GTX INC /DE/
Form 8-K
September 16, 2005

Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K
CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934
Date of Report (Date of earliest event reported): September 15, 2005
GTx, Inc.
(Exact name of registrant as specified in its charter)

Delaware	**000-50549**	**62-1715807**
(State or other jurisdiction of incorporation or organization)	(Commission File Number)	(I.R.S. Employer Identification No.)

3 N. Dunlap Street
3rd Floor, Van Vleet Building
Memphis, Tennessee 38163
(901) 523-9700
(Address, including zip code, and telephone number, including area code, of registrant s principal executive offices)

(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

TABLE OF CONTENTS

Table of Contents

ITEM 8.01 Other Events.

On September 15, 2005, GTx, Inc. (the Company) issued a press release announcing that it intended to offer and sell 5,000,000 shares of newly issued common stock pursuant to its effective shelf registration statement previously filed with the Securities and Exchange Commission. A copy of the press release is attached hereto as Exhibit 99.1 and incorporated herein by reference. Updated business information, including summaries of the Company s agreements with Ortho Biotech Products L.P. and Orion Corporation, and updated risk factors relating to the Company are set forth below.

Business Overview

The following disclosure supersedes the disclosure contained under the heading Business Overview in the Company s Annual Report on Form 10-K, as amended, filed with the Securities and Exchange Commission on August 3, 2005 (the Annual Report):

GTx, Inc.

GTx is a biopharmaceutical company dedicated to the discovery, development and commercialization of therapeutics for cancer and serious conditions related to men s health. Our lead drug discovery and development programs are focused on small molecules that selectively modulate the effects of estrogens and androgens, two essential classes of hormones. We have four clinical programs. We are developing ACAPODENE® (toremifene citrate), a selective estrogen receptor modulator, or SERM, in two separate clinical programs in men: (1) a pivotal Phase III clinical trial for the treatment of serious side effects of androgen deprivation therapy, or ADT, for advanced prostate cancer and (2) a pivotal Phase III clinical trial for the prevention of prostate cancer in high risk men with precancerous prostate lesions. In our third clinical program, we are developing ostarine, a selective androgen receptor modulator, or SARM, for the treatment of muscle wasting associated with acute conditions, such as burns, and chronic conditions, such as testosterone deficiency in aging men, or andropause. We plan to initiate our first Phase II clinical trial for ostarine in the fourth quarter of 2005. In our fourth clinical program, we and our collaborator, Ortho Biotech Products, L.P., a subsidiary of Johnson & Johnson, are developing andarine, another one of our SARMs, for the treatment of weight loss from various types of cancer, which is known as cancer cachexia. We are working with Ortho Biotech to plan a Phase II clinical trial of andarine.

We plan to build a specialized sales and marketing capability to market our product candidates directly to the relatively small and concentrated community of urologists and medical oncologists in the United States and to seek collaborators to commercialize our product candidates outside the United States and to broader target physician markets. We currently market FARESTON® (toremifene citrate 60 mg) tablets, which have been approved by the U.S. Food and Drug Administration, or FDA, for the treatment of metastatic breast cancer in post-menopausal women in the United States. The active pharmaceutical ingredient in Fareston is the same as in Acapodene, but at a different dose.

The following table summarizes key information about our product candidates:

Program	Product Candidate/Indication	Development Phase	Status
SERM	**Acapodene**		
	Side effects of androgen deprivation therapy	Pivotal Phase III clinical trial	Phase III clinical trial ongoing under an SPA; completion of patient enrollment anticipated in the third quarter of 2005; interim results expected in the fourth quarter of 2005
	Prevention of prostate cancer in high risk men with precancerous prostate lesions	Pivotal Phase III clinical trial	Phase III clinical trial ongoing under a proposed SPA;

	completion of patient enrollment anticipated in the first quarter of 2006

Table of Contents

Program	Product Candidate/Indication	Development Phase	Status
SARM	**Ostarine**		
	Muscle wasting associated with burns and andropause	Planning Phase II clinical trials	Phase I clinical trials completed; initial Phase II proof of concept clinical trial planned for the fourth quarter of 2005
	Andarine		
	Cancer cachexia	Planning Phase II clinical trial	Phase I clinical trials completed
	Prostarine		
	Benign prostatic hyperplasia	Preclinical	Preclinical studies ongoing
Anticancer	**Andromustine**		
	Prostate cancer that is not responsive to androgen deprivation therapy	Preclinical	Preclinical studies ongoing

Acapodene for the Treatment of Serious Side Effects of Androgen Deprivation Therapy

The standard medical treatment for men who have advanced, recurrent or metastatic prostate cancer is androgen deprivation therapy, which reduces blood levels of testosterone, a primary growth factor for prostate cancer. In the United States, we believe approximately 600,000 men are currently being treated by this therapy, with approximately 100,000 new patients started on this therapy each year. Androgen deprivation therapy has serious side effects, including: severe bone loss, or osteoporosis, leading to skeletal fractures; hot flashes; and breast pain and enlargement, or gynecomastia. We are developing Acapodene as a treatment for these side effects. Because there are no drugs approved by the FDA for the treatment of these multiple side effects, we believe that there could be a substantial market for Acapodene for this indication.

In November 2003, we initiated a randomized, double-blind, placebo-controlled pivotal Phase III clinical trial of orally-administered Acapodene in patients undergoing androgen deprivation therapy for advanced, recurrent or metastatic prostate cancer under a Special Protocol Assessment, or SPA, with the FDA that provides that this clinical trial should serve as an adequate basis for the submission of the effectiveness portion of a New Drug Application, or NDA. An SPA is designed to facilitate the FDA s review and approval of drug products by allowing the agency to evaluate the proposed design and size of clinical trials that are intended to form the primary basis for determining a drug product s efficacy. If agreement is reached with the FDA, an SPA documents the terms and conditions under which the design of the subject trial will be adequate for submission of the effectiveness portion of an NDA. In this clinical trial, approximately 1,200 patients with advanced, recurrent or metastatic prostate cancer who have been receiving androgen deprivation therapy for at least six months and who either have significant existing bone loss or are greater than 70 years of age are being randomized to receive either a placebo or a daily dose of 80 mg of Acapodene for 24 months. The primary endpoint is the incidence of vertebral skeletal fractures measured by x-ray. The secondary endpoints include bone mineral density, hot flashes, gynecomastia and lipid changes. Over 100 clinical sites across the United States and Mexico are participating in this clinical trial. We expect to complete patient enrollment in the third quarter of 2005. In the fourth quarter of 2005, we plan to conduct an interim analysis of the measurement of bone mineral density, a secondary

Table of Contents

endpoint, in approximately the first 200 patients to complete one year of this clinical trial. We expect that the last patient will complete this clinical trial in the second half of 2007. Following completion of the trial, we plan to conduct a three-year extension trial to gather additional fracture and survival data.

We designed our pivotal Phase III clinical trial principally based on the results of the Phase II clinical trial that we conducted to evaluate Acapodene in patients who had been receiving androgen deprivation therapy by treatment with luteinizing hormone releasing hormone agonists, known as LHRH agonists, for more than 12 months. In this trial, patients who received Acapodene at the highest tested dose experienced a 3.5% average increase in lumbar vertebral spine bone mineral density, an indicator of bone strength, while patients who received the placebo experienced a 0.24% average increase in lumbar vertebral spine bone mineral density. The difference in these measurements had a p-value of less than 0.05. A p-value of 0.05 or less generally represents a statistically significant difference in treatments. The results of our pivotal Phase III clinical trial of Acapodene for this indication may not be the same as the results of this Phase II clinical trial.

Acapodene for the Prevention of Prostate Cancer in High Risk Men with Precancerous Prostate Lesions

In the United States, prostate cancer is one of the most commonly diagnosed cancers and the second leading cause of cancer-related deaths in men. We believe that treating the precancerous lesions of prostate cancer known as high grade prostatic intraepithelial neoplasia, or high grade PIN, may be an effective approach to preventing prostate cancer. In the United States, there are over 115,000 new cases of high grade PIN diagnosed each year, and an estimated 15.0 million men under the age of 80 harbor this condition. As there is currently no therapy for the treatment of this condition, we believe this represents a significant unmet medical need.

