Altus Pharmaceuticals Inc.
Form 10-K
March 12, 2007

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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, 2006

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.)*
125 Sidney Street, 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 Global 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, or a non-accelerated filer. See definition of accelerated filer and large accelerated filer in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer o Accelerated filer o Non-accelerated filer þ

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 30, 2006 was $410,446,726.

The number of shares outstanding of the registrant s common stock as of February 28, 2007 was 23,995,477.

DOCUMENTS INCORPORATED BY REFERENCE

None.

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EX-3.1 Restated Certificates of Incorporation of the Registrant
EX-10.4 2002 Employee, Director and Consultant Stock Plan
EX-10.9 Director Compensation Policy dated February 2, 2007
EX-10.13 Agreement between Lauren Sabella, dated April 4, 2006
EX-10.14 Agreement between Burkhard Blank, dated June 2, 2006
EX-10.15 Agreement between John Sorvillo, dated July 31, 2006
EX-10.16 Agreement between Renato Fuchs, dated August 14, 2006
EX-10.17 Agreement between Bruce Leicher, dated October 31, 2006
EX-23.1 Consent of Independent Registered Public Accounting Firm
EX-31.1 Section 302 Certification of C.E.O.
EX-31.2 Section 302 Certification of C.F.O.
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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 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 anticipates, believes, could, estimates, expects, intends, may, plans, potential, predicts, projects, should, will, would and similar expressi 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.

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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 and us in this report refer to Altus Pharmaceuticals Inc. and our subsidiary.

Our principal executive offices are located at 125 Sidney Street, Cambridge, MA 02139, and our telephone number is (617) 299-2900. Our web site address is *www.altus.com.* The information contained on, or that can be accessed through, our web site is not incorporated by reference into this report. We have included our web site address as a factual reference and do not intend it to be an active link to our web site. 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 web site as soon as reasonably practicable after such materials have been electronically filed with, or furnished to, the Securities and Exchange Commission.

Altus is a trademark 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 two product candidates advancing toward late stage 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 degrade toxic metabolites in the gut or increase the amount of a protein that is in short supply in the body. We have successfully completed a Phase II clinical trial of ALTU-135 for the treatment of malabsorption due to exocrine pancreatic insufficiency and we have also successfully completed a Phase II clinical trial of ALTU-238 in adults for the treatment of growth hormone deficiency. We are developing ALTU-238 under an agreement with Genentech, Inc., or Genentech, relating to the development, manufacture and commercialization of this product candidate in North America. We have a pipeline of other product candidates in preclinical research and development. Our most advanced preclinical product candidate is ALTU-237, which 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.

ALTU-135 for Malabsorption due to Exocrine Pancreatic Insufficiency

Our lead product candidate, ALTU-135, 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 $739 million in 2006.

We believe that ALTU-135, if approved, will have significant competitive advantages compared to existing pancreatic enzyme replacement therapies. We believe these potential advantages include:

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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;

a pre-specified and consistent ratio of lipase, protease and amylase;

more consistent and reliable dosing;

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 is the largest well-controlled, scientifically rigorous prospective clinical trial conducted to date in 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. We believe that some of the manufacturers of these products may not be able to satisfy the FDA s requirements for NDAs for these products.

In 2005, we completed a prospective, randomized, double-blind, dose-ranging Phase II clinical trial of the capsule form of ALTU-135. The results of this trial demonstrated that ALTU-135 was well tolerated and in the two higher dose treatment arms ALTU-135 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. However, the results of our Phase II clinical trial may not be predictive of the results in our planned Phase III clinical trial of ALTU-135. We expect to initiate a pivotal Phase III clinical efficacy trial of the capsule form of ALTU-135 in patients with cystic fibrosis in the second quarter of 2007 and a long-term safety study in cystic fibrosis patients and chronic pancreatitis patients with pancreatic insufficiency in the second quarter of 2007. The FDA and the European Medicines Agency, or EMEA, have granted ALTU-135 orphan drug designation, which generally provides a drug being developed for a rare disease or condition with marketing exclusivity for seven years in the United States and ten years in the European Union if it is the first drug of its type approved for such indication. In December 2006, the FDA informed us of its intention to revoke our orphan drug designation because it found the prevalence of pancreatic insufficiency exceeded the statutory 200,000 patient limit if all HIV/AIDS patients who suffer from fat malabsorption were included in the patient population. We responded to the FDA that it was never our intent to include HIV/AIDS patients in the orphan population since the vast majority of these patients display malabsorption for reasons other than pancreatic insufficiency. We proposed, if necessary, modifying our orphan drug designation to clarify the exclusion of

HIV/AIDS patients. We believe this proposal will enable us to preserve our orphan drug designation in the United States. Additionally, the FDA has granted ALTU-135 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.

