Altus Pharmaceuticals Inc.
Form 10-K
March 11, 2008

Table of Contents

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

FORM 10-K

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2007

OR

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from to

Commission File No. 000-51711
ALTUS PHARMACEUTICALS INC.
(Exact Name of Registrant as Specified in its Charter)

Delaware	**04-3573277**
(State or Other Jurisdiction of Incorporation or Organization)	*(I.R.S. Employer Identification No.)*
640 Memorial Drive, Cambridge, Massachusetts	**02139**
(Address of Principal Executive Offices)	*(Zip Code)*

Registrant s telephone number, including area code:
(617) 299-2900

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, $.01 par value	The NASDAQ Stock Market LLC

Securities registered pursuant to Section 12(g) of the Act:
NONE
(Title of Class)

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES o NO þ

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. YES o NO þ

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES þ NO o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. þ

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer o	Accelerated filer þ	Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). YES o NO þ

The aggregate market value of the voting and non-voting common equity held by non-affiliates computed by reference to the price at which the common equity was last sold on The Nasdaq Global Market on June 29, 2007 was $353,628,990.

The number of shares outstanding of the registrant s common stock as of March 3, 2008 was 30,832,286.

DOCUMENTS INCORPORATED BY REFERENCE

Certain information required in Part III of this Annual Report on Form 10-K will be incorporated by reference either from the registrant s definitive Proxy Statement for the registrant s Annual Meeting of Stockholders to be held on June 12, 2008, or from a future amendment to this Form 10-K, to be filed with the Securities and Exchange Commission not later than 120 days after the end of the fiscal year covered by this Form 10-K.

INDEX TO FORM 10-K
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2007

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. The forward-looking statements are contained principally in, but not limited to, the sections entitled Business, Risk Factors and Management s Discussion and Analysis of Financial Condition and Results of Operations. These statements involve known and unknown risks, uncertainties and other important factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

- the expected timing, progress or success of our preclinical research and development and clinical programs;
- our ability to successfully obtain sufficient supplies of our product candidates for use in clinical trials and toxicology studies and secure sufficient commercial supplies of our product candidates;
- the timing, costs and other limitations involved in obtaining regulatory approval for any of our product candidates;
- the potential benefits of our product candidates over other therapies;
- our ability to market, commercialize and achieve market acceptance for any of our product candidates that we are developing or may develop in the future;
- our estimate of market sizes and anticipated uses of our product candidates;
- our ability to enter into and maintain collaboration agreements with respect to our product candidates and the performance of our collaborative partners under such agreements;
- our ability to protect our intellectual property and operate our business without infringing upon the intellectual property rights of others;
- our estimates of future performance;
- our ability to raise sufficient capital to fund our operations; and
- our estimates regarding anticipated operating losses, future revenue, expenses, capital requirements and our needs for additional financing.

In some cases, you can identify forward-looking statements by terms such as anticipate, assume, believe, could, estimate, expect, intend, may, plan, potential, predict, project, should, will, would and similar identify forward-looking statements. Forward-looking statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Because of these risks and uncertainties, the forward-looking events and circumstances discussed in this Annual Report on Form 10-K may not transpire. We discuss many of these risks in Item 1A of this Annual Report on Form 10-K under the heading Risk Factors beginning on page 39.

Given these uncertainties, you should not place undue reliance on these forward-looking statements. Also, forward-looking statements represent our estimates and assumptions only as of the date of this document. You should read this document and the documents that we reference in this Annual Report on Form 10-K with the understanding

that our actual future results may be materially different from what we expect. Except as required by law, we do not undertake any obligation to update or revise any forward-looking statements contained in this Annual Report on Form 10-K, whether as a result of new information, future events or otherwise.

Table of Contents

PART I

ITEM 1. *BUSINESS*

Our Corporate Information

We were incorporated in Massachusetts in October 1992 as a wholly-owned subsidiary of Vertex Pharmaceuticals Incorporated, or Vertex, from whom we exclusively license specified patents underlying some of our product candidates. In February 1999, we were reorganized as an independent company, and in August 2001 we reincorporated in Delaware. Prior to May 2004, we were named Altus Biologics Inc. We have one subsidiary, Altus Pharmaceuticals Securities Corp., a Massachusetts corporation. Unless the context requires otherwise, references to Altus, we, our , us and the Registrant in this report refer to Altus Pharmaceuticals Inc. and our subsidiary.

Our principal executive offices are located at 640 Memorial Drive, Cambridge, MA 02139, and our telephone number is (617) 299-2900. Our website address is *www.altus.com*. The information contained on, or that can be accessed through, our website is not incorporated by reference into this report. We have included our website address as a factual reference and do not intend it to be an active link to our website. Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and all amendments to those reports, are available to you free of charge through the Investor Relations section of our website as soon as reasonably practicable after such materials have been electronically filed with, or furnished to, the Securities and Exchange Commission.

Altus and Trizytek[tm] [porcine-free enzymes] are trademarks of Altus Pharmaceuticals Inc. Each of the other trademarks, trade names or service marks appearing in this report belongs to its respective holder.

Business Overview

We are a biopharmaceutical company focused on the development and commercialization of oral and injectable protein therapeutics for gastrointestinal and metabolic disorders, with three product candidates in clinical development. We use our proprietary protein crystallization technology to develop protein therapies which we believe will have significant advantages over existing products and will address unmet medical needs. Our product candidates are designed to either substitute a protein that is in short supply in the body or degrade toxic metabolites in the gut and remove them from the blood stream. We have initiated our Phase III clinical program for Trizytek (formerly ALTU-135) for the treatment of malabsorption due to exocrine pancreatic insufficiency and have successfully completed a Phase II clinical trial of ALTU-238 in adults for the treatment of growth hormone deficiency. We are also conducting a Phase I clinical trial for ALTU-237. ALTU-237 is designed to treat hyperoxalurias, a series of conditions in which too much oxalate is present in the body, resulting in an increased risk of developing kidney stones and, in rare instances, crystal formations in other organs. In addition, we have a pipeline of other product candidates in preclinical research and development.

Trizytek for Malabsorption due to Exocrine Pancreatic Insufficiency

Our lead product candidate, Trizytek, is an orally-administered enzyme replacement therapy consisting of three digestive enzymes, lipase, protease and amylase, for the treatment of malabsorption due to exocrine pancreatic insufficiency. Exocrine pancreatic insufficiency is a deficiency of digestive enzymes normally produced by the pancreas which leads to malabsorption of nutrients, malnutrition, impaired growth and shortened life expectancy. Exocrine pancreatic insufficiency can result from a number of diseases and conditions, including cystic fibrosis, chronic pancreatitis and pancreatic cancer. According to IMS Health, global prescription sales of existing pancreatic

enzyme replacement products were approximately $858 million in 2007.

Table of Contents

We believe that Trizytek, if approved, will have significant competitive advantages compared to existing pancreatic enzyme replacement therapies. We believe these potential advantages include:

- benefits associated with a drug that is microbially-derived and manufactured in a controlled environment, rather than a drug derived from pig pancreases, as is the case with existing pancreatic enzyme replacement therapies;
- a significantly lower pill burden, allowing patients to take, on average, one capsule per meal or snack compared to, on average, four or five larger capsules per meal or snack with existing products;
- more consistent and reliable dosing;
- a pre-specified and consistent ratio of lipase, protease and amylase;
- resistance to degradation early in the gastrointestinal tract, permitting enzyme activity later in the gastrointestinal tract where most digestion and absorption of fats, proteins and carbohydrates occurs;
- the potential for an alternative dosage formulation, such as a liquid oral form, which is currently unavailable with existing therapies, for children and adults who are unable to swallow pills or capsules; and
- testing in what we believe are the largest well-controlled, scientifically rigorous prospective clinical trials for the treatment of cystic fibrosis patients with pancreatic insufficiency.

We believe that many of these advantages are a result of our proprietary protein crystallization technology, which enables improved product consistency and stability, as well as higher concentration and purity.

Existing pancreatic enzyme replacement products have been marketed since before enactment of the Food, Drug and Cosmetic Act, or FDCA, in 1938 and are not marketed under new drug applications, or NDAs, approved by the United States Food and Drug Administration, or FDA. In April 2004, the FDA issued a notice that manufacturers of existing pancreatic enzyme replacement products will be subject to regulatory action if they do not obtain approved NDAs for those products by April 28, 2008. In October 2007, the FDA issued an update to the 2004 notice and announced that it has extended the deadline for unapproved pancreatic enzyme drug products from April 28, 2008 to April 28, 2010, but only if the manufacturers have investigational new drug applications on active status on or before April 28, 2008 and have submitted NDAs on or before April 28, 2009. We believe the FDA granted this extension in response to requests from the porcine enzyme manufacturers and to ensure the availability of the porcine-derived products during the additional time needed by manufacturers to obtain marketing approval. This extension reinforces our belief that some porcine enzyme manufacturers may have difficulty meeting the FDA s requirements, particularly the requirements relating to manufacturing processes and controls.

In 2005, we completed a prospective, randomized, double-blind, dose-ranging Phase II clinical trial of the capsule form of Trizytek. The results of this trial demonstrated that Trizytek was well tolerated, and in the two higher dose treatment arms Trizytek showed a statistically significant improvement in fat absorption (p-value<0.001), the trial s primary endpoint, as well as a statistically significant improvement in protein absorption (p-value<0.001) and a statistically significant decrease in stool weight (p-value<0.001), each of which was a secondary endpoint in the study. In addition, we observed a positive trend, although not statistically significant, in carbohydrate absorption. Based on these results, we initiated a pivotal Phase III efficacy trial of the capsule form of Trizytek in cystic fibrosis patients. However, the results of our Phase II clinical trial may not be predictive of the results in our ongoing Phase III efficacy trial of Trizytek. We are also conducting two long term safety studies, in cystic fibrosis patients and in chronic pancreatitis patients with pancreatic insufficiency. We expect to complete the efficacy trial in the second quarter of

2008 and report top-line efficacy trial results in the third quarter of 2008.

The European Medicines Agency, or EMEA, has granted Trizytek orphan drug designation, which generally provides a drug being developed for a rare disease or condition with marketing exclusivity for ten years in the European Union if it is the first drug of its type approved for such indication.

Table of Contents

In June 2007, we were notified by the Office of Orphan Products Development of the FDA that the orphan drug designation granted in 2002 to Trizytek for the treatment of pancreatic insufficiency was revoked. The FDA based its decision on a finding that if one includes all patients with HIV/AIDS who suffer from fat malabsorption due to pancreatic insufficiency, the patient population in the United States appears to exceed 200,000 persons and is thus ineligible for orphan drug designation. We believe that only a subset of patients with HIV/AIDS have fat malabsorption due to pancreatic insufficiency and that our original filing was correctly within the 200,000 person limit for this disease condition. The FDA, however, concluded otherwise. The principal anticipated advantage to us of an orphan drug designation was the availability of tax credits and the abatement of NDA filing fees. In addition, the holder of the first NDA approved for an orphan drug indication also receives marketing exclusivity for a period of seven years over other products that contain or constitute the same drug or active ingredient. We are not aware of other products in development that contain or constitute the same drug as Trizytek for orphan drug purposes. Given these facts and circumstances, we may consult with the Office of Orphan Products Development. If we conclude that re-filing with a more precisely defined indication has merit, we have the right to submit an application for orphan drug status on or before the filing of an NDA. We may also conclude that the advantages of continuing to seek orphan drug designation may not be warranted. The FDA has granted Trizytek fast track designation and admission into its Continuous Marketing Application, or CMA, Pilot 2 Program, both of which are designed to facilitate interactions between a drug developer and the FDA during the drug development process.

We have a strategic alliance agreement with Cystic Fibrosis Foundation Therapeutics, Inc., or CFFTI, which is funding a portion of the development of Trizytek.

ALTU-238 for Growth Hormone Deficiency and Related Disorders

Our next most advanced product candidate, ALTU-238, is a crystallized formulation of human growth hormone, or hGH, that is designed to be injected once-weekly with a fine gauge needle for the treatment of growth hormone deficiency and hGH-related disorders. Based on reported revenues of existing products, global sales of hGH products exceeded $2.8 billion in 2006, and the market grew at a compound annual growth rate of approximately 16% from 2003 to 2006. We are developing ALTU-238 for both adult and pediatric populations as an alternative to current therapies. Current medical guidelines for clinical practice generally recommend daily administration of existing therapies by subcutaneous injection. In our Phase I and Phase II clinical trials, ALTU-238 demonstrated pharmacokinetic and pharmacodynamic parameters that are consistent with once-weekly administration. In our Phase II clinical trial, we identified doses of ALTU-238 that maintained insulin-like growth factor 1, or IGF-1, levels within the normal range for age and gender over the course of the study. IGF-1 is a naturally occurring hormone that stimulates the growth of bone, muscle and other body tissues in response to hGH and, in turn, regulates hGH release from the pituitary gland. In addition, once-per-week dosing of ALTU-238 also appeared to result in a consistent, linear dose response of hGH and IGF-1 levels in the blood, which we believe will enable physicians and patients to correlate a given dose of ALTU-238 to desired levels of hGH and IGF-1 in the blood. We believe that the convenience of once-weekly administration of ALTU-238, if approved, would improve patient acceptance and compliance, and thereby effectiveness.

In December 2006, we entered into a Collaboration and License Agreement with Genentech, Inc., or Genentech, relating to the development, manufacture and commercialization of ALTU-238 and other pharmaceutical products containing crystallized hGH using our proprietary technology. The Collaboration and License Agreement covered development and commercialization rights in North America. Genentech had an option to extend the collaboration globally by providing notice to us within a specified timeframe. In consideration of the rights granted to Genentech under the agreement, Genentech paid us $15.0 million. In connection with the agreement, Genentech also purchased 794,575 shares of our common stock on February 27, 2007 for an aggregate purchase price of $15.0 million.

On December 19, 2007, Genentech and we entered into an agreement terminating the collaboration effective December 31, 2007. Under the termination agreement, we reacquired the North American development and commercialization rights to ALTU-238, and Genentech s option to expand the agreement to a global agreement expired unexercised. In addition, Genentech agreed to provide, for a limited time, supplies of hGH

Table of Contents

for future ALTU-238 clinical development in North America and for clinical development and commercial purposes outside North America, and to pay us a $4.0 million termination payment to fund the transition of the project back to us. During the period of the collaboration, we incurred $10.1 million of costs relating to the development of ALTU-238 which were paid or estimated to be due to us by Genentech. Upon commercialization, Genentech will be entitled to a nominal royalty on sales of ALTU-238. Our goal is to resume the clinical program for ALTU-238 in mid-2008.

ALTU-237 for Treatment of Hyperoxalurias and Kidney Stones

Our third product candidate in clinical development is ALTU-237, which we are developing to treat hyperoxalurias, a series of conditions in which excess oxalate is present in the body, resulting in an increased risk of developing kidney stones and, in rare instances, crystal formations in other organs. Increased oxalate in the body can be the result of a variety of factors including excess dietary intake of oxalate, genetic disorders of metabolism, and disease states such as inflammatory bowel disease. The oxalate combines with calcium in the urine causing formations of calcium oxalate crystals, which can grow into kidney stones. Kidney stones can be a serious medical condition. Kidney stones occur in 10% of adult men and 3% of adult women during their lifetimes. There are a variety of types of kidney stones, but calcium oxalate stones are the most common type in people who have kidney stone disease. We are currently conducting a Phase I clinical trial for ALTU-237.

Pipeline and Technology

We also have a pipeline of product candidates in preclinical research and development that we are designing to address other areas of unmet need in gastrointestinal and metabolic disorders.

We are currently testing our product candidate ALTU-236 in animal models for the treatment of phenylketonuria, or PKU. PKU is a rare, inherited, metabolic disorder that results from an enzyme deficiency that causes the accumulation of the amino acid phenylalanine in the body. If left untreated, PKU can result in mental retardation, swelling of the brain, delayed speech, seizures and behavior abnormalities.

We are also testing our product candidate ALTU-242 in animal models for the treatment of gout, a condition which we believe is in need of improved pharmaceutical therapies. Gout is caused by excess levels of urate in the body which can precipitate and form crystals in joints causing a painful and erosive arthritis. Gout is a common disorder that affects at least 1% of the population in Western countries and is the most common inflammatory joint disease in men older than 40 years of age. According to Ingenix, a division of United Healthcare, and based on incidence data extrapolated to the U.S. population, there are more than 1.6 million diagnoses of gout in the United States annually.

Our product candidates are based on our proprietary technology, which enables the large-scale crystallization of proteins for use as therapeutic drugs. We apply our technology to improve known protein drugs, as well as to develop other proteins into protein therapeutics. For example, our product candidate Trizytek is based on known enzymes to which we apply our proprietary crystallization technology with the goal of offering a new and improved drug. We have developed our product candidate ALTU-238 by applying our proprietary crystallization technology with the goal of offering an improved version of an approved drug. We believe that, by using our technology, we are able to overcome many of the limitations of existing protein therapies and deliver proteins in capsule and alternative dosage forms, such as a liquid oral form, and extended-release injectable formulations. Our product candidates are designed to offer improvements over existing products, such as greater convenience, better safety and efficacy and longer shelf life. In addition, we believe that we may be able to reduce the development risk and time to market for our drug candidates because we apply our technology to existing, well-understood proteins with well-defined mechanisms of action. We believe that our technology is broadly applicable to different classes of proteins, including enzymes, hormones, antibodies, cytokines and peptides. To date, we have crystallized more than 70 proteins for use in our

research and development programs. We currently hold worldwide rights to all of our product candidates.

Table of Contents

Our Strategy

Our goal is to become a leading biopharmaceutical company focused on developing and commercializing protein therapies to address unmet medical needs in gastrointestinal and metabolic disorders. Our strategy to achieve this objective includes the following elements:

Focus on advancing our lead product candidates. We have three product candidates in clinical development, including Trizytek, ALTU-238 and ALTU-237. Trizytek is currently in a pivotal Phase III clinical trial in cystic fibrosis patients and two long-term safety studies in cystic fibrosis patients and chronic pancreatitis patients with pancreatic insufficiency for the treatment of malabsorption due to exocrine pancreatic insufficiency. Based on our discussions with the FDA, we believe that the results of these clinical trials, combined with our Phase II results, will be sufficient to support an NDA filing for Trizytek with the FDA. In addition, we have completed a Phase II clinical trial of ALTU-238 in adult growth hormone deficient patients and are planning to resume the clinical development of ALTU-238 in mid-2008. We believe that these product candidates, if approved, will offer significant advantages over existing therapies. In addition, because these product candidates are based on well-understood proteins with known mechanisms of action, we believe we may be able to reduce their development risk and time to market. ALTU-237 is currently in a Phase I clinical trial which we expect to complete in the first half of 2008.

Continue to build and advance our product pipeline for gastrointestinal and metabolic disorders. In addition to our product candidates in clinical development, we have built a pipeline of preclinical product candidates based on our proprietary protein crystallization technology. These product candidates are designed to address unmet needs for the treatment of phenylketonuria, gout, and other gastrointestinal and metabolic diseases. We plan to apply the manufacturing, clinical and regulatory experience gained from our clinical stage product candidates to advance a number of these preclinical product candidates into clinical trials over the next few years.

Establish a commercial infrastructure. We plan to establish a commercial infrastructure and targeted specialty sales force to market Trizytek in North America. In addition, we plan to leverage our sales and marketing capabilities by targeting the same groups of physician specialists with additional products that we bring to market either through our own development efforts or by in-licensing from others.

Selectively establish collaborations for our product candidates with leading pharmaceutical and biotechnology companies. We intend to explore and evaluate collaborations in markets where we believe that having a collaborator will enable us to gain better access to those markets. We may also collaborate with other companies to accelerate the development of some of our early-stage product candidates, to co-commercialize our product candidates in North America in instances where we believe that a larger sales and marketing presence will expand the market or accelerate penetration, or to advance other business objectives.

Establish collaborations to apply our technology to other therapeutic proteins. We believe that our technology has broad applicability to many classes of proteins and can be used to enhance protein therapeutics developed by other parties. In the future, we may derive value from our technology by selectively collaborating with biotechnology and pharmaceutical companies that will use our technology for products that they are either currently marketing or developing.

Table of Contents

Our Product Candidates

The following table summarizes key information about our product candidates that are in clinical trials and our most advanced preclinical research and development programs. All of the product candidates are based on our crystallization technology and are the result of our internal research and development efforts. We currently have all commercial rights to each of our product candidates.

Product Candidate (Method of Delivery) Indication	Stage of Development	Status
Trizytek (oral) *Exocrine Pancreatic Insufficiency*	Phase III ongoing	Phase III clinical efficacy trial and two long-term safety studies to support FDA registration are ongoing. An alternative dosage form of Trizytek is in development for children and adults who have difficulty swallowing capsules.
ALTU-238 (injectable) *Growth Disorders*	Initial Phase I and Phase II trials completed	Manufacturing is planned for the first half of 2008, to enable a Phase Ic study to be followed by a Phase II pediatric study.
ALTU-237 (oral) *Hyperoxalurias*	Phase I ongoing	Top-line Phase I results expected to be reported in second quarter of 2008.
ALTU-236 (oral) *Phenylketonuria*	Preclinical	Preclinical testing in animal models
ALTU-242 (oral) *Gout*	Preclinical	Preclinical testing in animal models

Trizytek for Exocrine Pancreatic Insufficiency

Our lead product candidate, Trizytek, is an orally administered enzyme replacement therapy for which we have initiated Phase III clinical trials and successfully completed a Phase II clinical trial of its capsule form for the treatment of malabsorption due to exocrine pancreatic insufficiency. Pancreatic insufficiency is a deficiency of the digestive enzymes normally produced by the pancreas and can result from a number of disease conditions, including cystic fibrosis, chronic pancreatitis and pancreatic cancer. Patients with exocrine pancreatic insufficiency are currently treated with enzyme replacement products containing enzymes derived from pig pancreases. We believe that Trizytek represents a significant potential advancement as a therapeutic alternative for the treatment of these patients.

Trizytek contains three types of digestive enzymes derived from non-animal sources:

Lipase. We selected the lipase in Trizytek, which is used for the digestion of fats, because it demonstrated the ability in *in vitro* and animal testing to be active across a wide range of acidity levels and more resistant to degradation in the harsh environment of the gastrointestinal tract when compared to other lipases. It also demonstrated the ability to break down a broader range of fats than existing animal-derived lipases and other

microbial lipases. Because lipases are the most susceptible of the three enzymes to degradation in the gastrointestinal tract, we use our proprietary technology to both crystallize and cross-link this lipase for increased activity and stability;

Protease. We selected the protease in Trizytek, which is used for the digestion of proteins, because it demonstrated the ability in *in vitro* and animal testing to break down as many types of proteins as the multiple proteases contained in existing products. We crystallize the protease for greater stability and concentration; and

Table of Contents

Amylase. We selected the amylase in Trizytek, which is used for the digestion of carbohydrates, because it demonstrated the ability in *in vitro* testing to be active in the highly acidic environment of the upper gastrointestinal tract. Because the amylase is stable in soluble form, we do not crystallize it.

A contract manufacturer produces these enzymes for us from microbial sources using separate fermentation and purification processes. The enzymes are then blended to achieve a pre-specified and consistent ratio of lipase to protease to amylase in each capsule.