In January 2005, we initiated a randomized, double-blind, placebo-controlled pivotal Phase III clinical trial of orally-administered Acapodene for the prevention of prostate cancer in men with high grade PIN. Approximately 100 clinical sites across the United States and Canada are participating in this clinical trial. Approximately 1,260 patients with high grade PIN are being randomized to receive either a daily dose of 20 mg of Acapodene or placebo. Only patients who have confirmed high grade PIN and a prostate biopsy that excludes cancer in the past six months are eligible to participate. The primary endpoint is the incidence of prostate cancer. We expect to complete patient enrollment in the first quarter of 2006. We submitted our plan for this pivotal Phase III clinical trial to the FDA in October 2004 under a proposed SPA. We filed a revised SPA in response to comments from the FDA on our initial filing, and in September 2005 we received a response letter from the FDA related to the revised SPA. We agree with and intend to implement the FDA s recommendations under the SPA. We believe that upon submission of an amendment to the SPA file to implement the FDA s recommendations, the SPA will be complete and the trial would then be conducted under an agreed SPA. We will evaluate efficacy endpoints for this trial at 36 months, with an interim analysis at 24 months. If a sufficient reduction in prostate cancer at 24 months is achieved, we could potentially file an NDA, provided that we are also able to submit as part of the filing safety data for 36 months for a majority of patients in the trial and other safety data, as requested by the FDA. However, the results of the interim analysis may not be sufficiently favorable to support an application for regulatory approval. If the results of the interim analysis are not sufficiently favorable to support an application, we expect that the trial will continue for 36 months.

In 2004, we completed a randomized, double-blind, placebo-controlled, dose-finding Phase IIb clinical trial of Acapodene in men with recently diagnosed high grade PIN to determine the efficacy and safety of a daily dose of Acapodene for 12 months. The trial enrolled 514 men and was conducted at 64 clinical sites across the United States. The primary efficacy endpoint of this trial was incidence of prostate cancer at 12 months. Participants were randomized to receive a 20 mg, 40 mg or 60 mg dose of Acapodene or placebo. A screening biopsy was performed on each trial participant at the time of enrollment, and eligibility was limited to participants who did not show evidence of prostate cancer. A second biopsy was performed six months after enrollment in an effort

Table of Contents

to identify trial participants who had prostate cancer that was not detected by the initial biopsy. The intent-to-treat population consisted of all patients initially enrolled in the trial who returned for their six-month biopsy. We also analyzed trial results in a predefined subgroup of patients that excluded patients showing biopsy evidence of prostate cancer at six months and that also excluded patients who did not complete the full course of therapy in the trial.

We analyzed the results of this Phase IIb clinical trial on a stratified basis, in which we assessed the effect of individual clinical sites on the overall statistical analysis of the trial results, and on an unstratified basis, in which we did not assess such effect. In the stratified analysis of the per protocol population, which is the intent-to-treat population less two patients in the group that received 20 mg of Acapodene who were deemed to be not compliant with the protocol, the cumulative, or overall, risk of prostate cancer was 24.4% in the group that received 20 mg of Acapodene compared with 31.2% in the group that received placebo. The p-value for this result was less than 0.05. Thus, the cumulative risk of prostate cancer based on a stratified analysis of the per protocol population was 22.0% lower in the 20 mg treatment group, which would imply an annualized rate of prevention of cancers of 6.8 per 100 men treated. The p-value in the unstratified analysis of the per protocol population for the comparison between the group that received 20 mg of Acapodene and the group that received placebo was 0.132. In the stratified analysis of the intent-to-treat population, the cumulative risk of prostate cancer was 24.9% in the group that received 20 mg of Acapodene compared with 31.2% in the group that received placebo. The p-value for this result was 0.081, which was statistically significant under the protocol for this trial. Statistical significance under the protocol was defined as a p-value of 0.10 or less. The p-value in the unstratified analysis of the intent-to-treat population for the comparison between the group that received 20 mg of Acapodene and the group that received placebo was 0.148.

In a stratified analysis of the subgroup of patients who had no biopsy evidence of prostate cancer at their initial screening biopsy or their six-month biopsy and completed the full course of therapy in the trial, the cumulative risk of prostate cancer was 9.1% in the group that received 20 mg of Acapodene compared with 17.4% in the group that received placebo, a 48.2% reduction. The p-value for this result was less than 0.05. For the 40 mg and 60 mg treatment arms, in the intent-to-treat population, the per protocol population and the predefined patient subgroup, the cumulative risk of cancer was lower than the placebo group, although these results were not statistically significant.

The overall rates of drug-related adverse events and serious adverse events did not differ to a significant degree between any of the Acapodene dose groups and placebo. The results of our pivotal Phase III clinical trial of Acapodene for this indication may not be the same as the results of this Phase IIb clinical trial.

Ostarine for the Treatment of Muscle Wasting Associated with Burns and Andropause

Ostarine, a SARM, is a nonsteroidal, orally-available small molecule that binds to and modulates the same receptor as testosterone. Testosterone and other tissue building, or anabolic, agents have been proven to beneficially reverse involuntary weight loss in patients who have muscle wasting caused by burns and trauma, end-stage renal disease, chronic obstructive pulmonary disease and HIV. However, testosterone and anabolic steroids have major limitations, including unwanted side effects on the prostate in elderly men and masculinization in women, and testosterone is inconvenient to administer to patients. Ostarine is designed to have anabolic activity like testosterone, but in an orally-available formulation and without the unwanted side effects of testosterone and anabolic steroids on the prostate and skin sebaceous glands. We believe that ostarine has the potential to treat muscle wasting associated with chronic conditions, such as andropause, frailty and end-stage renal disease, as well as muscle wasting associated with acute conditions, such as burns.

We plan to initiate Phase II clinical trials of ostarine first for muscle wasting associated with burns because we believe that acute indications have a relatively expeditious and defined clinical

Table of Contents

development and regulatory pathway. Many burn patients are hypermetabolic and lose significant lean body weight, which adversely affects their healing and recovery. As a result, we believe that clinical results demonstrating that ostarine is effective in treating muscle wasting in burn patients could establish proof of concept of the potential efficacy of ostarine as a treatment for patients with other muscle wasting conditions. Anabolic steroidal agents are frequently used for the treatment of muscle wasting associated with burns. We expect to initiate Phase II clinical testing of ostarine for the treatment of muscle wasting associated with burns in the fourth quarter of 2005.

We also plan to initiate a Phase II clinical trial of ostarine for the treatment of muscle wasting associated with andropause in the first half of 2006. Andropause is a condition associated with aging men caused by declining testosterone levels and is characterized by the loss of muscle mass, osteoporosis, high cholesterol, hypogonadism and obesity. Men on average gain a pound of fat and lose one-half pound of muscle each year between the ages of 30 and 60, and muscle loss accelerates after age 60, with the average man losing 35% of his muscle between the ages of 20 and 80. This characteristic loss of muscle mass and bone in men with andropause is also known as frailty. Frailty is a condition that adversely effects the health of both men and women. A 2001 study of more than 5,000 elderly adults found that morbidity rates among the frail elderly population were significantly higher than among the non-frail elderly. The study found that over a three-year period, the rate of death among the frail elderly was 18%, versus a 3% rate among the non-frail elderly. The frail were also far more likely to experience falls, hospitalizations and loss of independence. In this study funded by the National Institutes of Health, which was designed to be representative of the elderly U.S. population, 7% of the patient population was found to be frail.

We have data from two Phase I clinical trials of ostarine: a double-blind, placebo-controlled, single-ascending dose clinical trial and a double-blind, placebo-controlled, multiple-ascending dose clinical trial. The single-ascending dose clinical trial included 96 healthy male volunteers. Ostarine was well tolerated by the participants in this clinical trial, and there were no drug-related serious adverse events. This clinical trial demonstrated that the average half life of ostarine was approximately 24 hours, which supports a daily dosing regimen.

The second Phase I clinical trial evaluated the safety, tolerability and specific pharmacodynamic characteristics of ostarine using multiple-ascending doses in 48 healthy male volunteers between the ages of 18 and 45 and 12 elderly males with truncal obesity who had an average age of 68 years. Data from an additional group of 11 elderly males with truncal obesity are being collected for the purpose of evaluating safety but not tolerability. Safety and pharmacodynamic measurements were taken at the beginning of the study and after 14 days of daily oral dosing. These measurements included routine blood chemistry and hematology, sex hormones and gonadotropins, serum prostate specific antigen, metabolic markers of bone and muscle, cutaneous sebum analysis and DEXA scanning for body composition. Overall, clinical laboratory values and hormonal effects for the 60 volunteers were consistent with anabolic activity. Comparisons of DEXA assessments from the beginning of the study to DEXA assessments after 14 days for the 60 volunteers showed positive changes in body composition, with lean body mass and fat mass moving in a direction consistent with anabolic activity. Ostarine did not appear to have unwanted side effects on the prostate or the skin for the 60 volunteers. We believe that these observations support the potential ability of ostarine to selectively modulate androgen receptors in a tissue-specific manner. Ostarine has been well tolerated by the participants in this Phase I clinical trial, and there have been no drug-related serious adverse events to date. However, Phase I clinical trials are not designed to show efficacy, and the results of future clinical trials may not be the same as these early observations.

