TERCICA INC
Form 10-K
March 16, 2006
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# UNITED STATES

# SECURITIES AND EXCHANGE COMMISSION

**WASHINGTON, D.C. 20549**

# FORM 10-K

**x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
**For the fiscal year ended December 31, 2005**

**OR**

**¨ 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. 000-50461**

# TERCICA, INC.

**(Exact name of Registrant as specified in its charter)**

| **Delaware** | **26-0042539** |
|---|---|
| **(State or other jurisdiction of incorporation or organization)** | **(I.R.S. Employer Identification Number)** |

**2000 Sierra Point Parkway, Suite 400**

**Brisbane, CA 94005**

**(650) 624-4900**

**(Address, including zip code, and telephone number, including area code, of registrant s principal executive offices)**

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**Securities registered pursuant to Section 12(b) of the Act: None**

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

**Common Stock, $0.001 par value**

**(Title of class)**

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Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ¨ No x

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 ¨ No x

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 x No ¨

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. ¨

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 file in Rule 12b-2 of the Exchange Act (Check one):

Large accelerated filer ¨ Accelerated filer x Non-accelerated filer ¨

Indicate by check mark whether registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ¨ No x

The aggregate market value of the registrant s common stock, $0.001 par value, held by non-affiliates of the registrant as of June 30, 2005 was $114,824,133 (based upon the closing sales price of such stock as reported in the Nasdaq National Market on such date). Excludes an aggregate of 18,357,639 shares of the registrant s common stock held by officers and directors and by each person known by the registrant to own 5% or more of the registrant s outstanding common stock as of June 30, 2005. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

As of February 24, 2006, there were 37,485,469 shares of the registrant s common stock, $0.001 par value, outstanding.

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the registrant s definitive Proxy Statement for the 2006 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission pursuant to Regulation 14A not later than 120 days after the end of the fiscal year covered by this Form 10-K are incorporated by reference in Part III, Items 10-14 of this Form 10-K.

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**TERCICA, INC.**

**FORM 10-K ANNUAL REPORT**

**FOR THE YEAR ENDED DECEMBER 31, 2005**

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**PART I**

*This report includes forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities and Exchange Act of 1934, as amended. All statements other than statements of historical facts are forward-looking statements for purposes of these provisions, including any projections of earnings, revenues or other financial items, any statement of the plans and objectives of management for future operations, any statements concerning proposed new products or licensing or collaborative arrangements, any statements regarding future economic conditions or performance, and any statement of assumptions underlying any of the foregoing. In some cases, forward-looking statements can be identified by the use of terminology such as may, will, expects, plans, anticipates, estimates, potential, or continue or the negative thereof or other comparable terminology. Although we believe that the expectations reflected in the forward-looking statements contained herein are reasonable, there can be no assurance that such expectations or any of the forward-looking statements will prove to be correct, and actual results could differ materially from those projected or assumed in the forward-looking statements. Our future financial condition and results of operations, as well as any forward-looking statements, are subject to inherent risks and uncertainties, including but not limited to the Risk Factors set forth under Item 1A, and for the reasons described elsewhere in this report. All forward-looking statements and reasons why results may differ included in this report are made as of the date hereof, and we assume no obligation to update these forward-looking statements or reasons why actual results might differ.*

**Item 1. Business.**

We are a biopharmaceutical company focused on the development and commercialization of new therapeutics for the treatment of short stature and other endocrine disorders. Our first commercial product is Increlex , (mecasermin [rDNA origin] injection), a DNA-derived recombinant human insulin-like growth factor-1, or rhIGF-1. We obtained approval for the long-term treatment of growth failure in children with severe primary insulin-like growth factor deficiency, or severe Primary IGFD, from the U.S. Food and Drug Administration, or FDA, in August 2005, based on Phase III clinical trial data. In January 2006, we launched Increlex in the United States. In December 2005, we submitted a Marketing Authorization Application to the European Medicines Agency, or EMEA, seeking approval of long-term Increlex replacement therapy for severe Primary IGFD.