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We have a collaboration with Dr. Falk Pharma GmbH, or Dr. Falk, a specialty pharmaceutical company headquartered in Germany, to commercialize ALTU-135 in Europe, the countries of the former Soviet Union, Israel and Egypt. We also have a strategic alliance agreement with Cystic Fibrosis Foundation Therapeutics, Inc., or CFFTI, which is funding a portion of the development of ALTU-135.

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 $2.5 billion in 2006, and the market grew at a compound annual growth rate of approximately 9.1% from 2002 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 study, we identified doses of ALTU-238 that achieved 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.

We recently entered into an agreement with Genentech to develop, manufacture and commercialize ALTU-238. The agreement, which became effective on February 21, 2007, provides for an exclusive North American collaboration and license arrangement, which Genentech has the option to expand to a global arrangement. In connection with the North American agreement, we anticipate receiving a $15 million up-front payment in March 2007. Genentech also purchased 794,575 shares of our common stock on February 27, 2007 for an aggregate purchase price of $15 million. We have the potential to receive additional payments of approximately $148 million based upon the achievement of all development and commercialization milestones for North America. If Genentech exercises its option to extend the collaboration globally, we have the potential to receive additional payments of approximately $110 million, comprising an option exercise fee and payments contingent upon the achievement of all development and commercialization milestones relating to countries outside of North America. Genentech will be responsible for all ALTU-238 development and commercialization costs in North America and, if Genentech exercises its option to make this a global agreement, all such costs. We have the option to co-promote ALTU-238 with Genentech in North America. If we exercise this option, Genentech will pay us for our co-promotion efforts for a limited period of time. We are entitled to receive royalties based on annual net sales of hGH-related products resulting from the collaboration. Genentech has control over the development and commercialization of ALTU-238.

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. Our most advanced preclinical product candidate is ALTU-237, which we are developing 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. 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

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in people who have kidney stone disease. We expect to file an investigational new drug application, or IND, for ALTU-237 for the treatment of hyperoxalurias in the first half of 2007.

We are currently testing our product candidate ALTU-236 in animal models for the treatment of phenylketonuria, or PKU, which currently lacks any approved pharmaceutical therapies. 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.

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 ALTU-135 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 preclinical product candidates.

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 two product candidates advancing toward late stage clinical development. We are preparing ALTU-135 for a pivotal Phase III clinical trial and a long-term safety study for the treatment of malabsorption due to exocrine pancreatic insufficiency. Based on our discussions with the FDA, we believe that the results of these two clinical trials will be sufficient to support an NDA filing for ALTU-135 with the FDA. In addition, we have completed a Phase II clinical trial of ALTU-238 in adult growth hormone deficient patients. We expect Genentech to advance ALTU-238 into a Phase III clinical trial in adults and Phase II and Phase III clinical trials in pediatric patients. 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.

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 hyperoxalurias, phenylketonuria, gout, and other gastrointestinal and metabolic diseases. We plan to apply the manufacturing, clinical and regulatory experience gained from our

two lead product candidates to advance a number of these preclinical product candidates into clinical trials over the next few years. We also plan to add additional product candidates to our pipeline through the application of our proprietary protein crystallization

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technology to existing protein therapeutics or known proteins with potential therapeutic use. We plan to file an IND for ALTU-237 for the treatment of hyperoxalurias in the first half of 2007.

Establish a commercial infrastructure. We plan to establish a commercial infrastructure and targeted specialty sales force to market ALTU-135 in North America. We may also exercise our right to co-promote ALTU-238 with Genentech 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 have established two such collaborations to date, including a collaboration with Dr. Falk for the commercialization of ALTU-135 in Europe, the countries of the former Soviet Union, Israel and Egypt and a collaboration with Genentech for the development and commercialization of ALTU-238 in North America. We intend to develop additional collaborations in markets outside of North America 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 additional 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.

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.

Product Candidate (Method of Delivery) Indication	Stage of Development	Commercial Rights	Status
ALTU-135 (oral) *Exocrine Pancreatic Insufficiency*	Phase II completed	Altus (United States and rest of world, except as noted below) Dr. Falk (Europe, the countries of the former Soviet Union, Israel and Egypt)	Phase III clinical efficacy trial and long-term safety study to support NDA submission are expected to begin in the second quarter of 2007. An alternative dosage form of ALTU-135 is in development for children and adults who have difficulty swallowing capsules.

ALTU-238 (injectable) *Growth Disorders*	Phase II completed	Altus (North America co-promote option, Europe and rest of world, subject to Genentech s option) Genentech (North America with option for rest of world)	Timing of a Phase III clinical trial in adults and Phase II and III clinical trials in pediatric patients expected to be finalized after the completion of a development plan with Genentech.