Andarine for the Treatment of Cancer Weight Loss

We are developing another one of our SARMs, andarine, under a collaboration agreement with Ortho Biotech. Together with Ortho Biotech, our strategy is to develop andarine for the treatment of cancer cachexia. We selected this indication because it represents a potentially large market and we believe it has a relatively well-defined clinical and regulatory process. There are approximately

Table of Contents

1.3 million patients diagnosed with cancer each year in the United States. Wasting weight loss afflicts approximately one-third of newly-diagnosed cancer patients. The weight loss attributable to cancer cachexia results from both the loss of lean body, or muscle, weight and the loss of fat. There are no drugs that have been approved by the FDA for the treatment of weight loss from cancer.

We are working with Ortho Biotech to initiate a Phase II clinical trial of andarine in 2006. We have completed four Phase I clinical trials of andarine in which andarine was well tolerated by all participants with no serious adverse events. We observed early indications in the multiple-dose Phase I clinical trial that andarine promoted growth activity, as measured by levels of IGF-1, a marker for muscle growth, without affecting the sebaceous glands. We believe that these observations support the potential ability of andarine to selectively modulate androgen receptors in a tissue-specific manner. However, Phase I clinical trials are not designed to show efficacy, and the results of future clinical trials may not be the same as these early observations.

In March 2004, we entered into a joint collaboration and license agreement with Ortho Biotech for andarine for indications related to men s health and other licensed SARM compounds meeting specified criteria which Ortho Biotech may ultimately choose to develop instead of, or in addition to, andarine. We retain the right to independently develop specific SARM compounds which are excluded from the collaboration, including ostarine. Under the terms of the agreement, we received an up-front licensing fee and reimbursement of certain andarine development expenses totaling approximately $6.7 million, which is being amortized into revenue over five years. We are entitled to receive additional licensing fees and milestone payments prior to product launch of (1) up to an aggregate of $76 million for licensed products containing andarine or any replacement compound, and (2) up to $45 million for each licensed product containing any other compound developed under the agreement, upon achievement of specific clinical development milestones or receipt of regulatory approvals. Johnson & Johnson Pharmaceutical Research & Development, an affiliate of Ortho Biotech, is responsible for further clinical development and related expenses for andarine and other licensed SARM compounds. If a licensed product containing andarine or any other SARM compound is approved for commercial sale, Ortho Biotech will have full and exclusive decision-making authority for marketing such product in the United States and in markets outside the United States. Under the agreement, we have the option, subject to meeting specified conditions, to co-promote andarine and other licensed products to urologists in the United States for indications specifically related to men s health. Ortho Biotech is obligated to pay us up to double digit royalties on worldwide net sales of andarine and other licensed products, and an additional royalty in excess of 20% on all co-promoted net sales to urologists in the United States. Ortho Biotech may terminate the development or commercialization of andarine or any other licensed SARM compound under the agreement upon 90 days notice, or 30 days notice if there are safety issues, or may terminate the agreement for our uncured material breach.

Fareston

In January 2005, we acquired from Orion Corporation the right to market Fareston (toremifene citrate 60 mg) tablets in the United States for the prevention and treatment of breast cancer. Fareston had been marketed in the United States by third parties since 1998. We also acquired a license to toremifene, the active pharmaceutical ingredient in Fareston and Acapodene, for all indications worldwide, except breast cancer outside of the United States. We do not have the right to manufacture toremifene, although we have specified rights to assume manufacture of toremifene under specified circumstances, and we rely on Orion for our clinical and commercial supply. We pay Orion a royalty on Fareston sales. For the six months ended June 30, 2005, we recognized approximately $1.8 million in net revenues from the sale of Fareston.

Orion Agreement

In March 2000, we entered into a license and supply agreement with Orion to develop and commercialize products containing toremifene, the active pharmaceutical ingredient in Fareston and

Table of Contents

Acapodene. Our rights under the original license agreement were limited to specific disease fields pertaining to prostate cancer. In December 2004, we entered into an agreement with Orion to purchase specified Fareston-related assets which Orion had re-acquired from another licensee. We also entered into an amended and restated license and supply agreement with Orion which replaces the original license agreement. We paid Orion approximately $5.2 million under the 2004 agreements for the assets and related license rights.

Under the amended and restated license agreement, we obtained an exclusive license from Orion to develop and commercialize toremifene-based products, including Fareston and Acapodene, for all human indications worldwide, except breast cancer outside of the United States. We are required to pay Orion a royalty on sales by us and our affiliates of Fareston for breast cancer in the United States. We are also required to pay Orion a royalty on sales by us, our affiliates and third-party sublicensees of other toremifene-based products, including Acapodene if approved for commercial sale. We are obligated to purchase all of our clinical and commercial requirements for toremifene from Orion at transfer prices specified in the amended and restated agreement. Orion may terminate its supply obligations under specified circumstances. However, we have specified rights to assume manufacture of toremifene if Orion terminates its supply of toremifene because it has ceased to manufacture toremifene, although we would have to engage another supplier to do so. The term of the amended and restated agreement lasts, on a country-by-country basis, until the later of expiration of our own patents claiming the method of use or manufacture of toremifene for prostate cancer or the end of all marketing or regulatory exclusivity which we may obtain for toremifene-based products. Orion may terminate the agreement as a result of our uncured material breach or bankruptcy.

Pipeline

We have an extensive preclinical pipeline generated from our own discovery program, which includes the specific product candidate prostarine, a SARM for benign prostatic hyperplasia, and andromustine, an anticancer drug candidate, for hormone-refractory prostate cancer.

We believe that our drug discovery capabilities position us well to design and develop non-steroidal small molecule drugs that modulate the effects of hormones.

Table of Contents

Joint Collaboration and License Agreement

The following disclosure supersedes the disclosure contained under the heading Business Licenses and Collaborative Relationships Ortho Biotech Products L.P., A Subsidiary of Johnson & Johnson in the Annual Report:

In March 2004, we entered into a joint collaboration and license agreement with Ortho Biotech for andarine for indications related to men s health and other licensed SARM compounds meeting specified criteria which Ortho Biotech may ultimately choose to develop instead of, or in addition to, andarine. Under the agreement, Ortho Biotech may also develop andarine or any replacement or additional licensed SARM compound for indications other than those related to men s health. We retain the right to independently develop specific SARM compounds which are excluded from the collaboration, including ostarine.

A joint development committee made up of equal members from Ortho Biotech and us oversees all development of licensed compounds under the agreement, although the committee only has an advisory role over development activities directed at indications unrelated to men s health. Ortho Biotech has final decision-making authority over any disputes concerning the development of licensed compounds directed at indications related to men s health.

Under the terms of the agreement, we received an up-front licensing fee and reimbursement of certain andarine development expenses totaling approximately $6.7 million, which is being amortized into revenue over five years. We are entitled to receive additional licensing fees and milestone payments prior to product launch of (1) up to an aggregate of $76 million for licensed products containing andarine or any replacement compound, and (2) up to $45 million for each licensed product containing any other compound developed under the agreement, upon achievement of specific clinical development milestones or receipt of regulatory approvals.

Johnson & Johnson Pharmaceutical Research & Development, an affiliate of Ortho Biotech, is responsible for further clinical development and related expenses for andarine and other licensed SARM compounds. If a licensed product containing andarine or any other SARM compound is approved for commercial sale, Ortho Biotech will have full and exclusive decision-making authority for marketing such product in the United States and in markets outside the United States, including setting the price. Under the agreement, we have the option, subject to meeting specified conditions, to co-promote andarine and other licensed products to urologists in the United States for indications specifically related to men s health. If we are acquired by a large pharmaceutical company or fail to conduct specified minimum detailing requirements, Ortho Biotech may terminate our right to co-promote andarine or other licensed products, in which case we would be eligible to receive certain royalty payments. Ortho Biotech is solely responsible for clinical and commercial supply of licensed products.