We licensed the rights of Genentech to develop, manufacture and commercialize rhIGF-1 products for a broad range of indications, including short stature, worldwide. Our current focus is on marketing and selling Increlex for the treatment of severe Primary IGFD and developing Increlex as a replacement therapy for primary IGF-1 deficiency, or Primary IGFD. We define the indication Primary IGFD to mean a child who has a height standard deviation score, or Height SDS, and an IGF-1 standard deviation score, or IGF-1 SDS, of less than minus two, and the indication severe Primary IGFD to mean a child who has a Height SDS and IGF-1 SDS of minus three or less, in each case in the presence of normal or elevated levels of growth hormone.

The endocrine system regulates metabolism through the use of hormones, including IGF-1. IGF-1 is a naturally occurring hormone that is necessary for normal human growth and metabolism. A deficiency of IGF-1 can result in short stature, which is characterized by children being shorter than approximately 97.5% of normal children, and can lead, in children and adults, to a range of other metabolic disorders. These metabolic disorders can include lipid abnormalities, decreased bone density, obesity and insulin resistance.

The cellular production of IGF-1 is regulated by growth hormone. Growth hormone deficiency, or GHD, leads to inadequate IGF-1 production, which results in short stature in children. Growth hormone replacement therapy, which increases IGF-1 levels, can be used to successfully treat GHD. However, we believe that many individuals with short stature, despite normal growth hormone secretion, are IGF-1 deficient because their cells do not respond normally to growth hormone. These children have Primary IGFD and are candidates for rhIGF-1

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replacement therapy. Increlex is identical to naturally occurring human IGF-1, and we believe it performs the same functions in the body.

Our most recent Phase III clinical trial results reflect the treatment of 76 children with severe Primary IGFD with rhIGF-1 replacement therapy for an average of 4.4 years, with some patients being treated for up to 12 years. None of the children withdrew from the study due to adverse events. Of these children, 62 completed at least one year of rhIGF-1 replacement therapy, which is the generally accepted minimum length of time required to adequately measure growth responses to drug therapy. A statistically significant increase in average growth rate from 2.8 cm per year prior to treatment to 8.0 cm per year after the first year of rhIGF-1 treatment was demonstrated in these patients ($p<0.0001$). Compared to pre-treatment growth rates, statistically significant increases were also observed during each of the next five years of rhIGF-1 treatment ($p<0.005$). We believe that these increases in growth rates were clinically meaningful and comparable to those observed in clinical trials of approved growth hormone treatments. Statistically significant increases in Height SDS compared to baseline were also observed for each of the first eight years of rhIGF-1 treatment ($p<0.001$).

We are also developing Increlex for use in the broad population of children with Primary IGFD. In late 2004, we initiated a Phase IIIb clinical trial of Increlex in children with Primary IGFD, which includes children with a less severe form of IGFD. In mid 2005 we initiated another Phase III study of Increlex in Primary IGFD, in which we are investigating once-daily dosing of Increlex. We are also assessing our Increlex development strategy for other indications.

Approximately one million children in the United States have short stature, and we believe that there are an equal number of children with short stature in Western Europe. Of the approximately 380,000 children in the United States referred to pediatric endocrinologists for evaluation of possible short stature, we believe that approximately 30,000 in the United States and an equal number in Western Europe, for a total of 60,000 children, have Primary IGFD. We believe that severe Primary IGFD constitutes approximately 20%, or 12,000, of the total population in the United States and Western Europe with Primary IGFD.