Disease Background and Market Opportunity

We have designed Trizytek to treat malabsorption resulting from exocrine pancreatic insufficiency. Malabsorption is the failure to absorb adequate amounts of nutrients, such as fats, proteins and carbohydrates, in food and is clinically manifested as malnutrition, weight loss or poor weight gain, impaired growth, abdominal bloating, cramping and chronic diarrhea. Exocrine pancreatic insufficiency is a deficiency of digestive enzymes normally produced by the pancreas that results in poor absorption of essential nutrients from food. If not treated appropriately, exocrine pancreatic insufficiency generally leads to malnutrition, impaired growth and shortened life expectancy.

According to IMS Health, the worldwide market for pancreatic enzyme replacement therapies grew at a compound annual growth rate of approximately 9.3% from $658 million in 2004 to approximately $858 million in 2007. The market for these products in 2007 was approximately $251 million in North America, $292 million in Europe and $315 million in the rest of the world according to IMS Health. Diseases and conditions with a prevalence of exocrine pancreatic insufficiency include:

Cystic fibrosis Cystic fibrosis is one of the most prevalent genetic disorders in the Caucasian population, according to the Medical Genetics Institute of Cedars-Sinai. According to the Cystic Fibrosis Foundation, this disease affects approximately 30,000 people in the United States. Approximately 90% of cystic fibrosis patients are prescribed pancreatic enzymes to treat exocrine pancreatic insufficiency. As of 2005, cystic fibrosis patients with exocrine pancreatic insufficiency had a median life expectancy of 31 years, compared to 50 years for those cystic fibrosis patients who have sufficient pancreatic enzymes.

Chronic pancreatitis In many patients, chronic pancreatitis is clinically silent and many patients with unexplained abdominal pain may have chronic pancreatitis that eludes diagnosis. As a result, according to The New England Journal of Medicine, the true prevalence of the disease is not known, although estimates range from 0.04% to 5.0% of the United States population. Based on survey data reported in Medscape General Medicine, we believe chronic pancreatitis results in more than 500,000 physician visits per year in the United States.

Pancreatic cancer The American Cancer Society estimates that approximately 30,000 people in the United States are diagnosed with pancreatic cancer each year. According to an industry estimate, approximately 65% of patients with pancreatic cancer will have some degree of fat malabsorption.

Limitations of Existing Products

Patients with exocrine pancreatic insufficiency are typically prescribed enzyme replacement products containing enzymes extracted from pig pancreases. Many of these products were available for human use prior to the passage of the FDCA in 1938, and all are currently marketed without NDAs approved by the FDA. In 1995, the FDA issued a final ruling requiring that these pancreatic enzyme products be marketed by prescription only, and in April 2004, the FDA issued a notice that manufacturers of these products will be subject to regulatory action if they do not obtain

approved NDAs for these products by April 28, 2008. In October 2007, the FDA issued an update to the 2004 notice and announced that it has extended the deadline for unapproved pancreatic enzyme drug products from April 28, 2008 to April 28, 2010, but only if the manufacturers have investigational new drug applications on active status on or before April 28, 2008 and have submitted NDAs on or before April 28, 2009. We believe the FDA granted this extension in response to requests from the porcine enzyme manufacturers and to ensure the availability of the porcine-derived products

Table of Contents

during the additional time needed by manufacturers to obtain marketing approval. This extension reinforces our belief that some porcine enzyme manufacturers may have difficulty meeting the FDA s requirements, particularly the requirements relating to manufacturing processes and controls. The FDA has also issued guidance titled Guidance for Industry Exocrine Pancreatic Drug Products Submitting NDAs, also termed the PEP Guidance, that existing manufacturers of pancreatic enzyme products can follow in order to obtain FDA approval.

Existing pancreatic enzyme replacement therapies are derived from pig pancreases and are supposed to be taken with every meal and snack in order to permit the digestion and absorption by the patient of sufficient amounts of fats, proteins and carbohydrates. We believe that these products have a number of significant limitations that affect their ease of administration, safety and effectiveness, including:

High pill burden. Patients on existing pancreatic enzyme therapies are generally required to take, on average, four or five large capsules per meal or snack, resulting in poor compliance and therefore reduced long-term efficacy, due to the following factors:

Degradation of enzymes in the gastrointestinal tract. A significant portion of the enzymes in existing products are degraded in the gastrointestinal tract prior to exerting their therapeutic effect. Some manufacturers have tried to address this issue by adding a protective coating to the enzymes, but this often results in a failure of the enzyme to dissolve and become active early enough in the gastrointestinal tract to break down foods and effectively assist with the digestive process.

Low concentration. Existing therapies are comprised of a mixture of enzymes and other materials found in a pig s pancreas. Based on comments submitted in response to the FDA s PEP Guidance in 2004 by manufacturers of existing products and the components of such products, we believe that manufacturers of these products are unable to concentrate the enzymes in the mixture to reduce the amount of material a patient must consume.

Variability of therapeutic effect. Because existing products are extracted from pig pancreases, there is significant variability between different manufacturing batches. As a result, we believe that the therapeutic effect of these therapies is also significantly variable. Each time a patient refills a prescription, the patient may need to experiment with the number of pills taken per meal or snack to achieve effective digestion of his or her food intake.

Short shelf life. Existing enzyme therapies tend to lose activity quickly relative to other types of drugs. For example, the lipase, which is generally the most sensitive component in these products, is often degraded by the proteases also found in these products. Many manufacturers try to overcome this limitation by filling each capsule with more drug than specified on the label in order to achieve the stated label claim over time. This leads to inconsistent efficacy and raises safety concerns. We believe this also contributes to patient uncertainty about the number of capsules to take per meal or snack.

Risk of viral contamination. Based on comments submitted in response to the FDA s PEP Guidance in 2004 by manufacturers of existing products, we believe they have been unable to develop viral inactivation or clearance steps and will not be able to eliminate the risk of viral contamination from the porcine-derived products. In those comments, at least one manufacturer identified the presence of viral contamination, and thus even with new manufacturing controls, these products may present a risk of viral contamination.

Product impurities. Existing enzyme therapies are poorly characterized and may contain impurities, including porcine viruses, tissue components and other contaminants. These impurities may increase the risk of antigenicity, or an immune system reaction.

Table of Contents

Anticipated Advantages of Trizytek

We believe that Trizytek, if approved, will offer patients a more convenient and effective long-term therapy for the treatment of malabsorption due to exocrine pancreatic insufficiency because of the following features:

Reduced pill burden. Trizytek is a highly concentrated, pure and stable enzyme replacement therapy designed to be as effective as existing products with significantly fewer capsules. Based on the clinical trials we have conducted to date, we believe that most patients will be effectively treated with, on average, one capsule per meal or snack. We believe that this dosing will result in greater convenience for the patient, which will improve compliance and, therefore, long-term effectiveness of therapy. We believe that Trizytek will reduce the pill burden for patients due to the following factors:

Stability of enzymes in the gastrointestinal tract. We have designed Trizytek to withstand degradation, maintain its activity across the different pH levels in the gastrointestinal tract, and exert its therapeutic effect in the first part of the small intestine, or the duodenum, where most fats, proteins and carbohydrates are broken down and absorbed. We believe this design will provide a more effective treatment for patients than current pancreatic enzyme replacement products, which are often degraded earlier or later in the gastrointestinal tract.

High concentration. Two of the three enzymes in Trizytek are crystallized, resulting in a highly concentrated product that requires less material to achieve a desired therapeutic effect.

Consistent activity and non-porcine enzymes. We have designed Trizytek to exhibit consistent enzyme activity from batch to batch. The enzymes in Trizytek are microbially derived and produced through fermentation. The amount of material and related enzyme activity in a capsule of Trizytek is tightly controlled, as each of the three enzymes in Trizytek is individually manufactured and added to the final drug product in a specific amount. We believe this will result in consistent product performance, eliminating the need for dose experimentation each time a patient refills a prescription, and avoiding the risk of viral contamination from animal-derived enzyme source material.

Longer shelf life. Based on stability studies performed as part of our development program, we believe that Trizytek capsules are significantly more stable than existing porcine-derived products, which offers the potential for a longer effective shelf life and more reliable and consistent dosing.

Alternative dosage formulation. We have completed a series of *in vivo* studies and are continuing formulation development activities of alternative dosage formulations of Trizytek. We believe that an alternative dosage formulation is an important option for children and adults who are unable to swallow capsules.

Trizytek Development Activities and Strategy

We have successfully completed a Phase II clinical trial of the capsule form of Trizytek and in May 2007, we announced the start of our Trizytek pivotal Phase III clinical efficacy trial in patients with cystic fibrosis and two long-term safety studies in cystic fibrosis patients and chronic pancreatitis patients with pancreatic insufficiency. The EMEA has granted Trizytek orphan drug designation for malabsorption due to exocrine pancreatic insufficiency. In June 2007, we were notified by the Office of Orphan Products Development of the FDA that the orphan drug designation granted in 2002 to Trizytek for the treatment of pancreatic insufficiency was revoked. The FDA based its decision on a finding that if one includes all patients with HIV/AIDS who suffer from fat malabsorption due to pancreatic insufficiency, the patient population in the United States appears to exceed 200,000 persons and is thus

ineligible for orphan drug designation.

The FDA has granted Trizytek fast track designation. Fast track designation is designed to facilitate the development of new drugs and may be granted to a product with a specific indication where the FDA agrees that the product is intended to treat a serious or life threatening condition and demonstrates the potential to address unmet medical needs for that condition. Fast track designation also permits drug developers to submit sections of an NDA as they become available. In February 2004, Trizytek was also admitted to the FDA s

Table of Contents

CMA Pilot 2 Program. Under the CMA Pilot 2 program, one fast track designated product from each review division of the Center for Drug Evaluation and Research, or CDER, the center at the FDA that regulates drugs and therapeutic biologics, and the Center for Biologics Evaluation and Research, or CBER, the center at the FDA that regulates other biologics, is selected for frequent scientific feedback and interactions with the FDA, with a goal of improving the efficiency and effectiveness of the drug development process.

We have completed four clinical trials of Trizytek, three of which were in cystic fibrosis patients and one of which was in healthy volunteers. The following table summarizes the clinical trials of Trizytek that we have completed to date:

Trial	Number of Subjects	Primary Study Objective
Phase Ia	20 healthy volunteers	Safety and tolerability over 7 days of dosing
Phase Ib	23 cystic fibrosis patients	Safety, tolerability and clinical activity over 3 days of dosing
Phase Ic	8 cystic fibrosis patients	Safety, tolerability and clinical activity over 14 days of dosing
Phase II	129 cystic fibrosis patients	Safety, tolerability and efficacy over 28 days of dosing

Our clinical trials with cystic fibrosis patients assessed a number of different measures, or endpoints, of digestion and absorption. We assessed fat absorption by measuring a patient s fat intake over a specified period of time and comparing that to the amount of fat in their stool during the same period. This comparison enabled us to calculate the amount of fat a patient absorbed, using a metric known as the coefficient of fat absorption, or CFA. The same process was applied to determine protein absorption, using a metric called the coefficient of nitrogen absorption, or CNA. We measured carbohydrate absorption by analyzing a patient s blood glucose levels after a starch meal, using a test we refer to as the starch challenge test. In our Phase Ib and Phase II clinical trials, we also measured the number and weight of the patients stools.

Phase I Clinical Trials

In our three Phase I clinical trials, the capsule form of Trizytek was generally well tolerated at doses of up to four times the maximum recommended clinical dose. In addition, in our Phase Ib trial, we observed statistically significant evidence of clinical activity based on CFA, CNA and stool results when all cohorts in the Phase Ib were considered together. In the Phase Ic trial, we observed evidence of amylase activity based on a treatment-associated increase in maximum glucose levels in a small number of subjects.

Phase II Clinical Trial

We successfully completed our Phase II clinical trial for Trizytek and presented the results of the trial at the North American Cystic Fibrosis Conference in October 2005. In the trial, Trizytek was well tolerated and showed a statistically significant improvement in fat absorption (p-value<0.001), the trial s primary endpoint, in the two higher dose treatment arms. In these treatment arms, we also observed a statistically significant improvement in protein absorption (p-value<0.001) and a statistically significant decrease in stool weight (p-value<0.001), each of which was a secondary endpoint in the study. In addition, we observed a positive trend, although not statistically significant, in carbohydrate absorption in these treatment arms.

Because we measured the impact of each active ingredient in Trizytek, we believe that this is the first clinical trial to demonstrate that the combination of the three enzymes, lipase, protease and amylase, may be effective in treating pancreatic insufficiency. We also believe that this trial is the only trial to concurrently evaluate the impact of a fixed dose of enzyme replacement therapy on the absorption of fats, proteins and carbohydrates.

After the completion of the Phase II clinical trial, we performed additional manufacturing development work on Trizytek. As part of this work, we evaluated the assays used to measure the enzymatic activity of Trizytek in our Phase II trial. We found that the standard US Pharmacopea, or USP, assay that was used to measure the lipase activity of porcine-derived lipase did not accurately measure the lipase activity of Trizytek. This USP assay, which is the standard for measuring lipase activity, is specified for porcine material and has

Table of Contents

been in existence for more than 50 years. We retested the Phase II clinical trial material utilizing an improved version of the USP assay that was developed to accurately measure the activity of our microbially derived, non-porcine lipase and found that the activity of the lipase doses used in the Phase II clinical trial were 6,500, 32,500 and 130,000 units, rather than 5,000, 25,000 and 100,000 units as measured in the USP assay that we utilized previously. Based on the results from our Phase II clinical trial and earlier trials for Trizytek, we believe that:

a formulation of Trizytek consisting of 32,500 units of lipase, 25,000 units of protease and 3,750 units of amylase, representing a ratio of approximately 1.0:0.8:0.12, provides a clinically meaningful improvement in fat and protein absorption;

most patients will be able to be treated with one small capsule of Trizytek per meal or snack; and

patients with the most severe fat and protein malabsorption will realize the greatest benefit from treatment with Trizytek.

Phase II Study Design and Demographics

The purpose of our Phase II clinical trial of Trizytek was to obtain initial efficacy data, select a dose level of Trizytek for further evaluation in our Phase III clinical trial and assess the safety and tolerability of Trizytek over a 28-day treatment period in cystic fibrosis patients with pancreatic insufficiency. We believe our Phase II clinical trial of Trizytek represents the largest, randomized, double-blind, dose-ranging trial conducted to date in the treatment of cystic fibrosis patients with pancreatic insufficiency.

To establish a baseline period measurement of fat, protein and carbohydrate absorption, at the beginning of the trial patients were tested during a 72-hour period when they were not taking enzyme replacement therapy. Following this baseline period, Trizytek in capsule form was orally administered to patients with each of five meals or snacks per day for a period of 28 days. In the middle of the trial, we performed an additional measurement of fat, protein and carbohydrate absorption to establish these measurements for the treatment period. For both the baseline and treatment period measurements, we assessed fat and protein absorption following a 72-hour, controlled, high-fat diet by examining stools collected from patients. The appropriate period for measuring fat and protein absorption was determined by using a blue dye stool marker, which facilitated accurate and complete stool collection. Changes in carbohydrate absorption were determined by measuring blood glucose responses using the starch challenge test. We assessed the clinical activity of the lipase component of Trizytek by measuring the change in CFA, the clinical activity of the protease component of Trizytek by measuring the change in CNA and the clinical activity of the amylase component of Trizytek by measuring the change in carbohydrate absorption.

The Phase II clinical trial for Trizytek enrolled a total of 129 subjects with cystic fibrosis and pancreatic insufficiency in 26 cystic fibrosis centers in the United States. We believe the demographics and baseline characteristics of the patients in the trial generally reflect the cystic fibrosis patient population. Ninety-five percent of the patients in the trial were Caucasian. The trial consisted of patients between the ages of 11 and 55, with a median age of 21.

The study included three treatment arms of approximately equal size, with patients in each arm receiving a fixed dose of Trizytek in capsule form administered orally:

Treatment arm 1 6,500 units lipase: 5,000 units protease: 750 units amylase per meal or snack;

Treatment arm 2 32,500 units lipase: 25,000 units protease: 3,750 units amylase per meal or snack, which is the dose we have selected to use in our ongoing Phase III clinical trials; and

Treatment arm 3	130,000 units lipase: 100,000 units protease: 15,000 units amylase per meal or snack.

The trial did not include a placebo arm, as we assessed efficacy based on the differences in fat, protein and carbohydrate absorption between the baseline period and the treatment period.

Table of Contents

Phase II Efficacy Results

Of the 129 patients who were enrolled in the trial, 117 patients had valid stool collections during the Trizytek treatment period. We used this subset of patients for our main efficacy analyses. The results of the Phase II clinical trial showed a statistically significant improvement in CFA from the baseline period to the treatment period (p-value<0.001) for patients in treatment arms 2 and 3. The results of the trial also showed a statistically significant difference between on-treatment CFAs for patients in treatment arms 2 and 3 relative to treatment arm 1; therefore, the trial achieved its primary efficacy endpoint. We also observed a statistically significant improvement in CNA from the baseline period to the treatment period (p-value<0.001) and a statistically significant decrease in stool weight from the baseline period to the treatment period (p-value<0.001) for patients in treatment arms 2 and 3. The trial results also indicated a trend, although not statistically significant, toward improvement in carbohydrate absorption for patients in treatment arms 2 and 3.

We also observed statistically significant improvements in CNA from the baseline period to the treatment period for patients in treatment arms 2 and 3, as compared to patients in treatment arm 1. In addition, changes in CFA and CNA were highly correlated (r=0.844, p-value<0.001), supporting the 1.0:0.8 ratio of the units of lipase and protease in the formulation. The correlation coefficient, r, is the measure of correlation between two sets of data. Based on the results of our Phase II clinical trial, we selected a formulation of Trizytek consisting of 32,500 units of lipase, 25,000 units of protease and 3,750 units of amylase as the dose level for testing in our Phase III clinical trial.

In treatment arm 2 there was an average 11.4 percentage point increase in CFA, from 55.6% to 67.0%, and an average 12.5 percentage point increase in CNA, from 58.8% to 71.3%, from the baseline period to the treatment period. In treatment arm 3 there was an average 17.3 percentage point increase in CFA, from 52.2% to 69.7%, and an average 17.5 percentage point increase in CNA, from 56.8% to 74.6%, from the baseline period to the treatment period. There was not a statistically significant difference between these results. Based on these increases in CFA and CNA, we believe that cystic fibrosis patients suffering from malabsorption who are treated with Trizytek may experience clinically meaningful improvements in fat and protein absorption, resulting in an overall improvement in nutritional status. We also believe that an improvement in nutritional status may lead to weight maintenance or weight gain in patients, both of which are important elements in the overall health of cystic fibrosis patients and others suffering from pancreatic insufficiency. According to the Cystic Fibrosis Foundation 2003 Patient Registry, more than 90% of cystic fibrosis patients take currently available pancreatic enzyme replacement therapies and approximately 35% of cystic fibrosis patients are in urgent need of improved nutrition.

Clinicians who treat cystic fibrosis patients typically recommend a high fat diet consistent with the diet in our Phase II clinical trial. Patients in our Phase II clinical trial consumed, on average, 100 grams of fat per day. In these patients, an average increase in fat absorption of 10 percentage points would equate to 10 grams of additional fat absorbed per day. According to the FDA, there are nine calories in a gram of fat. As a result, an improvement in CFA of 10 percentage points would equate to an additional 90 calories absorbed per day. Over a period of one year, such a 90 calorie per day increase would result in an improvement in weight of approximately nine pounds, allowing patients to either maintain weight that they may have otherwise lost or gain weight. For these reasons, we believe that an improvement in CFA of 10 percentage points or more represents a clinically meaningful benefit to patients with pancreatic insufficiency.

To gain a better understanding of the clinical impact of treatment with Trizytek, we further analyzed the data on CFA and CNA improvements in our Phase II clinical trial, specifically focusing on differences experienced by patients who began the trial with lower levels of fat and protein absorption during the baseline period, as compared with patients who began the trial with higher baseline levels of fat and protein absorption. We examined two groups: patients who absorbed 40% or less of their fat or protein intake during the baseline period, and patients who absorbed more than 40%, but less than 80%, of their fat or protein intake during the baseline period. In this retrospective analysis, we

looked only at data from patients in treatment arms 2 and 3, and we pooled these two groups for purposes of the analysis, as there were no statistically significant differences between these treatment arms in improvements in CFA and CNA.

Table of Contents

When we analyzed those patients who absorbed 40% or less of their fat or protein intake during the baseline period we observed the following results:

- an average increase in CFA of 31 percentage points for combined treatment arms 2 and 3, from the baseline period to the treatment period (number of patients, or n=21)

- an average increase in CNA of 36 percentage points for combined treatment arms 2 and 3, from the baseline period to the treatment period (n=9)

In patients with fat or protein absorption of more than 40%, but less than 80%, during the baseline period, we observed the following results:

- an average increase in CFA of 9 percentage points for combined treatment arms 2 and 3, from the baseline period to the treatment period (n=50)

- an average increase in CNA of 13 percentage points for combined treatment arms 2 and 3, from the baseline period to the treatment period (n=60)

Based on these data, we believe cystic fibrosis patients enrolled in our Phase II clinical trial had a clinically meaningful response to Trizytek. In particular, those subjects who had the most severe fat or protein malabsorption, which we define as patients with a CFA or CNA of 40% or less during the baseline period, responded the most from their treatment with Trizytek. Based on our discussions with the FDA to date, we expect that in our Phase III clinical trial of Trizytek, the FDA will look for Trizytek to provide patients who have a lower baseline CFA level a substantially greater percentage point increase in CFA than the percentage point increase in patients who have a higher baseline CFA level in order to demonstrate clinically meaningful improvement. We believe that a statistically significant improvement in carbohydrate absorption will not be required by the FDA in order to obtain approval for Trizytek.

As noted above, the trial results also indicated a trend toward improvement in carbohydrate absorption for patients in treatment arms 2 and 3. To obtain additional insight with respect to carbohydrate absorption, we further analyzed the data retrospectively by examining all three treatment arms using a responder analysis that excluded subjects with cystic fibrosis-related diabetes, because those subjects were receiving diabetes medications that could have confounded the results. In this subgroup (n=81), we observed a marked increase in the number of subjects whom we considered responders in treatment arms 2 and 3 compared to treatment arm 1. We defined responders as patients who achieved a minimum predetermined level of glucose change during the treatment period as compared to the pre-treatment period. The number of subjects achieving this response in treatment arm 2 was statistically significant when compared to treatment arm 1 (p-value<0.01) and was approaching statistical significance for treatment arm 3 (p-value=0.0644) compared to treatment arm 1.

Phase II Safety and Tolerability Results

There were no statistically significant differences among the three treatment arms in the incidence of adverse events, or AEs, the number of related AEs, or the number of serious adverse events, or SAEs. The majority of AEs were mild in intensity, similar to previous Trizytek studies in cystic fibrosis subjects, and the most frequently reported AEs were gastrointestinal disorders. There were no clear differences across the treatment arms for any AEs considered to be related to Trizytek. The majority of the SAEs were gastrointestinal and pulmonary related, which were consistent with the subjects underlying cystic fibrosis disease. Of the SAEs, only one was considered by an investigator in the trial as probably or possibly related to treatment with Trizytek.