Ortho Biotech is obligated to pay us up to double digit royalties on worldwide net sales of andarine and other licensed products, and an additional royalty in excess of 20% on all co-

Table of Contents

promoted net sales to urologists in the United States. Ortho Biotech is obligated to pay us royalties on a product-by-product and country-by-country basis until the later of expiration of the last-to-expire valid claim of a patent controlled by us or jointly owned with Ortho Biotech that claims the composition of matter for such product, or ten years from product launch.

The term of the agreement generally ends when Ortho Biotech is no longer obligated to pay royalties to us. Ortho Biotech may terminate the development or commercialization of andarine or any other licensed SARM compound under the agreement upon 90 days notice, or 30 days notice if there are safety issues. If Ortho Biotech so terminates development or commercialization of such compounds or products, it is required to transfer and assign ownership of certain regulatory applications, approvals and other documents related to such compounds and products to us, as well as grant us (1) an exclusive, royalty-free worldwide license, with the right to sublicense, to all joint patents developed under the agreement covering collaboration products; (2) an exclusive, worldwide, royalty-bearing license, with the right to sublicense, under Ortho Biotech patents covering collaboration products, subject to certain royalties under certain conditions; and (3) an exclusive, royalty-free worldwide license, with the right to sublicense, under all Ortho Biotech trademarks covering collaboration products. In addition, in the event of a non-safety related termination by Ortho Biotech, Ortho Biotech must continue manufacturing licensed product until we are able to secure an alternative commercial manufacturing source. Ortho Biotech may also terminate the agreement for our uncured material breach.

Amended and Restated License and Supply Agreement

The following disclosure supersedes the disclosure contained under the heading Business Licenses and Collaborative Relationships Orion Corporation in the Annual Report:

In March 2000, we entered into a license and supply agreement with Orion to develop and commercialize products containing toremifene, the active pharmaceutical ingredient in Fareston and Acapodene. Our rights under the original license agreement were limited to specific disease fields pertaining to prostate cancer. In December 2004, we entered into an agreement with Orion to purchase specified Fareston-related assets which Orion had re-acquired from another licensee. We also entered into an amended and restated license and supply agreement with Orion which replaces the original license agreement and expanded our rights to toremifene. We paid Orion approximately $5.2 million under the 2004 agreements for the assets and related license rights.

Under the amended and restated license agreement, we obtained an exclusive license from Orion to develop and commercialize toremifene-based products, including Fareston and Acapodene, for all human indications worldwide, except breast cancer outside of the United States. We are required to pay Orion a royalty on sales by us and our affiliates of Fareston for breast cancer in the United States, which royalty will be reduced upon the occurrence of specified circumstances. We are prohibited from using a third party to market or sell Fareston. We are also required to pay Orion a royalty on sales by us, our affiliates and third party sublicensees of other products, including Acapodene, containing toremifene as a therapeutically active ingredient if approved for commercial sale. We are also obligated to pay Orion a specified portion of any non-royalty income received from third party sublicensees to develop or commercialize Acapodene or other toremifene-based product for prostate cancer after applying a portion of such income to reimburse ourselves for specified license fees and clinical development costs incurred by us. In addition, we are required to pay Orion up to $1.0 million if we are acquired before receiving regulatory approval for the use of Acapodene or other toremifene-based product for prostate cancer.

Table of Contents

Under our amended and restated agreement with Orion, we must use commercially reasonable efforts to launch Acapodene or another toremifene-based product for prostate cancer as soon as practical in each major country where regulatory approval has been obtained and to market and sell such product in such major country. If we delay product launch in a major country other than due to potential adverse business effects in such country, Orion may terminate the agreement. We must also use commercially reasonable efforts to conduct development and registration of Acapodene or another toremifene-based product for prostate cancer in order to file applications for regulatory approval in the United States and all other major countries in accordance with our final development plans. Orion may require us to modify our final development plans if such development plans could reasonably be deemed to adversely affect Orion s or its other licensees activities related to Fareston for breast cancer outside the United States or toremifene-based animal health products.

We are also required to achieve minimum sales requirements in the United States for Acapodene or other toremifene-based product for prostate cancer during specified years after product launch. If we fail to do so, we must pay Orion royalties based on the amount of the shortfall below the applicable minimum sales requirement. We must also use commercially reasonable efforts to market Fareston for breast cancer in the United States in accordance with a specific sales and marketing plan. We and our affiliates are prohibited from marketing or selling a SERM-based product for human use in the United States and other major countries located outside the European Union during the term of Orion s patents in such countries and in major countries in the European Union through October 2006.

We are obligated to purchase all of our clinical and commercial requirements for toremifene from Orion at transfer prices specified in the amended and restated agreement. Orion may terminate its supply obligations, as well as its obligation to assist us in obtaining and maintaining regulatory approval of Acapodene and Fareston for breast cancer in the United States, if we do not obtain regulatory approval for toremifene-based product for prostate cancer in the United States by December 31, 2009. Orion may also terminate its supply obligations if Orion permanently ceases to manufacture toremifene. If Orion terminates its supply obligations to us, it is required to grant us specified licenses to applicable patents and know-how, and to assist us in transferring such know-how to us or another supplier chosen by us.

The term of the amended and restated agreement lasts, on a country-by-country basis, until the later of expiration of our own patents claiming the method of use or manufacture of toremifene for prostate cancer, including patents which we licensed from the University of Tennessee Research Foundation, or the end of all marketing or regulatory exclusivity which we may obtain for toremifene-based products. Orion may terminate the agreement as a result of our uncured material breach or bankruptcy.

Risk Factors

The following disclosure supersedes the disclosure contained under the heading Business Additional Factors That Might Affect Future Results in the Annual Report:

Table of Contents

Risks Related to Our Financial Results and Need for Additional Financing

We have incurred losses since inception and anticipate that we will incur continued losses for the foreseeable future.

We have a limited operating history. As of June 30, 2005, we had an accumulated deficit of $176.5 million, of which $96.3 million related to non-cash dividends and adjustments to the preferred stock redemption value. We have incurred losses in each year since our inception in 1997. Net losses were $22.3 million in 2004, $14.2 million in 2003 and $11.9 million in 2002. For the six months ended June 30, 2005, net losses were $19.1 million. We expect to continue to incur significant and increasing operating losses for the foreseeable future. These losses have had and will continue to have an adverse effect on our stockholders equity and working capital.

Because of the numerous risks and uncertainties associated with developing small molecule drugs, we are unable to predict the extent of any future losses or when we will become profitable, if at all. We have financed our operations and internal growth almost exclusively through sales of common stock and preferred stock. In addition, we received an upfront license fee from Ortho Biotech in March 2004 for our joint collaboration for the development and commercialization of andarine and other licensed SARM compounds that Ortho Biotech may choose to develop. Fareston is currently our only commercial product and, we expect, will account for all of our product revenue for the foreseeable future. For the six months ended June 30, 2005, we recognized approximately $1.8 million in net revenues from the sale of Fareston.

We expect our research and development expenses to increase in connection with our conduct of clinical trials. In addition, subject to regulatory approval of any of our product candidates, we expect to incur additional sales and marketing expenses and increased manufacturing expenses.

We will need substantial additional funding and may be unable to raise capital when needed, which would force us to delay, reduce or eliminate our product development programs or commercialization efforts.

We will need to raise additional capital to:

fund our operations and clinical trials;

continue our research and development; and

commercialize our product candidates, if any such product candidates receive regulatory approval for commercial sale.

We believe that the net proceeds from our proposed offering of 5,000,000 shares of common stock, our current cash resources, interest on these funds and product revenue from the sale of Fareston will be sufficient to meet our projected operating requirements through the first half of 2007. Our future funding requirements will depend on many factors, including:

the scope, rate of progress and cost of our clinical trials and other research and development activities;

Table of Contents

future clinical trial results;

the terms and timing of any collaborative, licensing and other arrangements that we may establish;

the cost and timing of regulatory approvals;

potential future licensing fees, milestone payments and royalty payments;

the cost and timing of establishing sales, marketing and distribution capabilities;

the cost of establishing clinical and commercial supplies of our product candidates and any products that we may develop;

the effect of competing technological and market developments;

the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights; and

the extent to which we acquire or invest in businesses, products and technologies, although we currently have no commitments or agreements relating to any of these types of transactions.

Until we can generate a sufficient amount of product revenue, if ever, we expect to finance future cash needs through public or private equity offerings, debt financings or corporate collaboration and licensing arrangements, such as our collaboration with Ortho Biotech, as well as through interest income earned on cash balances.