**Scientific Background**

***Role of IGF-1 in Growth and Metabolism***

The endocrine system regulates metabolism through the use of hormones, including IGF-1. IGF-1 is a naturally occurring hormone that is necessary for normal human growth and metabolism. A deficiency of IGF-1 can result in short stature, which is characterized by children being shorter than approximately 97.5% of normal children, and can lead, in children and adults, to a range of other metabolic disorders. These metabolic disorders can include lipid abnormalities, decreased bone density, obesity and insulin resistance. The cellular production of IGF-1 is regulated by growth hormone. Growth hormone deficiency leads to inadequate IGF-1 production, which results in short stature in children. Growth hormone replacement therapy, which increases IGF-1 levels, can often be used to successfully treat GHD. However, we believe many individuals with short stature, despite normal growth hormone secretion, are IGF-1 deficient, because their cells do not respond normally to growth hormone. These individuals have Primary IGFD, which is characterized clinically by short stature, IGF-1 deficiency and growth hormone sufficiency. Individuals with Primary IGFD are candidates for rhIGF-1 replacement therapy. Our product, Increlex, is identical to naturally occurring human IGF-1, and we believe it performs the same functions in the body.

IGF-1 is a 70 amino acid protein that must be present in tissues for normal growth and metabolism in humans. IGF-1 is normally produced as a result of a hormonal cascade beginning with the secretion of growth hormone by the pituitary gland. Growth hormone binds to a growth hormone receptor on a cell which initiates an intracellular process, known as intracellular signaling, that produces IGF-1. IGF-1 is released into the blood, and in the tissues stimulates cartilage and bone growth.

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Certain endocrine system disorders, including the failure of the pituitary gland to produce growth hormone, defective or nonexistent cell receptors that do not bind with growth hormone, or defects in the cell s growth hormone intracellular signaling, may inhibit the production of IGF-1. Insufficient blood levels of either IGF-1 or growth hormone in childhood result in short stature. Since the 1950s, children with low levels of growth hormone and resulting short stature have been given replacement growth hormone therapy, resulting in IGF-1 production and subsequent growth. However, there are children with short stature who, despite normal levels of growth hormone, have low levels of IGF-1. These children are IGF-1 deficient usually because of abnormalities in either their growth hormone receptors or in their growth hormone signaling pathways.

As children with IGFD become adults, they continue to suffer from the effects of IGF-1 deficiency. Since the growth plates in the long bones fuse and additional cartilage and bone growth can no longer occur after puberty, rhIGF-1 replacement therapy does not cause growth in adults. However, low levels of IGF-1 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 IGF-1 deficiency, as occurs in adulthood. We refer to this disorder as Adult IGFD.

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***Role of IGF-1 in Glucose Metabolism***

IGF-1 and insulin receptors have similar intracellular signaling pathways and overlapping metabolic effects. The clinical trial data we acquired from Genentech demonstrate that the use of rhIGF-1 significantly improved blood glucose control and insulin sensitivity in type 2 diabetic patients. We believe that rhIGF-1 may be useful in treating diabetic patients who are resistant to the effects of insulin.

The following diagram illustrates IGF-1 deficiency and the role of IGF-1 in growth and metabolism.

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**Indications**

| Increlex Indication | Development Status | Commercialization Rights |
|---|---|---|
| Severe Primary IGFD | Approved in the U.S.; Marketing Authorization Application submitted to the European Medicines Agency in December 2005 | Worldwide |
| Primary IGFD | Phase IIIb trial initiated late 2004 | Worldwide |
| Primary IGFD | Once-daily dosing trial initiated mid-2005 | Worldwide |
| Adult IGFD | Assessing potential development strategy | Worldwide |

***Short Stature***

Approximately one million children in the United States have short stature, and we believe that there are an equal number of children with short stature in Western Europe. Short stature is caused by a deficiency of IGF-1 or growth hormone, or other abnormalities such as genetic defects not associated with a deficiency of either hormone. Physicians use a height standard deviation score, or Height SDS, to indicate how many standard deviations a person s height is from the average height of the normal population of a similar age and gender. The American Academy of Pediatrics and the American Academy of Clinical Endocrinology define short stature as a height that is more than two standard deviations below the average population height. Children with short stature are shorter than approximately 97.5% of children of a similar age and gender, and if their deficit in growth continues unchanged, they will attain a final height of no more than approximately 5 4 for boys and 4 11 for girls. Similarly, in evaluating IGF-1 deficiency, physicians can use an IGF-1 standard deviation score, or IGF-1 SDS, to indicate how many standard deviations a person s IGF-1 level is from the average level of the population of a similar age and gender.