There were no major safety concerns identified regarding laboratory values, vital signs or physical exams. Abnormal liver transaminase values with frequent fluctuations were common among the subjects during the pre-treatment, treatment and follow-up periods, and are common in the cystic fibrosis population in general. We observed, however, more frequent liver transaminase elevations in subjects during the treatment and follow-up periods compared to the pre-treatment period. In a 1999 published study of 124 children with cystic fibrosis who were followed for four years, it was found that 80% had abnormal elevations in liver transaminases. Overall transaminase elevations experienced by patients in our Phase II trial were transient,

Table of Contents

asymptomatic and not associated with increases in bilirubin. Increases in bilirubin are typically associated with harm to the liver. In addition to normal to abnormal transaminase shifts, abnormal to normal transaminase shifts were also observed across treatment groups. A causal relationship between Trizytek treatment and elevated liver transaminases is unclear because of the underlying liver disease, which is estimated to occur in up to 37% of cystic fibrosis patients according to published studies, and other complicating factors in these patients, including diabetes and infections. We also believe that Trizytek is not absorbed into the body from the gastrointestinal tract.

Phase III Clinical Trial in Cystic Fibrosis Patients

Based on the results of our Phase II clinical trial and our discussions with the FDA, we initiated a Phase III program for Trizytek which includes an efficacy trial in cystic fibrosis patients and long term safety studies in cystic fibrosis patients and chronic pancreatitis patients with pancreatic insufficiency. We designed our pivotal Phase III clinical trial of Trizytek to be a multicenter, randomized, double-blind, placebo-controlled clinical study to determine, as the primary endpoint, the efficacy of Trizytek in the treatment of fat malabsorption in cystic fibrosis patients with exocrine pancreatic insufficiency through measurement of CFA. The trial also includes secondary efficacy endpoints, including the evaluation of Trizytek in the treatment of protein and carbohydrate absorption through measurement of CNA and use of the starch challenge test and in decreasing the weight and frequency of stools in patients. In the trial, we are also evaluating the safety and tolerability of Trizytek over an approximate two month dosing period.

The Phase III efficacy trial is designed to evaluate approximately 150 cystic fibrosis patients over the age of seven with exocrine pancreatic insufficiency at cystic fibrosis centers primarily in the United States, Europe and South America. This sample size is designed to allow demonstration of improvements in CFA in the overall study population, as well as in the subgroups of patients with off-enzyme, baseline CFAs of less than 40% and greater than or equal to 40%. Patients with baseline CFAs of greater than 80% are excluded from the trial. At the beginning of the trial, we obtain baseline measurements of fat, protein and carbohydrate absorption during a hospital stay of up to one week. This hospital stay begins with a 48-hour wash-out period during which the patient does not receive any enzyme replacement therapy. We then assess fat and protein absorption during a 72-hour, controlled, high-fat diet by examining stools collected from patients. We are using a similar high-fat diet and stool collection process as we used in our Phase II trial. The timing of the stool collection as well as the amount of stool collected is determined using a blue dye stool marker, which facilitates accurate and complete stool collection. Changes in carbohydrate absorption are determined by measuring blood glucose responses using the starch challenge test.

After the baseline period is complete, patients are released from the hospital and placed on open-label therapy with Trizytek. All of the patients in the trial take one capsule of Trizytek containing 32,500 units of lipase, 25,000 units of protease and 3,750 units of amylase with each meal or snack for approximately four weeks. The selected dose of lipase, protease and amylase is consistent with the middle dose in our Phase II clinical trial. After this four-week period, patients return to the hospital for up to one week for a second in-hospital stay. During this hospital stay, patients are randomized on a one-to-one basis, and stratified based on whether their baseline measurements of CFA place them in the subgroup of patients having absorption of less than 40% or the subgroup of patients having absorption of greater than or equal to 40% but not more than 80% to receive either Trizytek or placebo. Fat, protein and carbohydrate absorption are measured using the same process that was used to establish the baseline level during the first in-hospital stay. A comparison of each patient s measurements during the two in-hospital periods is performed in the analysis of the endpoints for the trial. After the second in-hospital stay, patients return to open-label therapy with Trizytek for one week to complete the study. We expect to complete the efficacy trial in the second quarter of 2008 and report top-line efficacy trial results in the third quarter of 2008.

Long-Term Safety Studies

We have initiated two clinical studies evaluating the long-term safety of Trizytek. One study is being conducted in cystic fibrosis patients and one study is being conducted in chronic pancreatitis patients with exocrine pancreatic insufficiency. The studies are designed to evaluate the safety of Trizytek following one

Table of Contents

year of open-label treatment in order to provide the necessary six-month and 12-month exposure data for approval of an NDA. Based on our discussions with the FDA, we expect that the initial NDA filing for Trizytek will be required to include 12-month safety data. We plan to enroll a total of approximately 240 patients with pancreatic insufficiency into the two studies, which will include some of the eligible patients from our Phase III efficacy trial of Trizytek. The safety of Trizytek will be evaluated based on adverse events, physical examinations, vital signs and standard clinical laboratory testing during the one-year study period.

ALTU-238 for Growth Hormone Deficiency and Related Disorders

ALTU-238 is a crystallized formulation of hGH that is designed to be administered once weekly through a fine-gauge needle for the treatment of hGH disorders in both pediatric and adult populations. Based on reported revenues of existing products, these indications generated approximately $2.8 billion in worldwide sales of hGH in 2006, and the market grew at a compound annual growth rate of approximately 16% from 2003 to 2006. We are developing ALTU-238 as a long-acting, growth hormone product that can allow patients to avoid the inconvenience of daily injections as recommended by current medical guidelines for existing products. We have used our proprietary protein crystallization technology and formulation expertise to develop ALTU-238 without altering the underlying molecule or requiring polymer encapsulation. Since hGH is a known protein molecule with an established record of safety and efficacy, we believe that ALTU-238 may have less development risk than most pharmaceutical product candidates at a similar stage of development.

We have successfully completed two clinical trials of ALTU-238, a Phase I trial in healthy adults and a Phase II trial in growth hormone deficient adults. Both trials were designed to determine the safety, pharmacokinetics and pharmacodynamics of ALTU-238. Pharmacokinetics refers to the process by which a drug is absorbed, distributed, metabolized and eliminated by the body. Pharmacodynamics refers to the process by which a drug exerts its biological effect. In the Phase II trial, ALTU-238 demonstrated a pharmacokinetic and pharmacodynamic profile that we believe is supportive of a once-per-week dosing regimen for growth hormone deficient adults. The study identified doses of ALTU-238 that maintained IGF-1 levels within the normal range for age and gender over the course of the study. IGF-1 is a naturally occurring hormone that stimulates the growth of bone, muscle and other body tissues in response to hGH and, in turn, regulates hGH release from the pituitary gland. The study also indicated that once-per-week dosing of ALTU-238 appeared to result in a consistent, linear dose response of hGH and IGF-1 levels in the blood. ALTU-238 was generally well tolerated, and there were no serious adverse events reported in either study.

In December 2006, we entered into a Collaboration and License Agreement with Genentech relating to the development, manufacture and commercialization of ALTU-238 and other pharmaceutical products containing crystallized hGH using our proprietary technology. The Collaboration and License Agreement covered development and commercialization rights in North America. Genentech had an option to extend the collaboration globally by providing notice to us within a specified timeframe. In consideration of the rights granted to Genentech under the agreement, Genentech paid us $15.0 million. In connection with the agreement, Genentech also purchased 794,575 shares of our common stock on February 27, 2007 for an aggregate purchase price of $15.0 million.

On December 19, 2007, Genentech and we entered into an agreement terminating the collaboration effective December 31, 2007. Under the termination agreement, we reacquired the North American development and commercialization rights to ALTU-238, and the option to expand the agreement to a global agreement expired unexercised. In addition, Genentech agreed to provide, for a limited time, supplies of hGH for future ALTU-238 clinical development in North America and for clinical development and commercial purposes outside North America and to pay us a $4.0 million termination payment to fund the transition of the project back to us. During the period of the collaboration, we incurred $10.1 million of costs relating to the development of ALTU-238 which were paid or estimated to be due to us by Genentech. Upon commercialization, Genentech will be entitled to a nominal royalty on sales of ALTU-238. Our goal is to resume the clinical program for ALTU-238 in mid-2008.

17

Table of Contents

Disease Background, Market Opportunity and Limitations of Existing Products

Growth hormone, which is secreted by the pituitary gland, is the major regulator of growth in the body. Growth hormone directly stimulates the areas of bones known as epiphyseal growth plates, which are responsible for bone elongation and growth. Growth hormone also causes growth indirectly by triggering the release of insulin-like growth factor 1, or IGF-1, from tissues throughout the body. In addition, growth hormone contributes to proper bone density and plays an important role in various metabolic functions, including lipid breakdown, protein synthesis and insulin regulation.

Growth hormone deficiency typically results from an abnormality within the pituitary gland that impairs its ability to produce or secrete growth hormone. A deficiency of growth hormone can result in reduced growth in children and lead to short stature. Because the growth plates in the long bones fuse and additional cartilage and bone growth can no longer occur after puberty, hGH replacement therapy does not cause growth in adults. However, low levels of hGH in adults are also frequently associated with other metabolic disorders, including lipid abnormalities, decreased bone density, obesity, insulin resistance, decreased cardiac performance and decreased muscle mass. These disorders typically become increasingly apparent after a prolonged period of hGH deficiency, as occurs in adulthood.

Patients with growth hormone deficiency are typically treated with growth hormone replacement therapy. Growth hormone is also prescribed for many patients suffering from a range of other diseases or disorders, including pediatric growth hormone deficiency, adult growth hormone deficiency, being small for gestational age and idiopathic short stature in children. According to industry estimates:

1 in 3,500 children suffer from growth hormone deficiency;

1 in 10,000 adults suffer from growth hormone deficiency;

between 3% and 10% of births annually are small for gestational age; and

between 2% and 3% of children are affected by idiopathic short stature.

Growth hormone is also used to treat Turner Syndrome, Prader Willi Syndrome and short bowel syndrome. The percentage of patients for whom hGH is prescribed varies significantly by indication. We believe that a once-weekly formulation of hGH, such as ALTU-238, may result in increased use in a number of these indications.

Currently, many of the FDA-approved hGH products are also in clinical development for additional indications, including Crohn s disease, female infertility, bone regeneration and a variety of other genetic and metabolic disorders. There are currently ten FDA-approved hGH products on the market in the United States from eight manufacturers, all of which use essentially the same underlying hGH molecule. Current medical guidelines for clinical practice generally recommend daily administration of existing products by subcutaneous injection. We believe that the primary differences between these products relate to their formulation and the devices employed for their delivery.

We believe that the burden of frequent injections significantly impacts quality of life for both adults and children being treated with hGH therapy and often leads to reduced compliance or a reluctance to initiate therapy. For example, we estimate that a standard course of treatment for pediatric growth hormone deficient patients typically lasts approximately six years and requires more than 1,800 injections. Faced with this protracted treatment regime, pediatric patients often take days off and miss treatment. For adults with growth hormone deficiency, the benefits of hGH treatment are more subtle and relate to metabolic function and organ health instead of increased height. As a consequence, and in contrast to hGH deficient children, many adults with growth hormone deficiency do not initiate hGH therapy, and of those who do, many fail to continue treatment.

Table of Contents

Anticipated Advantages of ALTU-238

We expect that ALTU-238, if approved, will offer patients a more convenient and effective long-term therapy because of the following features:

Convenience of once-weekly dosing. Based on the results of our Phase I and Phase II clinical trials, we believe that ALTU-238 will offer growth hormone deficient patients the convenience of a once-weekly injection. We believe this will improve compliance and thereby increase long-term effectiveness of therapy and potentially expand the market.

Administration with a fine gauge needle. ALTU-238 is designed to provide extended release without changing the chemical structure of the hGH molecules or using polymers to encapsulate the component hGH molecules. To date, there has not been an hGH therapy approved by the FDA for administration once per week. The only hGH therapy approved by the FDA for administration less frequently than once per week was withdrawn from the market and required polymeric encapsulation for its extended release formulation. This necessitated the use of a substantially larger needle and prolonged injection time. We have designed ALTU-238 using our protein crystallization technology so that, as the crystals dissolve, the hGH is released over an extended period. This allows ALTU-238 to be administered with a 29 or 30 gauge, insulin-like needle.

In addition, we have designed ALTU-238 to be manufactured using well-established equipment and processes consistent with other injectable protein products. We believe this will provide flexibility in the scale-up and commercial production of ALTU-238, if approved.

ALTU-238 Development Activities and Strategy

We have completed a Phase I clinical trial of ALTU-238 in healthy adults and a Phase II clinical trial in adults with growth hormone deficiency. The results of the completed trials are summarized in the tables below. Based on the results of these trials, we are planning a Phase Ic trial, which is intended to be a bridging study to confirm that our scaled-up manufacturing process produces crystallized growth hormone material that performs similarly to our ALTU-238 Phase I and Phase II clinical trial material. We believe that this study should confirm equivalence because we believe our technology does not alter the underlying human growth hormone. After the Phase Ic trial, we plan to advance ALTU-238 into a Phase II trial and then a Phase III clinical trial in growth hormone deficient children, as well as a Phase III clinical trial in growth hormone deficient adults.

Phase I Clinical Trial

In our Phase I clinical trial, we evaluated the safety, tolerability and the pharmacokinetic and pharmacodynamic profile of ALTU-238 in healthy adults. The following is a summary of our Phase I clinical trial for ALTU-238:

Table of Contents

ALTU-238 Phase I Clinical Trial Summary

Title	A Single Blind, Single Dose, Randomized, Placebo-Controlled, Parallel Group Study of ALTU-238 in Normal Healthy Adults to Determine Pharmacokinetics, Pharmacodynamics and Drug Safety
Design	Forty-five subjects received one of the following treatment regimens: a single injection of ALTU-238 at a dose of 2.8 mg, 8.4 mg or 16.8 mg of hGH, administered to 6 subjects at each dose; a single injection of ALTU-238 at a dose of 24.5 mg of hGH administered to 7 subjects; 7 daily injections of Nutropin AQ, a daily, FDA-approved hGH product, at a dose of 2.4 mg of hGH, administered to 6 subjects; a single injection of Nutropin AQ at a dose of 3.5 mg of hGH, administered to 6 subjects; and a single injection of placebo, administered to 8 subjects.
Administration	Each regimen was administered to patients as a subcutaneous injection.
Safety Results	ALTU-238 was generally well tolerated and easily administered through 29 and 30 gauge needles. There were no serious adverse events reported in the clinical trial, and the percentage of subjects who experienced adverse events was comparable among treatment groups. Subjects across all treatment groups, including subjects receiving Nutropin AQ and placebo, experienced injection site reactions, the most common of which were redness, hardening of the skin and swelling.
Clinical Activity Results	We observed a dose-dependent rise in hGH and IGF-1 concentrations following a single dose of ALTU-238. The pharmacokinetic profile of ALTU-238 at a dose of 16.8 mg indicated that the maximum concentration of hGH in the blood was achieved in approximately 51 hours and was less than the maximum concentration of hGH in the blood from a daily dose of 2.4 mg of Nutropin AQ. The IGF-1 pharmacodynamic profile over a seven-day period after a single injection of ALTU-238 at a dose of 16.8 mg was comparable to that observed with the same aggregate amount of hGH delivered through seven daily injections of Nutropin AQ.

Phase II Clinical Trial

In our Phase II clinical trial, we evaluated ALTU-238 in adults with growth hormone deficiency. The primary objective of the trial was to determine the safety and tolerability of ALTU-238, as well as its pharmacokinetic and pharmacodynamic profile, when administered over a three-week period. The goal of the pharmacokinetic and pharmacodynamic analyses was to confirm the once weekly dosing profile of ALTU-238 in growth hormone deficient adults. The following is a summary of our Phase II clinical trial:

Table of Contents

ALTU-238 Phase II Clinical Trial Summary

Title	A Phase II, Multi-Center, Multi-Dose, Randomized, Open-Label, Parallel Group Study of Extended Release Crystalline Formulation of Recombinant Human Growth Hormone
Design	Growth hormone deficient men and women between the ages of 16 and 60 were randomized to receive either 5.6 mg of ALTU-238 or 11.2 mg of ALTU-238 administered in three weekly subcutaneous injections. Enrollment for the study was planned for a minimum of 12 patients with a maximum of 20 patients, including at least 4 patients in the 5.6 mg dose group and at least 6 patients in the 11.2 mg dose group. A total of 13 patients were enrolled and analyzed for safety (6 patients in the 5.6 mg group and 7 patients in the 11.2 mg group); and 11 of these patients were analyzed for the pharmacokinetics and pharmacodynamics of ALTU-238 at the end of the first week, and 10 of these patients were analyzed for the pharmacokinetics and pharmacodynamics of ALTU-238 at the end of the third week. The patients who were enrolled but not analyzed were disqualified due to documentation issues.
Administration	For each dose level, three injections of ALTU-238 were administered as subcutaneous injections one week apart.
Safety Results	ALTU-238 was generally well tolerated. There were no serious adverse events, and no patients were discontinued due to an adverse event. The majority of adverse events were considered mild or moderate in severity. There was no apparent dose-related difference between the treatment groups for the overall reporting of adverse events. Mild to moderate injection site reactions were common. We also observed changes in serum insulin and glucose, which were expected following administration of growth hormone.
Clinical Activity Results	ALTU-238, administered through a subcutaneous injection, produced hGH and IGF-1 concentrations in the blood that support a once-per-week dosing regimen. A dose response was observed for both the maximum concentration and the total concentration for hGH and IGF-1 in the blood between the 5.6 mg and 11.2 mg dose levels. As a result, we believe the dose to patients can be adjusted without causing unexpectedly large changes in blood levels of either hGH or IGF-1. In addition, the IGF-1 profiles of the patients were relatively unchanged following 3 weekly injections, indicating that maximum IGF-1 concentration levels will be maintained in a consistent range following repeated weekly dosing with ALTU-238.

The pharmacokinetic and pharmacodynamic results from the Phase II clinical trial confirmed our view as to the appropriateness of once weekly dosing of ALTU-238 in adults with growth hormone deficiency and we believe that ALTU-238, if approved, can be administered once weekly.

Future Clinical Development

We have met with the FDA and EMEA to discuss the results of our Phase I and II clinical trials and future clinical development of ALTU-238 in growth hormone deficient adults in pediatric patients.

ALTU-237 for Treatment of Hyperoxalurias and Kidney Stones

ALTU-237 is an orally-administered crystalline formulation of an oxalate-degrading enzyme which we have designed for the treatment of hyperoxalurias including primary hyperoxaluria, enteric hyperoxaluria and kidney stones in individuals with a risk or history of recurrent kidney stones. Currently, there are limited effective pharmacological treatments for primary hyperoxaluria, enteric hyperoxaluria or recurrent kidney stones. We are currently conducting a Phase I clinical trial for ALTU-237.

Hyperoxalurias are a series of conditions where too much oxalate is present in the body resulting in an increased risk of kidney stones and, in rare instances, crystal formations in other organs. Increased oxalate in

Table of Contents

the body can result from eating foods that are high in oxalate, over-absorption of oxalate from the intestinal tract, and abnormalities of oxalate production by the body. Oxalate is a natural end-product of metabolism, does not appear to be needed for any human body process and is normally more than 90% excreted by the kidney. Since calcium is also continuously excreted by the kidney into the urine, oxalate can combine with calcium, causing formations of calcium-oxalate crystals which can grow into a kidney stone. In preclinical studies using rodent models, ALTU-237, delivered orally, demonstrated an ability to reduce oxalate levels in urine. We believe that reducing oxalate levels in urine may be indicative of a reduction of oxalate in the body and therefore may result in a decrease in kidney stones.

Over-absorption of oxalate from the intestinal tract, or enteric hyperoxaluria, is often associated with intestinal diseases such as inflammatory bowel disease and cystic fibrosis, or may occur in patients following gastric bypass surgery. Primary hyperoxaluria is a rare, inherited and, if left untreated, fatal metabolic disease that results in the accumulation of oxalate in the body. Although there are variations in the disease, primary hyperoxaluria is characterized by the shortage of an enzyme in the liver, which results in excess levels of oxalate production in the body. Unfortunately, oxalate cannot be further metabolized, and it can only be eliminated from the body by the kidney, leading to an increase in urinary excretion, and causing hyperoxaluria. Based on prevalence data from an industry article, we estimate that between 1-in-60,000 and 1-in-120,000 children in North America and Europe are born with primary hyperoxaluria.

According to the National Kidney Foundation, kidney stone disease is a common disorder of the urinary tract affecting approximately 20 million Americans. According to Disease Management, between 70% and 75% of kidney stones are composed of calcium oxalate crystals and up to 50% of patients who do not follow recommended guidelines will suffer from a repeated kidney stone incident within five years of their initial incident. According to the National Kidney and Urologic Diseases Information Clearinghouse, in 2000, kidney stones led to approximately 600,000 emergency room visits.

Preclinical Results

In a series of preclinical studies using rodent models, ALTU-237, delivered orally, demonstrated an ability to reduce oxalate levels in urine. One such study was designed to measure the impact of ALTU-237 on the reduction of hyperoxaluria in a genetic mouse model for primary hyperoxaluria. In this study, the mice were further challenged with ethylene glycol to mimic the human disease, which involves nephrocalcinosis, renal failure and potentially death. The four week study included 44 mice that received one of the following treatment regimens:

5mg, 25mg, or 80mg of ALTU-237 was orally administered to 11 mice at each dose

11 mice received no treatment and served as a control group

In the study, ALTU-237 therapy resulted in a sustained reduction of urinary oxalate levels as evidenced by a reduction in urinary oxalate of 30 to 50 percent in all treatment groups as compared to the control group. In addition, a reduction in nephrocalcinosis and an increase in survival rate was observed in mice in the two lower dose groups and there was no nephrocalcinosis, renal failure or death in any mouse in the high dose group.

Based in part on these results, we believe ALTU-237 could be the first effective oral therapeutic agent specifically designed to reduce oxalate levels and prevent the formation of kidney stones. Furthermore, we believe that these results suggest that we may be able to use our proprietary protein crystallization technology to orally deliver enzymes to the gastrointestinal tract, where they can exert a therapeutic effect by drawing out toxic metabolites from the body. This therapeutic approach is currently utilized by some existing drugs. For example, Renagel, marketed by Genzyme Corporation, removes excess levels of phosphate in the body in patients with chronic kidney disease by delivering drug to the gastrointestinal tract, where it binds to the phosphate and removes it from the body. If we are successful in

our design of ALTU-237, we believe that this program will provide a template for our other research and preclinical programs that are based on the same mechanism of action.

Table of Contents

Phase I Clinical Trial

In the third quarter of 2007, we initiated a Phase I clinical trial of ALTU-237, which is titled A Phase I, Single-Center, Double-blind, Placebo-Controlled, Dose Escalating Study Evaluating the Safety and Clinical Activity of ALTU-237 in Normal Healthy Adults on a Controlled, High Oxalate Diet. The primary objective of this trial is to determine the safety and tolerability of escalating dose levels of ALTU-237 in normal healthy adults. Secondary objectives are to determine the clinical activity of escalating dose levels of ALTU-237, as measured by changes in urinary oxalate level in normal healthy adults on a controlled, high oxalate diet, and to identify a dose of ALTU-237 for future studies based on safety and clinical activity.