If we raise additional funds by issuing equity securities, our stockholders will experience dilution. Debt financing, if available, may involve restrictive covenants. Any debt financing or additional equity that we raise may contain terms that are not favorable to us or our stockholders. If we raise additional funds through collaboration or licensing arrangements with third parties, it will be necessary to relinquish some rights to our technologies or our product candidates, or we may be required to grant licenses on terms that may not be favorable to us.

Risks Related to Development of Product Candidates

We will not be able to commercialize our product candidates if our preclinical studies do not produce successful results or our clinical trials do not demonstrate safety and efficacy in humans.

Preclinical and clinical testing is expensive, can take many years and has an uncertain outcome. Success in preclinical testing and early clinical trials does not ensure that later clinical trials will be successful, and interim results of a clinical trial do not necessarily predict final results. Typically, the failure rate for development candidates is high. Significant delays in clinical testing could materially impact our product development costs. We do not know whether planned clinical trials will begin on time, will need to be restructured or will be completed on schedule, if at all. We may experience numerous unforeseen events during, or as a result of, preclinical testing and the clinical trial process that could delay or prevent our ability to commercialize our product candidates, including:

regulators or institutional review boards may not authorize us to commence a clinical trial or conduct a clinical trial at a prospective trial site;

our preclinical or clinical trials may produce negative or inconclusive results, which may require us to conduct additional preclinical or clinical testing or to abandon projects that we expect to be promising;

Table of Contents

registration or enrollment in our clinical trials may be slower than we currently anticipate, resulting in significant delays;

we might have to suspend or terminate our clinical trials if the participating patients are being exposed to unacceptable health risks;

regulators or institutional review boards may suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements; and

our product candidates may not have the desired effects or may include undesirable side effects.

If any of these events were to occur and, as a result, we have significant delays in or termination of clinical trials, our costs could increase and our ability to generate revenue could be impaired, which would adversely impact our financial results.

Risks Related to Our Dependence on Third Parties

If third parties do not manufacture our product candidates in sufficient quantities and at an acceptable cost, clinical development and commercialization of our product candidates would be delayed.

We do not currently own or operate manufacturing facilities, and we rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our product candidates. Our current and anticipated future dependence upon others for the manufacture of our product candidates may adversely affect our future profit margins and our ability to develop product candidates and commercialize any product candidates on a timely and competitive basis.

We have agreed to purchase from Orion our worldwide requirements of toremifene, the active pharmaceutical ingredient in Acapodene, in finished tablet form at specified transfer prices under a license and supply agreement. We rely on Orion as a single source supplier for Acapodene. In the event that Orion terminates the agreement due to our uncured material breach or bankruptcy, we would not be able to manufacture Acapodene until Orion s patents with respect to the composition of matter of toremifene, the active pharmaceutical ingredient in Acapodene, expire. This could delay the development of and impair our ability to commercialize Acapodene. In addition, Orion may terminate its obligation to supply us with toremifene if Orion ceases its manufacture of toremifene permanently, or if Acapodene is not approved for commercial sale in the United States by December 31, 2009. If such termination occurs because Orion is no longer manufacturing toremifene, or because such regulatory approval is not obtained prior to the specified date, we will have the right to manufacture Acapodene, but we would be required to make arrangements with a qualified alternative supplier and obtain FDA approval of such supplier to do so.

We also rely on Orion to cooperate with us in the filing and maintenance of regulatory filings with respect to the manufacture of Acapodene. Orion may terminate its obligation to assist us in obtaining and maintaining regulatory approval of Acapodene if we do not receive regulatory approval for Acapodene by December 31, 2009. If Orion terminates its obligation to cooperate in these activities, or does not cooperate with us or otherwise does not successfully file or maintain these regulatory filings, we would be required to make arrangements with a qualified alternative supplier, which could delay or prevent regulatory approval of Acapodene.

We have not entered into an agreement for supply of andarine or ostarine. We currently rely on EaglePicher Pharmaceutical Services, a division of EaglePicher Technologies, LLC, which has filed for protection under the bankruptcy code, as our single supplier of andarine for clinical use. Under our joint collaboration and license agreement with Ortho Biotech, Ortho Biotech is responsible for the manufacture, packaging and supply of andarine for both clinical trials and commercialization. EaglePicher was our sole supplier of ostarine, which Metrics, Inc. packaged and supplied to our

Table of Contents

Phase I clinical trial site. We are seeking to transfer the manufacturing process for ostarine from EaglePicher to a new contract manufacturer, which could take as long as nine months. In the event that our current supply of ostarine is not sufficient to complete our planned Phase II clinical trials, or if we are unsuccessful in identifying a contract manufacturer or negotiating a manufacturing agreement on a timely basis or at all, we could experience a delay in receiving an adequate supply of ostarine for use in our clinical trials.

We may not be able to maintain or renew our existing or any other third-party manufacturing arrangements on acceptable terms, if at all. If we are unable to continue relationships with Orion for Acapodene and EaglePicher or Ortho Biotech for andarine, or to do so at an acceptable cost, or if these or other suppliers fail to meet our requirements for these product candidates or for ostarine for any reason, we would be required to obtain alternate suppliers. However, we may not be permitted to obtain alternate suppliers for Acapodene under our license agreement with Orion if Orion terminates its supply of Acapodene due to our uncured material breach or bankruptcy. Any inability to obtain alternate suppliers, including an inability to obtain approval of an alternate supplier from the FDA, would delay or prevent the clinical development and commercialization of these product candidates.

Use of third-party manufacturers may increase the risk that we will not have adequate supplies of our product candidates.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured product candidates or products ourselves, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party because of factors beyond our control;
- the possible termination or non-renewal of the agreement by the third party, based on its own business priorities, at a time that is costly or inconvenient for us;
- the possible exercise by Orion of its right to terminate its obligation to supply us with toremifene if it permanently ceases manufacture of toremifene or if we do not obtain regulatory approval of Acapodene prior to December 31, 2009; and
- if Orion terminates due to our uncured material breach or bankruptcy.

If we are not able to obtain adequate supplies of our product candidates, it will be more difficult for us to develop our product candidates and compete effectively. Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. For example, the active pharmaceutical ingredient in Acapodene is also the active pharmaceutical ingredient in Fareston. Orion also manufactures toremifene for third parties for sale outside the United States for the treatment of advanced breast cancer in post-menopausal women.

Our present or future manufacturing partners may not be able to comply with FDA-mandated current Good Manufacturing Practice regulations, other FDA regulatory requirements or similar regulatory requirements outside the United States. Failure of our third-party manufacturers or us to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, failure of regulatory authorities to grant marketing approval of our product candidates, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates.

Table of Contents

If third parties on whom we rely do not perform as contractually required or expected, we may not be able to obtain regulatory approval for or commercialize our product candidates.

We do not have the ability to independently conduct clinical trials for our product candidates, and we must rely on third parties, such as contract research organizations, medical institutions, clinical investigators and contract laboratories to conduct our clinical trials. In addition, we rely on third parties to assist with our preclinical development of product candidates. If these third parties do not successfully carry out their contractual duties or regulatory obligations or meet expected deadlines, if the third parties need to be replaced, or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our preclinical development activities or clinical trials may be extended, delayed, suspended or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates.

We are dependent on our collaborative arrangement with Ortho Biotech to develop and commercialize andarine, and we may be dependent upon additional collaborative arrangements to complete the development and commercialization of some of our other product candidates. These collaborative arrangements may place the development of our product candidates outside our control, may require us to relinquish important rights or may otherwise be on terms unfavorable to us.

Any loss of Ortho Biotech as a collaborator in the development or commercialization of andarine, dispute over the terms of the collaboration or other adverse development in our relationship with Ortho Biotech could materially harm our business and might accelerate our need for additional capital.

We may not be successful in entering into additional collaborative arrangements with third parties. If we fail to enter into additional collaborative arrangements on favorable terms, it could delay or impair our ability to develop and commercialize our product candidates and could increase our costs of development and commercialization.

Dependence on collaborative arrangements, including our arrangement with Ortho Biotech for the development of andarine, subjects us to a number of risks, including:

- we may not be able to control the amount and timing of resources that our collaborators may devote to the product candidates;
- our collaborators may experience financial difficulties;
- we may be required to relinquish important rights such as marketing and distribution rights;
- should a collaborator fail to develop or commercialize one of our compounds or product candidates, we may not receive any future milestone payments and will not receive any royalties for this compound or product candidate;
- business combinations or significant changes in a collaborator s business strategy may also adversely affect a collaborator s willingness or ability to complete its obligations under any arrangement;
- a collaborator could move forward with a competing product candidate developed either independently or in collaboration with others, including our competitors; and
- the collaborative arrangements are often terminated or allowed to expire, which would delay the development and may increase the cost of developing our product candidates.