Approximately 380,000 children in the United States are currently referred to pediatric endocrinologists for evaluation of possible short stature. Of these children, we believe that approximately 30,000 in the United States and an equal number in Western Europe, for a total of 60,000 children, suffer from Primary IGFD.

*Severe Primary IGFD.* We obtained approval of long-term Increlex replacement therapy for severe Primary IGFD from the FDA in August 2005, based on Phase III clinical trial data. In January 2006, we launched Increlex in the United States. In December 2005, we submitted a Marketing Authorization Application to the European Medicines Agency, or EMEA, seeking approval of long-term Increlex replacement therapy for severe Primary IGFD.

Our product label defines severe Primary IGFD to mean a child who has a Height SDS and IGF-1 SDS of minus three or less and normal growth hormone levels. These children do not respond or respond poorly to growth hormone therapy. If their deficit in growth continues unchanged, children with severe Primary IGFD who are untreated will typically attain a final height of no more than approximately 5 1 for boys and 4 9 for girls. We estimate that a total of 12,000 children in the United States and Western Europe have severe Primary IGFD.

We have Phase III results from the treatment of 76 children with severe Primary IGFD with rhIGF-1 replacement therapy for an average of 4.4 years, with some patients being treated for up to 12 years. None of the children withdrew from the study due to adverse events. Some patients experienced hypoglycemia, or low blood glucose levels. Enlargement of the tonsils or minor temporary hearing deficits were also noted in some patients.

Of these children, 62 have completed at least one year of rhIGF-1 replacement therapy, which is the generally accepted length of time required to adequately measure growth responses to drug therapy. A statistically significant increase in average growth rate from 2.8 cm per year prior to treatment to 8.0 cm per year after the first year of rhIGF-1 treatment was demonstrated in these patients ($p<0.0001$). A p-value of less than

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0.0001 means that the probability that this result occurred by chance was less than 1 in 10,000. A probability of 5 in 100 or less, or $p<0.05$, is considered to be statistically significant. Compared to pre-treatment growth rates, statistically significant increases were also observed during each of the next five years of rhIGF-1 treatment ($p<0.005$). We believe these increases in growth rates were clinically meaningful and comparable to those observed in clinical trials of other approved growth hormone treatments. Statistically significant increases in Height SDS compared to baseline were also observed for each of the first eight years of rhIGF-1 treatment ($p<0.001$).

*Primary IGFD.* We define the indication Primary IGFD to mean a child who has a Height SDS and IGF-1 SDS of less than minus two, in the presence of normal or elevated growth hormone. Although our first indication is for severe Primary IGFD, we intend to evaluate the use of Increlex for the treatment of all children with Primary IGFD. Children with Primary IGFD suffer from the same hormonal deficiency as those with severe Primary IGFD. If their deficit in growth continues unchanged, children with Primary IGFD who are untreated will typically attain a final height of no more than approximately 5 4 for boys and 4 11 for girls. Excluding children with severe Primary IGFD, we believe that approximately 48,000 children in the United States and Western Europe suffer from Primary IGFD.

We are enrolling a Phase IIIb clinical trial in Primary IGFD, which is intended to serve as the basis for a supplemental NDA filing for this indication. We are conducting this study in the United States and Europe. The principal purpose of this clinical trial is to ensure safety in the broader population and to evaluate the safety and efficacy of various doses of Increlex for patients with Primary IGFD. In mid 2005 we initiated another Phase III study in Primary IGFD to investigate once-daily dosing of Increlex.

