a Phase III study of over 700 patients with severe low-back pain. This study compares oxycodone against Oxytrex, a novel drug candidate being developed to provide superior and prolonged pain relief. We expect to announce initial Phase III clinical results from this study in the first quarter of 2005.

Remoxy Cleared for U.S. Clinical Trials

In September 2004, we received regulatory clearance to initiate clinical studies with Remoxy in the United States. We plan to meet with the FDA and to initiate a Phase III program with Remoxy by the end of 2004. We have been conducting clinical studies with Remoxy in England and pre-clinical studies in the U.S.

Grant Awarded for Neuropathic Pain Research

In July 2004, we were awarded an innovation research grant from the National Institutes of Health. The purpose of this grant is to encourage our research and development efforts in the area of neuropathic pain.

The Offering

Unless specifically stated, information in this prospectus supplement assumes the underwriters will not exercise their over-allotment option and no other person will exercise any other outstanding options or warrants.

Common stock offered by Pain Therapeutics, Inc.	8,000,000 shares
Common stock outstanding after the offering	43,610,818 shares
Use of proceeds	We intend to use the proceeds from this offering for general corporate purposes, including research and development, expansion of our commercial function, expansion of the use of our technology or acquisition of other technologies or products, and working capital.
Nasdaq National Market symbol	PTIE

The number of shares that will be outstanding after the offering is based on the number of shares outstanding as of September 13, 2004 and excludes:

- 7,840,740 shares of common stock authorized for issuance under our stock option plans, under which options to purchase 5,155,409 shares were outstanding and 2,685,331 shares were available for grant as of such date; and
- 220,000 shares of common stock reserved for issuance upon the exercise of warrants outstanding as of such date, at a weighted average exercise price of $1.00 per share.

* * *

We were incorporated in Delaware in May 1998. Our principal executive offices are located at 416 Browning Way, South San Francisco, California 94080. Our website address is www.paintrials.com. Information on our website is not a part of this prospectus supplement or the accompanying prospectus.

Summary Financial Data

The tables below set forth summary financial data for the periods indicated. The statement of operations data for the years ended December 31, 2002 and 2003 and the balance sheet data as of December 31, 2002 and 2003, are derived from our financial statements that have been audited by Ernst & Young LLP, independent auditors, and incorporated by reference into this prospectus supplement and the accompanying prospectus. The statement of operations data for the years ended December 31, 1999, 2000 and 2001, and the balance sheet data as of December 31, 1999, 2000 and 2001 are derived from our financial statements that have been audited by KPMG LLP, independent auditors. The summary statement of operations data for the six months ended June 30, 2003 and 2004 and the summary balance sheet data as of June 30, 2004 are derived from our unaudited financial statements, incorporated by reference into this prospectus supplement and the accompanying prospectus. You should read the following summary financial data together with "Management's Discussion and Analysis of Financial Condition and Results of Operations," the accompanying financial statements and related notes that are incorporated by reference into this prospectus supplement and the accompanying prospectus. Results for interim periods are not necessarily indicative of results to be expected during the remainder of the fiscal year or for any future period.

	Years ended December 31,					Six months ended June 30, 2003	Six months ended June 30, 2004
	1999	2000	2001	2002	2003		
	(in thousands, except per share data)						
Research and development expense	$ 3,967	$ 12,596	$ 11,668	$ 11,396	$ 18,913	$ 7,503	$ 17,677
General and administrative expense	693	7,710	5,647	5,523	3,338	1,720	2,044
Total operating expenses	4,660	20,306	17,315	16,919	22,251	9,223	19,721
Operating loss	(4,660)	(20,306)	(17,315)	(16,919)	(22,251)	(9,223)	(19,721)
Interest income	160	2,826	2,978	994	634	261	491
Net loss	(4,500)	(17,480)	(14,337)	(15,925)	(21,617)	(8,962)	(19,230)
Return to series C preferred stockholders for beneficial conversion feature	—	(14,231)	—	—	—	—	—
Loss available to common stockholders	$ (4,500)	$ (31,711)	$ (14,337)	$ (15,925)	$ (21,617)	$ (8,962)	$ (19,230)
Basic and diluted loss per common share	$ (1.35)	$ (2.33)	$ (0.57)	$ (0.59)	$ (0.73)	$ (0.33)	$ (0.54)
Weighted average shares used in computing basic and diluted loss per common share	3,345	13,635	25,332	27,039	29,483	27,250	35,463

	As of December 31,					As of June 30, 2004
	1999	2000	2001	2002	2003	
Balance sheet data:						
Cash, cash equivalents and marketable securities	$ 9,340	$ 78,927	$ 65,274	$ 50,146	$ 77,429	$ 60,992
Working capital	9,096	77,320	63,195	48,146	74,799	55,877
Total assets	9,441	81,147	68,136	53,325	80,513	62,904
Total liabilities	301	2,452	2,519	3,101	3,951	5,161
Stockholders' equity (deficit)	(563)	78,695	65,616	50,224	76,562	57,743

RISK FACTORS

You should carefully consider the risks described below before making a decision to buy our common stock. If any of the following risks actually occur, our business could be harmed, the trading price of our common stock could decline and you may lose all or part of your investment. You should also refer to the other information contained in or incorporated by reference into this prospectus supplement and the accompanying prospectus, including the financial statements and related notes.

Risks Relating to our Financial Position and Need for Financing

Our operating history may make it difficult for you to evaluate our business to date and to assess its future viability.

We were founded in May 1998 and are in the development stage. Our operations to date have been limited to organizing and staffing our company, acquiring, developing and securing our technology and undertaking preclinical studies and clinical trials of our drug candidates. We have not yet demonstrated our ability to obtain regulatory approval, formulate and manufacture our product candidates on a commercial scale or conduct sales and marketing activities. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

We have a history of losses and expect to incur substantial losses and negative operating cash flows for the foreseeable future.

We have incurred net losses each year since our inception. As a result of ongoing operating losses, we had an accumulated deficit of $93.5 million as of June 30, 2004. Even if we succeed in developing and commercializing one or more of our drug candidates, we expect to continue to incur substantial losses for the foreseeable future, and we may never become profitable. We anticipate that our expenses will increase substantially in the foreseeable future as we:

- continue to conduct preclinical and clinical trials for our drug candidates, including the Phase III trials of Oxytrex, PTI-901 and the Phase III clinical program and formulation and development activities for Remoxy;
- seek regulatory approvals for our drug candidates;
- develop, formulate, manufacture and commercialize our drug candidates;
- implement additional internal systems and develop new infrastructure;
- acquire or in-license additional products or technologies or expand the use of our technology;
- maintain, defend and expand the scope of our intellectual property; and
- hire additional personnel.

We will need to generate significant revenues to achieve and maintain profitability. If we cannot successfully develop, obtain regulatory approval for and commercialize our drug candidates, we will not be able to generate such revenues or achieve profitability in the future. Our failure to achieve or maintain profitability would have a material adverse impact on the market price of our common stock.

If we cannot raise additional capital on acceptable terms, we may be unable to complete planned clinical trials of any or some of our drug candidates or to pursue attractive business opportunities.

We have funded all of our operations and capital expenditures with the proceeds from public and private stock offerings. We expect that our current cash, cash equivalent and marketable securities on hand will be sufficient to meet our working capital and capital expenditure needs for at least the next 12 months. However, we may need to raise additional funds within such 12-month period or thereafter and additional financing may not be

available on favorable terms, if at all. Even if we succeed in selling additional securities to raise funds, our existing stockholders' ownership percentage would be reduced and new investors may demand rights, preferences or privileges senior to those of existing stockholders. If we raise additional capital through strategic alliance and license arrangements, we may have to trade our rights to our technology, intellectual property or drug candidates to others in such arrangements on terms that may not be favorable to us.

If we determine that we need to raise additional funds and we are not successful in doing so, we may be unable to complete the clinical development of some or all of our drug candidates or to seek or obtain FDA approval of our drug candidates. We then could be forced to discontinue product development, enter into a relationship with a strategic partner earlier than currently intended, reduce sales and marketing efforts or forego attractive business opportunities.

Clinical and Regulatory Risks

If we fail to obtain the necessary regulatory approvals, we will not be allowed to commercialize our drugs, and we will not generate product revenues.

Satisfaction of all regulatory requirements typically takes many years, is dependent upon the type, complexity and novelty of the drug candidate, and requires the expenditure of substantial resources for research and development and testing. Our research and clinical approaches may not lead to drugs that the FDA considers safe for humans and effective for indicated uses we are studying. The FDA may require us to conduct additional clinical testing, in which case we would have to expend additional time and resources and would likely delay the date of potentially receiving regulatory approval. In particular, the FDA may require additional toxicology studies for certain excipients used in Remoxy or any of our other drug candidates. The approval process may also be delayed by changes in government regulation, future legislation or administrative action or changes in FDA policy that occur prior to or during our regulatory review. Delays in obtaining regulatory approvals will:

- delay commercialization of, and product revenues from, our drug candidates; and
- diminish the competitive advantages that we may have otherwise enjoyed.

Even if we comply with all FDA regulatory requirements, we may never obtain regulatory approval for any of our drug candidates. If we fail to obtain regulatory approval for any of our drug candidates we will have fewer saleable products and corresponding lower product revenues. Even if we receive regulatory approval of our drug candidates, such approval may involve limitations on the indications and conditions of use or marketing claims we may make for our products. Further, later discovery of previously unknown problems or adverse events could result in additional regulatory restrictions, including withdrawal of products. The FDA may also require us to commit to perform lengthy Phase IV post-approval studies, for which we would have to expend additional resources, which could have an adverse effect on our operating results and financial condition.

In foreign jurisdictions, we must receive marketing authorizations from the appropriate regulatory authorities before we can commercialize our drugs. Foreign regulatory approval processes generally include all of the aforementioned requirements and risks associated with FDA approval.

If we are unable to design, conduct and complete clinical trials successfully, we will not be able to obtain regulatory approval for our drug candidates.

In order to obtain FDA approval for any of our drug candidates, we must submit to the FDA a new drug application, or NDA, that demonstrates that the drug candidate is safe and effective in humans for its intended use. This demonstration requires significant research and animal tests, which are referred to as preclinical studies, as well as human tests, which are referred to as clinical trials. Two of our drug candidates, Oxytrex and PTI-901, are in Phase III clinical trials. In September 2004, we received regulatory clearance to initiate clinical studies with Remoxy in the United States and we plan to initiate a Phase III program in December 2004.

Our Phase III trials may not demonstrate the safety or efficacy of our drug candidates. Success in pre-clinical testing and early clinical trials does not ensure that later clinical trials will be successful. Results of later clinical trials may not replicate the results of prior clinical trials and pre-clinical testing. FDA guidelines recommend that the efficacy of new painkillers be demonstrated in more than one clinical model of pain. This means that even if one of our Phase III trials demonstrates positive results for our drug candidates, we are likely to have to demonstrate positive results in one or more additional Phase III clinical trials prior to receiving broad label FDA approval for treatment of severe chronic pain. Even if the results of our Phase III trials are positive, we may have to commit substantial time and additional resources to conducting further preclinical and clinical studies before we can submit NDAs or obtain FDA approvals for our drug candidates.

Clinical trials are very expensive and difficult to design and implement, in part because they are subject to rigorous requirements. The clinical trial process is also time consuming. Furthermore, if participating patients in clinical studies suffer drug-related adverse reactions during the course of such trials, or if we or the FDA believe that participating patients are being exposed to unacceptable health risks, we will have to suspend or terminate our clinical trials. Failure can occur at any stage of the trials, and we could encounter problems that cause us to abandon clinical trials or to repeat clinical studies.

In addition, completion of clinical trials can be delayed by numerous factors, including:

- delays in identifying and agreeing on acceptable terms with prospective clinical trial sites;
- slower than expected rates of patient recruitment and enrollment;
- increases in time required to complete monitoring of patients during or after participation in a trial; and
- unexpected need for additional patient-related data.

Any of these delays, if significant, could impact the timing, approval and commercialization of our drug candidates and could significantly increase our overall costs of drug development.

Even if our clinical trials are completed as planned, their results may not support our expectations or intended marketing claims. The clinical trials process may fail to demonstrate that our drug candidates are safe and effective for indicated uses. Such failure would cause us to abandon a drug candidate and could delay development of other drug candidates.

Clinical trial designs that were discussed with authorities prior to their commencement may subsequently be considered insufficient for approval at the time of application for regulatory approval.

We discuss with and obtain guidance from regulatory authorities on certain of our clinical development activities. These discussions are not binding obligations on the part of regulatory authorities. Regulatory authorities may revise previous guidance or decide to ignore previous guidance at any time during the course of our clinical activities or after the completion of our clinical trials. Even with successful clinical safety and efficacy data, we may be required to conduct additional, expensive trials to obtain regulatory approval.

Developments by competitors may establish standards of care that affect our ability to conduct our clinical trials as planned.

We have conducted clinical trials of our drug candidates comparing our drug candidates to both placebo and other approved drugs. Changes in standards related to clinical trial design could affect our ability to design and conduct clinical trials as planned. For example, regulatory authorities may not allow us to compare our drug candidates to placebo in a particular clinical indication where approved products are available. In that case, both the cost and the amount of time required to conduct a trial could increase.

The Drug Enforcement Administration, or DEA, limits the availability of the active ingredients in certain of our current drug candidates and, as a result, our quota may not be sufficient to complete clinical trials, or to meet commercial demand or may result in clinical delays.