Table of Contents

Risks Related to Our Intellectual Property

Our license agreement with Orion excludes the use of toremifene in humans to treat breast cancer outside the United States and may limit our ability to market Acapodene for human uses of toremifene outside the United States.

Our exclusive license from Orion excludes the use of toremifene for the treatment of breast cancer outside the United States. Orion has licensed to other parties the right to market, sell and distribute toremifene for the treatment of advanced breast cancer outside the United States and could license additional parties to market, sell and distribute toremifene for this indication outside the United States.

Under the terms of our license agreement with Orion, Orion may require us to modify our final Acapodene development plans for specified major markets outside the United States if those development plans could adversely affect Orion s or Orion s other licensees activities related to Fareston for breast cancer outside the United States or toremifene-based animal health products. Although we do not believe that our development plans adversely affect these activities, any future modifications to our plans imposed by Orion may limit our ability to maximize the commercial potential of Acapodene.

Furthermore, we and our affiliates are prohibited from marketing or selling products containing toremifene or related SERM compounds for human use (1) in the United States and other major countries located outside the European Union during the term of Orion s patents covering toremifene in such countries and (2) in major countries in the European Union through October 2006, other than in the dosage forms or formulations which are, or may in the future be, manufactured by Orion under our agreement with Orion. The binding effect of this noncompetition provision on us and our affiliates may make it more difficult for us to be acquired by some potential buyers during the relevant time periods even if we determine that a sale of the company would be in the best interests of our stockholders.

If some or all of our, or our licensors , patents expire or are invalidated or are found to be unenforceable, or if some or all of our patent applications do not yield issued patents or yield patents with narrow claims, or if we are estopped from asserting that the claims of an issued patent cover a product of a third party, we may be subject to competition from third parties with products with the same active pharmaceutical ingredients as our product candidates.

Our commercial success will depend in part on obtaining and maintaining patent and trade secret protection for our product candidates, the methods for treating patients in the product indications using these product candidates and the methods used to synthesize these product candidates. We will be able to protect our product candidates and the methods for treating patients in the product indications using these product candidates from unauthorized use by third parties only to the extent that we or our exclusive licensors own or control such valid and enforceable patents or trade secrets. Our rights to specified patent applications relating to SARM compounds that we have licensed from the University of Tennessee Research Foundation, or UTRF, are subject to the terms of UTRF s license with The Ohio State University, or OSU, and our rights to future related improvements are subject to UTRF s exercise of an exclusive option under its agreement with OSU for such improvements, which UTRF can exercise at no additional cost to it. In addition, under the terms of our agreements with the diagnostic companies to which we provide clinical samples from our Phase IIb clinical trial of Acapodene, we will not obtain any intellectual property rights in any of their developments, including any test developed to detect high grade PIN or prostate cancer.

Even if our product candidates and the methods for treating patients in the product indications using these product candidates are covered by valid and enforceable patents and have claims with sufficient scope and support in the specification, the patents will provide protection only for a limited amount of time. For example, the patent that we have licensed from Orion covering the composition

Table of Contents

of matter of toremifene expires in the United States in 2009. Foreign counterparts of this patent have either already expired or will expire in Australia, Italy, Sweden and Switzerland in 2008, that is, before we commercialize Acapodene. As a result, outside the United States and in the United States after 2009, we will need to rely primarily on the protection afforded by method of use patents, relating to the use of Acapodene for the relevant product indications, that have been issued or may be issued from our owned or licensed patent applications. To date, most of our applications for method of use patents filed for Acapodene outside of the United States are still pending and have not yielded issued patents. Although we intend to apply, if appropriate, for regulatory market exclusivity and extensions of patent term under applicable European and United States laws, we might not be able to secure any such regulatory exclusivity or extension of patent term. We are not eligible for any such exclusivity or further extension of the composition of matter patent of toremifene in the United States.

Our and our licensors ability to obtain patents can be highly uncertain and involve complex and in some cases unsettled legal issues and factual questions. Furthermore, different countries have different procedures for obtaining patents, and patents issued in different countries provide different degrees of protection against the use of a patented invention by others. Therefore, if the issuance to us or our licensors, in a given country, of a patent covering an invention is not followed by the issuance, in other countries, of patents covering the same invention, or if any judicial interpretation of the validity, enforceability or scope of the claims in a patent issued in one country is not similar to the interpretation given to the corresponding patent issued in another country, our ability to protect our intellectual property in those countries may be limited. Changes in either patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property or narrow the scope of our patent protection.

Even if patents are issued to us or our licensors regarding our product candidates or methods of using them, those patents can be challenged by our competitors who can argue such patents are invalid or unenforceable or that the claims of the issued patents should be limited or narrowly construed. Patents also will not protect our product candidates if competitors devise ways of making or using these product candidates without legally infringing our patents. The Federal Food, Drug, and Cosmetic Act and FDA regulations and policies create a regulatory environment that encourages companies to challenge branded drug patents or to create noninfringing versions of a patented product in order to facilitate the approval of abbreviated new drug applications for generic substitutes. These same types of incentives encourage competitors to submit new drug applications that rely on literature and clinical data not prepared for or by the drug sponsor, providing another less burdensome pathway to approval.

We also rely on trade secrets to protect our technology, especially where we do not believe that patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. Our employees, consultants, contractors, outside scientific collaborators and other advisors may unintentionally or willfully disclose our confidential information to competitors, and confidentiality agreements may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. Enforcing a claim that a third party illegally obtained and is using our trade secrets is expensive and time-consuming, and the outcome is unpredictable. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how. Failure to obtain or maintain trade secret protection could adversely affect our competitive business position.

Off-label sale or use of toremifene products could decrease our sales of Acapodene and could lead to pricing pressure if such products become available at competitive prices and in dosages that are appropriate for the indications for which we are developing Acapodene.

In all countries in which we hold or have licensed rights to patents or patent applications related to Acapodene, the composition of matter patents we license from Orion will expire before our method of use patents, and in some countries outside the United States, the composition of matter patents have already expired. Our method of use patents may not protect Acapodene from the risk

Table of Contents

of off-label sale or use of other toremifene products in place of Acapodene. Physicians are permitted to prescribe legally available drugs for uses that are not described in the drug s labeling and that differ from those uses tested and approved by the FDA or its equivalent. Such off-label uses are common across medical specialties and are particularly prevalent for cancer treatments. Any off-label sales of toremifene may adversely affect our ability to generate revenue from the sale of Acapodene, if approved for commercial sale.

Even in the event that patents are issued from our pending method of use patent applications, after the expiration of the patent covering the composition of matter of toremifene in a particular country, competitors could market and sell toremifene products for uses for which Fareston has already been approved. Thus, physicians in such countries would be permitted to prescribe these other toremifene products for indications that are protected by our method of use patents or patents issuing from pending patent applications, even though these toremifene products would not have been approved for those uses, and in most cases the competitor would not be liable for infringing our patents. Moreover, because Orion has licensed and could further license other parties to market, sell and distribute toremifene for breast cancer outside the United States, physicians in such countries could prescribe these products sold pursuant to another Orion license off-label. This further increases the risk of off-label competition developing for Acapodene for the indications for which we are developing this product candidate. In addition, if no patents are issued with respect to our pending method of use patent applications related to the use of Acapodene, after the expiration of the patent covering the composition of matter of toremifene in a particular country, we would have no patent to prevent competitors from marketing and selling generic versions of toremifene at doses and in formulations equivalent to Acapodene for the indications covered by our pending method of use patent applications.

If we infringe intellectual property rights of third parties, it may increase our costs or prevent us from being able to commercialize our product candidates.

There is a risk that we are infringing the proprietary rights of third parties because numerous United States and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields that are the focus of our drug discovery and development efforts. Others might have been the first to make the inventions covered by each of our or our licensors pending patent applications and issued patents and might have been the first to file patent applications for these inventions. In addition, because patent applications can take many years to issue, there may be currently pending applications, unknown to us or our licensors, which may later result in issued patents that cover the production, manufacture, commercialization, formulation or use of our product candidates. In addition, the production, manufacture, commercialization, formulation or use of our product candidates may infringe existing patents of which we are not aware. Defending ourselves against third-party claims, including litigation in particular, would be costly and time consuming and would divert management s attention from our business, which could lead to delays in our development or commercialization efforts. If third parties are successful in their claims, we might have to pay substantial damages or take other actions that are adverse to our business.