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Product Candidate (Method of Delivery) Indication	Stage of Development	Commercial Rights	Status
ALTU-237 (oral) *Hyperoxalurias*	Preclinical	Altus	IND enabling work in progress, with IND filing expected in the first half of 2007.
ALTU-236 (oral) *Phenylketonuria*	Preclinical	Altus	Preclinical testing in animal models
ALTU-242 (oral) *Gout*	Preclinical	Altus	Preclinical testing in animal models

ALTU-135 for Exocrine Pancreatic Insufficiency

Our lead product candidate, ALTU-135, is an orally administered enzyme replacement therapy for which we have 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 ALTU-135 represents a significant potential advancement as a therapeutic alternative for the treatment of these patients.

ALTU-135 contains three types of digestive enzymes derived from non-animal sources:

Lipase. We selected the lipase in ALTU-135, 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 the lipase for increased activity and stability;

Protease. We selected the protease in ALTU-135, 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

Amylase. We selected the amylase in ALTU-135, 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 ALTU-135 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.

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According to IMS Health, the worldwide market for pancreatic enzyme replacement therapies grew at a compound annual growth rate of approximately 6% from $658 million in 2004 to approximately $739 million in 2006. The market for these products in 2006 was approximately $226 million in North America, $252 million in Europe and $261 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% 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. The FDA has also issued guidance, known as 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 larger 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.

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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.

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.

Anticipated Advantages of ALTU-135

We believe that ALTU-135, 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. ALTU-135 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 ALTU-135 will reduce the pill burden for patients due to the following factors:

Stability of enzymes in the gastrointestinal tract. We have designed ALTU-135 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 ALTU-135 are crystallized, resulting in a highly concentrated and pure product that requires less material to achieve a desired therapeutic effect.

Consistent activity. We have designed ALTU-135 to exhibit consistent enzyme activity from batch to batch. The enzymes in ALTU-135 are microbially derived and produced through fermentation. The amount of material and related enzyme activity in a capsule of ALTU-135 is tightly controlled, as each of the three enzymes in ALTU-135 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.

Longer shelf life. Based on stability studies performed as part of our development program, we believe that ALTU-135 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 ALTU-135. We believe that an alternative dosage formulation is an important option for children and adults who are unable to swallow capsules.

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ALTU-135 Development Activities and Strategy

We have successfully completed a Phase II clinical trial of the capsule form of ALTU-135 and are preparing to advance this product candidate into a pivotal Phase III clinical efficacy trial in patients with cystic fibrosis and a long-term safety study in cystic fibrosis patients and chronic pancreatitis patients with pancreatic insufficiency, each in the second quarter of 2007. The FDA and the EMEA have granted ALTU-135 orphan drug designation for malabsorption due to exocrine pancreatic insufficiency. In December 2006, the FDA informed us of its intention to revoke our orphan drug designation because it found the prevalence of pancreatic insufficiency exceeded the statutory 200,000 patient limit if all HIV/AIDS patients who suffer from fat malabsorption were included in the patient population. We responded to the FDA that it was never our intent to include HIV/AIDS patients in the orphan population since the vast majority of these patients display malabsorption for reasons other than pancreatic insufficiency. We proposed, if necessary, modifying our orphan drug designation to clarify the exclusion of HIV/AIDS patients. We believe this proposal will enable us to preserve our orphan drug designation in the United States. The FDA has also granted ALTU-135 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, ALTU-135 was also admitted to the FDA s 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. If the Phase III clinical trial is successful, we plan to submit our NDA for ALTU-135 to the FDA in the first half of 2009.

We have completed four clinical trials of ALTU-135, three of which were in cystic fibrosis patients and one of which was in healthy volunteers. The following table summarizes the clinical trials of ALTU-135 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 ALTU-135 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.

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Phase II Clinical Trial

We successfully completed our Phase II clinical trial for ALTU-135 and presented the results of the trial at the North American Cystic Fibrosis Conference in October 2005. In the trial, ALTU-135 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.

We believe that this is the first clinical trial to demonstrate that the combination of the three enzymes in ALTU-135, 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 ALTU-135. As part of this work, we evaluated the assays used to measure the enzymatic activity of ALTU-135 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 ALTU-135. This USP assay, which is the standard for measuring lipase activity, is specified for porcine material and has 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 ALTU-135, we believe that:

- a formulation of ALTU-135 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 ALTU-135 per meal or snack; and
- patients with the most severe fat and protein malabsorption will realize the greatest benefit from treatment with ALTU-135.

Study Design and Demographics

The purpose of our Phase II clinical trial of ALTU-135 was to obtain initial efficacy data, select a dose level of ALTU-135 for further evaluation in our Phase III clinical trial and assess the safety and tolerability of ALTU-135 over a 28-day treatment period in cystic fibrosis patients with pancreatic insufficiency. We believe our Phase II clinical trial of ALTU-135 represents the largest prospective, 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, ALTU-135 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 ALTU-135 by measuring the change in CFA, the clinical activity of the protease component of ALTU-135 by measuring the change in CNA and the clinical activity of the amylase component of ALTU-135 by measuring the change in carbohydrate absorption.

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The Phase II clinical trial for ALTU-135 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.