*Adult IGFD.* Children with Primary IGFD who attain adulthood are considered to have Adult IGFD. Adult IGFD patients may have decreased cardiac performance, impaired exercise performance, decreased muscle mass, decreased bone density, obesity and abnormalities of carbohydrate and lipid metabolism. Replacement therapy with Increlex may have beneficial effects with respect to these metabolic abnormalities. We believe that at least a total of 120,000 people in the United States and Western Europe suffer from Adult IGFD. This market does not include adults who become IGF-1 deficient as a result of other disorders, including anorexia nervosa, malabsorption and liver disease, which could represent additional opportunities that we may study in the future. We currently are assessing our development strategy and timing for the use of Increlex in Adult IGFD.

***Diabetes***

Genentech originally developed rhIGF-1 as a potential treatment for people with a broad range of type 1 and type 2 diabetes. In four Phase II clinical trials using rhIGF-1 in over 700 type 2 diabetic patients, long-term glucose control was improved, as indicated by statistically significant improvements of approximately 1% to 2% in glycated hemoglobin, which is an indicator of an individual s average blood glucose concentrations over a three to four month period. Improvements of approximately 0.5% in glycated hemoglobin are frequently considered clinically significant. However, during the course of these clinical trials, potential concerns were raised that long term use of rhIGF-1 in diabetic patients might lead to an increased incidence and/or severity of diabetic retinopathy. As a result of the scope and extended timeframe of the clinical trials necessary to address this concern, Genentech discontinued development of rhIGF-1 for treatment of type 1 and type 2 diabetes.

We are currently assessing our development and regulatory strategies and timing for the use of Increlex in diabetes. We have developed an integrated database of the results from the diabetes studies conducted by Genentech. We are analyzing these data to determine a diabetes patient population that may benefit from treatment with Increlex while minimizing the side effects observed in prior studies. This patient population may include diabetes patients with low IGF-1 levels or those in orphan diabetes indications.

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**Strategy**

Our goal is to capitalize on the opportunities presented by Increlex and to develop and commercialize additional new products for the treatment of endocrine disorders. Key elements of our strategy for achieving these goals include:

***Expand the severe Primary IGFD indication to Primary IGFD.*** Our goal is to capitalize on the opportunities presented by Increlex for the treatment of short stature. We intend to submit a supplemental NDA to expand the use of Increlex to encompass children with Primary IGFD. This will allow us to leverage our existing preclinical, clinical and manufacturing data from our FDA-approved NDA for severe Primary IGFD. We believe that this will expand the market for Increlex from the approximately 12,000 children with severe Primary IGFD to encompass the approximately 60,000 children with Primary IGFD**,** including severe Primary IGFD, in the United States and Western Europe. To support the supplemental NDA, in late 2004, we initiated a Phase IIIb clinical trial of Increlex in children with Primary IGFD.

***Grow Increlex revenues for severe Primary IGFD.*** Our sales and marketing force targets the approximately 500 active U.S.-based pediatric endocrinologists who treat children with short stature. Because these pediatric endocrinologists are primarily hospital-based and concentrated in major metropolitan areas, we believe that our focused marketing organization and specialized sales force can effectively serve them. In addition, we conduct medical education programs, medical symposia, and regional speaker programs aimed at establishing awareness of Increlex and severe Primary IGFD in the physician community. We also intend to conduct post-marketing studies and establish a patient registry to provide further data on the safety and efficacy of Increlex. We acquired certain international rights to rhIGF-1 from Genentech and are evaluating our international commercialization strategy. In December 2005, we submitted a Marketing Authorization Application to the EMEA seeking approval of long-term Increlex replacement therapy for severe Primary IGFD.

***Develop Increlex for additional indications.*** We intend to develop Increlex for those indications where preclinical or clinical data show significant promise as a potential treatment. These indications may include Adult IGFD and diabetes. We believe that the risks and time required to obtain FDA approval of Increlex for new disease indications may be reduced as a result of the FDA s approval of Increlex for the treatment of severe Primary IGFD.