The DEA regulates chemical compounds as Schedule I, II, III, IV or V substances, with Schedule I substances considered to present the highest risk of substance abuse and Schedule V substances the lowest risk. Certain active ingredients in our current drug candidates, such as oxycodone, are listed by the DEA as Schedule II under the Controlled Substances Act of 1970. Consequently, their manufacture, research, shipment, storage, sale and use are subject to a high degree of oversight and regulation. For example, all Schedule II drug prescriptions must be signed by a physician, physically presented to a pharmacist and may not be refilled without a new prescription. Furthermore, the amount of Schedule II substances we can obtain for clinical trials and commercial distribution is limited by the DEA and our quota may not be sufficient to complete clinical trials or meet commercial demand. There is a risk that DEA regulations may interfere with the supply of the drugs used in our clinical trials, and, in the future, our ability to produce and distribute our products in the volume needed to meet commercial demand.

Government agencies may establish and promulgate usage guidelines that directly apply to our drug candidates.

Government agencies, professional and medical societies, and other groups may establish usage guidelines that apply to our drug candidates. These guidelines could address such matters as usage and dose, among other factors. Application of such guidelines could limit the use of our drug candidates.

Conducting clinical trials of our drug candidates or potential commercial sales of a drug candidate may expose us to expensive product liability claims and we may not be able to maintain product liability insurance on reasonable terms or at all.

The risk of product liability is inherent in the testing of pharmaceutical products. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit or terminate testing of one or more of our products. Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of our products. We currently carry clinical trial insurance but do not carry product liability insurance. If we successfully commercialize one or more of our drug candidates, we may face product liability claims, regardless of FDA approval for commercial manufacturing and sale. We may not be able to obtain such insurance at a reasonable cost, if at all. If our agreements with any future corporate collaborators entitle us to indemnification against product liability losses, such indemnification may not be available or adequate should any claim arise.

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

Any regulatory approvals that we receive for our drug candidates may also be subject to limitations on the indicated uses for which the drug may be marketed or contain requirements for potentially costly post-marketing follow-up studies. In addition, if the FDA approves any of our drug candidates, the labeling, packaging, adverse event reporting, storage, advertising, promotion and record-keeping for the drug will be subject to extensive regulatory requirements. The subsequent discovery of previously unknown problems with the drug, including adverse events of unanticipated severity or frequency, may result in restrictions on the marketing of the drug, and could include withdrawal of the drug from the market.

The FDA's policies may change and additional government regulations may be enacted that could prevent or delay regulatory approval of our drug candidates. 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 may be subject to fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution. Any of these events could prevent us from marketing our drugs and our business could suffer.

Risks Relating to Commercialization

If physicians and patients do not accept and use our drugs, we will not achieve sufficient product revenues and our business will suffer.

Even if the FDA approves our drugs, physicians and patients may not accept and use them. Acceptance and use of our drugs will depend on a number of factors including:

- perceptions by members of the healthcare community, including physicians, about the safety and effectiveness of our drugs;
- published studies demonstrating the cost-effectiveness of our drugs relative to competing products;
- availability of reimbursement for our products from government or healthcare payers;
- our ability to implement a risk management plan prior to the distribution of any Schedule II drug; and
- effectiveness of marketing and distribution efforts by us and our licensees and distributors, if any.

Because we expect to rely on sales generated by our current lead drug candidates for substantially all of our product revenues for the foreseeable future, the failure of any of these drugs to find market acceptance would harm our business and could require us to seek additional financing.

If we are unable to develop our own sales, marketing and distribution capabilities, or if we are not successful in contracting with third parties for these services on favorable terms, or at all, our product revenues could be disappointing.

We currently have no sales, marketing or distribution capabilities. In order to commercialize our products, if any are approved by the FDA, we will either have to develop such capabilities internally or collaborate with third parties who can perform these services for us. If we decide to commercialize any of our drugs ourselves, we may not be able to hire the necessary experienced personnel and build sales, marketing and distribution operations which are capable of successfully launching new drugs and generating sufficient product revenues. In addition, establishing such operations will take time and involve significant expense.

If we decide to enter into co-promotion or other licensing arrangements with third parties, we may be unable to locate acceptable collaborators because the number of potential collaborators is limited and because of competition from others for similar alliances with potential collaborators. Even if we are able to identify one or more acceptable collaborators, we may not be able to enter into any collaborative arrangements on favorable terms, or at all.

In addition, due to the nature of the market for pain management products, it may be necessary for us to license all or substantially all of our drug candidates to a single collaborator, thereby eliminating our opportunity to commercialize other pain management products independently. If we enter into any collaborative arrangements, our revenues are likely to be lower than if we marketed and sold our products ourselves.

In addition, any revenues we receive would depend upon our collaborators' efforts which may not be adequate due to lack of attention or resource commitments, management turnover, change of strategic focus, further business combinations or other factors outside of our control. Depending upon the terms of our collaboration, the remedies we have against an under-performing collaborator may be limited. If we were to terminate the relationship, it may be difficult or impossible to find a replacement collaborator on acceptable terms, or at all.

If we cannot compete successfully for market share against other drug companies, we may not achieve sufficient product revenues and our business will suffer.

The market for our drug candidates is characterized by intense competition and rapid technological advances. If our drug candidates receive FDA approval, they will compete with a number of existing and future drugs and therapies developed, manufactured and marketed by others. Existing or future competing products may provide greater therapeutic convenience or clinical or other benefits for a specific indication than our products, or may offer comparable performance at a lower cost. If our products are unable to capture and maintain market share, we may not achieve sufficient product revenues and our business will suffer.

We will compete for market share against fully integrated pharmaceutical companies or other companies that are collaborating with larger pharmaceutical companies, academic institutions, government agencies and other public and private research organizations. Many of these competitors have opioid painkillers already approved or in development. In addition, many of these competitors, either alone or together with their collaborative partners, operate larger research and development programs and have substantially greater financial resources than we do, as well as significantly greater experience in:

- developing drugs;
- conducting preclinical testing and human clinical trials;
- obtaining FDA and other regulatory approvals of drugs;
- formulating and manufacturing drugs; and
- launching, marketing, distributing and selling drugs.

Our ability to generate product revenues will be diminished if we fail to obtain acceptable prices or an adequate level of reimbursement for our products from healthcare payers.

Our ability to commercialize our drugs, alone or with collaborators, will depend in part on the extent to which reimbursement will be available from:

- government and health administration authorities;
- private health maintenance organizations and health insurers; and
- other healthcare payers.

Significant uncertainty exists as to the reimbursement status of newly approved healthcare products. Healthcare payers, including Medicare, health maintenance organizations and managed care organizations, are challenging the prices charged for medical products and services and/or are seeking pharmacoeconomic data to justify formulary acceptance and reimbursement practices. We currently have not generated pharmacoeconomic data on any of our products. Government and other healthcare payers increasingly are attempting to contain healthcare costs by limiting both coverage and the level of reimbursement for drugs, and by refusing, in some cases, to provide coverage for uses of approved products for disease indications for which the FDA has or has not granted labeling approval. Adequate third-party insurance coverage may not be available to patients for any products we discover and develop, alone or with collaborators. If government and other healthcare payers do not provide adequate coverage and reimbursement levels for our products, market acceptance of our product candidates could be limited.

Risks Relating to our Intellectual Property

If we are unable to protect our intellectual property our competitors could develop and market products with similar features that may reduce demand for our products.

Our success, competitive position and potential future revenues will depend in part on our ability to protect our intellectual property. If we, Albert Einstein College of Medicine or our other collaborators fail to file, prosecute or maintain certain patents, our competitors could market products that contain features and clinical

benefits similar to those of our products, and demand for our products could decline as a result. In January 2003, the U.S. Patent and Trademark Office, or PTO, disclosed that a law firm for an unidentified third-party filed requests for an Ex Parte Reexamination related to certain claims on patents we exclusively licensed from Albert Einstein College of Medicine. In each of the reexaminations, the PTO issued a first/initial office action and responses to those office actions were filed. In certain of the reexaminations, the PTO issued second/final office actions in which the PTO affirmed the patentability of certain claims related to uses of our drugs under development while maintaining rejections with respect to other claims, and responses to those office actions have been filed. Reexamination certificates have been issued in certain of the proceedings confirming the patentability of the claims. We cannot provide any assurance as to the outcome of the remaining ongoing PTO proceedings. We may be involved in additional challenges to our intellectual property. An adverse outcome of the reexamination process or any other challenges to our intellectual property could result in loss of claims of these patents that pertain to certain drugs we currently have under development and could have a material adverse impact on our future revenues.

We intend to file additional patent applications relating to our technology, products and processes. We may direct Albert Einstein College of Medicine or our collaborators to file additional patent applications relating to the licensed technology or we may do so ourselves. However, our competitors may challenge, invalidate or circumvent any of our current or future patents. These patents may also fail to provide us with meaningful competitive advantages.

We may become involved in expensive litigation or other legal proceedings related to our existing intellectual property rights, including patents.

We expect that we will rely upon trade secrets, know-how, continuing technological innovations and licensing opportunities to develop and maintain our competitive position. Others may independently develop substantially equivalent proprietary information or be issued patents that may prevent the sale of our products or know-how or require us to license such information and pay significant fees or royalties in order to produce our products.

Our technology could infringe upon claims of patents owned by others. If we were found to be infringing on a patent held by another, we might have to seek a license to use the patented technology. In that case, we might not be able to obtain such a license on terms acceptable to us, or at all. If a legal action were to be brought against us or our licensors, we could incur substantial defense costs, and any such action might not be resolved in our favor. If such a dispute were to be resolved against us, we could have to pay the other party large sums of money and our use of our technology and the testing, manufacture, marketing or sale of one or more of our proposed products could be restricted or prohibited.

Risks Relating to our Business and Strategy

Competition for qualified personnel in the pharmaceutical industry is intense, and if we are not successful in attracting and retaining qualified personnel, we could experience delays in completing necessary clinical trials, in the regulatory approval process or in formulating, manufacturing, marketing and selling our potential products.

We will need to hire additional qualified personnel with expertise in clinical research, preclinical testing, government regulation, formulation and manufacturing and sales and marketing. We compete for qualified individuals with numerous biopharmaceutical companies, universities and other research institutions. Competition for such individuals, particularly in the San Francisco Bay area, is intense, and our search for such personnel may not be successful. Attracting and retaining qualified personnel will be critical to our success.

Our employees and consultants are generally subject to confidentiality or other agreements with their former employers and they may inadvertently or otherwise violate those agreements.

Many of our employees and consultants were previously employed at universities or biotechnology or pharmaceutical companies. While we require our employees and consultants to honor any agreements they may

have entered into prior to working with us, we may be subject to claims that we inadvertently or otherwise used or disclosed trade secrets or other confidential information belonging to former employers. Failure to defend such claims could result in loss of valuable rights or personnel, which in turn could harm or prevent commercialization of our product candidates. Successful defense against such claims can be expensive and might distract us from our execution of our strategies.

Law enforcement concerns over diversion of opioids and social issues around abuse of opioids may make the regulatory approval process very difficult for our drug candidates.

Media stories regarding the diversion of opioids and other controlled substances are commonplace. Law enforcement agencies or regulatory agencies may apply policies that seek to limit the availability of opioids. Such efforts may adversely affect the regulatory approval process for our drug candidates.

Developments by competitors may render our products or technologies obsolete or non-competitive.

Alternative technologies and products are being developed to improve or replace the use of opioids for pain management, several of which are in clinical trials or are awaiting approval from the FDA. In addition, the active ingredients in nearly all opioid drugs are available in generic form. Drug companies that sell generic opioid drugs represent substantial competition. Many of these organizations competing with us have substantially greater capital resources, larger research and development staffs and facilities, greater experience in drug development and in obtaining regulatory approvals and greater manufacturing and marketing capabilities than we do. Our competitors may market less expensive or more effective drugs that would compete with our product candidates or reach market with competing drugs before we are able to reach market with our drug candidates. These organizations also compete with us to attract qualified personnel and partners for acquisitions, joint ventures or other collaborations.

Business interruptions could limit our ability to operate our business.

Our operations as well as those of our collaborators on which we depend are vulnerable to damage or interruption from computer viruses, human error, natural disasters, electrical and telecommunication failures, international acts of terror and similar events. We have not established a formal disaster recovery plan and our back-up operations and our business interruption insurance may not be adequate to compensate us for losses we may suffer. A significant business interruption could result in losses or damages incurred by us and require us to cease or curtail our operations.

Risks Relating to Manufacturing

If third-party manufacturers of our drug candidates fail to devote sufficient time and resources to our concerns, or if their performance is substandard, our clinical trials and product introductions may be delayed and our costs may be higher than expected.

We have no manufacturing facilities and have limited experience in drug product development and commercial manufacturing. We lack the resources and expertise to formulate, manufacture or test the technical performance of our drug candidates. We currently rely on a limited number of experienced personnel and a small number of contract manufacturers and other vendors to formulate, test, supply, store and distribute drug supplies for our clinical trials. Our reliance on a limited number of vendors exposes us to the following risks, any of which could delay our clinical trials, and, consequently, FDA approval of our drug candidates and commercialization of our products, result in higher costs, or deprive us of potential product revenues:

- Contract commercial manufacturers, their sub-contractors or other third parties we rely on, may encounter difficulties in achieving the volume of production needed to satisfy clinical needs or commercial demand, may experience technical issues that impact quality or compliance with applicable and strictly enforced regulations governing the manufacture of pharmaceutical products, and may experience shortages of qualified personnel to adequately staff production operations.

- Our contract manufacturers could default on their agreements with us to provide clinical supplies or meet our requirements for commercialization of our products.
- The use of alternate manufacturers may be difficult because the number of potential manufacturers that have the necessary governmental licenses to produce narcotic products is limited. Additionally, the FDA and the DEA must approve any alternative manufacturer of our product before we may use the alternative manufacturer to produce our supplies. It may be difficult or impossible for us to find a replacement manufacturer on acceptable terms quickly, or at all. Our contract manufacturers and vendors may not perform as agreed or may not remain in the contract manufacturing business for the time required to successfully produce, store and distribute our products.
- If any third-party manufacturer makes improvements in the manufacturing process for our products, we may not own, or may have to share, the intellectual property rights to such innovation.