The study enrolled approximately 60 normal healthy adults that are being randomized into four cohorts. During a baseline period, subjects in each cohort consume a low oxalate, high calcium diet to establish a consistent, low urinary oxalate baseline level prior to treatment. After the baseline period, subjects are randomized at a 3:1 ratio to receive either ALTU-237 or placebo during a seven day, double blind treatment period. During this treatment period, subjects consume a high oxalate, low calcium diet. Dose escalation proceeds to the next higher dose only after the safety and tolerability of the lower dose is assessed. Safety assessments are performed throughout the study period and include physical examination, AE assessment, standard clinical laboratory testing (hematology, serum chemistry, coagulation and urine analysis), vital signs measurements, electrocardiogram testing, and concomitant medication assessment.

In addition to evaluating the safety of ALTU-237, we expect the trial to provide important information on the clinical activity of the product candidate. We also expect the broad range of doses to provide valuable information on the dose levels for future trials. We will evaluate clinical activity by examining oxalate excretion levels and the occurrence of crystals in urine. Finally, we will evaluate and compare the levels of oxalate in the urine of subjects from before and after they take ALTU-237, and we will make comparisons of these levels between the cohorts.

Our Preclinical Research and Development Programs

We are currently developing a pipeline of preclinical product candidates that are designed to either substitute protein that is in short supply in the body or degrade the toxic metabolites in the gut and remove them from the blood stream. We are developing all of these product candidates for oral delivery to address areas of unmet need in gastrointestinal and metabolic disorders, including an enzyme that degrades phenylalanine for the treatment of phenylketonuria and an enzyme that degrades urate for the treatment of gout. We believe that our proprietary, crystallized formulations of these product candidates will represent novel or improved therapies for the treatment of these disorders. Our two most advanced preclinical product candidates are described below.

ALTU-236 for Treatment of Hyperphenylalanemia

We are developing ALTU-236, an orally-administered enzyme replacement therapy designed to reduce the long-term effects associated with excess levels of phenylalanine, also known as hyperphenylalanemia. According to the National Institutes of Health, phenylketonuria, or PKU, which is the most severe form of hyperphenylalanemia, affects approximately 1-in-15,000 newborns in the United States. PKU is a rare, inherited, metabolic disorder that results from an enzyme deficiency that causes the accumulation of the amino acid phenylalanine in the body. If left untreated, PKU can result in mental retardation, swelling of the brain, delayed speech, seizures and behavior abnormalities. Virtually all newborns in the United States and in many other countries are screened prior to leaving the hospital for PKU. There is currently one approved drug to treat certain patients with PKU. However, the majority of patients suffering from PKU and hyperphenylalanemia are currently treated with a phenylalanine restricted diet. This diet is expensive and difficult to maintain and does not avoid many of the long-term effects of PKU. We are currently testing ALTU-236 in animal models.

Table of Contents

ALTU-242 for Treatment of Gout

We are also developing ALTU-242, an orally-administered enzyme designed to reduce the long-term effects associated with excess levels of urate, the cause of gout. Excess levels of urate can precipitate and form crystals in joints causing a painful erosive arthritis commonly referred to as gout. Gout is a common disorder that affects at least 1% of the population in Western countries and is the most common inflammatory joint disease in men older than 40 years of age. We are currently testing ALTU- 242 in animal models. According to Ingenix, a division of United Healthcare, and based on incidence data extrapolated to the U.S. population, there are more than 1.6 million diagnoses of gout in the United States annually.

Our Protein Crystallization Technology and Approach

Historically, scientists have crystallized proteins primarily for use in x-ray crystallography to examine the structure of proteins in small batches. In contrast, we are using our technology to crystallize proteins in significantly larger amounts for use as therapeutic drugs. This requires the crystallization process to be both reproducible and scalable, and our technology is designed to enable large scale crystallization with batch-to-batch consistency.

Crystallized proteins are more stable, pure and concentrated than proteins in solution. For example, one protein crystal may contain several billion molecules of the underlying protein. We believe that these characteristics will enable improved storage and delivery, permitting delivery of the protein molecules with fewer capsules or smaller injection volumes.

Once a protein is in the crystallized state, we formulate it for either oral or injectable delivery. For our product candidates that will be delivered orally, we use our crystallization technology to deliver proteins to the gastrointestinal tract, where they can exert their therapeutic effect locally. In situations where we need to confer a higher level of stability to a protein, such as in the lipase component of Trizytek, we cross-link protein molecules in crystals together using multi-functional cross-linking agents. For our product candidates that are injected, we use our crystallization technology to develop highly concentrated and stable proteins that can be formulated for extended release.

Our approach to developing therapeutic product candidates using crystallized proteins is comprised of the following general elements:

Establish initial crystallization conditions. Once we choose a target protein, we rapidly screen hundreds of crystallization conditions both manually and using robotics. We define the conditions under which a soluble protein could crystallize, including protein concentration, pH and temperature of crystallization.

Identify key crystallization conditions and initial crystallization scale up. After we identify the initial conditions, we focus on the critical crystallization conditions to define a robust and reproducible crystallization process. We then scale the process from single drops, to microliter scale, to milliliter scale, and finally, to liter scale.

Select crystallization process and crystal. If there is more than one successful crystallization process and resulting crystals, we use our target product profile to choose the best protein crystal for the given application based on crystal size, shape and other characteristics.

We apply our proprietary protein crystallization technology to existing, well-understood proteins in the development of our product candidates. We believe our technology is broadly applicable to all classes of proteins, including enzymes, hormones, antibodies, cytokines and peptides. To date, we have crystallized more than 70 proteins for evaluation in our product candidates and preclinical research and development programs.

Table of Contents

Collaborations

Cystic Fibrosis Foundation Therapeutics, Inc.

In February 2001, we entered into a strategic alliance agreement with CFFTI, an affiliate of the Cystic Fibrosis Foundation. Under this agreement, which was amended in 2001 and 2003, we and CFFTI have agreed to collaborate for the development of Trizytek and specified derivatives of Trizytek in North America for the treatment of malabsorption due to exocrine pancreatic insufficiency in patients with cystic fibrosis and other indications. The agreement, in general terms, provides us with funding from CFFTI for a portion of the development costs of Trizytek upon the achievement of specified development and regulatory milestones, up to a total of $25.0 million, in return for specified payment obligations described below and our obligation to use commercially reasonable efforts to develop and bring Trizytek to market in North America for the treatment of malabsorption due to exocrine pancreatic insufficiency in patients with cystic fibrosis and other indications. CFFTI has also agreed to provide us with reasonable access to its network of medical providers, patients, researchers and others involved in the care and treatment of cystic fibrosis patients, and to use reasonable efforts to promote the involvement of these parties in the development of Trizytek. In connection with the agreement, we also issued CFFTI warrants to purchase a total of 261,664 shares of common stock at an exercise price of $0.02 per share. We believe that our relationship with the Cystic Fibrosis Foundation will help facilitate our development of Trizytek.

As of December 31, 2007, we had received a total of $18.4 million of the $25.0 million available under the agreement. In addition, we may receive an additional milestone payment of $6.6 million, less an amount determined by when we achieve the milestone. The alliance is managed by a steering committee, comprised of an equal number of representatives from us and CFFTI, which generally oversees the progress of our clinical development of Trizytek and reviews the schedule and achievement of milestones under our agreement.

Under the terms of the agreement, we granted CFFTI an exclusive license under our intellectual property rights covering Trizytek and specified derivatives for use in all applications and indications in North America, and CFFTI granted us back an exclusive sublicense of the same scope, including the right to grant further sublicenses. Our exclusive license to CFFTI continues in effect until the earliest to occur of our payment in full of all license fees due under the agreement, as described below; our termination of the agreement on account of a material default or bankruptcy of CFFTI; the parties mutual agreement not to proceed with development following a deadlock of the alliance steering committee; or the alliance steering committee s determination that Trizytek is not safe or effective for the treatment of exocrine pancreatic insufficiency; or, solely due to scientific or medical reasons, that Trizytek should not be developed or marketed.

Our exclusive sublicense from CFFTI continues in effect until our license to CFFTI terminates or CFFTI terminates the agreement on account of our failure to meet specified milestones, our determination not to continue development after an unresolved deadlock of the alliance steering committee, or our material default or bankruptcy. If CFFTI terminates the agreement due to our breach, it would retain its exclusive license to Trizytek and our sublicense from CFFTI would terminate. Upon termination of the agreement by us due to a breach by CFFTI, the license granted to CFFTI by us to Trizytek will terminate.

If Trizytek is approved by the FDA, we are obligated to pay CFFTI a license fee equal to the aggregate amount of milestone payments we have received from CFFTI, plus interest, up to a maximum of $40.0 million, less the fair market value at the time of approval of the shares of stock underlying the warrants we issued to CFFTI. This fee, together with accrued interest, will be due in four annual installments, commencing 30 days after the approval date. We are required to pay an additional $1.5 million to CFFTI within 30 days after the approval date. In addition, we are obligated to pay royalties to CFFTI on worldwide net sales by us or our sublicensees of Trizytek for any and all indications until the expiration of specified United States patents covering Trizytek. We have the option to terminate

our ongoing royalty obligation by making a one-time payment to CFFTI, but we currently do not expect to do so. We are also required to pursue, prosecute, maintain and defend all patents covered by the agreement at our own expense.

Table of Contents

Dr. Falk Pharma GmbH

In December 2002, we entered into a development, commercialization and marketing agreement with Dr. Falk Pharma GmbH, or Dr. Falk, for the development by us of Trizytek and the commercialization by Dr. Falk of Trizytek, if approved, in Europe, the countries of the former Soviet Union, Israel and Egypt. Under the agreement, we granted Dr. Falk an exclusive, sublicensable license under specified patents that cover Trizytek to commercialize Trizytek for the treatment of symptoms caused by exocrine pancreatic insufficiency.

In June 2007, we reacquired from Dr. Falk the development and commercialization rights to Trizytek and ended the development and commercialization collaboration in Europe and countries of the former Soviet Union, Israel and Egypt. Dr. Falk and we had differing views regarding the optimal development and commercialization path for Trizytek, and ultimately concluded that acquisition of the development and commercialization rights by us would be in the best interest of both parties.

Under the termination agreement, we regained control of all of the assets created in the collaboration. In addition, Dr. Falk has agreed to transfer the July 2004 Orphan Medicinal Product Designation granted to Dr. Falk by the European Agency for the Evaluation of Medicinal Products. In exchange, we will pay Dr. Falk 12.0 million over three years. As of the termination of the collaboration agreement, we had received a total of 11 million in milestone payments from Dr. Falk. Had we continued the collaboration with Dr. Falk, we could have received an additional 15 million in potential milestone payments based upon the achievement of specified clinical and regulatory milestones, and we would have had the right to receive royalties on net sales of Trizytek by Dr. Falk and to supply bulk capsules of Trizytek to Dr. Falk.

Genentech, Inc.

In December 2006, we entered into a collaboration and license agreement with Genentech relating to the development, manufacture and commercialization of ALTU-238 and other pharmaceutical products containing crystallized hGH using our proprietary technology. The collaboration and license agreement covered development and commercialization rights for ALTU-238 in North America. Genentech had an option to extend the collaboration globally by providing notice to us within a specified timeframe. In consideration of the rights granted to Genentech under the agreement, Genentech paid us $15.0 million. In connection with the agreement, Genentech also purchased 794,575 shares of our common stock on February 27, 2007 for an aggregate purchase price of $15.0 million.

On December 19, 2007, Genentech and we entered into an agreement terminating the collaboration effective December 31, 2007. Under the termination agreement, we reacquired the North American development and commercialization rights to ALTU-238, and the option to expand the agreement to a global agreement expired unexercised. In addition, Genentech agreed to provide, for a limited time, supplies of hGH for future ALTU-238 clinical development in North America and for clinical development and commercial purposes outside North America and to pay us a $4.0 million termination payment to fund the transition of the project back to us. During the period of the collaboration, we incurred $10.1 million of costs relating to the development of ALTU-238 which were paid or estimated to be due to us by Genentech. Upon commercialization, Genentech will be entitled to a nominal royalty on sales of ALTU-238. Our goal is to resume ALTU-238 clinical trials by mid-2008.

Manufacturing

We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of any of our product candidates. We currently have no plans to build our own clinical- or commercial-scale manufacturing capabilities, and we expect for the foreseeable future to rely on contract manufacturers for both clinical and commercial supplies of our products. Although we rely on contract manufacturers, we have personnel with

manufacturing experience to oversee the relationships with our contract manufacturers.

Table of Contents

Amano

Amano Enzyme, Inc., or Amano, manufactures our clinical supplies of the crystallized and cross-linked lipase, the crystallized protease, and the amylase enzymes that comprise the active pharmaceutical ingredients, or APIs, for Trizytek.

Amano has built a plant near Nagoya, Japan to produce the enzymes for Trizytek in large-scale batches using microbial fermentation. The plant has not been inspected or approved by the FDA, EMEA or the Japanese Ministry of Health, Labour and Welfare. Amano has supplied the APIs for Trizytek for our non-clinical and clinical trials to date and has agreed to supply us with APIs for our Phase III clinical trial and additional toxicology studies at a specified transfer price. We use a third party, Patheon Inc., to perform fill, finish and packaging services for Trizytek.

Under the terms of our original agreement with Amano, each party contributed technology used for the production of the APIs in Trizytek. Each party owns intellectual property created solely by it, and jointly owns any intellectual property created jointly. In connection with our entry into the agreement with Lonza Ltd., or Lonza, described below, Amano has agreed to transfer technology relating to Trizytek to Lonza.

On December 20, 2007, we and Amano entered into an additional agreement. Under this agreement, Amano granted to us a royalty-bearing license to technology owned by Amano to manufacture proteins in bulk form for use by us in preparing the supply of Trizytek for clinical and commercial purposes. The agreement grants to Amano an option to supply a portion of our requirements for such proteins for clinical and commercial purposes. The agreement also provides that Amano will provide regulatory, technology transfer and other support to us in connection with the development and registration of Trizytek. Under our agreements, Amano may not sell the APIs used in Trizytek to third parties for use in specified competitive products.

Lonza

In November 2006, we entered into a six-year manufacturing and supply agreement with Lonza for the manufacturing and supply of commercial quantities of the crystallized and cross-linked lipase, the crystallized protease and the amylase enzymes that comprise the APIs for Trizytek. This agreement provides for the transfer of manufacturing technology to Lonza, the installation of specialized manufacturing equipment for the manufacturing process, the validation of the manufacturing facility, and the supply of these enzymes for commercial purposes. We plan to continue to use a third party to perform fill, finish and packaging services for the commercial supply of Trizytek.

Under the agreement, Lonza has agreed to manufacture the APIs in accordance with defined specifications and applicable cGMP and international regulatory requirements. Subject to customary notice, reservation and forecasting procedures, Lonza has agreed to reserve capacity at its facility for supply of the APIs that we believe will meet our needs for APIs for use in the commercial launch of Trizytek. We must provide binding purchase orders to Lonza annually, and we have committed to purchase a specified number of batches, and a specified percentage of our requirements, from Lonza during specified periods. However, if Lonza is unable to meet specified production and delivery requirements, we have the right to reduce payments or engage third-party suppliers, depending on the extent of the shortfall. If Lonza builds or acquires more capacity that is appropriate for the manufacture of the APIs, we agreed to use commercially reasonable efforts to purchase additional batches of the APIs from Lonza.

The agreement is subject to automatic renewal at the expiration of its six-year term for successive two year terms unless we provide Lonza with notice prior to expiration of each term of our decision to terminate. Each party has the right to terminate the agreement upon the occurrence of an uncured material breach or the bankruptcy of the other party. We have the right to terminate the agreement in the event that we cease development or commercialization of Trizytek due to toxicity, efficacy or other technical or business considerations, in which case we must make a payment

to Lonza if we have not already purchased from Lonza a specified value of APIs. Lonza has the right to terminate the agreement in the event that we do not order a defined quantity of enzymes for delivery from the capacity reserved for us by Lonza for the production of

Table of Contents

Trizytek. Lonza also has the right to terminate the agreement if we fail to arrange for the delivery of certain materials and technology that are necessary for Lonza to manufacture the enzymes in accordance with the specifications for production.

ALTU-238

Prior to entering into the Genentech collaboration, we purchased hGH from Sandoz GmbH, or Sandoz, a subsidiary of Novartis AG. However, under the termination agreement with Genentech, Genentech agreed to supply the hGH for the continued clinical development of ALTU-238 in North America and for clinical development and commercial purposes outside North America for a limited period of time. We are currently evaluating sources for a long term hGH supply.

We have completed small-scale cGMP runs of ALTU-238 at a contract manufacturer for our completed Phase I and II clinical trials. However, we will need to produce ALTU-238 for our future clinical trials at a larger scale. To do so, we entered into a drug production and clinical supply agreement with Althea Technologies, Inc., or Althea, in August 2006. Under this agreement, Althea has agreed to modify an existing production facility, and test and validate its manufacturing operations for the production of ALTU-238. Althea initiated the testing and validation of the facility in 2007 and we expect to complete validation and produce ALTU-238 for our future clinical trials in the first half of 2008. The agreement terminates following the production of a defined number of manufacturing runs of ALTU-238, from which we intend to supply planned clinical trials. The agreement is subject to early termination by either party in the event of an uncured material breach by or bankruptcy of the other party. Althea s liability to us for any breach of the agreement is limited to an obligation to replace those products which do not conform to requirements.

In addition, we and Althea have agreed to negotiate an agreement under which Althea will provide ALTU-238 for commercial supply. Alternatively, if within one year after the termination or expiration of the agreement, other than a termination due to Althea s uncured breach, we enter into an agreement with a third party to provide commercial supply of ALTU-238, we must make a one-time payment to Althea.

Sales and Marketing

We periodically review our product candidates to determine the most appropriate commercialization strategy for each product candidate. If we receive regulatory approval for any of our product candidates that we believe we can effectively commercialize ourselves, we would build a focused sales and marketing organization in order to commercialize those product candidates. Our sales and marketing strategy is comprised of the following elements:

Build our own North American sales force. We plan to establish a commercial infrastructure and targeted specialty sales force to market our product candidates in North America. Our sales efforts for Trizytek, if approved, will initially be focused on the 500 pediatric pulmonologists who are in approximately 100 cystic fibrosis care centers throughout the United States, as well as the 5,000 key gastroenterologists and pancreatologists who prescribe products for exocrine pancreatic insufficiency. For ALTU-238, we would initially focus on the approximately 400 key prescribing pediatric endocrinologists and approximately 3,000 adult endocrinologists who treat patients with growth hormone deficiency. Because the target groups for ALTU-238 are primarily hospital-based and concentrated in major metropolitan areas, we believe that the market for ALTU-238 can be addressed with a specialized sales force that targets these key prescribers. We also plan to leverage our sales and marketing capabilities by targeting the same groups of physician specialists with multiple products that we bring to market either through our own development efforts or by in- licensing from others.

Assemble a commercial organization. We plan to continue to build a marketing, managed care and sales management organization to create and implement marketing strategies for Trizytek, ALTU-238 and other product candidates in our product pipeline. We expect that our marketing organization will oversee any products that we market through our own sales force and oversee and support our sales and reimbursement efforts. The responsibilities of the marketing organization will include developing educational initiatives with respect to approved products and establishing appropriate product messaging

Table of Contents

according to the product label. We also plan to conduct post-approval marketing studies for our products to provide further data on the safety and efficacy. As we develop our pipeline products, we will evaluate whether to expand our marketing and sales efforts.

Selectively establish collaborations for our product candidates with leading pharmaceutical and biotechnology companies. We may enter into additional collaborations in markets outside of North America for our product candidates, where we believe that having a partner will enable us to gain better access to those markets. In addition, we may co-commercialize our product candidates in North America with pharmaceutical and biotechnology companies to achieve a variety of business objectives, including expanding the market or accelerating penetration. We may also collaborate with such companies to accelerate the development of selected early-stage product candidates.

Competition

Our major competitors are pharmaceutical and biotechnology companies in the United States and abroad that are actively engaged in the discovery, development and commercialization of products to treat gastrointestinal and metabolic disorders. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

Many of the entities developing and marketing potentially competing products may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing than we do. These entities also compete with us in recruiting and retaining qualified scientific and management personnel, as well as in acquiring technologies complementary to our programs.

Our commercial opportunity will be reduced or eliminated if our competitors develop and commercialize products that are more effective, have fewer side effects, are more convenient or are less expensive than any products that we may develop. In addition, our ability to compete may be affected because in some cases insurers and other third-party payors seek to encourage the use of generic products. This may have the effect of making branded products less attractive, from a cost perspective, to buyers.

If our clinical-stage product candidates are approved for commercial sale, they will compete with currently marketed drugs and potentially with drug candidates currently in development for the same indications, including the following:

Trizytek. If approved, Trizytek, the product candidate we are developing for the treatment of malabsorption due to exocrine pancreatic insufficiency, will compete with currently marketed porcine-derived pancreatic enzyme replacement therapies from Axcan Pharma, Johnson & Johnson, and Solvay Pharmaceuticals, as well as from generic drug manufacturers such as KV Pharmaceutical and IMPAX Laboratories. In April 2004, the FDA issued a notice that manufacturers of existing pancreatic enzyme replacement products will be subject to regulatory action if they do not obtain approved NDAs for these products by April 28, 2008. In October 2007, the FDA issued an update to the 2004 notice and announced that it has extended the deadline for unapproved pancreatic enzyme drug products from April 28, 2008 to April 28, 2010, but only if the manufacturers have investigational new drug applications on active status on or before April 28, 2008 and have submitted NDAs on or before April 28, 2009. We believe the FDA granted this extension in response to requests from the porcine enzyme manufacturers and to ensure the availability of pancreatic insufficiency drug products during the additional time needed by manufacturers to obtain marketing approval. This extension reinforces our belief that some porcine enzyme manufacturers may have difficulty meeting the FDA s requirements, particularly the requirements relating to manufacturing processes and controls. In addition, we understand that Biovitrum, Eurand and Meristem Therapeutics have product candidates in clinical development that could compete with

Trizytek. However, the product candidates from Biovitrum and Meristem contain only lipase and we believe that the product candidate from Eurand is porcine-derived. We understand that Eurand completed the initial submission of its rolling NDA filing for its porcine-derived product candidate in December 2007, and Axcan Pharma has completed the initial submission of its rolling NDA for its porcine-derived product candidate.

Table of Contents

ALTU-238. If approved, ALTU-238, the product candidate we are developing as a once-weekly treatment for hGH deficiency and related disorders, will compete with approved hGH therapies from companies such as BioPartners, Eli Lilly, Genentech, Novo Nordisk, Pfizer, Sandoz, Serono and Teva Pharmaceutical Industries. In addition, we understand that ALTU-238 may compete with product candidates in clinical development from some of these companies and from others, including LG Life Sciences, which is developing a long-acting hGH therapy based on an encapsulated microparticle technology.

ALTU-237. If approved, ALTU-237, the product candidate we are developing for the treatment of hyperoxalurias, may compete with products in development at companies such as Amsterdam Molecular Therapeutics, Medix, NephroGenex, and OxThera.