***Broaden endocrinology portfolio based on our expertise.*** We intend to pursue the development and commercialization of additional products for the treatment of significant unmet medical needs, principally endocrine disorders. We have an opportunistic approach to in-licensing products and product candidates. We are seeking to in-license products that may benefit from our expertise. We believe our scientific expertise in endocrinology may make us an attractive licensee. We actively maintain ongoing discussions with academic research institutions and other companies regarding preclinical and clinical development projects in the endocrinology area.

**Genentech Relationship**

We entered into a U.S. License and Collaboration Agreement with Genentech in April 2002, which was amended in July and November 2003. In addition, we entered into an International License and Collaboration Agreement with Genentech in July 2003, which expands certain of the rights granted to us under the U.S. agreement to the remaining territories of the world outside of the United States. Under these agreements, we have certain rights and licenses to Genentech s intellectual property to research, develop, use, manufacture and market rhIGF-1, alone or in combination with IGF binding protein-3, which we refer to in this document as IGFBP-3, for a broad range of indications. The rights are exclusive with respect to our development and sale of rhIGF-1 and non-exclusive with respect to our manufacture of rhIGF-1. Indications not covered by our licenses from Genentech include diseases and conditions of the central nervous system. In addition, we need to enter into a written agreement with another company if we desire to commercialize rhIGF-1 for diabetes outside of the United States.

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Under both the U.S. and International License and Collaboration Agreements with Genentech, Genentech agreed to transfer to us its preclinical and clinical data related to rhIGF-1. This includes data resulting from extensive animal testing as well as Phase I, Phase II and Phase III clinical trials with respect to rhIGF-1. In addition, under these agreements Genentech agreed to transfer its manufacturing technology and know-how to us. In consideration of this transfer, we paid Genentech $1.0 million in cash and approximately $4.1 million in Series A preferred stock upon execution of the United States License and Collaboration Agreement. We paid Genentech $1.7 million upon execution of the International License and Collaboration Agreement and $1.4 million related to rights related to the license to Genentech s rights to IGF-1 combined with IGFBP-3. In connection with the approval of our NDA in August 2005, we paid Genentech a $1.0 million milestone payment related to the United States License and Collaboration Agreement. We also agreed to pay to Genentech royalties on the sales of rhIGF-1 products and certain one-time payments upon the occurrence of specified milestone events, such as attaining rhIGF-1 indication approvals and aggregate sales levels with respect to rhIGF-1. We are subject to the following milestone payments to Genentech as of December 31, 2005:

In addition to the amounts already paid to Genentech, if we achieve all of the additional milestones for rhIGF-1 under the U.S. and International License and Collaboration Agreements, we will owe Genentech up to an aggregate of approximately $33 million.

If we develop rhIGF-1 in combination with IGFBP-3, we would be subject to these same milestone events and, upon achievement of all of the milestones, would owe Genentech up to an additional aggregate of approximately $32.5 million.

Accordingly, we would owe Genentech up to an aggregate of approximately $65.5 million in milestone payments if we achieved all of these milestone events for both rhIGF-1 and for rhIGF-1 in combination with IGFBP-3. Both agreements require us to fulfill certain obligations to maintain our licenses. These obligations include a requirement to use reasonable business efforts to meet specified milestones, including filing for regulatory approval with the FDA for either diabetes or a substitute indication, subject to Genentech s consent, by December 31, 2008. If we fail to use reasonable business efforts to meet our obligations under either agreement, Genentech may terminate that agreement and we would have no further rights to utilize the technology and intellectual property covered by that agreement to develop, manufacture and commercialize rhIGF-1 for any indications. This may prevent us from continuing our business.