As a result of intellectual property infringement claims, or to avoid potential claims, we might:

- be prohibited from selling or licensing any product that we may develop unless the patent holder licenses the patent to us, which the patent holder is not required to do;
- be required to pay substantial royalties or grant a cross license to our patents to another patent holder; or
- be required to redesign the formulation of a product candidate so it does not infringe, which may not be possible or could require substantial funds and time.

Table of Contents

Risk Related to Regulatory Approval of Our Product Candidates

If we are not able to obtain required regulatory approvals, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization are subject to comprehensive regulation by the FDA, and other regulatory agencies in the United States and by comparable authorities in other countries. Failure to obtain regulatory approval for a product candidate will prevent us from commercializing the product candidate. We have not received regulatory approval to market any of our product candidates in any jurisdiction and have only limited experience in preparing and filing the applications necessary to gain regulatory approvals. The process of obtaining regulatory approvals is expensive, often takes many years, if approval is obtained at all, and can vary substantially based upon the type, complexity and novelty of the product candidates involved.

Changes in the regulatory approval policy during the development period, changes in or the enactment of additional regulations or statutes, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Even if the FDA approves a product candidate, the approval may impose significant restrictions on the indicated uses, conditions for use, labeling, advertising, promotion, marketing and/or production of such product, and may impose ongoing requirements for post-approval studies, including additional research and development and clinical trials. The FDA also may impose various civil or criminal sanctions for failure to comply with regulatory requirements, including withdrawal of product approval.

Furthermore, the approval procedure and the time required to obtain approval varies among countries and can involve additional testing beyond that required by the FDA. Approval by one regulatory authority does not ensure approval by regulatory authorities in other jurisdictions.

The FDA has substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. For example, we believe that if the results of our ongoing Phase III clinical trial of Acapodene for the reduction in the incidence of prostate cancer in men with high grade PIN are sufficiently positive, that trial will be sufficient to serve as a single pivotal Phase III clinical trial for this indication. We submitted our plan for the Phase III clinical trial to the FDA under an SPA, filed a revised SPA in response to comments from the FDA on our initial filing, and received a response letter from the FDA related to the SPA in September 2005. An SPA is designed to facilitate the FDA s review and approval of drug products by allowing the agency to evaluate the proposed design and size of clinical trials that are intended to form the primary basis for determining a drug product s efficacy. If agreement is reached with the FDA, an SPA documents the terms and conditions under which the design of the subject trial will be adequate for submission of the effectiveness portion of an NDA. We agree with and intend to implement the FDA s September 2005 recommendations under the SPA, which we expect will be sufficient to support the submission of the effectiveness portion of an NDA. However, there are circumstances under which we may not receive the benefits of the SPA, notably including if the FDA subsequently identifies a substantial scientific issue essential to determining the product s safety or efficacy. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent regulatory approval of a product candidate. Furthermore, even if we file an application with the FDA for marketing approval of a product candidate, it may not result in marketing approval from the FDA.

We do not expect to receive regulatory approval for the commercial sale of any of our product candidates that are in development for the next few years. The inability to obtain FDA approval or approval from comparable authorities in other countries for such candidates would prevent us from

Table of Contents

commercializing our product candidates in the United States or other countries. See the section entitled Business Government Regulation in our Annual Report on Form 10-K, as amended, filed with the Securities and Exchange Commission, for additional information regarding risks associated with approval, as well as risks related to post-approval requirements.

Risks Related to Commercialization

The commercial success of any products that we may develop will depend upon the degree of market acceptance among physicians, patients, health care payors and the medical community.

Any products that we may develop may not gain market acceptance among physicians, patients, health care payors and the medical community. If these products do not achieve an adequate level of acceptance, we may not generate material product revenues, and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

the prevalence and severity of any side effects;

potential advantages over alternative treatments;

the ability to offer our product candidates for sale at competitive prices;

relative convenience and ease of administration;

the strength of marketing and distribution support; and

sufficient third-party coverage or reimbursement.

Our only marketed product generating revenue is Fareston. Fareston is subject to a number of risks that may cause sales of Fareston to continue to decline.

Fareston is currently our only marketed product generating sales. Sales of Fareston in the United States have been declining. Continued sales of Fareston could be impacted by many factors. The occurrence of one or more of the following risks may cause sales of Fareston to decline:

the loss of the availability of Orion s website to market Fareston, which is an important source of advertising;

the loss of one or more of our three largest wholesale drug distributors, which accounted for approximately 96% of our revenue generated from the sale of Fareston for the six months ended June 30, 2005;

the continued success of competing products, including aromatase inhibitors;

the loss of coverage or reimbursement for Fareston from Medicare and Medicaid, private health insurers or other third-party payors;

exposure to product liability claims related to the commercial sale of Fareston, which may exceed our product liability insurance;

the failure of Orion to maintain regulatory filings or comply with applicable FDA requirements with respect to Fareston;

the ability of third parties to market and sell generic toremifene products that will compete with Fareston for the treatment of breast cancer after the composition of matter patents that we license from Orion expire in the United States in 2009;

the loss of Orion, upon which we rely as a single source, as our supplier of Fareston; and

Table of Contents

our inability to manufacture Fareston until Orion s patents with respect to the composition of matter of toremifene expire if Orion terminates our license and supply agreement due to our uncured material breach or bankruptcy.

If we are unable to expand our sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate product revenue from such candidates.

We have limited experience as a company in the sales, marketing and distribution of pharmaceutical products. There are risks involved with building our own sales and marketing capabilities, as well as entering into arrangements with third parties to perform these services. For example, building a sales force is expensive and time-consuming and could delay any launch of a product candidate. In addition, to the extent that we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenues are likely to be lower than if we market and sell any products that we develop ourselves.

If we are unable to obtain adequate coverage and reimbursement from third-party payors for products we sell at acceptable prices, our revenues and prospects for profitability will suffer.

Many patients will not be capable of paying for any products that we may develop and will rely on Medicare and Medicaid, private health insurers and other third-party payors to pay for their medical needs. If third-party payors do not provide coverage or reimbursement for any products that we may develop, our revenues and prospects for profitability may suffer. In December 2003, the President of the United States signed into law legislation creating a prescription drug benefit program for Medicare recipients. The prescription drug program established by the legislation may have the effect of reducing the prices that we are able to charge for products we develop and sell through the program. This prescription drug legislation may also cause third-party payors other than the federal government, including the states under the Medicaid program, to discontinue coverage for products that we may develop or to lower the amount that they pay.

State Medicaid programs generally have outpatient prescription drug coverage, subject to state regulatory restrictions, for the population eligible for Medicaid. The availability of coverage or reimbursement for prescription drugs under private health insurance and managed care plans varies based on the type of contract or plan purchased.

A primary trend in the United States health care industry is toward cost containment. In addition, in some foreign countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take six to 12 months or longer after the receipt of regulatory marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our product candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization. Third-party payors are challenging the prices charged for medical products and services, and many third-party payors limit reimbursement for newly-approved health care products. In particular, third-party payors may limit the indications for which they will reimburse patients who use any products that we may develop or products we sell. Cost-control initiatives could decrease the price we might establish for products that we may develop or that we sell, which would result in lower product revenues to us.

Another development that may affect the pricing of drugs is proposed Congressional action regarding drug reimportation into the United States. The Medicare Prescription Drug, Improvement and Modernization Act of 2003 gives discretion to the Secretary of Health and Human Services to allow drug reimportation into the United States under some circumstances from foreign countries, including countries where the drugs are sold at a lower price than in the United States. Proponents of drug reimportation may attempt to pass legislation which would directly allow reimportation under

Table of Contents

certain circumstances. If legislation or regulations were passed allowing the reimportation of drugs, they could decrease the price we receive for any products that we may develop, negatively affecting our revenues and prospects for profitability.

If product liability lawsuits are brought against us, we will incur substantial liabilities and may be required to limit commercialization of any products that we may develop.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any product that we may develop. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

decreased demand for any product candidates or products;

injury to our reputation;

withdrawal of clinical trial participants;

costs to defend the related litigation;

substantial monetary awards to trial participants or patients;

loss of revenue; and

the inability to commercialize any products for which we obtain or hold approvals.