We rely on third-party commercial drug manufacturers for drug supply.

Approved third-party commercial drug manufacturers may subsequently be stopped from producing, storing, shipping or testing our drug products due to their non-compliance with federal, state or local regulations. Drug manufacturers are subject to ongoing periodic unannounced inspection by the FDA, the DEA, and corresponding state and foreign government agencies to ensure strict compliance with good manufacturing practice and other government regulations and corresponding foreign standards. We do not have control over third-party manufacturers' compliance with these regulations and standards. If our drug supply for one of our product candidates was interrupted, our operations could be negatively affected.

If we cannot formulate and scale-up a wide range of dosage forms of Remoxy, we might determine that the commercial opportunity for Remoxy is too limited to warrant further investment in clinical testing and development.

We plan to formulate and scale-up a wide range of dosage forms of Remoxy. We may not be able to successfully complete our formulation or scale-up activities or we may determine that the commercial opportunity for Remoxy in certain dosage forms is too limited to warrant further investment.

Risks Relating to our Collaboration Agreements

If outside collaborators fail to devote sufficient time and resources to our drug development programs, or if their performance is substandard, our regulatory submissions and our product introductions may be delayed.

We depend on independent investigators and collaborators, such as universities and medical institutions, to conduct our clinical trials under agreements with us. These collaborators are not our employees and we cannot control the amount or timing of resources that they devote to our programs. These investigators may not assign as great a priority to our programs or pursue them as diligently as we would if we were undertaking such programs ourselves. If outside collaborators fail to devote sufficient time and resources to our drug development programs, or if their performance is substandard, the approval of our regulatory submissions and our introductions of new drugs will be delayed.

Our collaborators may also have relationships with other commercial entities, some of which may compete with us. If outside collaborators assist our competitors to our detriment, the approval of our regulatory submissions will be delayed and the sales from our products will be less than expected.

We may not succeed at in-licensing drug candidates or technologies to expand our product pipeline.

We may not successfully in-license drug candidates or technologies to expand our product pipeline. The number of such candidates or technologies may be limited. Competition among large pharmaceutical companies

and biopharmaceutical companies for promising drug candidates or technologies is intense because such companies generally desire to expand their product pipelines through in-licensing.

Our collaborative agreements may not succeed or may give rise to disputes over intellectual property or other issues.

Our strategy to focus on development of novel drug candidates discovered by third parties requires us to enter into license agreements with such third parties. In addition, we may enter into collaborative agreements to commercialize our products. Such agreements are generally complex and contain provisions that could give rise to legal disputes. Such disputes can delay the development of potential new drug products, or can lead to lengthy, expensive litigation or arbitration. Other factors relating to collaborative agreements may adversely affect the success of our drug candidates, including:

- the development of parallel products by our collaborators or by a competitor;
- arrangements with collaborative partners that limit or preclude us from developing certain products or technologies;
- premature termination of a collaborative agreement; or
- failure by a collaborative partner to devote sufficient resources to the development of our potential products.

Risks Relating to an Investment in our Common Stock

Our stock price has been volatile and could experience a sudden decline in value.

Our common stock has experienced significant price and volume fluctuations and may continue to experience volatility in the future. You may not be able to sell your shares quickly or at the latest market price if trading in our stock is not active or the volume is low. The following factors, in addition to other risk factors described in this section, may have a significant impact on the market price of our common stock:

- results of or delays in our preclinical and clinical trials;
- publicity regarding actual or potential medical results relating to products under development by us or others;
- announcements of technological innovations or new commercial products by us or others;
- developments in patent or other proprietary rights by us or others;
- comments or opinions by securities analysts or major stockholders;
- future sales of our common stock by existing stockholders;
- regulatory developments or changes in regulatory guidance;
- litigation or threats of litigation;
- economic and other external factors or other disaster or crises;
- the departure of any of our officers, directors or key employees;
- period-to-period fluctuations in financial results; and
- limited daily trading volume.

The National Association of Securities Dealers, Inc., or NASD, and the Securities and Exchange Commission, or SEC, have adopted certain new rules. If we were unable to continue to comply with the new rules, we could be delisted from trading on the NASDAQ National Market, or Nasdaq, and thereafter trading in

our common stock, if any, would be conducted through the over-the-counter market or on the Electronic Bulletin Board of the NASD. As a consequence of such delisting, an investor would likely find it more difficult to dispose of, or to obtain quotations as to the price of, our common stock. Delisting of our common stock could also result in lower prices per share of our common stock than would otherwise prevail.

Our charter documents contain provisions that may prevent or delay removal of incumbent management or a change of control.

Provisions of our amended and restated certificate of incorporation and amended and restated bylaws may have the effect of deterring or delaying attempts by our shareholders to remove or replace management, engage in proxy contests and effect changes in control. These provisions include:

- a classified board so that only one third of the board of directors is elected each year;
- elimination of cumulative voting in the election of directors;
- procedures for advance notification of shareholder nominations and proposals;
- the ability of our board of directors to amend our bylaws without shareholder approval; and
- the ability of our board of directors to issue up to 10,000,000 shares of preferred stock without shareholder approval upon the terms and conditions and with the rights, privileges and preferences as the board of directors may determine.

In addition, as a Delaware corporation, we are subject to Delaware law, including Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years following the date that the stockholder became an interested stockholder unless certain specific requirements are met as set forth in Section 203.

These provisions, alone or together, could have the effect of deterring or delaying changes in incumbent management, proxy contests or changes in control.

Volatility in the stock prices of other companies may contribute to volatility in our stock price.

The stock market in general, Nasdaq and the market for technology companies in particular, have experienced significant price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of those companies. Further, there has been particular volatility in the market prices of securities of early stage and development stage life sciences companies. These broad market and industry factors may seriously harm the market price of our common stock, regardless of our operating performance. In the past, following periods of volatility in the market price of a company's securities, securities class action litigation has often been instituted. A securities class action suit against us could result in substantial costs, potential liabilities and the diversion of management's attention and resources.

Our share ownership is concentrated, and our officers, directors and principal stockholders can exert significant control over matters requiring stockholder approval.

Due to their combined stock holdings, our officers, directors and principal stockholders (stockholders holding greater than 5% of our common stock) acting collectively may have the ability to exercise significant influence over matters requiring stockholder approval including the election of directors and approval of significant corporate transactions. In addition, this concentration of ownership may delay or prevent a change in control of the Company and may make some transactions more difficult or impossible to complete without the support of these stockholders.

Publicly available information regarding stockholders' ownership may not be comprehensive because the SEC does not require certain large stockholders to publicly disclose their stock ownership positions.

Our operating results may fluctuate from quarter to quarter and this fluctuation may cause our stock price to decline.

Our quarterly operating results have fluctuated in the past and are likely to fluctuate in the future. Factors contributing to these fluctuations include, among other items, the timing and enrollment rates of clinical trials for our drug candidates, our need for clinical supplies and the re-measurement of certain deferred stock compensation. Thus, quarter-to-quarter comparisons of our operating results are not indicative of what we might expect in the future. As a result, in some future quarters our clinical, financial or operating results may not meet the expectations of securities analysts and investors that could result in a decline in the price of our stock.

There may not be an active, liquid trading market for our common stock.

There is no guarantee that an active trading market for our common stock will be maintained on Nasdaq. Investors may not be able to sell their shares quickly or at the latest market price if trading in our stock is not active.

FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus contain forward-looking statements. We use words like “anticipates,” “believes,” “plans,” “expects,” “future,” “intends” and similar expressions to identify these forward-looking statements. Examples of such statements include:

- We expect our third drug candidate to enter a Phase III clinical program by the end of 2004.
- We expect to unblind our first Phase III Oxytrex study and to announce clinical results in the first quarter of 2005.
- We plan to enroll over 700 patients with severe osteoarthritic pain in our second Phase III Oxytrex study.
- We expect to complete patient enrollment for our second Phase III Oxytrex study in the first quarter of 2005 and to announce clinical results of this study in the second quarter of 2005.
- If approved by the FDA for this indication, we believe PTI-901 will target a market in excess of $1 billion per year.
- The first Phase III study for PTI-901 plans to enroll 600 women, while the second Phase III study for PTI-901 study plans to enroll 600 men.
- We expect to complete patient enrollment for the PTI-901 Phase III study in women in the second quarter of 2005 and patient enrollment for the PTI-901 Phase III study in men in the second half of 2005.
- We plan to announce new anti-abuse data in human volunteers with Remoxy in the fourth quarter of 2004.
- We also plan to initiate a Phase III clinical program with Remoxy in the United States in December 2004.
- Using our Remoxy platform technology, we will seek to develop anti-abuse versions of one or more additional opioid painkillers.
- We believe our focus on clinical development and late stage products will enable us to generate product revenues earlier than if we were focused on early-stage research and discovery activities.
- In general, we intend to independently develop our drug candidates through late-stage clinical trials.
- We intend to continue to outsource pre-clinical studies, clinical trials and formulation and manufacturing activities.
- We intend to evaluate promising drug candidates or technologies to further expand our product pipeline.
- We expect to announce initial Phase III clinical results from our Phase III study with Oxytrex in the first quarter of 2005.
- We plan to meet with the FDA and to initiate a Phase III program with Remoxy by the end of 2004.
- Even if we succeed in developing and commercializing one or more of our drug candidates, we expect to continue to incur substantial losses for the foreseeable future, and we may never become profitable.
- We anticipate that our expenses will increase substantially in the foreseeable future.
- We expect that our current cash, cash equivalent and marketable securities on hand will be sufficient to meet our working capital and capital expenditure needs for at least the next 12 months.
- We expect to rely on sales generated by our current lead drug candidates for substantially all of our product revenues for the foreseeable future.

- We intend to file additional patent applications relating to our technology, products and processes.
- We expect that we will rely upon trade secrets, know-how, continuing technological innovations and licensing opportunities to develop and maintain our competitive position.

We have based these forward-looking statements on our current expectations and projections about future events. These forward-looking statements involve risks and uncertainties, including, but not limited to, the following:

- those risks and uncertainties relating to difficulties or delays in development, testing, regulatory approval, production and marketing of our drug candidates;
- unexpected adverse side effects or inadequate therapeutic efficacy of our drug candidates that could slow or prevent product approval (including the risk that current and past results of clinical trials are not indicative of future results of clinical trials);
- the uncertainty of patent protection for our intellectual property or trade secrets;
- potential infringement of the intellectual property rights or trade secrets of third parties; and
- our ability to obtain additional financing if necessary; and those risks and uncertainties relating to an investment in our common stock.

In light of those risks, uncertainties and assumptions, the forward-looking events discussed in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus might not occur.

USE OF PROCEEDS

We estimate our net proceeds from the sale of the 8,000,000 shares of our common stock offered in this offering will be approximately $ million based on the public offering price of $ per share and after deducting the underwriting discount and estimated offering expenses.

We intend to use the proceeds from this offering for general corporate purposes, including research and development, expansion of our commercial function, expansion of the use of our technology or acquisition of other technologies or products, and working capital. Pending use, we intend to invest the net proceeds in short term, investment grade, interest bearing securities.

CAPITALIZATION

The following table sets forth our unaudited cash, cash equivalents and marketable securities and other capitalization as of June 30, 2004:

- on a historical basis; and
- on an as adjusted basis to give effect to this offering.

	As of June 30, 2004	
	Historical	As Adjusted
	(in thousands)	
Cash, cash equivalents and marketable securities	$ 60,992	$ 119,752
Total debt	$ —	$ —
Stockholders' equity:		
Convertible preferred stock, $.001 par value; 10,000,000 shares authorized, no shares issued and outstanding	—	—
Common stock, $.001 par value; actual—120,000,000 shares authorized, 35,572,629 shares issued and outstanding; as adjusted—43,572,629 shares issued and outstanding	36	44
Additional paid-in capital	151,452	210,204
Accumulated other comprehensive income (loss)	(267)	(267)
Deficit accumulated during the development stage	(93,478)	(93,478)
Total stockholders' equity	57,743	116,503
Total capitalization	57,743	116,503

DILUTION

The net tangible book value of our common stock as of June 30, 2004 was approximately $57.7 million, or $1.62 per share. Net tangible book value per share represents the amount of our total assets, excluding net intangible assets, less our total liabilities, divided by the total number of shares of our common stock outstanding.

Without taking into account any other changes in net tangible book value, other than to give effect to the sale of eight million shares of common stock offered by us in this prospectus supplement at the assumed public offering price of $7.84, and after deducting the estimated underwriting discount and estimated offering expenses payable by us, our as adjusted net tangible book value as of June 30, 2004 would have been approximately $116.5 million, or $2.67 per share. This represents an immediate increase in net tangible book value of $1.05 per share to existing stockholders and an immediate dilution of $5.17 per share to investors purchasing shares of common stock in this offering. The following table illustrates this per share dilution:

Assumed public offering price per share		$7.84
Net tangible book value per share as of June 30, 2004	$1.62	
Increase per share attributable to new investors	1.05	
Net tangible book value per share after this offering		2.67
Dilution per share to new investors		$5.17

The calculation of net tangible book value and other computations above assume that no options or warrants were exercised after June 30, 2004. As of June 30, 2004, 4,336,197 shares of common stock were issuable upon exercise of outstanding options at a weighted average exercise price of $6.76 per share and warrants outstanding to purchase a total of 220,000 shares of common stock at a weighted average exercise price of $1.00 per share. If all these options and warrants had been exercised as of June 30, 2004, our net tangible book value on that date would have been $87.3 million or $2.17 per share, the increase in net tangible book value attributable to new investors would have been $0.86 per share and the dilution in net book value to new investors would have been $4.81 per share.

DIVIDEND POLICY

To date, we have not paid any cash dividends on our common stock. We currently anticipate that we will retain any available funds to finance the growth and operation of our business and we do not anticipate paying any cash dividends in the foreseeable future. Certain present or future agreements may limit or prevent the payment of dividends on our common stock.