Under the U.S. License and Collaboration Agreement, Genentech has exclusively licensed to us its right to develop and commercialize rhIGF-1 products in the United States for all indications other than diseases and conditions of the central nervous system. Genentech has a right, which we refer to as the Opt-In Right, to elect, within a limited period of time following an NDA-enabling clinical trial, to participate jointly with us in the development and commercialization of rhIGF-1 products we develop for diabetes indications and for all non-orphan indications. Orphan indications are generally diseases or conditions that affect fewer than 200,000 individuals in the United States. If Genentech elects to exercise its Opt-In Right for a particular indication, Genentech will pay us more than 50% of the past development costs associated with that indication, which would have a one-time positive impact on our operating results. In addition, after Genentech exercises its Opt-In Right for a particular indication, we would share with Genentech the ongoing net operating losses and profits resulting from the joint development and commercialization effort for that indication. Pursuant to this arrangement, we would fund less than 50% of such operating losses and we would receive less than 50% of any profits associated with any joint indication. In addition, if we elect to discontinue the development of rhIGF-1 products for diabetes or a substitute indication selected by us, subject to Genentech s consent, Genentech has the right to assume development of such indication. Any substitute indication agreed to by Genentech, under the terms of the current agreement, must have a potential market greater than $250 million and not be an indication for the central nervous system. In such event, our rights under the agreement for such indication would terminate and Genentech would be granted a non-exclusive license under our rhIGF-1 intellectual property and technology to manufacture, use and sell rhIGF-1 products for diabetes, or if applicable the substitute indication, subject to an obligation to pay us milestone payments and/or royalties to be negotiated by Genentech and us in good faith on sales of these products.

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With respect to those indications in the United States for which Genentech does not have an Opt-In-Right or for which Genentech has not exercised its Opt-In-Right to jointly develop and commercialize rhIGF-1, we have the final decision on disputes relating to development and commercialization of rhIGF-1. With respect to those indications in the United States for which Genentech has exercised its Opt-In-Right, or for which its Opt-In-Right has not expired or been waived by Genentech, Genentech has the final decision on disputes relating to development and commercialization of rhIGF-1.

Under the International License and Collaboration Agreement, Genentech has exclusively licensed to us its right to develop and commercialize rhIGF-1 products outside of the United States for all indications other than diseases and conditions of the central nervous system. In addition, we need to enter into a written agreement with another company if we desire to commercialize rhIGF-1 for diabetes outside of the United States. Unlike the U.S agreement, Genentech does not have the right to participate in any of our development or commercialization efforts for rhIGF-1 products outside of the United States.

Upon an uncured material breach of either the U.S. or International License and Collaboration Agreement, the non-breaching party may terminate the agreement. We also have the right to terminate either agreement at our sole discretion upon 60 days prior written notice to Genentech. If Genentech terminates either agreement because of our material breach, or if we terminate either agreement for any reason other than a material breach by Genentech, the rights and licenses granted to us under the respective agreement would terminate. In such event, Genentech would be granted a non-exclusive license under our rhIGF-1 intellectual property and technology to manufacture, use and sell rhIGF-1 products, subject to an obligation to pay us royalties on sales of these products to be negotiated by Genentech and us in good faith.

**Manufacturing**

We have a manufacturing and services agreement with Cambrex Bio Science Baltimore, Inc., or Cambrex Baltimore, for the manufacture and supply of bulk rhIGF-1. This agreement terminates in December 2008. Under this agreement, Cambrex Baltimore is obligated to provide us with up to 24 kilograms of rhIGF-1 per year, subject to the establishment and validation of the manufacturing process for rhIGF-1, which we have completed as of 2005. We currently believe that this quantity will be sufficient to supply our expected requirements through at least 2008. We executed a Quality Agreement with Cambrex Baltimore to ensure that we maintain product quality, compliance with cGMP and oversight over all critical aspects of rhIGF-1 production, testing and release.

Our U.S. License and Collaboration Agreement with Genentech provides us with rights and access to Genentech s manufacturing technology and documentation associated with Genentech s manufacture and testing of rhIGF-1, including Genentech s proprietary large-scale manufacturing process for producing bulk rhIGF-1. This includes production cell banks, production batch records, development reports, analytical methods and regulatory documents describing improvements and changes to the production process.