Key differentiating elements affecting the success of all of our product candidates are likely to be their convenience of use and efficacy and safety profile compared to other therapies.

Intellectual Property

We actively seek patent protection for the proprietary technology that we consider important to our business, including compounds, compositions and formulations, their methods of use and processes for their manufacture. In addition to seeking patent protection in the United States, we generally file patent applications in Canada, Europe, Japan and additional countries on a selective basis in order to further protect the inventions that we consider important to the development of our business worldwide. We also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop and maintain our proprietary position. Our success depends in part on our ability to obtain and maintain proprietary protection for our product candidates, technology and know-how, to operate without infringing the proprietary rights of others, and to prevent others from infringing our proprietary rights.

Our patent portfolio includes patents and patent applications with claims relating to protein crystals, both cross-linked and non-cross-linked, as well as compositions of specific protein crystals, such as lipase and hGH, and methods of making and using these compositions. In addition, we currently have patent applications relating to compositions and formulations containing both cross-linked and non-cross-linked protein crystals and patent applications relating to some of our later stage pipeline products.

As of December 31, 2007, our patent estate on a worldwide basis includes 13 patents issued in the United States and 65 issued in other countries, many of which are foreign counterparts of our United States patents, as well as more than 100 pending patent applications, with claims covering all of our product candidates.

Four of our issued United States patents, expiring between 2014 and 2016, relate to Trizytek and have claims covering cross-linked protein crystals, cross-linked enzyme crystals and methods of using those crystals in enzyme and oral protein therapy. We also have five pending United States patent applications relating to Trizytek, which if issued as patents, would expire between 2017 and 2025. Some of these applications include claims covering a combination of lipase, protease and amylase in specific formulations and methods of treatment using these formulations. We also have 43 issued foreign patents, expiring between 2011 and 2021, relating to Trizytek and pending foreign patent applications, which if issued as patents, would expire between 2011 and 2025.

We have five pending United States patent applications relating to ALTU-238, which if issued as patents, would expire between 2019 and 2027, and include claims relating to hGH crystals with an extended release profile and methods of treating hGH deficiency associated disorders using such hGH crystals. We also have pending foreign patent applications relating to ALTU-238, which if issued as patents, would expire between 2019 and 2027.

Five of our United States patents, which have claims covering cross-linked protein or enzyme crystals and methods of using those crystals in enzyme and oral protein therapy and methods of making cross-linked crystals with controlled dissolution properties, also relate to ALTU-237. These patents expire between 2014 and 2017. Additionally, we have two pending United States patent applications relating to ALTU-237, which if issued as patents, would expire between 2026 and 2027. Some of these applications include claims covering

specific oxalate degrading enzyme formulations, methods of making formulations, and methods of treatment using these formulations.

Our patent estate includes patent applications relating to some of our other product candidates. These patent applications, assuming they issue as patents, would expire between 2021 and 2024. We also have eight other issued United States patents and various foreign counterparts that relate to cross-linked protein crystal biosensors, methods of using cross-linked crystals of thermolysin as a catalyst, stabilized protein crystals, protein crystal formulations as catalysts in organic solvents and cross-linked glycoprotein crystals.

We hold an exclusive, royalty-free, fully-paid license from Vertex to patents relating to cross-linked enzyme crystals, including the four issued United States patents relating to Trizytek and ALTU-237 and two other issued United States patents relating to biosensors and thermolysin, as well as to a number of corresponding foreign patents and patent applications and know-how, including improvements developed by Vertex or its collaborators through February 2004. Under this license, Vertex retains non-exclusive rights to use the licensed Vertex patents and know-how to develop and commercialize small molecule drugs for human or animal therapeutic uses. We also granted to Vertex a non-exclusive, royalty-free, fully-paid license, under our patents and know-how with respect to cross-linked protein crystals that we have acquired, developed or licensed through February 2004, for Vertex s use in small molecule drug development and commercialization for human or animal therapeutic uses. The licenses with respect to patents, unless otherwise terminated earlier for cause, terminate on a country-by-country basis upon the expiration of each patent covered by the license.

We also have rights to specified technology developed by Amano under our cooperative development agreement with Amano, as described above under the section entitled Manufacturing.

Individual patents extend for varying periods depending on the effective date of filing of the patent application or the date of patent issuance, and the legal term of the patents in the countries in which they are obtained. Generally, patents issued in the United States are effective for:

the longer of 17 years from the issue date or 20 years from the earliest effective filing date, if the patent application was filed prior to June 8, 1995; and

20 years from the earliest effective filing date, if the patent application was filed on or after June 8, 1995.

The term of foreign patents varies in accordance with provisions of applicable local law, but typically is 20 years from the earliest effective filing date. In addition, in some instances, a patent term in the United States and outside of the United States can be extended to recapture a portion of the term effectively lost as a result of the health authority regulatory review period. These extensions, which may be as long as five years, are directed to the approved product and its approved indications. We intend to seek such extensions as appropriate.

The patent positions of companies like ours are generally uncertain and involve complex legal and factual questions. Our ability to maintain and solidify our proprietary position for our technology will depend on our success in obtaining effective claims and enforcing those claims once granted. We do not know whether any of our patent applications or those patent applications that are licensed to us will result in the issuance of any patents or if issued will assist our business. Our issued patents and those that may issue in the future, or those licensed to us, may be challenged, invalidated or circumvented. This could limit our ability to stop competitors from marketing related products and reduce the length of term of patent protection that we may have for our products. In addition, the rights granted under any of our issued patents may not provide us with proprietary protection or competitive advantages against competitors with similar technology. Our competitors may develop similar technologies, duplicate any technology developed by us, or use their patent rights to block us from taking the full advantage of the market.

Because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that a related patent may remain in force for a short period following commercialization, thereby reducing the advantage of the patent to our business and products.

Table of Contents

In addition to patents, we may rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets are difficult to protect. We seek to protect the trade secrets in our proprietary technology and processes, in part, by entering into confidentiality agreements with commercial partners, collaborators, employees, consultants, scientific advisors and other contractors and into invention assignment agreements with our employees and some of our commercial partners and consultants. These agreements are designed to protect our proprietary information and, in the case of the invention assignment agreements, to grant us ownership of the technologies that are developed. These agreements may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors.

Many of our employees, consultants and contractors have worked for others in the biotechnology or pharmaceutical industries. We try to ensure that, in their work for us, they do not use the proprietary information or know-how of others. To the extent that our employees, consultants or contractors use proprietary information owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local level, and other countries extensively regulate, among other things, the research, development, testing, manufacture, labeling, packaging, promotion, storage, advertising, distribution, marketing and export and import of products such as those we are developing.

United States Government Regulation

In the United States, the information that must be submitted to the FDA in order to obtain approval to market a new drug varies depending on whether the drug is a new product whose safety and effectiveness has not previously been demonstrated in humans or a drug whose active ingredients and some other properties are the same as those of a previously approved drug. A new drug will follow the NDA route, and a new biologic will follow the biologic license application, or BLA, route.

NDA and BLA Approval Processes

In the United States, the FDA regulates drugs and some biologics under the FDCA, and in the case of the remaining biologics, also under the Public Health Service Act, and implementing regulations. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include:

the FDA s refusal to approve pending applications;

license suspension or revocation;

withdrawal of an approval;

a clinical hold;

warning letters;

product recalls;

product seizures;

total or partial suspension of production or distribution; or

injunctions, fines, civil penalties or criminal prosecution.

Any agency or judicial enforcement action could have a material adverse effect on us. The process of obtaining regulatory approvals and the subsequent substantial compliance with appropriate federal, state, local, and foreign statutes and regulations require the expenditure of substantial time and financial resources.

Table of Contents

The process required by the FDA before a drug or biologic may be marketed in the United States generally involves the following:

completion of nonclinical laboratory tests according to good laboratory practice regulations, or GLP;

submission of an IND, which must become effective before human clinical trials may begin;

performance of adequate and well-controlled human clinical trials according to good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug for its intended use;

submission to the FDA of a NDA or BLA;

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP to assure that the facilities, methods and controls are adequate to preserve the drug s identity, strength, quality and purity or to meet standards designed to ensure the biologic s continued safety, purity and potency; and

FDA review and approval of the NDA or BLA.

Once a pharmaceutical candidate is identified for development, it enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information and analytical data, to the FDA as part of the IND. Some preclinical or non-clinical testing may continue even after the IND is submitted. In addition to including the results of the preclinical studies, the IND will also include a protocol detailing, among other things, the objectives of the first phase of the clinical trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated if the first phase lends itself to an efficacy determination. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, specifically places the clinical trial on clinical hold. The FDA can also place a trial on clinical hold at any time after it commences. In these cases, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin or resume.

All clinical trials must be conducted under the supervision of one or more qualified investigators in accordance with GCP regulations. These regulations include the requirement that all research subjects provide informed consent. Further, an Institutional Review Board, or IRB, at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution. Each new clinical protocol must be submitted to the FDA as part of the IND. Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur.

Human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

Phase I: The drug is initially introduced into healthy human subjects or patients with the disease and tested for safety, dosage tolerance, pharmacokinetics, pharmacodynamics, absorption, metabolism, distribution and excretion. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

Phase II: Involves studies in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase III: Clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical study sites. These studies are intended to establish the overall risk-benefit ratio of the product and provide, if appropriate, an adequate basis for product labeling.

Phase I, Phase II and Phase III testing may not be completed successfully within any specified period, if at all. The FDA or an IRB or the sponsor may suspend or terminate a clinical trial at any time for various

Table of Contents

reasons, including a finding that the research subjects or patients are being exposed to an unacceptable health risk.

Concurrent with clinical trials, companies usually complete additional animal studies and must also must develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the product in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and the manufacturer must develop methods for testing the quality, purity and potency of the final drugs. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf-life.

The results of product development, preclinical studies and clinical studies, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug, results of chemical studies and other relevant information are submitted to the FDA as part of an NDA or BLA requesting approval to market the product. The submission of an NDA or BLA is subject to the payment of user fees, but a waiver of such fees may be obtained under specified circumstances. The FDA reviews all NDAs and BLAs submitted before it accepts them for filing. It may request additional information rather than accept an NDA or BLA for filing. In this event, the NDA or BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing.

Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA may refuse to approve an NDA or BLA if the applicable regulatory criteria are not satisfied or may require additional clinical or other data. Even if such data is submitted, the FDA may ultimately decide that the NDA or BLA does not satisfy the criteria for approval. The FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacture is cGMP-compliant to assure and preserve the product s identity, strength, quality and purity. The FDA reviews a BLA to determine, among other things whether the product is safe, pure and potent and the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product s continued safety, purity and potency. Before approving an NDA or BLA, the FDA will inspect the facility or facilities where the product is manufactured and tested.

Satisfaction of FDA requirements or similar requirements of state, local and foreign regulatory authorities typically takes at least several years and the actual time required may vary substantially, based upon, among other things, the type, complexity and novelty of the product or disease. Government regulation may delay or prevent marketing of potential products for a considerable period of time and impose costly procedures upon our activities. Success in early stage clinical trials does not assure success in later stage clinical trials. Data obtained from clinical activities are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval on a timely basis, or at all. Even if a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited which could restrict the commercial application of the products. Further, even after regulatory approval is obtained, later discovery of previously unknown problems with a product may result in restrictions on the product or even complete withdrawal of the product from the market. Delays in obtaining, or failures to obtain regulatory approvals for any drug candidate could substantially harm our business and cause our stock price to drop significantly. In addition, we cannot predict what adverse governmental regulations may arise from future United States or foreign governmental action.

Expedited Review and Approval

The FDA has various programs, including fast track, priority review and accelerated approval, that are intended to expedite or simplify the process for reviewing drugs and provide for approval on the basis of surrogate endpoints. Even if a drug qualifies for one or more of these programs, the FDA may later decide that the drug no longer meets

the conditions for qualification or that the time period for FDA review or approval will be shortened. Generally, drugs that may be eligible for these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs, and those that offer

meaningful benefits over existing treatments. Fast track designation applies to the combination of the product and the specific indication for which it is being studied. Although fast track and priority review do not affect the standards for approval, the FDA will attempt to facilitate early and frequent meetings with a sponsor of a fast-track designated drug and expedite review of the application for a drug designated for priority review. Drugs that receive an accelerated approval may be approved on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug receiving accelerated approval perform post-marketing clinical trials.

Continuous Marketing Applications Pilot 2

In conjunction with the reauthorization of the Prescription Drug User Fee Act of 1992, or PDUFA, the FDA agreed to meet specific performance goals, one of which was to conduct pilot programs to explore CMAs. Under one of the CMA pilot programs called Pilot 2, one fast-track designated product from each review division of CDER and CBER is selected for frequent scientific feedback and interactions with the FDA, with a goal of improving the efficiency and effectiveness of the drug development process. In order to be eligible for participation, the drug or biologic must (1) have been designated fast track, (2) have been the subject of an end-of-Phase I meeting or another type of meeting that FDA determines is equivalent, and (3) not be on clinical hold. Applicants must make a formal application as described in an FDA Guidance on the subject and will be evaluated based on the FDA s overall assessment of:

the potential value of enhanced interaction, emphasizing the potential public health benefit resulting from development of the product;

the likelihood that concentrated scientific dialogue will facilitate the availability of a promising novel therapy; and

the applicant s demonstration of commitment to product development as evidenced by a thorough consideration of the rationale for participation in Pilot 2.

A maximum of one fast-track product per review division in CDER and CBER will be chosen to participate.

Once an applicant is selected for participation in Pilot 2, the review division and the applicant will finalize an agreement on the nature of the timelines for feedback and interactions between the applicant and the FDA. Pilot 2 agreements and activities for each application continued through September 30, 2007, the pilot program completion date, unless (1) an NDA or BLA is submitted, (2) the applicant withdraws the product from the pilot program, or (3) the agreement is terminated by the FDA because the drug or biologic no longer meets the pre-application criteria or the applicant deviates significantly from the negotiated developmental plan or has other significant disagreements with the FDA.

As the Pilot 2 program has ended, we will continue to communicate with the FDA via the standard regulatory pathways.

In November 2003, Trizytek was granted a fast track designation for treatment of malabsorption in patients with partial or complete exocrine pancreatic insufficiency. In February 2004, Trizytek was accepted into the Pilot 2 program pending agreement on a schedule of interactions with the FDA.

Orphan Drug Designation

The FDA initially granted orphan drug designation for Trizytek. In June 2007, we were notified by the Office of Orphan Products Development of the FDA that the orphan drug designation granted in 2002 to Trizytek for the treatment of pancreatic insufficiency was revoked. The FDA based its decision on a finding that if all patients with HIV/AIDS who suffer from fat malabsorption due to pancreatic insufficiency, the patient population in the United States appears to exceed 200,000 persons and is thus ineligible for orphan drug designation. We believe that only a subset of patients with HIV/AIDS have fat malabsorption due to

Table of Contents

pancreatic insufficiency and that our original filing was correctly within the 200,000 person limit for this disease condition. The FDA, however, concluded otherwise. The principal anticipated advantage to us of an orphan drug designation was the availability of tax credits and the abatement of NDA filing fees. In addition, the holder of the first NDA approved for an orphan drug indication also receives marketing exclusivity for a period of seven years over other products that contain or constitute the same drug or active ingredient. We are not aware of other products in development that contain or constitute the same drug as Trizytek for orphan drug purposes. Given these facts and circumstances, we may consult with the Office of Orphan Products Development. If we conclude that re-filing with a more precisely defined indication has merit, we have the right to submit an application on or before the filing of an NDA. We may also conclude that the advantages of continuing to seek orphan drug designation may not be warranted.

Pediatric Exclusivity

The FDA Modernization Act of 1997 included a pediatric exclusivity provision that was extended by the Best Pharmaceuticals for Children Act of 2002. Pediatric exclusivity is designed to provide an incentive to manufacturers for conducting research about the safety of their products in children. Pediatric exclusivity, if granted, provides an additional six months of market exclusivity in the United States for new or currently marketed drugs. Under Section 505A of the FDCA, six months of market exclusivity may be granted in exchange for the voluntary completion of pediatric studies in accordance with an FDA-issued Written Request. The FDA may not issue a Written Request for studies on unapproved or approved indications where it determines that information relating to the use of a drug in a pediatric population, or part of the pediatric population, may not produce health benefits in that population.

We have not requested or received a Written Request for such pediatric studies, although we may ask the FDA to issue a Written Request for such studies in the future. To receive the six-month pediatric market exclusivity, we would have to receive a Written Request from the FDA, conduct the requested studies, and submit reports of the studies in accordance with a written agreement with the FDA or, if there is no written agreement, in accordance with commonly accepted scientific principles. The FDA may not issue a Written Request for such studies if we ask for one, and it may not accept the reports of the studies. The current pediatric exclusivity provision is scheduled to end on October 1, 2012, and it may not be reauthorized, or may be reauthorized in a more limited form.

FDA Policy on Drugs to Treat Exocrine Pancreatic Insufficiency

Drugs to treat exocrine pancreatic insufficiency have been marketed in the United States since before the passage of the FDCA in 1938. Most of these drugs were available as over the counter, or OTC, drug products. As part of an OTC drug review, and between 1979 and 1991, the FDA evaluated the safety and effectiveness of drug products used to treat exocrine pancreatic insufficiency. In July 1991, the FDA announced that it had concluded that all exocrine pancreatic insufficiency drug products, whether marketed on an OTC or a prescription basis, were new drugs for which an approved application would be required for marketing. On April 28, 2004, the FDA published a notice in the Federal Register reiterating its determination that all pancreatic extract drug products are new drugs requiring an approved NDA for marketing, indicating that they should be marketed as prescription drugs only, and stating that after April 28, 2008, any prescription exocrine pancreatic insufficiency drug product being marketed without an approved NDA will be subject to regulatory action. In October 2007, the FDA issued an update to the 2004 notice announcing that it has extended the deadline for unapproved pancreatic enzyme drug products from April 28, 2008 to April 28, 2010, but only if the manufacturers have investigational new drug applications on active status on or before April 28, 2008 and have submitted NDAs on or before April 28, 2009. We believe the FDA granted this extension in response to requests from the porcine enzyme manufacturers and to ensure the availability of pancreatic insufficiency drug products during the additional time needed by manufacturers to obtain marketing approval. This extension reinforces our belief that some of the porcine enzyme manufacturers may have difficulty meeting the FDA s requirements, particularly the requirements relating to manufacturing processes and controls.

In 2006, the FDA issued the PEP Guidance. The PEP Guidance represents the FDA s current thinking on the topic, but does not bind the FDA or any other person. An alternative approach may be used to submit an

Table of Contents

NDA if the approach satisfies the requirements of the applicable law and regulations. The FDA has approved an NDA for only one pancreatic enzyme product, although the product is not currently on the market.

Post-Approval Requirements

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory standards is not maintained or if problems occur after the product reaches the market. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further FDA review and approval. In addition, the FDA may require testing and surveillance programs to monitor the effect of approved products that have been commercialized, and the FDA has the power to prevent or limit further marketing of a product based on the results of these post-marketing programs.

Any drug products manufactured or distributed by us pursuant to FDA approvals are subject to continuing regulation by the FDA, including, among other things:

- record-keeping requirements;
- reporting of adverse experiences with the drug;
- implementation of risk management plans and providing the FDA with updated safety and efficacy information;
- drug sampling and distribution requirements;
- notifying the FDA and gaining its approval of specified manufacturing or labeling changes;
- complying with certain electronic records and signature requirements; and
- complying with FDA promotion and advertising requirements.

Drug manufacturers and their subcontractors are required to register their manufacturing facilities with the FDA and some state agencies, and are subject to periodic unannounced inspections by the FDA and some state agencies for compliance with cGMP and other laws.

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products. Future FDA and state inspections may identify compliance issues at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct.

From time to time, legislation is passed in Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of products regulated by the FDA. In addition, FDA regulations and guidance are often revised or reinterpreted by the agency in ways that may significantly affect our business and our products. It is impossible to predict whether legislative changes will be enacted, or FDA regulations, guidance or interpretations changed or what the impact of such changes, if any, may be.

Foreign Regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sale and distribution of our products. Whether or not we obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of foreign countries before we can commence clinical

trials or marketing of the product in those countries. The approval process varies from country to country and the time may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country.

Under European Union regulatory systems, we may submit marketing authorization applications either under a centralized or decentralized procedure. The centralized procedure, which is compulsory for medicines produced by biotechnology and optional for those which are highly innovative, provides for the grant of a

Table of Contents

single marketing authorization that is valid for all European Union member states. The decentralized procedure provides for mutual recognition of national approval decisions. Under this procedure, the holder of a national marketing authorization may submit an application to the remaining member states. Within 90 days of receiving the applications and assessments report each member state must decide whether to recognize approval. If a member state does not recognize the marketing authorization, the disputed points are eventually referred to the European Commission, whose decision is binding on all member states.

As in the United States, we may apply for designation of our products as orphan drugs for the treatment of specific indications in the European Union before the application for marketing authorization is made. Orphan drugs in the European Union enjoy economic and marketing benefits, including a 10-year market exclusivity period for the approved indication for the same or similar drug, unless another applicant can show that its product is safer, more effective or otherwise clinically superior to the orphan-designated product. EMEA has granted Trizytek orphan drug designation.

Reimbursement

Sales of biopharmaceutical products depend in significant part on the availability of coverage through third-party payment systems. We anticipate third-party payors will provide coverage and reimbursement for our products. It will be time consuming and expensive for us to seek coverage from third-party payors for newly-approved drugs, and the scope of such coverage might be more limited than the purposes for which the FDA approves the drug. Eligibility for coverage does not imply that any drug will be reimbursed in all cases or at a rate that would be sufficient to allow us to sell our products on a competitive and profitable basis. Interim payments for new drugs, if applicable, might not be sufficient to cover our costs, and such payment might not be made permanent. Reimbursement rates vary according to the use of the drug, the clinical setting in which it is used, and whether it is administered by a physician in connection with a specific service or procedure. Reimbursement rates may be based upon payments allowed for lower-cost products that are already covered; may be incorporated into unprofitable composite rates for other services; and may reflect budgetary constraints, political considerations, and imperfections in data affecting government-funded health care programs. Drug prices may be reduced by mandatory discounts or rebates imposed by third party payors. Third party payors often follow the coverage and reimbursement policies established by government-funded health care programs such as Medicare. As a result, Medicare coverage and reimbursement policies may affect the pricing and profitability of drugs whether or not Medicare beneficiaries are expected to comprise a significant portion of the patients using the drug.

The levels of revenues and profitability of biopharmaceutical companies may also be affected by the continuing efforts of government and third party payors to contain or reduce the costs of health care through various means. For example, in some foreign markets, pricing reimbursement or profitability of therapeutic and other pharmaceutical products is subject to governmental control. In Canada, this practice has led to lower priced drugs than in the United States. As a result, importation of drugs from Canada into the United States may result in reduced product revenues.