PRICE RANGE OF COMMON STOCK

Our common stock has been traded in The Nasdaq Stock Market under the symbol PTIE since our initial public offering on July 14, 2000. As of September 20, 2004 we had approximately 88 holders of record of our common stock. The following table sets forth the high and low sales prices per share of our common stock as reported on The Nasdaq National Market for the periods indicated:

	Sales Price	
	High	Low
2002:		
First Quarter	$10.61	$7.46
Second Quarter	12.12	6.10
Third Quarter	10.00	3.86
Fourth Quarter	4.76	2.00
2003:		
First Quarter	3.90	1.68
Second Quarter	8.11	1.68
Third Quarter	8.95	5.90
Fourth Quarter	7.71	4.44
2004:		
First Quarter	9.86	5.77
Second Quarter	9.34	6.54
Third Quarter (through September 20, 2004)	8.39	6.22

SELECTED FINANCIAL DATA

The table below sets forth selected financial data for the periods indicated. The statement of operations data for the year ended December 31, 2003 and 2002 and the balance sheet data as of December 31, 2002 and 2003 are derived from our financial statements that have been audited by Ernst & Young LLP, independent auditors and incorporated by reference into this prospectus supplement and the accompanying prospectus. The statement of operations data for the years ended December 31, 1999, 2000 and 2001, and the balance sheet data as of December 31, 1999, 2000 and 2001 are derived from our audited financial statements that have been audited by KPMG LLP, independent auditors. The summary statement of operations data for the six months ended June 30, 2004 and 2003 and the period from inception (May 4, 1998) through June 30, 2004 and the summary balance sheet data as of June 30, 2004 are derived from our unaudited financial statements, incorporated by reference into this prospectus supplement and the accompanying prospectus. In the opinion of management, all adjustments, consisting only of normal recurring adjustments, necessary for a fair presentation have been included in preparing the unaudited financial statements. You should read the following selected financial data together with "Management's Discussion and Analysis of Financial Condition and Results of Operations" and the accompanying financial statements and related notes that are incorporated by reference into this prospectus supplement and the accompanying prospectus. Results for interim periods are not necessarily indicative of results to be expected during the remainder of the fiscal year or for any future period.

	Year ended December 31,					Six months ended June 30, 2003	Six months ended June 30, 2004	Inception (May 4, 1998) through June 30, 2004
	1999	2000	2001	2002	2003			
	(in thousands, except per share data)							
Statement of operations data:								
Research and development expense	$ 3,967	$ 12,596	$ 11,668	$ 11,396	$ 18,913	$ 7,503	$ 17,677	$ 76,517
General and administrative expense	693	7,710	5,647	5,523	3,338	1,720	2,044	25,078
Total operating expenses	4,660	20,306	17,315	16,919	22,251	9,223	19,721	101,595
Operating loss	(4,660)	(20,306)	(17,315)	(16,919)	(22,251)	(9,223)	(19,721)	(101,595)
Interest income	160	2,826	2,978	994	634	261	491	8,117
Net loss	(4,500)	(17,480)	(14,337)	(15,925)	(21,617)	(8,962)	(19,230)	(93,478)
Return to series C preferred stockholders for beneficial conversion feature	—	(14,231)	—	—	—	—	—	(14,231)
Loss available to common stockholders	$ (4,500)	$ (31,711)	$ (14,337)	$ (15,925)	$ (21,617)	$ (8,962)	$ (19,230)	$ (107,709)
Basic and diluted loss per common share	$ (1.35)	$ (2.33)	$ (0.57)	$ (0.59)	$ (0.73)	$ (0.33)	$ (0.54)	
Weighted average shares used in computing basic and diluted loss per common share	3,345	13,635	25,332	27,039	29,483	27,250	35,463	

	As of December 31,					As of June 30, 2003
	1999	2000	2001	2002	2003	
Balance sheet data:						
Cash, cash equivalents and marketable securities	$ 9,340	$ 78,927	$ 65,274	$ 50,146	$ 77,429	$ 60,992
Working capital	9,096	77,320	63,195	48,146	74,799	55,877
Total assets	9,441	81,147	68,136	53,325	80,513	62,904
Total liabilities	301	2,452	2,519	3,101	3,951	5,161
Stockholders' equity (deficit)	(563)	78,695	65,616	50,224	76,562	57,743

MATERIAL UNITED STATES FEDERAL TAX CONSIDERATIONS FOR NON-U.S. HOLDERS OF COMMON STOCK

This section summarizes certain material U.S. federal income and estate tax considerations relating to the ownership and disposition of common stock. This summary does not provide a complete analysis of all potential tax considerations. The information provided below is based on existing authorities. These authorities may change, or the IRS might interpret the existing authorities differently. In either case, the tax considerations of owning or disposing of common stock could differ from those described below. For purposes of this summary, a "non-U.S. holder" is any holder other than a citizen or resident of the United States, a corporation organized under the laws of the United States or any state, a trust that is (i) subject to the primary supervision of a U.S. court and the control of one of more U.S. persons or (ii) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person or an estate whose income is subject to U.S. income tax regardless of source. If a partnership or other flow-through entity is a beneficial owner of common stock, the tax treatment of a partner in the partnership or an owner of the entity will depend upon the status of the partner or other owner and the activities of the partnership or other entity. This summary generally does not address tax considerations that may be relevant to particular investors because of their specific circumstances, or because they are subject to special rules. Finally, this summary does not describe the effects of any applicable foreign, state, or local laws.

INVESTORS CONSIDERING THE PURCHASE OF COMMON STOCK SHOULD CONSULT THEIR OWN TAX ADVISORS REGARDING THE APPLICATION OF THE U.S. FEDERAL INCOME AND ESTATE TAX LAWS TO THEIR PARTICULAR SITUATIONS AND THE CONSEQUENCES OF FOREIGN, STATE, OR LOCAL LAWS, AND TAX TREATIES.

Dividends

Any dividends paid to a non-U.S. holder on common stock will generally be subject to U.S. withholding tax at a 30 percent rate. The withholding tax might not apply, however, or might apply at a reduced rate, under the terms of an applicable income tax treaty between the United States and the non-U.S. holder's country of residence. A non-U.S. holder must demonstrate its entitlement to treaty benefits by certifying its nonresident status. A non-U.S. holder can meet this certification requirement by providing a Form W-8BEN or appropriate substitute form to us or our paying agent. If the holder holds the stock through a financial institution or other agent acting on the holder's behalf, the holder will be required to provide appropriate documentation to the agent. The holder's agent will then be required to provide certification to us or our paying agent, either directly or through other intermediaries. For payments made to a foreign partnership or other flow-through entity, the certification requirements generally apply to the partners or other owners rather than to the partnership or other entity, and the partnership or other entity must provide the partners' or other owners' documentation to us or our paying agent. Special rules, described below, apply if such dividends are effectively connected with a U.S. trade or business conducted by the non-U.S. holder.

Sale of Common Stock

Non-U.S. holders will generally not be subject to U.S. federal income tax on any gains realized on the sale, exchange, or other disposition of common stock. This general rule, however, is subject to several exceptions. For example, the gain would be subject to U.S. federal income tax if:

- the gain is effectively connected with the conduct by the non-U.S. holder of a U.S. trade or business (in which case the special rules described below apply);
- the non-U.S. holder was a citizen or resident of the United States and thus is subject to special rules that apply to expatriates; or
- the rules of the Foreign Investment in Real Property Tax Act (or FIRPTA) (described below) treat the gain as effectively connected with a U.S. trade or business.

The FIRPTA rules may apply to a sale, exchange or other disposition of common stock if we are, or were within five years before the transaction, a "U.S. real property holding corporation" (or USRPHC). In general, we

would be a USRPHC if interests in U.S. real estate comprised most of our assets. We do not believe that we are a USRPHC or that we will become one in the future.

Dividends or Gain Effectively Connected With a U.S. Trade or Business

If any dividends on common stock, or gain from the sale, exchange or other disposition of common stock is effectively connected with a U.S. trade or business conducted by the non-U.S. holder, then the dividends or gain will be subject to U.S. federal income tax at the regular graduated rates. If the non-U.S. holder is eligible for the benefits of a tax treaty between the United States and the holder's country of residence, any "effectively connected" dividends or gain would probably be subject to U.S. federal income tax only if it is also attributable to a permanent establishment or fixed base maintained by the holder in the United States. Payments of dividends that are effectively connected with a U.S. trade or business, and therefore included in the gross income of a non-U.S. holder, will not be subject to the 30 percent withholding tax. To claim exemption from withholding, the holder must certify its qualification, which can be done by filing a Form W-8ECI. If the non-U.S. holder is a corporation, that portion of its earnings and profits that is effectively connected with its U.S. trade or business would generally be subject to a "branch profits tax." The branch profits tax rate is generally 30 percent, although an applicable income tax treaty might provide for a lower rate.

U.S. Federal Estate Tax

The estates of nonresident alien individuals are generally subject to U.S. federal estate tax on property with a U.S. situs. Because we are a U.S. corporation, our common stock will be U.S. situs property and therefore will be included in the taxable estate of a nonresident alien decedent. The U.S. federal estate tax liability of the estate of a nonresident alien may be affected by a tax treaty between the United States and the decedent's country of residence.

Backup Withholding and Information Reporting

The Code and the Treasury regulations require those who make specified payments to report the payments to the IRS. Among the specified payments are dividends and proceeds paid by brokers to their customers. The required information returns enable the IRS to determine whether the recipient properly included the payments in income. This reporting regime is reinforced by "backup withholding" rules. These rules require the payors to withhold tax from payments subject to information reporting if the recipient fails to cooperate with the reporting regime by failing to provide his taxpayer identification number to the payor, furnishing an incorrect identification number, or repeatedly failing to report interest or dividends on his returns. The withholding tax rate is currently 28 percent. The backup withholding rules do not apply to payments to corporations, whether domestic or foreign.

Payments to non-U.S. holders of dividends on common stock will generally not be subject to backup withholding, and payments of proceeds made to non-U.S. holders by a broker upon a sale of common stock will not be subject to information reporting or backup withholding, in each case so long as the non-U.S. holder certifies its nonresident status. Some of the common means of certifying nonresident status are described under "—Dividends." We must report annually to the IRS any dividends paid to each non-U.S. holder and the tax withheld, if any, with respect to such dividends. Copies of these reports may be made available to tax authorities in the country where the non-U.S. holder resides.

Any amounts withheld from a payment to a holder of common stock under the backup withholding rules can be credited against any U.S. federal income tax liability of the holder.

THE PRECEDING DISCUSSION OF U.S. FEDERAL INCOME TAX CONSIDERATIONS IS FOR GENERAL INFORMATION ONLY. IT IS NOT TAX ADVICE. EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS OWN TAX ADVISOR REGARDING THE PARTICULAR U.S. FEDERAL, STATE, LOCAL, AND FOREIGN TAX CONSEQUENCES OF PURCHASING, HOLDING, AND DISPOSING OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES OF ANY PROPOSED CHANGE IN APPLICABLE LAWS.

UNDERWRITING

Citigroup Global Markets Inc. and UBS Securities LLC are acting as joint bookrunning managers of the offering, and, together with CIBC World Markets Corp. and Rodman & Renshaw, LLC, are acting as representatives of the underwriters named below. Subject to the terms and conditions stated in the underwriting agreement dated the date of this prospectus supplement, each underwriter named below has agreed to purchase, and we have agreed to sell to that underwriter, the number of shares set forth opposite the underwriter's name.

Underwriter	Number of Shares
Citigroup Global Markets Inc.	
UBS Securities LLC	
CIBC World Markets Corp.	
Rodman & Renshaw, LLC	
Total	8,000,000

The underwriting agreement provides that the obligations of the underwriters to purchase the shares included in this offering are subject to approval of legal matters by counsel and to other conditions. The underwriters are obligated to purchase all the shares (other than those covered by the over-allotment option described below) if they purchase any of the shares.

The underwriters propose to offer some of the shares directly to the public at the public offering price set forth on the cover page of this prospectus supplement and some of the shares to dealers at the public offering price less a concession not to exceed $ per share. The underwriters may allow, and dealers may reallow, a concession not to exceed $ per share on sales to other dealers. If all of the shares are not sold at the initial offering price, the representatives may change the public offering price and the other selling terms.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to 1,200,000 additional shares of common stock at the public offering price less the underwriting discounts. The underwriters may exercise the option solely for the purpose of covering over-allotments, if any, in connection with this offering. To the extent the option is exercised, each underwriter must purchase a number of additional shares approximately proportionate to that underwriter's initial purchase commitment.

We, our officers and directors and an affiliate have agreed that, for a period of 90 days from the date of this prospectus supplement, we and they will not, without the prior written consent of Citigroup and UBS Securities LLC, dispose of or hedge any shares of our common stock or any securities convertible into or exchangeable for our common stock, subject to certain exceptions. The exceptions permit our officers and directors, subject to certain conditions, to transfer common stock for estate planning purposes or for the purpose of making a charitable contribution to a not-for-profit organization; provided, however, that the recipients of any such shares agree to be bound by the transfer restrictions for the remainder of the 90 day period. Citigroup and UBS Securities LLC in their sole discretion may release any of the securities subject to these lock-up agreements at any time without notice.

Each underwriter has represented, warranted and agreed that:

- it has not offered or sold and, prior to the expiry of a period of six months from the closing date, will not offer or sell any shares included in this offering to persons in the United Kingdom except to persons whose ordinary activities involve them in acquiring, holding, managing or disposing of investments (as principal or agent) for the purposes of their businesses or otherwise in circumstances which have not resulted and will not result in an offer to the public in the United Kingdom within the meaning of the Public Offers of Securities Regulations 1995;

- it has only communicated and caused to be communicated and will only communicate or cause to be communicated any invitations or inducement to engage in investment activity (within the meaning of section 21 of the Financial Services and Markets Act 2000 ("FSMA")) received by it in connection with the issue or sale of any shares included in this offering in circumstances in which section 21(1) of the FSMA does not apply to us;
- it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the shares included in this offering in, from or otherwise involving the United Kingdom; and
- the offer in The Netherlands of the shares included in this offering is exclusively limited to persons who trade or invest in securities in the conduct of a profession or business (which include banks, stockbrokers, insurance companies, pension funds, other institutional investors and finance companies and treasury departments of large enterprises.