We have product liability insurance that covers our clinical trials and commercial products up to a $20 million annual aggregate limit. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost and we may not be able to obtain insurance coverage that will be adequate to satisfy any liability that may arise.

If our competitors are better able to develop and market products than any products that we may develop, our commercial opportunity will be reduced or eliminated.

We face competition from established pharmaceutical and biotechnology companies, as well as from academic institutions, government agencies and private and public research institutions. Our commercial opportunities will be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer side effects or are less expensive than any products that we may develop. In addition, significant delays in the development of our product candidates could allow our competitors to bring products to market before us and impair our ability to commercialize our product candidates.

Various products are currently marketed or sold and used off-label for some of the diseases and conditions that we are targeting, and a number of companies are or may be developing new treatments. The occurrence of such off-label uses could significantly reduce our ability to market and sell any products that we may develop. For example, although there are no products that have been approved by the FDA to treat multiple side effects of advanced prostate cancer therapy, we are aware of a number of drugs marketed by Eli Lilly, Merck, Aventis, Proctor & Gamble, Wyeth Pharmaceuticals, Boehringer and Bristol Myers Squibb that are prescribed off-label to treat single side effects of this therapy, that external beam radiation is used to treat breast pain and enlargement and that Amgen Inc. may be developing a product candidate for the treatment of bone loss in post-cancer patients. Similarly, while there are no drugs that have been approved by the FDA for the treatment of muscle wasting weight loss from cancer, there are drugs marketed by Steris Laboratories and Savient Pharmaceuticals that are being prescribed off-label for the treatment of some types of muscle wasting weight loss from cancer. Testosterone and other anabolic agents are used to treat involuntary weight loss in patients who have acute muscle wasting. In addition, there may be product candidates of which we are not aware at an earlier stage of development that may

Table of Contents

compete with our product candidates. If any are successfully developed and approved, they could compete directly with our product candidates. This could result in reduced sales and pricing pressure on our product candidates, if approved, which in turn would reduce our ability to generate revenue and have a negative impact on our results of operations.

Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies and technology licenses complementary to our programs or advantageous to our business.

Risks Related to Employees and Growth

If we fail to attract and keep senior management and key scientific personnel, we may be unable to successfully develop or commercialize our product candidates.

Our success depends on our continued ability to attract, retain and motivate highly qualified management, clinical and scientific personnel and on our ability to develop and maintain important relationships with leading academic institutions, clinicians and scientists. If we are not able to attract and keep senior management and key scientific personnel, particularly Dr. Mitchell S. Steiner, we may not be able to successfully develop or commercialize our product candidates. All of our employees are at-will employees and can terminate their employment at any time. We do not carry key person insurance covering members of senior management, other than $15 million of insurance covering Dr. Steiner.

We will need to hire additional employees in order to continue our clinical trials and commercialize our product candidates. Any inability to manage future growth could harm our ability to commercialize our product candidates, increase our costs and adversely impact our ability to compete effectively.

In order to continue our clinical trials and commercialize our product candidates, we will need to expand the number of our managerial, operational, financial and other employees. We currently anticipate that we will need between 150 and 250 additional employees by the time that Acapodene or ostarine is initially commercialized, including 50 to 80 sales representatives. While to date we have not experienced difficulties in recruiting and hiring qualified individuals, the competition for qualified personnel in the biotechnology field is intense.

Future growth will impose significant added responsibilities on members of management, including the need to identify, recruit, maintain and integrate additional employees. Our future financial performance and our ability to commercialize our product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively.

Risks Related To Our Common Stock

Market volatility may cause our stock price and the value of your investment to decline.

The market prices for securities of biotechnology companies in general have been highly volatile and may continue to be highly volatile in the future. The following factors, in addition to other

Table of Contents

risk factors described in this section, may have a significant impact on the market price of our common stock:

adverse results or delays in our clinical trials;

the timing of achievement of our clinical, regulatory and other milestones, such as the commencement of clinical development, the completion of a clinical trial or the receipt of regulatory approval;

announcement of FDA approval or non-approval of our product candidates or delays in the FDA review process;

actions taken by regulatory agencies with respect to our product candidates or products, our clinical trials or our sales and marketing activities;

the commercial success of any product approved by the FDA or its foreign counterparts;

the terms and timing of any collaborative, licensing or other arrangements that we may establish;

regulatory developments in the United States and foreign countries;

changes in the structure of health care payment systems;

any intellectual property infringement lawsuit involving us;

announcements of technological innovations or new products by us or our competitors;

market conditions for the biotechnology or pharmaceutical industries in general;

actual or anticipated fluctuations in our results of operation;

changes in financial estimates or recommendations by securities analysts;

sales of large blocks of our common stock;

sales of our common stock by our executive officers, directors and significant stockholders;

changes in accounting principles; and

the loss of any of our key scientific or management personnel.

The stock markets in general, and the markets for biotechnology stocks in particular, have experienced significant volatility that has often been unrelated to the operating performance of particular companies. These broad market fluctuations may adversely affect the trading price of our common stock. In the past, class action litigation has often been instituted against companies whose securities have experienced periods of volatility in market price. Any such litigation brought against us could result in substantial costs, which would hurt our financial condition and results of operations and divert management s attention and resources, which could result in delays of our clinical trials or commercialization efforts.

Our officers, directors and largest stockholders will maintain the ability to control all matters submitted to stockholders for approval.

As of June 30, 2005, our officers, directors and holders of 5% or more of our outstanding common stock beneficially owned approximately 79% of our outstanding common stock. As a result, these stockholders, acting together, will be able to control all matters requiring approval by our stockholders, including the election of directors and the approval of mergers or other business combination transactions. The interests of this group of stockholders

may not always coincide with our interests or the interests of other stockholders.

Table of Contents

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our certificate of incorporation and our bylaws may delay or prevent an acquisition of us or a change in our management. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our Board of Directors. Because our Board of Directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team. These provisions include:

a classified Board of Directors;

a prohibition on actions by our stockholders by written consent;

the ability of our Board of Directors to issue preferred stock without stockholder approval, which could be used to institute a poison pill that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our Board of Directors; and

limitations on the removal of directors.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. Finally, these provisions establish advance notice requirements for nominations for election to our Board of Directors or for proposing matters that can be acted upon at stockholder meetings. These provisions would apply even if the offer may be considered beneficial by some stockholders.

A significant portion of our total outstanding shares are restricted from immediate resale but may be sold into the market in the near future. This could cause the market price of our common stock to drop significantly, even if our business is doing well.

For the 12-month period ended August 31, 2005, the average daily trading volume of our common stock on the Nasdaq National Market was less than 39,000 shares. As a result, future sales of a substantial number of shares of our common stock in the public market, or the perception that such sales may occur, could adversely affect the then-prevailing market price of our common stock. As of June 30, 2005, we had 24,664,716 shares of common stock outstanding.

In connection with the proposed offering of 5,000,000 shares of our common stock, all of our executive officers and directors and their affiliated entities have entered into lock-up agreements with the underwriters of this proposed offering. As a result of these lock-up agreements, approximately 17.1 million shares will be subject to contractual restriction on resale through the date 90 days after the date of the prospectus supplement related to the proposed offering.

Table of Contents

The market price for shares of our common stock may drop significantly if stockholders subject to the lock-up agreements sell a substantial number of shares when the restrictions on resale lapse, or if the underwriters waive the lock-up agreements and allow the stockholders to sell some or all of their shares. Based on information currently available to us, all of the shares to be outstanding after this proposed offering of 5,000,000 shares of our common stock will be eligible for sale in the public market following expiration of the lock-up agreements in connection with this proposed offering, subject in some cases to volume and other limitations under federal securities laws.

Moreover, J.R. Hyde, III, Oracle Partners, L.P. and Memphis Biomed Ventures I, L.P., three of our largest stockholders, and their affiliates, who hold in the aggregate approximately 11.1 million shares of common stock, have rights, subject to some conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. Additionally, all shares of common stock that we may issue under our employee benefit plans can be freely sold in the public market upon issuance.

Item 9.01. Financial Statements and Exhibits

(c) Exhibits

99.1 Press release entitled GTx Announces Public Offering of Common Stock, issued by the Company on September 15, 2005

Table of Contents

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

GTx, Inc.

Date: September 16, 2005

By: /s/ Henry P. Doggrell

Name: Henry P. Doggrell
Title: Vice President, General Counsel/Secretary

Table of Contents

Exhibit Index

99.1	Press release entitled GTx Announces Public Offering of Common Stock, issued by the Company on September 15, 2005