In the United States there have been, and we expect that there will continue to be, a number of federal and state proposals to implement governmental pricing reimbursement controls. The Medicare Prescription Drug and Modernization Act of 2003 imposed new requirements for the distribution and pricing of prescription drugs that may affect the marketing of our products, if we obtain FDA approval for those products. Under this law, Medicare was extended to cover a wide range of prescription drugs other than those directly administered by physicians in a hospital or medical office. Competitive regional private drug plans were authorized to establish lists of approved drugs, or formularies, and to negotiate rebates and other price control arrangements with drug companies. Proposals to allow the government to directly negotiate Medicare drug prices with drug companies, if enacted, might further constrain drug prices, leading to reduced revenues and profitability. While we cannot predict whether any future legislative or regulatory proposals will be adopted, the adoption of such proposals could have a material adverse effect on our

business, financial condition and profitability.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For

Table of Contents

example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market.

Employees

We believe that our success will depend greatly on our ability to identify, attract and retain capable employees. As of December 31, 2007, we had 160 employees, of whom 32 hold Ph.D. or M.D. degrees. We have 112 employees primarily engaged in research and development activities, and 48 primarily engaged in general, administrative and operations activities. We believe that relations with our employees are good. None of our employees is represented under a collective bargaining agreement.

On February 4, 2008, Sheldon Berkle, our President and Chief Executive Officer, resigned. The Chairman of our Board of Directors, David D. Pendergast, Ph.D., has been appointed to lead our senior management team on an interim basis, as Executive Chairman. We are currently recruiting a President and Chief Executive Officer.

ITEM 1A. *RISK FACTORS*

Our business is subject to numerous risks. We cannot assure investors that our assumptions and expectations about our business will prove to have been correct. Important factors could cause our actual results to differ materially from those indicated or implied by forward-looking statements. Such factors that could cause or contribute to such differences include those factors discussed below. We undertake no intention or obligation to update or revise any forward-looking statements in this Annual Report on Form 10-K, whether as a result of new information, future events or otherwise.

Our existing and potential stockholders should consider carefully the risks described below and the other information in this Annual Report, including the Special Note Regarding Forward Looking Statements, our Management s Discussion and Analysis of Financial Condition and Results of Operations and our consolidated financial statements and the related notes appearing elsewhere in this Annual Report. We may be unable, for many reasons, including those that are beyond our control, to implement our current business strategy. If any of the following risks actually occur, they may materially harm our business, our financial condition and our results of operations. In that event, the market price of our common stock could decline.

Risks Related to Our Business and Strategy

If we fail to obtain the additional capital necessary to fund our operations, we will be unable to successfully develop and commercialize our product candidates and may be restricted in our ability to finance discovery of our next generation of product candidates.

We will require substantial future capital in order to continue to complete clinical development of and commercialize our clinical-stage product candidates, Trizytek, ALTU-238 and ALTU-237 and to conduct the research and development and clinical and regulatory activities necessary to bring our other product candidates into clinical development. Our future capital requirements will depend on many factors, including:

- the progress and results of our Phase III clinical efficacy trial and long-term safety studies for Trizytek, our planned toxicology studies and any other studies we may initiate based on the results of these studies or additional discussions with regulatory authorities;

the results and costs of future clinical trials for ALTU-238 that we may initiate;

the progress and results of the Phase I clinical trial for ALTU-237 and any other trials we may initiate based on the results of this trial or additional discussions with regulatory authorities;

the timing, progress and results of ongoing manufacturing development work for Trizytek, ALTU-238 and ALTU-237;

Table of Contents

- the results of our preclinical studies and testing for our earlier stage research products and product candidates, and any decisions to initiate clinical trials if supported by the preclinical results;

- the costs, timing and outcome of regulatory review of our product candidates in clinical development, and any of our preclinical product candidates that progress to clinical trials;

- the cost of obtaining clinical and commercial supplies of APIs and finished drug product;

- the costs of establishing commercial operations, including sales and marketing functions, should any of our product candidates approach marketing approval and/or be approved, and of establishing commercial manufacturing and distribution arrangements;

- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our issued patents, ensuring freedom to operate under any third party intellectual property rights, and defending intellectual property-related claims;

- our ability to establish and maintain collaborative or other financing arrangements and obtain milestone, royalty and other payments from collaborators or third parties; and

- the extent to which we acquire or invest in new businesses, products or technologies.

Additional funds may not be available when we need them on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, or we decide it is necessary to preserve existing resources, we may find it necessary or appropriate to:

- terminate or delay preclinical studies, clinical trials or other development activities for one or more of our product candidates; or

- delay our establishment of sales, marketing and commercial operations capabilities or other activities that may be necessary to commercialize our product candidates.

Based on our operating plans, we estimate that our net cash used in operating activities will be between $85 million and $95 million in 2008. We currently expect that our existing capital resources will be sufficient to maintain our current and planned operations into mid-2009. However, our operating plan may change as a result of many factors, including factors currently unknown to us, and we may need additional funds sooner than planned. In particular, because of the termination of our collaboration with Genentech, we will now be required to fund all costs related to the development of ALTU-238 unless and until we enter into a new collaboration agreement with another collaborative partner or secure alternative funding to support the development of this product candidate. The failure to obtain additional financing or enter into a new collaboration could lead to a delay in the planned clinical trials for ALTU-238.

We do not expect our available funds to be sufficient to fund the completion of the development and commercialization of any of our product candidates, and we expect that we will need to raise additional funds prior to being able to market any products. Additional funding may not be available to us on acceptable terms, or at all.

We are obligated under our agreement with CFFTI and under the terms of our redeemable preferred stock to make significant payments upon the occurrence of specified events. We may not have sufficient resources to make these payments when they become due.

If we receive FDA approval for Trizytek or related products, we must pay our collaborator, CFFTI, an amount equal to CFFTI s aggregate funding to us plus interest, up to a maximum of $40.0 million, less the fair market value of the shares of common stock underlying the warrants we issued to CFFTI. This amount, together with accrued interest, will be due in four annual installments, commencing 30 days after the approval date. We will also be required to pay an additional $1.5 million to CFFTI within 30 days after the approval date. These initial payments to CFFTI, if we receive FDA approval of Trizytek, will be due before we receive revenue from any commercial sales of the product, which could require us to raise additional funds or make it difficult for us to make the payments in a timely manner. In addition, if Vertex, the holder of our redeemable preferred stock, elects to redeem those shares on or after December 31, 2010, we will be required to pay an

Table of Contents

aggregate of $7.2 million plus dividends accrued after that date. We may require additional funding to make any such payments. Funds for these purposes may not be available to us on acceptable terms, or at all.

We have a history of net losses, which we expect to continue for at least several years and, as a result, we are unable to predict the extent of any future losses or when, if ever, we will achieve, or be able to maintain, profitability.

We have incurred significant losses since 1999, when we were reorganized as a company independent from Vertex. At December 31, 2007, our accumulated deficit was $239.0 million and we expect to continue to incur losses for at least the next several years. We have only been able to generate limited amounts of revenue from license and milestone payments under our collaboration agreements, and payments for funded research and development, as well as revenue from products we no longer sell. We expect that our annual operating losses will continue to increase over the next several years as we expand our research, development and commercialization efforts.

We must generate significant revenue to achieve and maintain profitability. All of our product candidates are still in development. Even if we succeed in developing and commercializing one or more of our product candidates, we may not be able to generate sufficient revenue or achieve or maintain profitability. Our failure to become and remain profitable would depress the market price of our common stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations.

Raising additional capital by issuing securities or through collaboration and licensing arrangements may cause dilution to existing stockholders, restrict our operations or require us to relinquish proprietary rights.

We may seek the additional capital necessary to fund our operations through public or private equity offerings, debt financings, and collaboration and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, existing stock ownership interests will be diluted, and the terms of such securities may include liquidation or other preferences that adversely affect the rights of our existing stockholders. In addition, many of the warrants that we have issued contain anti-dilution provisions that result in the issuance of additional shares of common stock upon exercise, and thus further dilution, to the extent we issue or are deemed to issue equity at a per share price less than the exercise price of the warrants. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions such as incurring additional debt, making capital expenditures, or declaring dividends. If we raise additional funds through collaboration and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates, or grant licenses on terms that are not favorable to us.

Our competitors may develop products that are less expensive, safer or more effective, which may diminish or prevent the commercial success of any product candidate that we bring to market.

Competition in the pharmaceutical and biotechnology industries is intense. We face competition from pharmaceutical and biotechnology companies, as well as numerous academic and research institutions and governmental agencies engaged in drug discovery activities or funding, both in the United States and abroad. Some of these competitors have greater financial resources than us, greater experience in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing than we do, and have products or are pursuing the development of product candidates that target the same diseases and conditions that are the focus of our drug development programs, including those set forth below. In addition, there may be others of which we are unaware.

Trizytek. If approved, Trizytek, the product candidate we are developing for the treatment of malabsorption due to exocrine pancreatic insufficiency, will compete with currently marketed porcine-derived pancreatic enzyme replacement therapies from companies such as Axcan Pharma, Johnson & Johnson, and Solvay

Pharmaceuticals, as well as from generic drug manufacturers such as KV Pharmaceutical and IMPAX Laboratories. In addition, we understand that Axcan Pharma, Biovitrum,

Table of Contents

Eurand, Meristem Therapeutics, and Solvay Pharmaceuticals have product candidates in development, some more advanced than Trizytek, that could compete with Trizytek. For example, Axcan Pharma completed the initial submission of the NDA for its porcine-derived pancrealipase product candidate and Eurand has completed the initial submission of its rolling NDA for its porcine-derived pancrealipase product candidate. If any of the existing porcine products is successful in satisfying the requirements of the FDA notice and obtains market approval, such product or products may share some of the competitive advantages that Trizytek may offer over the existing products and could generate significant sales and competition. Existing products to treat exocrine pancreatic insufficiency have been marketed in the United States since before the passage of the FDCA in 1938 and are currently marketed without FDA-approved NDAs. In 1995, the FDA issued a final rule requiring that these pancreatic enzyme products be marketed by prescription only, and in April 2004, the FDA issued a notice that manufacturers of these products will be subject to regulatory action if they do not obtain approved NDAs for their products by April 28, 2008. On October 26, 2007, the FDA provided additional notice to manufacturers of pancreatic enzyme products announcing that it has extended the required approval date for unapproved pancreatic enzyme products to April 28, 2010 as long as the manufacturers have INDs on active status on or before April 28, 2008 and have submitted NDAs on or before April 28, 2009. Despite the FDA s announced position, the agency may not pursue regulatory action against these companies if they fail to meet the 2008 deadline because there are currently no other products on the market for the treatment of exocrine pancreatic insufficiency. The level of competition that Trizytek, if approved, will face from these products in the United States will depend on whether the manufacturers of these products obtain approved NDAs by the deadline set by the FDA and, if they are unable to do so, whether the FDA takes regulatory action against these manufacturers and the nature of any such action. The nature of the competition that Trizytek, if approved, faces from existing pancreatic enzyme products could affect the market acceptance of Trizytek or require us to lower the price of Trizytek, which would negatively impact our margins and our ability to achieve profitability.

ALTU-238. If approved, ALTU-238, the product candidate we are developing as a once-weekly treatment for human growth hormone, or hGH deficiency and related disorders, will compete with existing approved hGH therapies from companies such as BioPartners, Eli Lilly, Genentech, Merck Serono, Novo Nordisk, Pfizer, Sandoz, and Teva Pharmaceutical Industries. In addition, we understand that ALTU-238 may compete with product candidates in clinical development from some of these companies and others, including LG Life Sciences, which is developing a long-acting hGH therapy based on an encapsulated microparticle technology.

*ALTU-*237. If approved, ALTU-237, the product candidate we are developing for the treatment of hyperoxalurias, may compete with product candidates in development at companies such as Amsterdam Molecular Therapeutics, Medix, NephroGenex, and OxThera.

We may not be successful in maintaining our existing collaboration or in establishing and maintaining additional collaborations on acceptable terms, which could adversely affect our ability to develop and commercialize our products.

An element of our business strategy is to establish collaborative arrangements with third parties, particularly with regard to development, regulatory approval, sales, marketing and distribution of our products outside of North America. We currently have one collaboration with CFFTI for Trizytek. We may also collaborate with other companies to accelerate the development of some of our early-stage product candidates, to co-commercialize our product candidates in North America in instances where we believe that a larger sales and marketing presence will expand the market or accelerate penetration, or to advance other business objectives. The process of establishing new collaborative relationships is difficult, time-consuming and involves significant uncertainty. We face, and will continue to face, significant competition in seeking appropriate collaborators. Moreover, if we do establish collaborative relationships, our collaborators may fail to fulfill their responsibilities or seek to renegotiate or terminate

their relationships with us due to unsatisfactory clinical results, a change in business strategy, a change of control or other reasons. In the event of a termination, we may incur termination payments or other expenses in connection with any reacquisition of

Table of Contents

rights. If we are unable to establish and maintain collaborative relationships on acceptable terms, we may have to delay or discontinue further development of one or more of our product candidates, undertake development and commercialization activities at our own expense or find alternative sources of funding.

For example, under our collaboration agreement with CFFTI, we have received significant funding for the development of Trizytek. We are also eligible to receive an additional payment if we achieve a specified milestone under the agreement. Additionally, the collaboration provides us with access to the Cystic Fibrosis Foundation s network of medical providers, patients, researchers and others involved in the care and treatment of cystic fibrosis patients. Our agreement with CFFTI provides for an exclusive license from us to CFFTI, and an exclusive sublicense back with a right to further sublicense from CFFTI, of intellectual property rights covering the development and commercialization of Trizytek in North America. The agreement with CFFTI requires us to use commercially reasonable efforts to develop and commercialize Trizytek in North America for the treatment of malabsorption due to exocrine pancreatic insufficiency in patients with cystic fibrosis and other indications. We are also required to meet specified milestones under the agreement by agreed upon dates. If we are unable to satisfy our obligations under the agreement, we may lose further funding under the agreement and lose our exclusive sublicense to Trizytek in North America, which will materially harm our business.

In addition, in December 2007, Genentech and we terminated our collaboration and license agreement, under which Genentech had agreed to fund the continued development and commercialization of ALTU-238 in North America. Because of the termination, we will not earn the milestones that were payable under the agreement, and we are now responsible for all the development costs for ALTU-238. As a result, we must now fund the further development of ALTU-238 and will require additional financing or a new collaborative partner to advance the ALTU-238 program into Phase III clinical trials.

If we enter into new collaborative agreements, our collaborators and we may not achieve our projected research and development goals in the time frames we announce and expect, which could have an adverse impact on our business and could cause our stock price to decline.

If we enter into new collaborative agreements for our product candidates, we expect to set goals for and make public statements regarding the timing of activities, such as the commencement and completion of preclinical studies and clinical trials, anticipated regulatory approval dates and developments and milestones under those collaboration agreements. The actual timing of such events can vary dramatically due to a number of factors such as delays or failures in our or our collaborators preclinical studies or clinical trials, delays or failures in manufacturing process development activities or in manufacturing product candidates, the amount of time, effort and resources to be committed to our programs by our future collaborators and the uncertainties inherent in the regulatory approval process. We cannot be certain that our or our collaborators preclinical studies and clinical trials will advance or be completed in the time frames we announce or expect, that our collaborators or we will make regulatory submissions or receive regulatory approvals as planned or that our collaborators or we will be able to adhere to our current schedule for the achievement of key milestones under any of our internal or collaborative programs. If our collaborators or we fail to achieve one or more of these milestones as planned, our business will be materially adversely affected and the price of our common stock could decline.

Risks Related to Development of Our Product Candidates

If we, or if we enter into collaborative agreements, our collaborators, are unable to commercialize our lead product candidates, or experience significant delays in doing so, our business will be materially harmed.

We have invested a significant portion of our time and financial resources to date in the development of oral and injectable crystallized protein therapies, including Trizytek, ALTU-238, and ALTU-237, for the treatment of

gastrointestinal and metabolic disorders. Our ability and the ability of a collaborative partner to

Table of Contents

develop and commercialize our product candidates successfully, and therefore our ability to generate revenues, will depend on numerous factors, including:

- successfully scaling up the manufacturing processes for our product candidates, successfully completing stability testing and release of our product candidates, and obtaining sufficient supplies of, our product candidates, in order to complete our clinical trials and toxicology studies on a timely basis;

- receiving marketing approvals from the FDA and foreign regulatory authorities;

- arranging for commercial-scale supplies of our product candidates with contract manufacturers whose manufacturing facilities operate in compliance with current good manufacturing practice regulations, or cGMPs, including the need to scale up the manufacturing process for commercial scale supplies;

- establishing sales, marketing and distribution capabilities on our own, through collaborative agreements or through third parties;

- obtaining commercial acceptance of our product candidates, if approved, in the medical community and by third-party payors and government pricing authorities; and

- establishing favorable pricing from foreign regulatory authorities.

If we are not successful in commercializing Trizytek, ALTU-238 or ALTU-237, or are significantly delayed in doing so, our business will be materially harmed.

Because our product candidates are in clinical development, there is a significant risk of failure.

Of the large number of drugs in development, only a small percentage result in the submission of an NDA to the FDA, and even fewer are approved for commercialization. We will only receive regulatory approval to commercialize a product candidate if we can demonstrate to the satisfaction of the FDA or the applicable foreign regulatory authority, in well-designed and conducted clinical trials, that the product candidate is safe and effective and otherwise meets the appropriate standards required for approval for a particular indication. Clinical trials are lengthy, complex and extremely expensive programs with uncertain results. A failure of one or more of our clinical trials may occur at any stage of testing. We have limited experience in conducting and managing the clinical trials necessary to obtain regulatory approvals, including approval by the FDA.

We have not yet completed Phase III clinical trials for any of our product candidates in clinical development, and we have not advanced, and may never advance, our product candidates that are currently in preclinical testing into clinical trials. We have completed a Phase II clinical trial for the capsule form of Trizytek and initiated a Phase III efficacy trial in May 2007. In order for Trizytek to be approved by the FDA, we will be required to demonstrate in the Phase III efficacy trial, to a statistically significant degree, that Trizytek improves absorption of fat in patients suffering from malabsorption as a result of exocrine pancreatic insufficiency. We will also be required to demonstrate the safety of Trizytek in a long-term study and have commenced two Phase III studies of Trizytek to evaluate its long-term safety. However, we may not be successful in meeting the primary or secondary endpoints for the Phase III efficacy trial or the goal of the long-term safety studies. The possibility exists that even if these trials are successful, we may still be required or may determine it is desirable to perform additional studies for approval or in order to achieve a broad indication for the labeling of the drug. In addition, we will need to complete specified toxicology studies in animals before submitting an NDA, and the results of those studies may not demonstrate sufficient safety.

The ability to continue to recruit and enroll patients in our Phase III clinical trial and our safety studies for Trizytek depends on the availability and willingness of patients to participate in experimental research, the conduct of recruitment activities that respect human subject protection, and recommendations by physicians to their patients to participate in our clinical trials. We have limited experience from conducting earlier stage clinical trials, and we are still developing our capabilities to conduct Phase III clinical trials, which usually involve a larger number of patients. In addition, in the execution of any Phase III clinical trial, we intend to rely in part on third party contractors to assist with these activities. The design of our Phase III clinical trial for Trizytek includes two in-hospital participation periods as well as one off-enzyme period for all patients and

Table of Contents

an additional off-enzyme period for half of the patients, which may make it difficult to enroll patients and, if enrolled, may cause them to drop out of the trial. In-hospital periods can be inconvenient, and off-enzyme periods can be uncomfortable for these patients. The design of our safety studies for Trizytek requires patients to participate for approximately 12 months. It is possible that some subjects may decide, after they have enrolled, that they no longer wish to participate in the trial, which could require us to enroll new patients at a later date, thereby delaying completion of the trial. Any predictions about the timing of enrollment or the completion of clinical trials are subject to the risks inherent in these activities.

For ALTU-238, we have completed Phase I clinical trials in healthy adults and a Phase II clinical trial in adults with hGH deficiency. The efficacy of ALTU-238 has not yet been tested in a human clinical trial, and ALTU-238 may prove not to be clinically effective as an extended-release formulation of hGH. In addition, it is possible that patients receiving ALTU-238 will suffer additional or more severe side effects than we observed in our Phase I and Phase II clinical trials, which could delay or preclude regulatory approval of ALTU-238 or limit its commercial use.

In August 2007, we initiated our first Phase I human clinical trial of ALTU-237, and its safety and efficacy have yet to be determined.

If we observe serious or other adverse events during the time our product candidates are in development or after our products are approved and on the market, we may be required to perform lengthy additional clinical trials, may be denied regulatory approval of such products, may be forced to change the labeling of such products or may be required to withdraw any such products from the market, any of which would hinder or preclude our ability to generate revenues.

In connection with our completed Phase II clinical trial of Trizytek, there was one serious adverse event considered by an investigator in our clinical trials as probably or possibly related to treatment with that product candidate. As the size of our clinical trials increase or the medical conditions of the population in which we are testing our products vary, the potential for serious or other adverse events related or unrelated to our product candidates could vary and possibly increase.

The one serious adverse event in our Phase II clinical trial of Trizytek involved a subject in the lowest dose group who developed distal intestinal obstructive syndrome, or DIOS, which resolved itself without further complications. DIOS is a condition that is unique to cystic fibrosis and occurs due to the accumulation of viscous mucous and fecal material in the colon. According to a 1987 study, DIOS is relatively common in cystic fibrosis patients, occurring in about 16% of those patients. In our Phase II clinical trial of Trizytek, we also observed elevated levels of liver transaminases, which can be associated with harm to the liver. These elevations were transient and asymptomatic and were not reported as drug-related serious adverse events. Elevation of liver transaminases is common among cystic fibrosis patients. The elevations we observed may or may not have been caused by Trizytek. The increases we observed were not associated with increases in bilirubin, which are typically associated with harm to the liver.

If the incidence of these events increases in number or severity, if a regulatory authority believes that these events constitute an adverse effect caused by the drug, or if other effects are identified either during future clinical trials or after any of our drug candidates are approved and on the market:

- we may be required to conduct additional pre-clinical or clinical trials, make changes in clinical trial brochures or, if a product is approved, make changes to the labeling of any such products, reformulate any such products, or implement changes to or obtain new approvals of our or our contractors or collaborators manufacturing facilities or processes;

regulatory authorities may be unwilling to approve our product candidates or may withdraw approval of our products;

we may experience a significant drop in the sales of the affected products;

our reputation in the marketplace may suffer; and

we may become the target of lawsuits, including class action suits.

Table of Contents

Any of these events could prevent approval or harm sales of the affected products or could substantially increase the costs and expenses of commercializing and marketing any such products.

If clinical trials for our product candidates are prolonged or delayed, we may be unable to commercialize our product candidates on a timely basis, or at all, which would require us to incur additional costs and delay our receipt of any revenue from potential product sales.