The common stock is quoted on the Nasdaq National Market under the symbol "PTIE."

The following table shows the underwriting discounts and commissions that we are to pay to the underwriters in connection with this offering. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares of common stock.

	Paid by Pain Therapeutics, Inc.	
	No Exercise	Full Exercise
Per share	$	$
Total	$	$

In connection with the offering, Citigroup on behalf of the underwriters, may purchase and sell shares of common stock in the open market. These transactions may include short sales, syndicate covering transactions and stabilizing transactions. Short sales involve syndicate sales of common stock in excess of the number of shares to be purchased by the underwriters in the offering, which creates a syndicate short position. "Covered" short sales are sales of shares made in an amount up to the number of shares represented by the underwriters' over-allotment option. In determining the source of shares to close out the covered syndicate 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. Transactions to close out the covered syndicate short involve either purchases of the common stock in the open market after the distribution has been completed or the exercise of the over-allotment option. The underwriters must close out any naked short position by purchasing shares of common stock in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the shares in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of bids for or purchases of shares in the open market while the offering is in progress.

The underwriters also may impose a penalty bid. Penalty bids permit the underwriters to reclaim a selling concession from a syndicate member when Citigroup repurchases shares originally sold by that syndicate member in order to cover syndicate short positions or make stabilizing purchases.

Any of these activities may have the effect of preventing or retarding a decline in the market price of the common stock. They may also cause the price of the common stock to be higher than the price that would otherwise exist in the open market in the absence of these transactions. The underwriters may conduct these transactions on the Nasdaq National Market or in the over-the-counter market, or otherwise. If the underwriters commence any of these transactions, they may discontinue them at any time.

In addition, in connection with this offering, some of the underwriters (and selling group members) may engage in passive market making transactions in the common stock on the Nasdaq National Market, prior to the pricing and completion of the offering. Passive market making consists of displaying bids on the Nasdaq National market no higher than the bid prices of independent market makers and making purchases at prices no higher than those independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are limited to a specified percentage of the passive market maker's average daily trading volume in the common stock during a specified period and must be discontinued when that limit is reached. Passive market making may cause the price of the common stock to be higher than the price that otherwise would exist in the open market in the absence of those transactions. If the underwriters commence passive market making transactions, they may discontinue them at any time.

We estimate that our portion of the total expenses of this offering will be $.

The underwriters have performed investment banking and advisory services for us from time to time for which they have received customary fees and expenses. The underwriters may, from time to time, engage in transactions with and perform services for us in the ordinary course of their business.

This prospectus supplement and the accompanying prospectus in electronic format may be made available on the websites maintained by one or more of the underwriters. The representatives may agree to allocate a number of shares to underwriters for sale to their online brokerage account holders. The representatives will allocate shares to underwriters that may make Internet distributions on the same basis as other allocations. In addition, shares may be sold by the underwriters to securities dealers who resell shares to online brokerage account holders.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act of 1933, or to contribute to payments the underwriters may be required to make because of any of those liabilities.

LEGAL MATTERS

Certain legal matters relating to the validity of the securities offered hereby will be passed upon by Wilson Sonsini Goodrich & Rosati, Professional Corporation, Palo Alto, California. Wilson Sonsini Goodrich & Rosati is corporate counsel to Pain Therapeutics, Inc. Michael J. O'Donnell, a member of Wilson Sonsini Goodrich & Rosati is a Director and a Secretary of Pain Therapeutics, Inc. In addition, certain individual attorneys employed by Wilson Sonsini Goodrich & Rosati beneficially own shares of Pain Therapeutics, Inc. common stock. As of September 13, 2004, such individuals beneficially owned an aggregate of approximately 64,714 shares of Pain Therapeutics, Inc. common stock. The validity of the common stock offered by this prospectus supplement will be passed upon for the underwriters by Cleary, Gottlieb, Steen & Hamilton, New York, New York.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and special reports, proxy statements and other information with the Securities and Exchange Commission. You may read and copy any document we file at the SEC's Public Reference Rooms in Washington, D.C., New York, New York and Chicago, Illinois. The Public Reference Room in Washington, D.C. is located at 450 Fifth Street, N.W. Please call the SEC at 1-800-SEC-0330 for further information on the public conference rooms. Our SEC filings are also available to the public from the SEC's web site at http://www.sec.gov.

We have filed a registration statement under the Securities Act of 1933 with the SEC with respect to the shares to be sold hereunder. The accompanying prospectus has been filed as part of the registration statement. This prospectus supplement and the accompanying prospectus do not contain all of the information set forth in the registration statement because certain parts of the registration statement are omitted in accordance with the rules and regulations of the SEC. The registration statement is available for inspection and copying as set forth below.

INCORPORATION 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. The information incorporated by reference is considered to be part of this prospectus, and later information filed with the SEC will update and supersede this information. We incorporate by reference the documents listed below and any future filings made by us with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934 until our offering is completed.

(1) Our Annual Report on Form 10-K for the year ended December 31, 2003, as amended.

(2) Our Quarterly Report on Form 10-Q for the quarter ended March 31, 2004.

(3) Our Quarterly Report on Form 10-Q for the quarter ended June 30, 2004.

(4) Our Definitive Notice and Proxy Statement filed on Schedule 14A on April 26, 2004.

(5) The description of our common stock contained in our Registration Statement on Form 8-A, filed with the Securities and Exchange Commission on March 15, 2000, and any further amendment or report filed hereafter for the purpose of updating any such description.

You may request a copy of any or all of the information that has been incorporated in this prospectus but that has not been delivered, at no cost, by writing or telephoning us at the following address or phone number:

Pain Therapeutics, Inc.
416 Browning Way
South San Francisco, California 94080
(650) 624-8200

You should rely only on the information incorporated by reference or provided in this prospectus. We have authorized no one to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus is accurate as of any date other than the date on the front of the document.

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

SUBJECT TO COMPLETION, DATED MAY 7, 2004

PROSPECTUS

15,000,000 Shares

Pain Therapeutics, Inc.

COMMON STOCK

Pain Therapeutics, Inc. may offer shares of its common stock from time to time. We will specify in an accompanying prospectus supplement the terms of any offering. Our common stock is traded on the Nasdaq National Market "PTIE." On May 6, 2004 the last reported sale price of our common stock on the Nasdaq National Market was $8.05 per share.

You should read this prospectus, any prospectus supplement and the documents incorporated by reference in this prospectus and any prospectus supplement carefully before you invest. **This prospectus may not be used to offer or sell any securities unless accompanied by a prospectus supplement**.

Investing in our common stock involves a high degree of risk. You should carefully consider the Risk Factors beginning on page 6 of this prospectus before you make an investment decision.

The common stock offered by this prospectus may be offered in amounts, at prices and at terms determined at the time of the offering and may be sold directly by us to investors, through agents designated from time to time or to or through underwriters or dealers. We will set forth the names of any underwriters or agents in the accompanying prospectus supplement. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution." The net proceeds we expect to receive from such sale will also be set forth in a prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved 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 , 200

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No person has been authorized to give any information or make any representations in connection with this offering other than those contained or incorporated by reference in this prospectus and any accompanying prospectus supplement in connection with the offering described herein and therein, and, if given or made, such information or representations must not be relied upon as having been authorized by us. Neither this prospectus nor any prospectus supplement shall constitute an offer to sell or a solicitation of an offer to buy offered securities in any jurisdiction in which it is unlawful for such person to make such an offering or solicitation. Neither the delivery of this prospectus or any prospectus supplement nor any sale made hereunder shall under any circumstances imply that the information contained or incorporated by reference herein or in any prospectus supplement is correct as of any date subsequent to the date hereof or of such prospectus supplement.

SUMMARY

The following summary is qualified in its entirety by the more detailed information, including our consolidated financial statements and related notes, included in this prospectus and incorporated in this prospectus by reference. You should carefully consider the information set forth in this entire prospectus, including the "Risk Factors" section, the applicable prospectus supplement for such securities and the other documents we refer to and incorporate by reference, including but not limited to the section entitled "Risk Factors" in our 2003 Annual Report on Form 10-K. Unless the context otherwise requires, the terms "Pain Therapeutics," "we," "us" and "our" refer to Pain Therapeutics, Inc., Inc., a Delaware corporation.

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 process, we may, from time to time, sell up to 15,000,000 shares of our common stock in one or more offerings. Each time we sell common stock, we will provide a prospectus supplement that will contain specific information about the terms of that offering. This prospectus does not contain all of the information included in the registration statement. For a more complete understanding of the offering of our common stock, you should refer to the registration statement, including its exhibits. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and any prospectus supplement, including the risk factors, together with the additional information described under the headings "Where You Can Find Information" and "Information Incorporated by Reference."

Pain Therapeutics, Inc.

Overview

We are a biopharmaceutical company that develops novel drugs. Our drugs target severe chronic pain, such as pain associated with advanced osteoarthritis, low-back pain or irritable bowel syndrome. We have three proprietary drug candidates in clinical development: Oxytrex™, Remoxy™ and PTI-901. Our two most advanced drugs, Oxytrex and PTI-901, are in Phase III clinical trials. Remoxy is in Phase I clinical trials in the United Kingdom. We believe the target market for our three drug candidates exceeds $3 billion per year. We currently retain all commercial rights to our drug candidates.

Our Drug Candidates

Oxytrex

Our lead candidate is a novel oral opioid called Oxytrex. Oxytrex is a small molecule drug that is currently in a Phase III clinical program. We are developing Oxytrex to treat severe chronic pain, such as low back, osteoarthritic pain or cancer pain.

If the Food and Drug Administration, or FDA, approves Oxytrex, we believe it could be an effective substitute for oxycodone. Oxycodone is widely used today to treat severe chronic pain. Sales of oxycodone exceed $1.5 billion a year. We own all commercial rights to Oxytrex.

Previous clinical results have shown that Oxytrex provides enhanced pain relief and prolonged pain relief. In a previously announced Phase II study with 350 patients suffering from severe osteoarthritic pain, Oxytrex reduced patients' pain scores by over 40% ($p<0.001$ vs. placebo and $p=0.006$ vs. oxycodone) over a 21-day treatment period. By comparison, oxycodone reduced patients' pain scores by 24%. Published pre-clinical results also demonstrate that the technology used in Oxytrex results in a lack of opioid addiction, tolerance, physical dependence or withdrawal symptoms in animals.

The FDA guidelines recommend that we demonstrate the efficacy of Oxytrex in more than one clinical model of pain. We plan to study Oxytrex in at least two Phase III efficacy studies.

In June 2003, we announced the initiation of our first Phase III efficacy study. This randomized, double-blinded study compares the analgesic efficacy of Oxytrex against placebo and oxycodone over a three-month treatment period in up to 700 patients with severe chronic low back pain.

In the first quarter of 2004, we initiated a second Phase III clinical study of Oxytrex. This randomized, double-blinded study will compare the analgesic efficacy of Oxytrex against placebo and oxycodone over a three-month treatment period in up to 700 patients with severe chronic osteoarthritic pain.

Oxytrex is formulated with two active drug ingredients: oxycodone and low-dose naltrexone. We believe we have produced sufficient clinical materials necessary to complete two Phase III trials of Oxytrex. We rely on a limited number of third-party manufacturers to manufacture, fill, label, ship or store Oxytrex.

Remoxy

In November 2003, we announced our second novel drug candidate, which we named Remoxy. Remoxy is an abuse-deterrent, long-acting version of oxycodone. Sales of oxycodone exceed $1.5 billion a year. We own all commercial rights to Remoxy.

Oxycodone is a strong narcotic painkiller that is widely used today to treat patients suffering from severe chronic pain. However, oxycodone has an abuse potential similar to morphine. The U.S. Drug Enforcement Agency, or DEA, and the national media have linked illicit oxycodone use to widespread patterns of drug abuse, addiction, diversion and drug overdose. Oxycodone is also the active ingredient in OxyContin©, a branded controlled-release narcotic painkiller. Remoxy's novel capsule formulation is specifically designed to foil abusers who attempt to tamper with the drug in order to induce a powerful euphoric high. Given a choice between prescribing abuse-resistant Remoxy or more easily abusable forms of oxycodone, we believe physicians will choose a less abusable alternative, such as Remoxy.

In November 2003, we filed an Investigational New Drug Application, or IND, for Remoxy with the FDA. The FDA has requested additional information on certain excipients used in formulations of Remoxy. We are responding to the FDA's requests for additional data prior to initiating any clinical studies in the United States.

In January 2004, we initiated a Phase I clinical program of Remoxy in the United Kingdom. Our phase I program is designed to assess the pharmacokinetics and pharmacological profile of several different formulations of Remoxy against placebo and active drug in healthy volunteers.

Remoxy is formulated with Durect Corporation's SABER™ technology under a joint development and license agreement. Under the terms of our license agreement with Durect, we have exclusive worldwide rights to develop and to commercialize Remoxy and certain other opioid drugs formulated with Durect's SABER technology. We plan to formulate and scale-up a wide range of dosage forms of Remoxy. We reimburse Durect for formulation and related work, and will make milestone payments based on the achievement of certain technical, clinical or regulatory milestones. We will also pay Durect royalties on related drug sales.

We believe we can produce sufficient clinical materials necessary to complete our Phase I trials of Remoxy. We rely on Durect Corporation and a limited number of third-party manufacturers to formulate, manufacture, fill, label, ship or store Remoxy.