We may encounter problems with our ongoing or planned clinical trials that could cause us or a regulatory authority to delay or suspend those clinical trials or delay the analysis of data derived from them. A number of events or factors, including any of the following, could delay the completion of our ongoing and planned clinical trials and negatively impact our ability to obtain regulatory approval for, and to market and sell, a particular product candidate, including our clinical-stage product candidates:

- conditions imposed by us or imposed on us by the FDA or any foreign regulatory authority regarding the scope or design of our clinical trials;
- delays in obtaining, or our inability to obtain or maintain, required approvals from institutional review boards, or IRBs, or other reviewing entities at clinical sites selected for participation in our clinical trials;
- delays in the completion of manufacturing development work for our product candidates, such as the delays we experienced in 2006 relating to Trizytek and ALTU-238;
- any dispute that arises under our current or future collaborative agreements or our agreements with third parties;
- insufficient supply or deficient quality of our product candidates or other materials necessary to conduct our clinical trials;
- difficulties enrolling subjects in our clinical trials, including, for example, recruiting patients in our Phase III trials for Trizytek, or finding pediatric subjects with hGH deficiency who have not previously received hGH therapy for our pediatric trials of ALTU-238;
- negative or inconclusive results from clinical trials, or results that are inconsistent with earlier results, that necessitate additional clinical studies;
- serious or unexpected side effects experienced by subjects in clinical trials; or
- failure of our third-party contractors or our investigators to comply with regulatory requirements or otherwise meet their contractual obligations to us in a timely manner.

Our clinical trials and those of our collaborators may not begin as planned, may need to be redesigned, and may not be completed on schedule, if at all. For example, on July 24, 2006, we announced that we expected to perform additional manufacturing development work before initiating the planned Phase III clinical trial of Trizytek in order to ensure a consistent production process for that product candidate. In addition, on that same date, we announced that the schedule for delivery of equipment for the production of ALTU-238 had been delayed due to several changes to the design specifications for that equipment, which would result in a delay in the initiation of planned Phase III trials of ALTU-238. In addition, in December 2007, we announced that Genentech and we had terminated our ALTU-238 collaboration agreement. This may result in a delay in our planned clinical trials, and preclude our ability to enter into

Phase III clinical trials unless we are able to procure additional funds to finance the costs of such trials. Delays in our clinical trials may result in increased development costs for our product candidates, which could cause our stock price to decline and could limit our ability to obtain additional financing. In addition, if one or more of our clinical trials are delayed, our competitors may be able to bring products to market before we do, and the commercial advantage, profitability or viability of our product candidates, including our clinical-stage product candidates, could be significantly reduced.

Table of Contents

Conducting clinical studies in Eastern Europe involves risks not typically associated with U.S. studies which may result in timing, cost and/or quality problems in our planned clinical trials for our product candidates.

We have enrolled several patients from Eastern Europe into our Phase III clinical trials for Trizytek and expect that a significant number of the patients in our upcoming clinical trials for ALTU-238 will be enrolled in Eastern European countries. We plan to conduct these trials in compliance with good clinical practices. However, ensuring compliance with good clinical practices at Eastern European clinical sites will involve risks, including risks associated with language barriers and the fact that some European clinical investigators have only limited experience in conducting clinical studies in accordance with standards set forth by the FDA and the European Medicines Agency, or EMEA. Although we will seek to mitigate this risk by monitoring and auditing the ongoing performance of our studies, using both our employees and outside contract research organizations, to ensure compliance with good clinical practices and all other regulatory requirements, we may not be able to mitigate these risks effectively. Failure to attain and document good clinical practices compliance would adversely impact the value of any data generated from these trials. In addition, should it require more time or money than we currently anticipate to perform any required site training, monitoring or auditing activities, these trials could be delayed, exceed their budgets, or both, which could have a material adverse impact on our business.

We may fail to select or capitalize on the most scientifically, clinically or commercially promising or profitable indications or therapeutic areas for our product candidates.

We have limited technical, managerial and financial resources to determine the indications on which we should focus the development efforts related to our product candidates. We may make incorrect determinations. Our decisions to allocate our research, management and financial resources toward particular indications or therapeutic areas for our product candidates may not lead to the development of viable commercial products and may divert resources from better opportunities. Similarly, our decisions to delay or terminate drug development programs may also be incorrect and could cause us to miss valuable opportunities. For example, we will need to allocate our financial, capital and human resources among Trizytek, ALTU-238 and ALTU-237, and our preclinical product candidates. If we invest in the advancement of a candidate which proves not to be viable, we will have fewer resources available for potentially more promising candidates. In particular, because we are now solely responsible for the development of ALTU-238, we will need to commit additional financial and human resources to the ALTU-238 program. Because our resources are limited, we may be unable to commit the necessary resources to this program without negatively impacting other programs.

Risks Related to Regulatory Approval of Our Product Candidates and Other Government Regulations

If we or our future collaborators do not obtain required regulatory approvals, we will be unable to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Trizytek, ALTU-238, ALTU-237 and any other product candidates we may discover or acquire and seek to commercialize, either alone or in conjunction with a collaborator, are subject to extensive regulation by the FDA and other regulatory authorities in the United States and other countries relating to the testing, manufacture, safety, efficacy, recordkeeping, labeling, packaging, storage, approval, advertising, promotion, sale and distribution of drugs. In the United States and in many foreign jurisdictions, we must successfully complete rigorous preclinical testing and clinical trials and an extensive regulatory review process before a new drug can be sold. We have not obtained regulatory approval for any product. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays.

The time required to obtain approval by the FDA is unpredictable but typically takes many years following the commencement of clinical trials, depending upon numerous factors, including the complexity of the product candidate

and the disease to be treated. Our product candidates may fail to receive regulatory approval for many reasons, including:

- a failure to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a product candidate is safe and effective for a particular indication;

Table of Contents

- the results of clinical trials may not meet the level of statistical significance required by the FDA or other regulatory authorities for approval;

- an inability to demonstrate that a product candidate s benefits outweigh its risks;

- an inability to demonstrate that the product candidate presents an advantage over existing therapies;

- the FDA s or comparable foreign regulatory authorities disagreement with the manner in which our collaborators or we interpret the data from preclinical studies or clinical trials;

- the FDA s or comparable foreign regulatory authorities failure to approve the manufacturing processes or facilities of third-party contract manufacturers of clinical and commercial supplies; and

- a change in the approval policies or regulations of, or the specific advice provided to us by, the FDA or comparable foreign regulatory authorities or a change in the laws governing the approval process.

The FDA or comparable foreign regulatory authorities might decide that the data are insufficient for approval and require additional clinical trials or other studies. Furthermore, even if we do receive regulatory approval to market a commercial product, any such approval may be subject to limitations on the indicated uses for which our collaborative partner or we may market the product. It is possible that none of our existing or future product candidates will ever obtain the appropriate regulatory approvals necessary for us or our collaborators to begin selling them.

Failure to obtain regulatory approvals or to comply with regulatory requirements in foreign jurisdictions would prevent us or any collaborator from marketing our products internationally.

We intend to have our product candidates marketed outside the United States. In order to market products in the European Union and many other non-United States jurisdictions, our collaborators or we must obtain separate regulatory approvals and comply with numerous and varying regulatory requirements. We have no experience in obtaining foreign regulatory approvals for our product candidates. The approval procedures vary among countries and can involve additional and costly preclinical and clinical testing and data review. The time required to obtain approval in other countries may differ from that required to obtain FDA approval. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. Approval by the FDA does not ensure approval by regulatory authorities in other countries, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. Our collaborators or we may not receive necessary approvals to commercialize our products in any market. The failure to obtain these approvals could harm our business and result in decreased revenues from the sale of products or from milestones or royalties associated with any collaboration agreements we may enter into in the future.

We also face challenges arising from the different regulatory requirements imposed by United States and foreign regulators with respect to clinical trials. The EMEA often imposes different requirements than the FDA with respect to the design of a pivotal Phase III clinical trial. For example, we believe that, based on our discussions with the EMEA, a collaborator or we will be required to conduct a trial comparing Trizytek with a currently marketed pancreatic enzyme replacement therapy in order to obtain regulatory approval in the European Union. If a comparator study is undertaken and Trizytek does not demonstrate equivalent efficacy to the comparator product, Trizytek may not obtain regulatory approval; further, if Trizytek does not demonstrate an advantage over the comparator, the commercial profitability and viability of Trizytek could be materially and adversely affected in Europe as well as the United States. These factors could in turn adversely impact the opportunity to enter into a future Trizytek collaboration in Europe.

Our product candidates will remain subject to ongoing regulatory requirements even if they receive marketing approval, and if we fail to comply with these requirements, we could lose these approvals, and the sales of any approved commercial products could be suspended.

Even if we receive regulatory approval to market a particular product candidate, the product will remain subject to extensive regulatory requirements, including requirements relating to manufacturing, labeling,

Table of Contents

packaging, adverse event reporting, storage, advertising, promotion, distribution and record keeping. In addition, the approval may be subject to limitations on the uses for which the product may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product, which could reduce our revenues, increase our expenses and render the approved product candidate not commercially viable.

In addition, as clinical experience with a drug increases after approval because it is typically used by a larger and more diverse group of patients after approval than during clinical trials, side effects and other problems may be observed after approval that were not seen or anticipated during pre-approval clinical trials or other studies. Any adverse effects observed after the approval and marketing of a product candidate could result in limitations on the use of or withdrawal of any approved products from the marketplace. Absence of long-term safety data may also limit the approved uses of our products, if any. If we fail to comply with the regulatory requirements of the FDA and other applicable United States and foreign regulatory authorities, or previously unknown problems with any approved commercial products, manufacturers or manufacturing processes are discovered, we could be subject to administrative or judicially imposed sanctions or other setbacks, including:

- restrictions on the products, manufacturers or manufacturing processes;
- warning letters;
- civil or criminal penalties;
- fines;
- injunctions;
- product seizures or detentions;
- import or export bans or restrictions;
- voluntary or mandatory product recalls and related publicity requirements;
- suspension or withdrawal of regulatory approvals;
- total or partial suspension of production; and
- refusal to approve pending applications for marketing approval of new products or supplements to approved applications.

If we are slow to adapt, or are unable to adapt, to changes in existing regulatory requirements or adoption of new regulatory requirements or policies, we may lose marketing approval for our products when and if any of them are approved, resulting in decreased revenue from milestones, product sales or royalties.

We deal with hazardous materials and must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our activities and those of our third-party manufacturers on our behalf involve the controlled storage, use and disposal of hazardous materials, including microbial agents, corrosive, explosive and flammable chemicals and other hazardous compounds. Our manufacturers and we are subject to federal, state and local laws and regulations

governing the use, manufacture, storage, handling and disposal of these hazardous materials. Although we believe that the safety procedures for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials.

In the event of an accident, state or federal authorities may curtail our use of these materials and interrupt our business operations. In addition, we could be liable for any resulting civil damages which may exceed our financial resources and may seriously harm our business. While we believe that the amount of insurance we currently carry, providing coverage of $1 million, should be sufficient for typical risks regarding our handling of these materials, it may not be sufficient to cover pollution conditions or other extraordinary or unanticipated

Table of Contents

events. Furthermore, an accident could damage, or force us to shut down, our operations. In addition, if we develop a manufacturing capacity, we may incur substantial costs to comply with environmental regulations and would be subject to the risk of accidental contamination or injury from the use of hazardous materials in our manufacturing process.

Risks Related to Our Dependence on Third Parties

We have no manufacturing capacity, and we have relied and expect to continue to rely on third-party manufacturers to produce our product candidates.

We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates or any of the compounds that we are testing in our preclinical programs, and we lack the internal resources and the capabilities to do so. As a result, we currently rely, and we expect to rely in the future, on third-party manufacturers to supply the active pharmaceutical ingredients, or APIs, for our product candidates and to produce and package final drug products, if and when they are approved for marketing. 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 manufacturing process development, sourcing of key raw materials, regulatory compliance and quality assurance;
- limitations on supply availability resulting from capacity and scheduling constraints of the third party;
- the possible breach of the manufacturing agreement by the third party because of factors beyond our control; and
- 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.

For example, on July 24, 2006, we announced that the schedule for delivery of equipment for the production of ALTU-238 had been delayed due to several changes to the design specifications for that equipment, which would result in a delay in the initiation of the planned Phase III clinical trial of ALTU-238. 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 our product candidates and commercialize any products that receive regulatory approval on a timely basis.

We currently rely on a limited number of manufacturers for the clinical and commercial supply of each of our product candidates, which could delay or prevent the clinical development and commercialization of our product candidates.

We currently depend on single source suppliers for each of our product candidates. Any disruption in production, inability of a supplier to produce adequate quantities of clinical and other material to meet our needs or other impediments could adversely affect our ability to successfully complete the clinical trials and other studies of our product candidates, delay submissions of our regulatory applications or adversely affect our ability to commercialize our product candidates in a timely manner, or at all.

We currently rely on two contract manufacturers to provide us with Trizytek for our Phase III clinical trials. Amano Enzyme Inc., or Amano, located in Nagoya, Japan, is the sole supplier of the enzymes that comprise the APIs for Trizytek. Patheon Inc., or Patheon, located in Ontario, Canada, is the sole manufacturer of the Trizytek drug product

which contains the three APIs. Both Amano and Patheon have only supplied us with materials for our clinical trials and our toxicology studies. In addition, Amano s manufacturing facility that produces the APIs for Trizytek has not been inspected or approved by the FDA, EMEA or the Japanese Ministry of Health, Labour and Welfare. Pursuant to our agreement with Amano, it has notified us that it will not be the primary manufacturer of the APIs for the initial commercial supply of Trizytek, but it may elect to supply some of the APIs for Trizytek in the future. Any dispute over the terms of, or decisions regarding, our collaboration with Amano or other adverse developments in our relationship with Amano would materially harm our business and might accelerate our need for additional capital.

Table of Contents

We entered into an agreement with Lonza in November 2006 for the commercial scale-up and supply of Trizytek. We are in the process of working with Lonza to transfer from Amano and us the technology required to manufacture the APIs for Trizytek. Switching manufacturers requires the cooperation of Amano, training of personnel, sourcing and quality assurance of key raw materials, and validation of Lonza s processes. Neither Lonza s nor Amano s facilities has been inspected or approved by the FDA, the EMEA or other relevant regulatory authorities. Changes in manufacturing processes or procedures, including a change in the location where the drug is manufactured or a change of a third-party manufacturer, may require prior review and approval from the FDA and satisfaction of comparable foreign requirements. This review may be costly and time-consuming and, if we obtain the required marketing approvals, could delay or prevent the launch of a product. If we are unable to successfully transition the manufacture of the APIs for Trizytek from Amano and ourselves to Lonza, our commercialization of Trizytek could be delayed, prevented or impaired and the costs related to Trizytek may increase. In addition, if Amano elects to become a commercial supplier of Trizytek, we will have the added difficulty of managing two suppliers of the same materials.

With respect to ALTU-238, we have purchased the hGH, the API in ALTU-238, for our prior clinical trials from Sandoz. In February 2008, we purchased hGH from a third-party supplier for both our Phase Ic trial and our Phase II pediatric trial. The Phase Ic trial is designed to confirm that ALTU-238 material produced at the current manufacturing scale performs similarly to the material used in previous ALTU-238 Phase I and Phase II trials. We have not identified a long term supplier for the hGH that we will need for our future Phase III trials and commercial needs, and we cannot be sure that we will be able to enter into an agreement with a suitable alternative supplier on suitable terms, or at all.

We have an agreement with Althea for Althea to use the hGH supplied to it to produce the clinical supplies for our planned clinical trials of ALTU-238. We have transferred the manufacturing process for ALTU-238 to Althea and are currently validating this process. Furthermore, prior to the initiation of manufacturing activities for ALTU-238 at Althea we will need to complete additional activities including the testing and qualification of specialized manufacturing equipment specific to ALTU-238. Delays in these activities, particularly in the delivery of specialized manufacturing equipment, have in the past delayed our clinical trials of ALTU-238 and unsuccessful testing, qualification and performance of such equipment could further delay the planned clinical trials for ALTU-238 and result in additional unforeseen expenses.

Our agreement with Althea covers only the manufacture of ALTU-238 for the planned clinical trials of ALTU-238. We will need to negotiate an additional agreement under which Althea would provide the commercial supply of ALTU-238 or find an alternative commercial manufacturer. Switching manufacturers would require cooperation with Althea, technology transfers, training, and validation of the alternative manufacturer s processes, and, under some circumstances, will require us to make a specified payment to Althea. Changes in manufacturing processes or procedures, including a change in the location where the drug is manufactured or a change of a third-party manufacturer, may require prior review and approval from the FDA and satisfaction of comparable foreign requirements. This review may be costly and time-consuming and could delay or prevent the launch of a product. If we are unable to secure another contract manufacturer for ALTU-238 at an acceptable cost, the commercialization of ALTU-238 could be delayed, prevented or impaired, and the costs related to ALTU-238 may increase. Any dispute over the terms of, or decisions regarding, our collaboration with Althea or other adverse developments in our relationship would materially harm our business and might accelerate our need for additional capital.

We do not have any agreements in place to manufacture our product candidates, other than the APIs for Trizytek, on a commercial scale. In order to commercialize these product candidates, our existing suppliers will need to scale up their manufacturing of our product candidates and/or transfer the technology to a commercial supplier. We may be required to fund capital improvements to support scale-up of manufacturing and related activities. Our existing manufacturers may not be able to increase their manufacturing capacity successfully for any of our product candidates for which we obtain marketing approval in a timely or economic manner, or at all. We may need to engage other

manufacturers to provide commercial supplies of our product candidates. It may be difficult for us to enter into commercial supply arrangements on a timely basis or on acceptable terms, which could delay or prevent our ability to commercialize our product candidates. If our existing manufacturers are unable or unwilling to increase their manufacturing capacity or

Table of Contents

we are unable to establish alternative arrangements, the development and commercialization of our product candidates may be delayed or there may be a shortage in supply.

Any performance failure on the part of a contract manufacturer could delay clinical development or regulatory approval of our product candidates or commercialization of any approved products.

The failure of a contract manufacturer to achieve and maintain high manufacturing standards could result in patient injury or death, product liability claims, product recalls, product seizures or withdrawals, delays or failures in testing or delivery, cost overruns, failure of regulatory authorities to grant marketing approvals, delays, suspensions or withdrawals of approvals, injunctions, fines, civil or criminal penalties, or other problems that could seriously harm our business. Contract manufacturers may encounter difficulties involving production yields, quality control and quality assurance. These manufacturers are subject to ongoing periodic unannounced inspection by the FDA and corresponding state and foreign agencies which audit strict compliance with cGMP and other applicable government regulations and corresponding foreign standards. However, we or a future collaborator may have limited control over third-party manufacturers compliance with these regulations and standards. Present or future manufacturers might not be able to comply with cGMP and other FDA or international regulatory requirements.

We rely on third parties to conduct, supervise and monitor our clinical trials, and those third parties may not perform satisfactorily, including failing to meet established deadlines for the completion of such trials.

We rely on third parties such as contract research organizations, medical institutions and clinical investigators to enroll qualified patients and conduct, supervise and monitor our clinical trials. Our reliance on these third parties for clinical development activities reduces our control over these activities. Our reliance on these third parties, however, does not relieve us of our regulatory responsibilities, including ensuring that our clinical trials are conducted in accordance with good clinical practice regulations, or GCP, and the investigational plan and protocols contained in the IND. Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. In addition, they may not complete activities on schedule, or may not conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our trial design. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, our efforts to obtain regulatory approvals for, and commercialize, our product candidates may be delayed or prevented.

Because we may enter into in the future sales or collaboration transactions, we may be dependent upon our collaborators, and we may be unable to prevent them from taking actions that may be harmful to our business or inconsistent with our business strategy.

Any future licensing and collaboration agreements that we may enter into with respect to our product development candidates may reduce or eliminate the control we have over the development and commercialization of our product candidates. Our future collaborators may decide to terminate a development program under circumstances where we might have continued such a program, or may be unable or unwilling to pursue ongoing development and commercialization activities as quickly as we would prefer. A collaborator may follow a different strategy for product development and commercialization that could delay or alter development and commercial timelines and likelihood of success. A collaborator may also be unwilling or unable to fulfill its obligations to us, including its development and commercialization responsibilities. Any future collaborators will likely have significant discretion in determining the efforts and level of resources that they dedicate to the development and commercialization of our product candidates. In addition, although we seek to structure our agreements with potential collaborators to prevent the collaborator from developing and commercializing a competitive product, we are not always able to negotiate such terms and the possibility exists that our collaborators may develop and commercialize, either alone or with others or through an in-license or acquisition, products that are similar to or competitive with the products that are the subject of the collaboration with us. If any collaborator terminates its collaboration with us or fails to perform or satisfy its

obligations to us, the development, regulatory approval or commercialization of our product candidate would

Table of Contents

be delayed or may not occur and our business and prospects could be materially and adversely affected for that reason. Likewise, if we fail to fulfill our obligations under a collaboration and license agreement, our collaborator may be entitled to damages, to terminate the agreement, or terminate or reduce its financial payment obligations to us under our collaborative agreement.

Our collaborations with outside scientists and consultants may be subject to restriction and change.

We work with chemists, biologists and other scientists at academic and other institutions, and consultants who assist us in our research, development, regulatory and commercial efforts. These scientists and consultants have provided, and we expect that they will continue to provide, valuable advice on our programs. These scientists and consultants are not our employees, may have other commitments that would limit their future availability to us and typically will not enter into non-compete agreements with us. If a conflict of interest arises between their work for us and their work for another entity, we may lose their services. In addition, we will be unable to prevent them from establishing competing businesses or developing competing products. For example, if a key principal investigator identifies a potential product or compound that is more scientifically interesting to his or her professional interests, his or her availability could be restricted or eliminated.

Risks Related to Commercialization of Our Product Candidates

If we are unable to establish 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.

We have no commercial products, and we do not currently have an organization for the sales and distribution of pharmaceutical products. In order to successfully commercialize any products that may be approved in the future by the FDA or comparable foreign regulatory authorities, we must build our sales and marketing capabilities or make arrangements with third parties to perform these services. Though we currently plan to retain North American commercialization rights to our products in circumstances where we believe that we can successfully commercialize such products on our own or with a partner, we may not be able to successfully develop our own sales and marketing force for product candidates for which we have retained marketing rights. In addition, we may co-promote our product candidates in North America with any future collaborators, or we may rely on other third parties to perform sales and marketing services for our product candidates, in order to achieve a variety of business objectives, including expanding the market or accelerating penetration. If we develop our own sales and marketing capability, we may be competing with other companies that currently have experienced and well-funded sales and marketing operations.

If we do enter into arrangements with third parties to perform sales and marketing services, our product revenues may be lower than if we directly sold and marketed our products and any revenues received under such arrangements will depend on the skills and efforts of others. If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not be able to generate product revenue and may not become profitable.

If physicians and patients do not accept our future products, we may be unable to generate significant revenue, if any.

Even if we or a future collaborator receives regulatory approval for our product candidates, these product candidates may not gain market acceptance among physicians, healthcare payors, government pricing agencies, patients and the medical community. Physicians may elect not to recommend or patients may elect not to use these products for a variety of reasons, including:

- prevalence and severity of adverse side effects;

ineffective marketing and distribution support;

timing of market introduction of competitive products;

lack of availability of, or inadequate reimbursement from managed care plans and other third-party or government payors;

Table of Contents

lower demonstrated clinical safety and efficacy compared to other products;

other potential advantages of alternative treatment methods; and

lack of cost-effectiveness or less competitive pricing.

If our approved drugs fail to achieve market acceptance, we will not be able to generate significant revenue, if any.

If the government and third-party payors fail to provide coverage and adequate payment rates for our future products, if any, our revenue and prospects for profitability will be harmed.