PTI-901

Our third drug candidate is called PTI-901 and treats Irritable Bowel Syndrome, or IBS. PTI-901 is a proprietary drug candidate that consists of an oral low-dose opioid antagonist. If approved by the FDA to treat men and women with IBS, we believe PTI-901 will target a market in excess of $1 billion per year. We own all commercial rights to PTI-901.

Chronic IBS is a painful abdominal disorder that leads to major changes in bowel habits. IBS causes some patients to have constipation, diarrhea or in some cases both. The causes of IBS are not known, and as yet there is no cure. People with chronic IBS may be unable to attend social events, hold a job, or travel away from home. Over 10 percent of the U.S. population suffers from IBS. For unknown reasons, IBS predominantly affects women.

There are no FDA-approved drugs to treat men with IBS. There are two FDA-approved drugs to treat women with IBS: Lotronex® (GlaxoSmithKline) and Zelnorm® (Novartis). The FDA approved Lotronex® in February 2000 for use in female patients with diarrhea-predominant IBS. The FDA approved Zelnorm® in July 2002 for short-term use by female patients who have constipation-predominant IBS.

We believe PTI-901 represents a novel approach to treat patients with IBS. We believe an appropriate dose of PTI-901 modulates aberrant neuronal communication within the gut, thus restoring proper bowel function and relieving pain in IBS patients.

Results from a 50-patient pilot study with PTI-901 in men and women were announced in May 2003 and presented at the American College of Gastroenterology meeting in October 2003. In this open-label study, patients with IBS reported a 76% response rate to PTI-901. This response rate was observed in both men and women and occurred without drug-related safety issues.

In November 2003, we announced the initiation of a Phase III program with PTI-901. The Phase III program consists of two clinical studies that are identical in all respects, except for gender. One study will enroll 600 women and the other will enroll 600 men, all of whom have been diagnosed with chronic IBS by a gastroenterologist according to clinically accepted criteria. Each Phase III study is randomized, double-blinded and will assess the clinical effect of PTI-901 against placebo during a three-month treatment period.

We believe we have produced sufficient clinical materials necessary to complete two Phase III trials with PTI-901. We rely on a limited number of third-party manufacturers to manufacture, fill, label, ship and store PTI-901.

Strategy

Our commercial goal is to build a franchise in pain management by developing novel drugs that target severe, chronic pain such as pain associated with advanced osteoarthritis, low-back pain or IBS. We intend to achieve this goal by developing proprietary drugs that are more effective or safer than drugs used in the clinic today. Our strategy includes:

- *Focusing on Clinical Development and Late Stage Products.* We believe this focus will enable us to generate product revenues earlier than if we were focused on early-stage research and discovery activities.
- *Retaining Significant Rights to Our Drugs.* We currently retain worldwide commercialization rights to all of our technology and drug candidates in all markets and indications. In general, we intend to independently develop our drug candidates through late-stage clinical trials. As a result, we expect to capture a greater percentage of the profits from drug sales than we would if we outlicensed our drug

candidates earlier in the development process. In market segments that require large or specialized sales forces, such as the market for oxycodone products, we may seek sales and marketing alliances with third parties.

- *Outsourcing Key Functions.* We intend to continue to outsource pre-clinical studies, clinical trials and formulation and manufacturing activities. We believe outsourcing permits significant timesavings and allows for more efficient deployment of our resources.
- *Pursue In-licensing or Acquisition Opportunities.* We intend to evaluate promising drug candidates or technologies to further expand our product pipeline. Our in-licensing strategy consists of evaluating clinical or pre-clinical stage opportunities in therapeutic areas that are related to our core expertise in drug development. We believe this strategy could diversify some of the risks inherent in drug development and increase our probability of commercial success.

Our Science and Technology

Our science was developed at Albert Einstein College of Medicine. It is well known that opioid painkillers produce their pain relieving effect by inhibiting the transmission of pain signals in certain nerve cells in the central nervous system. This inhibition of pain is achieved by inhibiting nerve cells that have opioid receptors on their membranes, via an inhibitory signaling pathway linked to the receptor. Scientists at Albert Einstein College of Medicine, however, have published results suggesting that opioid painkillers also activate an excitatory signaling pathway linked to opioid receptors, thereby stimulating the transmission of pain. This excitatory pathway counteracts pain inhibition and is believed to be a major cause of adverse side effects associated with opioid use, including the development of tolerance and addiction.

We believe that the excitatory pathway of opioid receptors contributes greatly to the adverse effects of chronic opioid use, such as tolerance, physical dependence and addiction. After repeated administration of morphine, oxycodone or other opioid painkillers, increasing doses of opioids are required in order to obtain the same level of pain relief, a process known as tolerance. If chronic opioid treatment is terminated abruptly, withdrawal symptoms rapidly appear. Continued administration of opioids prevents the appearance of withdrawal symptoms, at which point a patient is considered physically dependent. Published results in rodents also show that tolerance and physical dependence can be prevented by coadministration of low-dose naltrexone, an opioid antagonist. We believe low-dose naltrexone blocks the excitatory pathway, thus minimizing tolerance, physical dependence and addiction. In addition, recent pre-clinical work using animal models of addiction suggests that very low doses of opioid antagonists decrease the pleasurable effects and addictive potential of opioid drugs such as morphine or oxycodone.

Optimal dose ratios of low-dose opioid antagonist to opioid painkiller depend on their specific pharmacology and the mode of administration. Published pre-clinical and clinical dose response studies provide guidance in formulating optimal ratios of low-dose opioid antagonist to opioid painkiller for clinical development.

Oxytrex is a proprietary combination of two active drug ingredients. The first component is the opioid agonist oxycodone. The second component is an extremely low dose of the opioid antagonist naltrexone. Adding an antagonist to an agonist at usual clinical doses blocks the action of the agonist. This effect is clinically useful, for example, to reverse heroin overdose. At a very low dose, however, studies indicate that this effect is different: a very low-dose of an opioid antagonist can enhance pain relief and attenuate the development of tolerance or addiction. Oxytrex takes advantage of this effect by combining opioid agonists with low doses of opioid antagonists.

PTI-901 is a proprietary drug candidate that consists of oral low-dose opioid antagonist. We use PTI-901 to treat IBS. The precise causes of IBS are unknown. The two FDA-approved drugs attempt to slow down the gastrointestinal tract for diarrhea-predominant IBS in the case of Lotronex®, or speed up the gastrointestinal tract for constipation-predominant IBS in the case of Zelnorm®.

Scientific evidence suggests IBS is a disorder of the nervous system. In this scenario, patients with IBS suffer from aberrant neuronal communication within the gut due to an imbalance of opioid peptides in the gut. Since opioid peptides contribute to the proper function of the gut, an imbalance results in a broad range of gastrointestinal problems, including abdominal pain, diarrhea or constipation. We believe PTI-901 modulates aberrant neuronal communication within the gut, thus restoring proper bowel function and relieving pain in IBS patients.

Company sponsored research and development expenditures were $11.7 million, $11.4 million, $18.9 million and $9.5 million in 2001, 2002 and 2003 and the first three months of 2004, respectively.

We were incorporated in Delaware in May 1998. Our principal executive offices are located at 416 Browning Way, South San Francisco, California 94080 and our telephone number at that address is (650) 624-8200.

The butterfly design/logo is registered as a trademark of Pain Therapeutics, Inc. Oxytrex and Remoxy are trademarks of Pain Therapeutics, Inc. This prospectus also includes product names, trade names and trademarks of other companies. All other product names, trade names and trademarks appearing in this prospectus are the property of their respective holders.

RISK FACTORS

An investment in our securities involves a high degree of risk. You should carefully consider the risks described below before making an investment decision. You should also refer to the other information in this prospectus, including our financial statements and the related notes incorporated by reference into this prospectus. The risks and uncertainties described below are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations. If any of the following risks actually occur, our business, results of operations and financial condition could suffer. In that event, the trading price of our common stock could decline, and you may lose all or part of your investment in our common stock. The risks discussed below also include forward-looking statements and our actual results may differ substantially from those discussed in these forward-looking statements.

Risks Relating to our Financial Position and Need for Financing

Our operating history may make it difficult for you to evaluate the success of our business to date and to assess its future viability.

We were founded in May 1998 and are in the development stage. Our operations to date have been limited to organizing and staffing our company, acquiring, developing and securing our technology and undertaking preclinical studies and clinical trials of our drug candidates. We have not yet demonstrated our ability to obtain regulatory approval, formulate and manufacture commercial-scale product or conduct sales and marketing activities. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

We have a history of losses and expect to incur substantial losses and negative operating cash flows for the foreseeable future.

We have incurred net losses each year since our inception. As a result of ongoing operating losses, we had an accumulated deficit of $84.4 million as of March 31, 2004. Even if we succeed in developing and commercializing one or more of our drug candidates, we expect to continue to incur substantial losses for the foreseeable future, and we may never become profitable. We anticipate that our expenses will increase substantially in the foreseeable future as we:

- continue to conduct preclinical and clinical trials for our drug candidates, including the Phase III trials of Oxytrex and PTI-901 and formulation activities and Phase I trials of Remoxy;
- seek regulatory approvals for our drug candidates;
- develop, formulate, manufacture and commercialize our drugs;
- implement additional internal systems and develop new infrastructure;
- acquire or in-license additional products or technologies or expand the use of our technology;
- maintain, defend and expand the scope of our intellectual property; and
- hire additional personnel.

We will need to generate significant revenues to achieve and maintain profitability. If we cannot successfully develop and commercialize our products, we will not be able to generate such revenues or achieve profitability in the future. Our failure to achieve or maintain profitability could negatively impact the market price of our common stock.

If we cannot raise additional capital on acceptable terms, we may be unable to complete planned additional clinical trials of any or some of our drug candidates.

We have funded all of our operations and capital expenditures with the proceeds from public and private stock offerings. We expect that our current cash, cash equivalent and marketable securities on hand will be

sufficient to meet our working capital and capital expenditure needs for at least the next twelve months. However, we may need to raise additional funds sooner and additional financing may not be available on favorable terms, if at all. Even if we succeed in selling additional securities to raise funds, our existing stockholders' ownership percentage would be reduced and new investors may demand rights, preferences or privileges senior to those of existing stockholders.

If we determine that we need to raise additional funds and we are not successful in doing so, we may be unable to complete the clinical development of some or all of our drug candidates or to obtain FDA approval of our drug candidates, and we could be forced to discontinue product development, enter into a relationship with a strategic partner earlier than currently intended, reduce sales and marketing efforts and forego attractive business opportunities.

Clinical and Regulatory Risks

If we fail to obtain the necessary regulatory approvals, we will not be allowed to commercialize our drugs, and we will not generate product revenues.

Satisfaction of all regulatory requirements typically takes many years, is dependent upon the type, complexity and novelty of the drug candidate, and requires the expenditure of substantial resources for research and development and testing. Our research and clinical approaches may not lead to drugs that the FDA considers safe for humans and effective for indicated uses we are studying. The FDA may require us to conduct additional clinical testing, in which case we would have to expend additional time and resources. The approval process may also be delayed by changes in government regulation, future legislation or administrative action or changes in FDA policy that occur prior to or during our regulatory review. Delays in obtaining regulatory approvals will:

- delay commercialization of, and product revenues from, our drug candidates; and
- diminish the competitive advantages that we may have otherwise enjoyed.

Even if we comply with all FDA regulatory requirements, we may never obtain regulatory approval for any of our drug candidates. If we fail to obtain regulatory approval of any of our drug candidates we will have fewer saleable products and corresponding lower product revenues. Even if we receive regulatory approval of our products, such approval may involve limitations on the indicated uses or marketing claims we may make for our products. Further, later discovery of previously unknown problems could result in additional regulatory restrictions, including withdrawal of products. The FDA may also require us to commit to perform lengthy post-approval studies, for which we would have to expend additional resources, which could have an adverse effect on our operating results and financial condition.

In foreign jurisdictions, we must receive marketing authorizations from the appropriate regulatory authorities before we can commercialize our drugs. Foreign regulatory approval processes generally include all of the aforementioned requirements and risks associated with FDA approval.

If we are unable to design, conduct and complete clinical trials successfully, we will not be able to obtain regulatory approval for our products.

In order to obtain FDA approval of any of our drug candidates, we must submit to the FDA a New Drug Application, or NDA, that demonstrates that the drug candidate is safe and effective in humans for its intended use. This demonstration requires significant research and animal tests, which are referred to as preclinical studies, as well as human tests, which are referred to as clinical trials. Two of our drug candidates, Oxytrex and PTI-901, are in Phase III clinical trials. Remoxy is in Phase I clinical trials.

Our Phase III trials may not demonstrate the safety or efficacy of our drug candidates. Success in pre-clinical testing and early clinical trials does not ensure that later clinical trials will be successful. Results of

later clinical trials may not replicate the results of prior clinical trials and pre-clinical testing. FDA guidelines recommend that the efficacy of new painkillers be demonstrated in more than one clinical model of pain. Even if the results of our Phase III trials are positive, we may have to commit substantial time and additional resources to conducting further preclinical and clinical studies before we can submit NDAs or obtain FDA approvals for our drug candidates.

Clinical trials are very expensive and difficult to design and implement, in part because they are subject to rigorous requirements. The clinical trial process is also time consuming. Furthermore, if participating patients in clinical studies suffer drug-related adverse reactions during the course of such trials, or if we or the FDA believe that participating patients are being exposed to unacceptable health risks, we will have to suspend our clinical trials. Failure can occur at any stage of the trials, and we could encounter problems that cause us to abandon clinical trials or to repeat clinical studies.

Even if our clinical trials are completed as planned, their results may not support our product claims. The clinical trials process may fail to demonstrate that our drug candidates are safe and effective for indicated uses. Such failure would cause us to abandon a drug candidate and could delay development of other drug candidates.