In both domestic and foreign markets, our sales of any future products will depend in part upon the availability of reimbursement from third-party payors. Such third-party payors include government health programs such as Medicare and Medicaid, managed care providers, private health insurers and other organizations. These third-party payors are increasingly attempting to contain healthcare costs by demanding price discounts or rebates and limiting both coverage on which drugs they will pay for and the amounts that they will pay for new drugs. As a result, they may not cover or provide adequate payment for our drugs.

We might need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of any future products to such payors satisfaction. Such studies might require us to commit a significant amount of clinical development resources and management time as well as incur significant financial and other expense. Our future products might not ultimately be considered cost-effective. Adequate third-party reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

In the United States there have been, and we expect that there will continue to be, a number of federal and state proposals to implement governmental pricing reimbursement controls. The Medicare Prescription Drug and Modernization Act of 2003 imposed new requirements for the distribution and pricing of prescription drugs that may affect the marketing of our products, if we obtain FDA approval for those products. Under this law, Medicare was extended to cover a wide range of prescription drugs other than those directly administered by physicians in a hospital or medical office. Competitive regional private drug plans were authorized to establish lists of approved drugs, or formularies, and to negotiate rebates and other price control arrangements with drug companies. Proposals to allow the government to negotiate Medicare drug prices with drug companies directly, if enacted, might further constrain drug prices, leading to reduced revenues and profitability. While we cannot predict whether any future legislative or regulatory proposals will be adopted, the adoption of such proposals could have a material adverse effect on our business, financial condition and profitability.

Foreign governments tend to impose strict price controls on pharmaceutical products, which may adversely affect our revenues, if any.

In some foreign countries, particularly the countries of the European Union, Canada and Japan, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of 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 candidate to other available therapies. In some countries, the pricing is limited by the pricing of existing or comparable therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to enter into collaborative development and commercialization agreements and our revenues from these agreements could be adversely affected.

There is a substantial risk of product liability claims in our business. If we are unable to obtain sufficient insurance, a product liability claim against us could adversely affect our business.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face even greater risks upon any commercialization by us of our product

Table of Contents

candidates. We have product liability insurance covering our clinical trials in the amount of $10 million, which we believe is adequate to cover any current product liability exposure we may have. However, liabilities may exceed the extent of our coverage, resulting in material losses. Clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to obtain sufficient insurance or increase our existing coverage at a reasonable cost to protect us against losses that could have a material adverse effect on our business. An individual may bring a product liability claim against us if one of our products or product candidates causes, or is claimed to have caused, an injury or is found to be unsuitable for consumer use. Any product liability claim brought against us, with or without merit, could result in:

liabilities that substantially exceed our product liability insurance, which we would then be required to pay from other sources, if available;

an increase of our product liability insurance rates or the inability to maintain insurance coverage in the future on acceptable terms, or at all;

withdrawal of clinical trial volunteers or patients;

damage to our reputation and the reputation of our products, resulting in lower sales;

regulatory investigations that could require costly recalls or product modifications;

litigation costs; and

the diversion of management s attention from managing our business.

Risks Related to Our Intellectual Property

If the combination of patents, trade secrets and contractual provisions that we rely on to protect our intellectual property is inadequate to provide us with market exclusivity, our ability to successfully commercialize our product candidates will be harmed and we may not be able to operate our business profitably.

Our success depends, in part, on our ability to obtain, maintain and enforce our intellectual property rights both domestically and abroad. The patent position of biotechnology companies is generally highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. The validity, enforceability and commercial value of these rights, therefore, are highly uncertain.

Our patents may not protect us against our competitors. The issuance of a patent is not conclusive as to its scope, validity or enforceability. The scope, validity or enforceability of our patents can be challenged in litigation. Such litigation is often complex, can involve substantial costs and distraction and the outcome of patent litigation is often uncertain. If the outcome is adverse to us, third parties may be able to use our patented inventions and compete directly with us, without payment to us. Third parties may also be able to circumvent our patents by design innovations. We may not receive any additional patents based on the applications that we have filed and are currently pending.

Because patent applications in the United States and many foreign jurisdictions are typically not published until 18 months after filing or, in some cases, not at all, and because publications of discoveries in the scientific literature often lag behind actual discoveries, neither we nor our licensors or collaborators can be certain that they or we were the first to make the inventions claimed in patents or pending patent applications, or that they or we were the first to file for protection of the inventions set forth in these patent applications. Assuming the other requirements for

patentability are met, in the United States, the first to make the claimed invention is entitled to the patent, and outside the United States, the first to file is entitled to the patent.

Many of the proteins that are the APIs in our product candidates are off-patent. Therefore, we have obtained and are seeking to obtain patents directed to novel compositions of matter, formulations, methods of manufacturing and methods of treatment to protect some of our products. Such patents may not, however, prevent our competitors from developing products using the same APIs but different manufacturing methods or formulation technologies that are not covered by our patents.

Table of Contents

If third parties successfully assert that we have infringed their patents and proprietary rights or challenge the validity of our patents and proprietary rights, we may become involved in intellectual property disputes and litigation that would be costly, time consuming, and could delay or prevent the development or commercialization of our product candidates.

Our ability to commercialize our product candidates depends on our ability to develop, manufacture, market and sell our product candidates without infringing the proprietary rights of third parties. Third parties may allege our product candidates infringe their intellectual property rights. Numerous United States and foreign patents and pending patent applications, which are owned by third parties, exist in fields that relate to our product candidates and our underlying technology, including patents and patent applications claiming compositions of matter of, methods of manufacturing, and methods of treatment using, specific proteins, combinations of proteins, and protein crystals. For example, we are aware of some issued United States and/or foreign patents that may be relevant to the development and commercialization of our product candidates. However, we believe that, if these patents were asserted against us, it is likely that we would not be found to infringe any valid claim of the patents relevant to our development and commercialization of these products. If any of these patents were asserted against us and determined to be valid and construed to cover any of our product candidates, including, without limitation, Trizytek, ALTU-238 and ALTU-237, our development and commercialization of these products could be materially adversely affected.

Although we believe it is unlikely that we would be found to infringe any valid claim of these patents, we may not succeed in any action in which the patents are asserted against us. In order to successfully challenge the validity of any United States patent, we would need to overcome a presumption of validity. This burden is a high one requiring clear and convincing evidence. If any of these patents were found to be valid and we were found to infringe any of them, or any other patent rights of third parties, we would be required to pay damages, stop the infringing activity or obtain licenses in order to use, manufacture or sell our product candidates. Any required license might not be available to us on acceptable terms, or at all. If we succeeded in obtaining these licenses, payments under these licenses would reduce any earnings from our products. In addition, some licenses might be non-exclusive and, accordingly, our competitors might gain access to the same technology as that which was licensed to us. If we failed to obtain a required license or were unable to alter the design of our product candidates to make the licenses unnecessary, we might be unable to commercialize one or more of our product candidates, which could significantly affect our ability to establish and grow our commercial business.

In order to protect or enforce our patent rights, defend our activities against claims of infringement of third-party patents, or to satisfy contractual obligations to licensees of our own intellectual property, we might be required to initiate patent litigation against third parties, such as infringement suits or nullity, opposition or interference proceedings. Our collaborators or we may enforce our patent rights under the terms of our major collaboration and license agreements, but neither we nor our collaborators is required to do so. In addition, others may sue us for infringing their patent rights or file nullity, opposition or interference proceedings against our patents, even if such claims are without merit.

Intellectual property litigation is relatively common in our industry and can be costly. Even if we prevail, the cost of such litigation could deplete our financial resources. Litigation is also time consuming and could divert management s attention and resources away from our business. Furthermore, during the course of litigation, confidential information may be disclosed in the form of documents or testimony in connection with discovery requests, depositions or trial testimony. Disclosure of our confidential information and our involvement in intellectual property litigation could materially adversely affect our business. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. In addition, any uncertainties resulting from the initiation and continuation of any litigation could significantly limit our ability to continue our operations.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. While we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have inadvertently or otherwise used or disclosed intellectual property, trade

Table of Contents

secrets or other proprietary information of any such employee s former employer. Litigation may be necessary to defend against these claims and, even if we are successful in defending ourselves, could result in substantial costs or be distracting to management. If we fail in defending such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel.

If we are unable to protect our trade secrets, we may be unable to protect our interests in proprietary technology, processes and know-how that is not patentable or for which we have elected not to seek patent protection.

In addition to patented technology, we rely upon unpatented proprietary technology, processes and know-how, including particularly our manufacturing know-how relating to the production of the crystallized proteins used in the formulation of our product candidates. In an effort to protect our unpatented proprietary technology, processes and know-how, we require our employees, consultants, collaborators, contract manufacturers and advisors to execute confidentiality agreements. These agreements, however, may not provide us with adequate protection against improper use or disclosure of confidential information, in particular as we are required to make such information available to a larger pool of people as we seek to increase production of our product candidates and their component proteins. These agreements may be breached, and we may not become aware of, or have adequate remedies in the event of, any such breach. In addition, in some situations, these agreements may conflict with, or be subject to, the rights of third parties with whom our employees, consultants, collaborators, contract manufacturers or advisors have previous employment or consulting relationships. Also, others may independently develop substantially equivalent technology, processes and know-how or otherwise gain access to our trade secrets. If we are unable to protect the confidentiality of our proprietary technology, processes and know-how, competitors may be able to use this information to develop products that compete with our products, which could adversely impact our business.

If we fail to comply with our obligations in the agreements under which we licensed development, commercialization or other technology rights to products or technology from third parties, we could lose license rights that are important to our business or incur financial obligations based on our exercise of such license rights.

Some of our license agreements provide for licenses to us of technology that is important to our business, and we may enter into additional agreements in the future that provide licenses to us of valuable technology. These licenses impose, and future licenses may impose, various commercialization, milestone and other obligations on us. If we fail to comply with these obligations, the licensor may have the right to terminate the license even where we are able to achieve a milestone or cure a default after a date specified in an agreement, in which event we would lose valuable rights and our ability to develop our product candidates. For example, under the terms of our strategic alliance agreement with CFFTI, we granted CFFTI an exclusive license under our intellectual property rights covering Trizytek and specified derivatives for use in all applications and indications in North America, and CFFTI granted us back an exclusive sublicense of the same scope, including the right to grant sublicenses. CFFTI has the right to retain its exclusive license and terminate our sublicense if we fail to meet specified development milestones, there occurs an unresolved deadlock under the agreement and we discontinue our development activities, there occurs a material default in our obligations under the agreement not cured on a timely basis, including a failure to make required license fee payments to CFFTI on a timely basis if Trizytek is approved by the FDA, or a bankruptcy or similar proceeding is filed by or against us. The retention by CFFTI of its exclusive license to Trizytek and termination of our sublicense would have a material adverse effect on our business.

In addition, we rely on Amano s intellectual property relating to the manufacturing process used to produce the APIs for Trizytek, as well as upon technology jointly developed by us and Amano related to the production of those enzymes. Amano has granted a license to us of its proprietary technology and its rights under technology jointly developed during our collaboration, which we may sublicense to contract manufacturers we select. Our agreement with Amano requires us to pay Amano a royalty based on the cost of the materials supplied to us by other contract manufacturers. If we were to breach our agreement with Amano, we

57

Table of Contents

would be required to pay Amano a higher royalty based on net sales of Trizytek to retain our rights to Amano s independently and jointly-developed process technology.

Risks Related to Our Employees and Growth

Our future success depends on our ability to attract, retain and motivate key executives and personnel and to attract, retain and motivate qualified personnel.

We are a small company with 160 employees as of December 31, 2007. Our success depends on our ability to attract, retain and motivate highly qualified management, development and scientific personnel. Our President and Chief Executive Officer, Sheldon Berkle, resigned on February 4, 2008. We are currently recruiting a President and Chief Executive Officer, and the Chairman of our Board of Directors, David D. Pendergast, Ph.D., has been appointed to lead our senior management team on an interim basis as Executive Chairman. Our future success is dependent on Dr. Pendergast s leadership during this transition period, and on attracting a new President and Chief Executive Officer in a timely manner.

All of the arrangements we have with the key members of our executive, development and scientific teams may be terminated by us or the employee at any time without notice. Although we do not have any reason to believe that we may lose the services of any of these persons in the foreseeable future, the loss of the services of any of these persons might impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining qualified development and scientific personnel and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of development and scientific personnel from universities and research institutions. We do not maintain key person insurance on any of our employees.

As we evolve from a company primarily involved in drug research and development into one that may become involved in the commercialization of drug products, we may have difficulty managing our growth, which could disrupt our operations.

As we advance our drug candidates through the development process, we will need to expand our development, regulatory, manufacturing, sales and marketing capabilities or contract with other organizations to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various contract manufacturers, collaborative partners, suppliers and other organizations. Our ability to manage our operations and growth requires us to continue to improve our operational, financial and management controls, reporting systems and procedures. Such growth could place a strain on our management, administrative and operational infrastructure. We may not be able to make improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls. In addition, the physical expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Risks Related to Our Common Stock and Public Company Compliance Requirements

Our stock price has been and is likely to continue to be volatile.

Investors should consider an investment in our common stock as risky and subject to significant loss and wide fluctuations in market value. Our common stock has only been publicly traded since January 26, 2006, and

accordingly there is a limited history on which to gauge the volatility of our stock price. Our stock price has, however, been volatile since we began to be publicly traded. For example, our stock price declined approximately 50% following our announcement that our collaboration with Genentech had been terminated in December 2007. The stock market as a whole has experienced significant volatility, particularly with respect to pharmaceutical, biotechnology and other life sciences company stocks. The volatility of pharmaceutical, biotechnology and other life sciences company stocks may not relate to the operating performance of the

Table of Contents

companies represented by the stock. Some of the factors that may cause the market price of our common stock, which has been between $4.80 and $25.70 per share from the time of our initial public offering until March 3, 2008, to continue to fluctuate include:

- delays in or results from our clinical trials or studies;
- our entry into or the loss of a significant collaboration or the expansion or contraction of a significant collaboration, disputes with a collaborator, or delays in the progress of a collaborative development program;
- competitive product information such as results of clinical trials conducted by others on drugs that would compete with our product candidates or the regulatory filing or approval of such competitive products;
- delays or other problems with manufacturing our product candidates or approved products;
- failure or delays in advancing product candidates from our preclinical programs, or other product candidates we may discover or acquire in the future, into clinical trials;
- failure or discontinuation of any of our research programs;
- regulatory review delays, changes in regulatory requirements, new regulatory developments or enforcement policies in the United States and foreign countries;
- developments or disputes concerning patents or other proprietary rights;
- introduction of technological innovations or new commercial products by us or our competitors;
- changes in estimates or recommendations by securities analysts, if any, who cover our common stock;
- failure to meet estimates or recommendations by securities analysts, if any, who cover our common stock;
- positive or negative publicity regarding our product candidates or any approved products;
- litigation;
- sales, future sales or anticipated sales of our common stock by us or our stockholders;
- changes in the structure of health care payment systems;
- failure of any of our product candidates, if approved, to achieve commercial success;
- economic and other external factors or other disasters or crises;
- period-to-period fluctuations in our financial results; and
- general market conditions.

These and other external factors may cause the market price and demand for our common stock to fluctuate substantially, which may limit or prevent investors from readily selling their shares of common stock and may otherwise negatively affect the liquidity of our common stock. In addition, in the past, when the market price of a

stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our stockholders brought a lawsuit against us, we could incur substantial costs defending the lawsuit regardless of the validity of the claims or the ultimate outcome. Such a lawsuit could also divert the time and attention of our management and create additional volatility in our common stock price.

Table of Contents

We have limited experience attempting to comply with public company obligations. Attempting to comply with these requirements will increase our costs and require additional management resources, and we still may fail to comply.

We face and will continue to face substantial growth in legal, accounting, administrative and other costs and expenses as a public company that we did not incur as a private company. Compliance with the Sarbanes-Oxley Act of 2002, as well as other rules of the SEC, the Public Company Accounting Oversight Board and The Nasdaq Stock Market has resulted in a significant initial cost to us as well as an ongoing increase in our legal, audit and financial compliance costs. We are required to include the reports required by Section 404 of the Sarbanes-Oxley Act relating to internal controls over financial reporting in our SEC reports. We have completed a formal process to evaluate our internal controls over financial reporting for purposes of Section 404, and although we believe that our internal control over financial reporting are effective, we cannot assure that this will prove to be the case. Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Given the status of our efforts, coupled with the fact that guidance from regulatory authorities in the area of internal controls continues to evolve, we cannot be certain that we will be able to comply with the applicable regulations and deadlines. Any failure to implement required new or improved internal controls over financial reporting, or difficulties encountered in their implementation, could harm our operating results or cause us to fail to meet our reporting obligations. Ineffective internal controls over financial reporting could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our common stock.

If the estimates we make and the assumptions on which we rely in preparing our financial statements prove inaccurate, our actual results and our stock price may vary significantly.

Our financial statements have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires us to make estimates, accruals and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses and related disclosure. Such estimates and judgments include the carrying value of our property, equipment and other assets, revenue recognition under our collaboration agreement and the value of certain accrued expenses. We base our estimates, accruals and judgments on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. However, these estimates and judgments, or the assumptions underlying them, may change over time. For example, since the inception of our collaboration agreement with CFFTI, we have adjusted our estimated costs to complete the development program for Trizytek on five occasions resulting in cumulative changes in our revenue at each time of the change in the estimate. During the third quarter of 2007, we increased our estimated total development costs for Trizytek from $137.5 million to $157.5 million, which resulted in a $2.0 million decrease in our cumulative revenue in the third quarter of 2007. During the third quarter of 2006, we increased our estimated development costs for Trizytek, which resulted in a $3.7 million decrease in our cumulative revenue in the third quarter of 2006. Given the possibility that our estimates may change, our actual financial results may vary significantly from the estimates contained in our financial statements, our capital requirements may increase and our stock price could be adversely affected.

Insiders have substantial influence over us which could delay or prevent a change in corporate control or result in the entrenchment of management and the board of directors.

Our directors and executive officers, together with their affiliates and related persons as of March 3, 2008, beneficially owned, in the aggregate, approximately 26% of our outstanding common stock. As a result, these stockholders, if acting together, may have the ability to influence significantly the outcome of matters submitted to our stockholders for approval, including the election and removal of directors and any merger, consolidation or sale of all or substantially all of our assets. In addition, these persons, acting together, may have the ability to control the management and affairs of our company. Accordingly, this concentration of ownership may harm the market price of

our common stock by:

- delaying, deferring or preventing a change in control;
- entrenching our management and the board of directors;

Table of Contents

impeding a merger, consolidation, takeover or other business combination involving us; or

discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us.

Entities affiliated with Warburg Pincus Private Equity VIII, L.P., or Warburg Pincus, one of our principal stockholders, are entitled to designate up to two individuals as candidates to our board of directors, for so long as Warburg Pincus owns at least 2,691,935 shares of our common stock, or one individual for so long as Warburg Pincus owns at least 1,794,623 shares of our common stock. We have agreed to nominate and use our reasonable efforts to cause the election of such candidates. Currently, Stewart Hen and Jonathan S. Leff are the members of our board of directors designated by Warburg Pincus.

A significant portion of our total outstanding shares 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.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. We had 30,832,286 shares of common stock outstanding as of March 3, 2008. Holders of up to an aggregate of 17,216,958 shares of our common stock, assuming the exercise of warrants to purchase shares of our 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. We have registered all shares of common stock issuable under our equity compensation plans and they can now be freely sold in the public market upon issuance. A decline in the price of shares of our common stock might impede our ability to raise capital through the issuance of additional shares of our common stock or other equity securities, and may cause our stockholders to lose part or all of their investments in our shares of common stock.

Provisions of our charter, bylaws, and Delaware law may make an acquisition of us or a change in our management more difficult.

Certain provisions of our certificate of incorporation and bylaws could discourage, delay or prevent a merger, acquisition or other change in control that stockholders may consider favorable, including transactions in which stockholders might otherwise receive a premium for their shares. These provisions could limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. Stockholders who wish to participate in these transactions may not have the opportunity to do so. Furthermore, these provisions could prevent or frustrate attempts by our stockholders to replace or remove our management. These provisions:

allow the authorized number of directors to be changed only by resolution of our board of directors;

establish a classified board of directors, such that not all members of the board are elected at one time;

authorize our board of directors to issue without stockholder approval blank check preferred stock that, if issued, could operate as a poison pill to dilute the stock ownership of a potential hostile acquirer to prevent an acquisition that is not approved by our board of directors;

require that stockholder actions must be effected at a duly called stockholder meeting and prohibit stockholder action by written consent;

establish advance notice requirements for stockholder nominations to our board of directors or for stockholder proposals that can be acted on at stockholder meetings;

limit who may call stockholder meetings; and

require the approval of the holders of 80% of the outstanding shares of our capital stock entitled to vote in order to amend certain provisions of our restated certificate of incorporation and restated bylaws.

Table of Contents

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which may, unless certain criteria are met, prohibit large stockholders, in particular those owning 15% or more of our outstanding voting stock, from merging or combining with us for a prescribed period of time.

ITEM 1B. ***UNRESOLVED STAFF COMMENTS***

None.

ITEM 2. ***PROPERTIES***

As of March 3, 2008, we leased or subleased a total of approximately 272,470 square feet of office and laboratory space. The leased and subleased properties are described below:

Location	Approximate Square Footage	Use	Expiration Date
610 Lincoln Street North, Waltham, MA(1)	63,880(2)	Laboratory and Office	3/31/18
333 Wyman Street, Waltham, MA(1)	83,405	Office	3/31/18
640 Memorial Drive, Cambridge, MA	72,935	Laboratory and Office	(3)
625 Putnam Avenue, Cambridge, MA	15,750	Laboratory and Office	(4)
195 Albany Street, Cambridge, MA	16,000	Laboratory and Office	12/31/08
125 Sidney Street, Cambridge, MA	20,500	Office	(5)

(1) We entered into lease agreements for these neighboring facilities in Waltham, MA in October 2007, which will serve as our office headquarters and laboratory space. These leases commence on April 1, 2008 and we plan to occupy the facilities in the third quarter of 2008 after leasehold improvements are complete. At that time, we intend to vacate our three Cambridge facilities and consolidate our operations at the Waltham facilities.

(2) Under the terms of the lease for our facility at 610 Lincoln Street North, our initial leased area is approximately 63,880 square feet. Beginning in June 2009, our leased area increases to 85,430 square feet for the remainder of the lease term.

(3) This lease has an original expiration date of March 31, 2008 and converts to a monthly lease until December 31, 2008. We can terminate this lease at anytime between March 31, 2008 and December 31, 2008 with 60 days written notice to the landlord of this facility.

(4) We have informed our landlord for the 625 Putnam Avenue facility of our intent to terminate our lease effective October 31, 2008, as is permitted by the lease agreement.

(5) We have informed our landlord for the 125 Sidney Street facility of our intent to terminate our lease effective November 30, 2008, as is permitted by the lease agreement.

ITEM 3. ***LEGAL PROCEEDINGS***

We are not currently a party to any material legal proceedings.

ITEM 4. ***SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS***

No matters were submitted to a vote of our security holders during the quarter ended December 31, 2007.

Table of Contents

PART II

ITEM 5. *MARKET FOR REGISTRANT S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES*

Market Information

Our common stock is traded on The Nasdaq Global Market under the s