If we are unable to satisfy the FDA's request for additional information on Remoxy, we will not be allowed to conduct clinical testing of this product in the United States.

In November 2003, we filed an IND for Remoxy with the FDA. The FDA responded to our IND with a request for additional information on certain excipients used in formulations of Remoxy. We are not able to conduct human clinical studies with Remoxy in the United States until the FDA notifies us that their request for additional information is satisfied. If we are unable to conduct human clinical studies of Remoxy in the United States, we may determine that the commercial opportunity for Remoxy in certain dosage forms is too limited to warrant further investment.

Clinical trial designs that were discussed with authorities prior to their commencement may subsequently be considered insufficient for approval at the time of application for regulatory approval.

We discuss with and obtain guidance from regulatory authorities on certain of our clinical development activities. These discussions are not binding obligations on the part of regulatory authorities. Regulatory authorities may revise previous guidance or decide to ignore previous guidance at any time during the course of our clinical activities or after the completion of our clinical trials. Even with successful clinical safety and efficacy data, we may be required to conduct additional, expensive trials to obtain regulatory approval.

Developments by competitors may establish standards of care that affect our ability to conduct our clinical trials as planned.

We have conducted clinical trials of our drug candidates comparing our drug candidates to both placebo and other approved drugs. Changes in standards related to clinical trial design could affect our ability to design and conduct clinical trials as planned. For example, regulatory authorities may not allow us to compare our drug candidates to placebo in a particular clinical indication where approved products are available. In that case, both the cost and the amount of time required to conduct a trial could increase.

The DEA limits the availability of the active ingredients in our current drug candidates and, as a result, our quota may not be sufficient to complete clinical trials, meet commercial demand or may result in clinical delays.

The DEA regulates chemical compounds as Schedule I, II, III, IV or V substances, with Schedule I substances considered to present the highest risk of substance abuse and Schedule V substances the lowest risk. Certain active ingredients in our current drug candidates, such as oxycodone, are listed by the DEA as Schedule II or III substances under the Controlled Substances Act of 1970. Consequently, their manufacture,

research, shipment, storage, sale and use are subject to a high degree of regulation. For example, all Schedule II drug prescriptions must be signed by a physician, physically presented to a pharmacist and may not be refilled without a new prescription. Furthermore, the amount of Schedule II substances we can obtain for clinical trials and commercial distribution is limited by the DEA and our quota may not be sufficient to complete clinical trials or meet commercial demand. There is a risk that DEA regulations may interfere with the supply of the drugs used in our clinical trials, and in the future, our ability to produce and distribute our products in the volume needed to meet commercial demand.

Government agencies may establish and promulgate usage guidelines that directly apply to our products.

Government agencies, professional and medical societies, and other groups may establish usage guidelines that apply to our drugs. These guidelines could address such matters as usage and dose, among other factors. Application of such guidelines could limit the use of our drugs.

Conducting clinical trials of our drug candidates exposes us to expensive product liability claims and we may not be able to maintain product liability insurance on reasonable terms or at all.

The risk of product liability is inherent in the testing of pharmaceutical products. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit or terminate testing of one or more of our products. Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of our products. We currently carry clinical trial insurance but do not carry product liability insurance. We may not be able to obtain such insurance at a reasonable cost, if at all. If our agreements with any future corporate collaborators entitle us to indemnification against product liability losses, such indemnification may not be available or adequate should any claim arise.

Risks Relating to Commercialization

If physicians and patients do not accept and use our drugs, we will not achieve sufficient product revenues and our business will suffer.

Even if the FDA approves our drugs, physicians and patients may not accept and use them. Acceptance and use of our drugs will depend on a number of factors including:

- perceptions by members of the healthcare community, including physicians, about the safety and effectiveness of our drugs;
- cost-effectiveness of our drugs relative to competing products;
- availability of reimbursement for our products from government or healthcare payers;
- our ability to implement a risk management plan prior to the distribution of any Schedule II drug; and
- effectiveness of marketing and distribution efforts by us and our licensees and distributors, if any.

Because we expect to rely on sales generated by our current lead drug candidates for substantially all of our product revenues for the foreseeable future, the failure of any of these drugs to find market acceptance would harm our business and could require us to seek additional financing.

If we are unable to develop our own sales, marketing and distribution capabilities, or if we are not successful in contracting with third parties for these services on favorable terms, our product revenues could be disappointing.

We currently have no sales, marketing or distribution capabilities. In order to commercialize our products, if any are approved by the FDA, we will either have to develop such capabilities internally or collaborate with third

parties who can perform these services for us. If we decide to commercialize any of our drugs ourselves, we may not be able to hire the necessary experienced personnel and build sales, marketing and distribution operations which are capable of successfully launching new drugs and generating sufficient product revenues. In addition, establishing such operations will take time and involve significant expense.

If we decide to enter into co-promotion or other licensing arrangements with third parties, we may be unable to locate acceptable collaborators because the significant number of recent business combinations among pharmaceutical companies has resulted in a reduced number of potential future collaborators. Even if we are able to identify one or more acceptable collaborators, we may not be able to enter into any collaborative arrangements on favorable terms, or at all.

In addition, due to the nature of the market for pain management products, it may be necessary for us to license all or substantially all of our drug candidates to a single collaborator, thereby eliminating our opportunity to commercialize other pain management products independently. If we enter into any collaborative arrangements, our product revenues are likely to be lower than if we marketed and sold our products ourselves.

In addition, any revenues we receive would depend upon our collaborators' efforts which may not be adequate due to lack of attention or resource commitments, management turnover, change of strategic focus, further business combinations or other factors outside of our control. Depending upon the terms of our collaboration, the remedies we have against an under-performing collaborator may be limited. If we were to terminate the relationship, it may be difficult or impossible to find a replacement collaborator on acceptable terms, or at all.

If we cannot compete successfully for market share against other drug companies, we may not achieve sufficient product revenues and our business will suffer.

The market for our drug candidates is characterized by intense competition and rapid technological advances. If our drug candidates receive FDA approval, they will compete with a number of existing and future drugs and therapies developed, manufactured and marketed by others. Existing or future competing products may provide greater therapeutic convenience or clinical or other benefits for a specific indication than our products, or may offer comparable performance at a lower cost. If our products are unable to capture and maintain market share, we may not achieve sufficient product revenues and our business will suffer.

We will compete for market share against fully integrated pharmaceutical companies or other companies that are collaborating with larger pharmaceutical companies, academic institutions, government agencies and other public and private research organizations. Many of these competitors have opioid painkillers already approved or in development. In addition, many of these competitors, either alone or together with their collaborative partners, operate larger research and development programs and have substantially greater financial resources than we do, as well as significantly greater experience in:

- developing drugs;
- conducting preclinical testing and human clinical trials;
- obtaining FDA and other regulatory approvals of drugs;
- formulating and manufacturing drugs; and
- launching, marketing, distributing and selling drugs.

Our ability to generate product revenues will be diminished if we fail to obtain acceptable prices or an adequate level of reimbursement for our products from healthcare payers.

Our ability to commercialize our drugs, alone or with collaborators, will depend in part on the extent to which reimbursement will be available from:

- government and health administration authorities;

- private health maintenance organizations and health insurers; and
- other healthcare payers.

Significant uncertainty exists as to the reimbursement status of newly approved healthcare products. Healthcare payers, including Medicare, health maintenance organizations and managed care organizations, are challenging the prices charged for medical products and services and/or are seeking pharmacoeconomic data to justify formulary acceptance and reimbursement practices. Government and other healthcare payers increasingly are attempting to contain healthcare costs by limiting both coverage and the level of reimbursement for drugs, and by refusing, in some cases, to provide coverage for uses of approved products for disease indications for which the FDA has or has not granted labeling approval. Third-party insurance coverage may not be available to patients for any products we discover and develop, alone or with collaborators. If government and other healthcare payers do not provide adequate coverage and reimbursement levels for our products, market acceptance of them could be limited.

Risks Relating to our Intellectual Property

If we are unable to protect our intellectual property our competitors could develop and market products with similar features that may reduce demand for our products.

Our success, competitive position and potential future revenues will depend in part on our ability to protect our intellectual property. If we, Albert Einstein College of Medicine or our other collaborators fail to file, prosecute or maintain certain patents, our competitors could market products that contain features and clinical benefits similar to those of our products, and demand for our products could decline as a result. In January 2003, the U.S. Patent and Trademark Office, or PTO, disclosed that a law firm for an unidentified third-party filed requests for an Ex Parte Reexamination related to certain claims on patents we exclusively licensed from Albert Einstein College of Medicine. In each of the reexaminations, the PTO issued a first/initial office action and responses to those office actions were filed. In certain of the reexaminations, the PTO issued second/final office actions in which the PTO affirmed the patentability of certain claims related to uses of our drugs under development while maintaining rejections with respect to other claims, and responses to those office actions have been filed. Reexamination certificates have been issued in certain of the proceedings confirming the patentability of the claims. We cannot provide any assurance as to the outcome of the remaining ongoing PTO proceedings. An adverse outcome of the reexamination process could result in loss of claims of these patents that pertain to certain drugs we currently have under development and could have a material adverse impact on our future revenues.

We intend to file additional patent applications relating to our technology, products and processes. We may direct Albert Einstein College of Medicine or our collaborators to file additional patent applications relating to the licensed technology or we may do so ourselves. However, our competitors may challenge, invalidate or circumvent any of our current or future patents. These patents may also fail to provide us with meaningful competitive advantages.

We may become involved in expensive litigation or other legal proceedings related to our existing intellectual property rights, including patents.

We expect that we will rely upon trade secrets, know-how, continuing technological innovations and licensing opportunities to develop and maintain our competitive position. Others may independently develop substantially equivalent proprietary information or be issued patents that may prevent the sale of our products or know-how or require us to license such information and pay significant fees or royalties in order to produce our products.

Our technology could infringe upon claims of patents owned by others. If we were found to be infringing on a patent held by another, we might have to seek a license to use the patented technology. In that case, we might

not be able to obtain such a license on terms acceptable to us, or at all. If a legal action were to be brought against us or our licensors, we could incur substantial defense costs, and any such action might not be resolved in our favor. If such a dispute were to be resolved against us, we could have to pay the other party large sums of money and our use of our technology and the testing, manufacture, marketing or sale of one or more of our proposed products could be restricted or prohibited.

Risks Relating to our Business and Strategy

Competition for qualified personnel in the pharmaceutical industry is intense, and if we are not successful in attracting and retaining qualified personnel, we could experience delays in completing necessary clinical trials, in the regulatory approval process or in formulating, manufacturing, marketing and selling our potential products.

We will need to hire additional qualified personnel with expertise in clinical research, preclinical testing, government regulation, formulation and manufacturing and sales and marketing. We compete for qualified individuals with numerous biopharmaceutical companies, universities and other research institutions.

Competition for such individuals, particularly in the San Francisco Bay area, is intense, and our search for such personnel may not be successful. Attracting and retaining qualified personnel will be critical to our success.

Law enforcement concerns over diversion of opioids and social issues around abuse of opioids may make the regulatory approval process very difficult for our drug candidates.

Media stories regarding the diversion of opioids and other controlled substances are commonplace. Law enforcement agencies or regulatory agencies may apply policies that seek to limit the availability of opioids. Such efforts may adversely affect the regulatory approval process for our drug candidates.

Developments by competitors may render our products or technologies obsolete or non-competitive.

Alternative technologies and products are being developed to improve or replace the use of opioids for pain management, several of which are in clinical trials or are awaiting approval from the FDA. In addition, the active ingredients in nearly all opioid drugs are available in generic form. Drug companies that sell generic opioid drugs represent substantial competition. Many of these organizations competing with us have substantially greater capital resources, larger research and development staffs and facilities, greater experience in drug development and in obtaining regulatory approvals and greater manufacturing and marketing capabilities than we do. These organizations also compete with us to attract qualified personnel and partners for acquisitions, joint ventures or other collaborations.

Business interruptions could limit our ability to operate our business.

Our operations as well as those of our collaborators on which we depend are vulnerable to damage or interruption from computer viruses, human error, natural disasters, electrical and telecommunication failures, international acts of terror and similar events. We have not established a formal disaster recovery plan and our back-up operations and our business interruption insurance may not be adequate to compensate us for losses we may suffer. A significant business interruption could result in losses or damages incurred by us and require us to cease or curtail our operations.

Risks Relating to Manufacturing

If third-party manufacturers of our drug candidates fail to devote sufficient time and resources to our concerns, or if their performance is substandard, our clinical trials and product introductions may be delayed and our costs may be higher than expected.

We have no manufacturing facilities and have limited experience in drug product development and commercial manufacturing. We lack the resources and expertise to formulate, manufacture or test the technical

performance of our drug candidates. We currently rely on a limited number of experienced personnel and a small number of contract manufacturers and other vendors to formulate, test, supply, store and distribute drug supplies for our clinical trials. Our reliance on a limited number of vendors exposes us to the following risks, any of which could delay our clinical trials, and, consequently, FDA approval of our drug candidates and commercialization of our products, result in higher costs, or deprive us of potential product revenues:

- Contract commercial manufacturers, their sub-contractors or other third parties we rely on, may encounter difficulties in achieving the volume of production needed to satisfy clinical needs or commercial demand, may experience technical issues that impact quality, and may experience shortages of qualified personnel to adequately staff production operations.
- Our contract manufacturers could default on their agreements with us to provide clinical supplies or meet our requirements for commercialization of our products.
- The use of alternate manufacturers may be difficult because the number of potential manufacturers that have the necessary governmental licenses to produce narcotic products is limited. Additionally, the FDA and the DEA must approve any alternative manufacturer of our product before we may use the alternative manufacturer to produce our supplies. It may be difficult or impossible for us to find a replacement manufacturer on acceptable terms quickly, or at all. Our contract manufacturers and vendors may not perform as agreed or may not remain in the contract manufacturing business for the time required to successfully produce, store and distribute our products.
- If any third-party manufacturer makes improvements in the manufacturing process for our products, we may not own, or may have to share, the intellectual property rights to such innovation.

We rely on third-party commercial drug manufacturers for drug supply.

Approved third-party commercial drug manufacturers may subsequently be stopped from producing, storing, shipping or testing our drug products due to their non-compliance with federal, state or local regulations. Drug manufacturers are subject to ongoing periodic unannounced inspection by the FDA, the DEA, and corresponding state and foreign government agencies to ensure strict compliance with good manufacturing practice and other government regulations and corresponding foreign standards. We do not have control over third-party manufacturers' compliance with these regulations and standards.

If we cannot formulate and scale-up a wide range of dosage forms of Remoxy, we might determine that the commercial opportunity for Remoxy is too limited to warrant further investment in clinical testing and development.

We plan to formulate and scale-up a wide range of dosage forms of Remoxy. We may not be able to successfully complete our formulation or scale-up activities or we may determine that the commercial opportunity for Remoxy in certain dosage forms is too limited to warrant further investment.

Risks Relating to our Collaboration Agreements

If outside collaborators fail to devote sufficient time and resources to our drug development programs, or if their performance is substandard, our regulatory submissions and our product introductions may be delayed.

We depend on independent investigators and collaborators, such as universities and medical institutions, to conduct our clinical trials under agreements with us. These collaborators are not our employees and we cannot control the amount or timing of resources that they devote to our programs. These investigators may not assign as great a priority to our programs or pursue them as diligently as we would if we were undertaking such programs ourselves. If outside collaborators fail to devote sufficient time and resources to our drug development programs, or if their performance is substandard, the approval of our regulatory submissions and our introductions of new drugs will be delayed.

Our collaborators may also have relationships with other commercial entities, some of which may compete with us. If outside collaborators assist our competitors to our detriment, the approval of our regulatory submissions will be delayed and the sales from our products will be less than expected.

Our collaborative agreements may not succeed or may give rise to disputes over intellectual property or other issues.

Our strategy to focus on development of novel drug candidates discovered by third parties requires us to enter into license agreements with such third parties. In addition, we may enter into collaborative agreements to commercialize our products. Such agreements are generally complex and contain provisions that could give rise to legal disputes. Such disputes can delay the development of potential new drug products, or can lead to lengthy, expensive litigation or arbitration. Other factors relating to collaborative agreements may adversely affect the success of our drug candidates, including:

- the development of parallel products by our collaborators or by a competitor;
- arrangements with collaborative partners that limit or preclude us from developing certain products or technologies;
- premature termination of a collaborative agreement; or
- failure by a collaborative partner to devote sufficient resources to the development of our potential products.

Risks Relating to an Investment in our Common Stock

Our stock price has been volatile and could experience a sudden decline in value.

Our common stock has experienced significant price and volume fluctuations and may continue to experience volatility in the future. You may not be able to sell your shares quickly or at the latest market price if trading in our stock is not active or the volume is low. The following factors, in addition to other risk factors described in this section, may have a significant impact on the market price of our common stock:

- results of our preclinical and clinical trials;
- publicity regarding actual or potential medical results relating to products under development by us or others;
- announcements of technological innovations or new commercial products by us or others;
- developments in patent or other proprietary rights by us or others;
- comments or opinions by securities analysts or major stockholders;
- future sales of our common stock by existing stockholders;
- regulatory developments or changes in regulatory guidance;
- litigation or threats of litigation;
- economic and other external factors or other disaster or crises;
- the departure of any of our officers, directors or key employees;
- period-to-period fluctuations in financial results; and
- limited daily trading volume.

The National Association of Securities Dealers, Inc., or NASD, and the SEC have adopted certain new rules. If we were unable to continue to comply with the new rules, we could be delisted from trading on such market,

and thereafter trading in our common stock, if any, would be conducted through the over-the-counter market or on the Electronic Bulletin Board of the NASD. As a consequence of such delisting, an investor would likely find it more difficult to dispose of, or to obtain quotations as to the price of, our common stock. Delisting of our common stock could also result in lower prices per share of our common stock than would otherwise prevail.

Volatility in the stock prices of other companies may contribute to volatility in our stock price.

The stock market in general, and the Nasdaq National Market and the market for technology companies in particular, have experienced significant price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of those companies. Further, there has been particular volatility in the market prices of securities of early stage and development stage life sciences companies. These broad market and industry factors may seriously harm the market price of our common stock, regardless of our operating performance. In the past, following periods of volatility in the market price of a company's securities, securities class action litigation has often been instituted. A securities class action suit against us could result in substantial costs, potential liabilities and the diversion of management's attention and resources.

Our stock ownership is concentrated, and our officers, directors and principal stockholders can exert significant control over matters requiring stockholder approval.

Due to their combined stock holdings, our officers, directors and principal stockholders (stockholders holding greater than 5% of our common stock) acting collectively may have the ability to exercise significant influence over matters requiring stockholder approval including the election of directors and approval of significant corporate transactions. In addition, this concentration of ownership may delay or prevent a change in control of the Company and may make some transactions more difficult or impossible to complete without the support of these stockholders.

Our operating results may fluctuate from quarter to quarter and this fluctuation may cause our stock price to decline.

Our quarterly operating results have fluctuated in the past and are likely to fluctuate in the future. Factors contributing to these fluctuations include, among other items, the timing and enrollment rates of clinical trials for our drug candidates, our need for clinical supplies and the re-measurement of certain deferred stock compensation. Thus, quarter-to-quarter comparisons of our operating results are not indicative of what we might expect in the future. As a result, in some future quarters our operating results may not meet the expectations of securities analysts and investors, which could result in a decline in the price of our stock.

There may not be an active, liquid trading market for our common stock.

There is no guarantee that an active trading market for our common stock will be maintained on the Nasdaq National Market. Investors may not be able to sell their shares quickly or at the latest market price if trading in our stock is not active.

Our charter documents contain provisions that may prevent or delay removal of incumbent management or a change of control.

Provisions of our amended and restated certificate of incorporation and amended and restated bylaws may have the effect of deterring or delaying attempts by our shareholders to remove or replace management, engage in proxy contests and effect changes in control. These provisions include:

- a classified board so that only one third of the board of directors is elected each year;
- elimination of cumulative voting in the election of directors;

- procedures for advance notification of shareholder nominations and proposals;
- the ability of our board of directors to amend our bylaws without shareholder approval; and
- the ability of our board of directors to issue up to 10,000,000 shares of preferred stock without shareholder approval upon the terms and conditions and with the rights, privileges and preferences as the board of directors may determine.

In addition, as a Delaware corporation, we are subject to Delaware law, including Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years following the date that the stockholder became an interested stockholder unless certain specific requirements are met as set forth in Section 203.

These provisions, alone or together, could have the effect of deterring or delaying changes in incumbent management, proxy contests or changes in control.

DISCLOSURE REGARDING FORWARD-LOOKING STATEMENTS

In addition to the other information contained or incorporated by reference in this prospectus, you should carefully consider the risk factors disclosed in this prospectus or any prospectus supplement when evaluating an investment in our common stock. This prospectus contains forward-looking statements that are based upon current expectations that are within the meaning of the Private Securities Reform Act of 1995. It is the Company's intent that such statements be protected by the safe harbor created thereby.

Forward-looking statements involve risks and uncertainties and our actual results and the timing of events may differ significantly from the results discussed in the forward-looking statements. Examples of such forward-looking statements include, but are not limited to:

- statements about future operating losses and anticipated operating and capital expenditures;
- statements about the potential benefits of our drug candidates;
- statements relating to the timing, substance, sufficiency of materials required for or anticipated results of our clinical development of our drug candidates;
- statements about the size of the potential market for our products;
- statements about upcoming announcements by the Company;
- statements relating to the utility of our intellectual property;
- statements about expected future sources of revenue and capital;
- statements about potential competitors or products;
- statements about future market acceptance of our drug candidates;
- statements about expenses increasing substantially or fluctuating;
- statements about future expectations regarding trade secrets, technological innovations, licensing agreements and outsourcing of certain business functions;
- statements about anticipated hiring;
- statements about the sufficiency of our current resources to fund our operations over the next twelve months;
- statements about increasing cash requirements; statements about fluctuations in our operating results;
- statements about potential future dividends; and
- statements about development of our internal systems and infrastructure.

USE OF PROCEEDS

Unless otherwise indicated in a prospectus supplement, the net proceeds from the sale of securities offered by this prospectus will be used for general corporate purposes and working capital requirements. We may also use a portion of the net proceeds to fund possible investments in and acquisitions of complementary businesses, partnerships, minority investments, products or technologies. Currently, there are no commitments or agreements regarding such acquisitions or investments that are material. Pending their ultimate use, we intend to invest the net proceeds in money market funds, commercial paper and governmental and non-governmental debt securities with maturities of up to three years.

PLAN OF DISTRIBUTION

We may sell our common stock:

- through one or more underwriters or dealers;
- through agents;
- directly to one or more purchasers; or
- through a combination of the above.

If underwriters are used in the sale, they will acquire the common stock for their own account and may resell the stock from time to time in one or more transactions at a fixed public offering price. The obligations of the underwriters to purchase the common stock will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the common stock to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Each prospectus supplement will identify any underwriter, dealer or agent, and describe any compensation received by them from us. Any initial public offering price and any discounts or concessions allowed or reallowed or paid to dealers may be changed from time to time.

Underwriters, dealers or agents may receive compensation in the form of discounts, concessions or commissions from us or our purchasers as their agents in connection with the sale of the common stock. These underwriters, dealers or agents may be considered to be underwriters under the Securities Act. As a result, discounts, commissions or profits on resale received by underwriters, dealers or agents may be treated as underwriting discounts and commissions.

Underwriters or agents and their associates may be customers of, engage in transactions with or perform services for us in the ordinary course of business. We will describe in the prospectus supplement, naming the underwriter, the nature of any such relationship.

We may grant underwriters who participate in the distribution of the common stock an option to purchase additional securities to cover over-allotments, if any, in connection with the distribution. We will identify the amount of any such over-allotment option in the applicable prospectus supplement.

We will name any agent involved in the offering and sale of common stock and we will describe any commissions we will pay the agent and the terms of any agency relationship in the prospectus supplement. We may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase 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. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.

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 prevailing market prices; and
- at negotiated prices.

A prospectus supplement or supplements will describe the method of distribution of each distribution of common stock in the applicable prospectus supplement.

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 underwriters' obligations in the related supplement to this prospectus.

Underwriters, dealers and agents may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution with respect to payments made by the underwriters, dealers or agents, under agreements between us and the underwriters, dealers and agents.

In connection with the offering of the common stock, certain persons participating in such offering may engage in transactions that stabilize, maintain or otherwise affect the market price, including over-allotment, stabilizing transactions, short covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the common stock in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the common stock originally sold by the dealer is purchased in a covering transaction to cover short positions. Those activities may cause the price of the common stock to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Any underwriters who are qualified market makers on the Nasdaq National Market may engage in passive market making transactions in the common stock on the Nasdaq National Market in accordance with Rule 103 of Regulation M, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded.

To the extent required, this prospectus may be amended and supplemented from time to time to describe a specific plan of distribution.

LEGAL MATTERS

The validity of common stock offered hereby will be passed upon by Wilson Sonsini Goodrich & Rosati, Professional Corporation, Palo Alto, California.

EXPERTS

The financial statements of Pain Therapeutics, Inc. at December 31, 2003 and 2002, and for each of the two years in the period ended December 31, 2003 and for the period from May 4, 1998 (inception) through December 31, 2003, appearing in Pain Therapeutics, Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2003, have been audited by Ernst & Young LLP, independent auditors, as set forth in their report thereon included therein and incorporated herein by reference which, as to the period from May 4, 1998 (inception) through December 31, 2001, is based in part on the report of KPMG LLP, independent auditors. The financial statements referred to above are included in reliance upon such reports given on the authority of such firms as experts in accounting and auditing.

The financial statements of Pain Therapeutics, Inc. for the year ended December 31, 2001 have been incorporated by reference in the registration statement in reliance upon the report of KPMG LLP, independent auditors, incorporated by reference herein and upon the authority of said firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. 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. This prospectus does 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, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement. You may read and copy the registration statement, as well as our reports, proxy statements and other information, at the SEC's public reference room at 450 Fifth Street, N.W., Washington, D.C. 20549. You can request copies of these documents by writing to the SEC and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference rooms. Our SEC filings are also available at the SEC's web site at "http://www.sec.gov."

INFORMATION INCORPORATED BY REFERENCE

The SEC allows us to "incorporate by reference" into this prospectus the information we filed with the SEC. This means that we can disclose important information by referring you to those documents. The information incorporated by reference is considered to be a part of this prospectus. Information that we file later with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings made by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (other than reports or portions furnished under Items 9 or 12 of Form 8-K) until we complete our offering of the common stock:

- our annual report on Form 10-K for the fiscal year ended December 31, 2003;
- our quarterly report on Form 10-Q for the fiscal quarter ended March 31, 2004; and
- the description of our common stock contained in our Registration Statement on Form 8-A, filed with the Securities and Exchange Commission on March 15, 2000, and any further amendment or report filed hereafter for the purpose of updating any such description.

Copies of documents incorporated by reference, excluding exhibits except to the extent such exhibits are specifically incorporated by reference, are available from us without charge, upon oral or written request to:

Pain Therapeutics, Inc.
416 Browning Way
South San Francisco, California 94080
United States of America
Attn: Investor Relations
(650) 624-8200

8,000,000 Shares

Pain Therapeutics, Inc.

Common Stock

PROSPECTUS SUPPLEMENT
(to prospectus dated May 7, 2004)

, 2004

Joint Book-Running Managers

Citigroup **UBS Investment Bank**

CIBC World Markets **Rodman & Renshaw**