We believe that there is an increasing acceptance by the FDA and European Medicines Agency of a comparability-based assessment without the need to repeat clinical studies, if appropriate analytical methods are available to fully characterize the product. There can be no assurance, however, that such regulatory bodies will permit us to proceed with our marketing applications based solely on comparability- based laboratory assessments. There are a number of regulatory agency guidelines providing guidance to the industry on the demonstration of comparability for human therapeutic products. Specific FDA guidances enable manufacturers to assess changes to manufacturing processes based on the potential impact on final product safety and efficacy, to develop a comparability assessment program appropriate to the molecule, and to verify the impact of the changes.

**Sales and Marketing**

Our sales and marketing efforts are focused on the market for endocrine growth disorders, targeting the approximately 500 active pediatric endocrinologists practicing in the United States. Pediatric endocrinologists

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are the physicians who generally treat children with severe Primary IGFD. Because these pediatric endocrinologists are primarily hospital-based and concentrated in major metropolitan areas, we believe that our focused marketing organization and specialized sales force can effectively serve them. We are conducting a variety of programs aimed at establishing physician awareness of Increlex as a treatment for severe Primary IGFD, including medical education, symposiums and regional speaker programs. We are also conducting post-marketing studies and are developing a patient registry in order to provide further data on the safety and efficacy. In addition, we are evaluating our international commercialization strategy. As we develop Increlex for indications other than severe Primary IGFD and Primary IGFD, we will evaluate expanding our sales and marketing efforts as appropriate.

**Research and Development**

Our principal experience has been developing a late-stage product candidate and commercializing it. We do not conduct any of our own preclinical laboratory research. However, we actively maintain ongoing discussions with academic research institutions and other companies regarding both IGF-1 and non-IGF-1 related projects in endocrinology. Our current product, Increlex, is FDA-approved for the long-term treatment of growth failure in children with severe Primary IGFD, and we intend to develop other potential indications for rhIGF-1 for which we may contract with third parties for support. Research and development expenses consist primarily of costs associated with manufacturing development activities and clinical and regulatory activities. Manufacturing development activities include pre-FDA approval preparation activities for current good manufacturing practices (cGMP), regulatory inspection preparation, technology transfer, process development and validation, quality control and assurance activities, analytical services, personnel and related benefits and depreciation. Clinical and regulatory activities include the preparation, implementation, management of our clinical trials and assay development, as well as regulatory compliance, data management and biostatistics. Our research and development expenses were $21.6 million for the year ended December 31, 2005, $27.9 million for the year ended December 31, 2004 and $19.2 million for the year ended December 31, 2003.

**Patents and Proprietary Rights**

Our policy is to enforce our licensed patents to the extent Genentech has granted us such rights, and protect our proprietary technology. We intend to continue to file U.S. and foreign patent applications to protect technology, inventions and improvements that are considered important to the development of our business. There can be no assurance that any of these patent applications will result in the grant of a patent either in the United States or elsewhere, or that any patents granted will be valid and enforceable, or will provide a competitive advantage or will afford protection against competitors with similar technologies. Our success could depend, in part, on our ability to obtain additional patents, protect our proprietary rights and operate without infringing third party patents. We will be able to protect our licensed patents or proprietary technologies from unauthorized use by third parties only to the extent that such patents or proprietary rights are covered by valid and enforceable patents or are effectively maintained as trade secrets and such third party does not have any valid defense.

We have licensed from Genentech their intellectual property rights, including patent rights and preclinical and clinical data, and manufacturing know-how, to develop and commercialize rhIGF-1 worldwide for a broad range of indications. Such U.S. patents expire between 2010 and 2020. Our U.S. patent No. 6,331,414 B1 licensed from Genentech is directed to methods for bacterial expression of rhIGF-1 and expires in 2018. We have no equivalent European patent. The European Patent Office has determined that the claims of Genentech s corresponding European patent application are not patentable under European patent law in view of public disclosures made before the application was filed.

There has been increasing litigation in the biopharmaceutical industry with respect to the manufacture and sale of new therapeutic products. The validity and breadth of claims in biotechnology patents may involve complex factual and legal issues for which no consistent policy exists. In particular, the patent protection

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available for protein-based products, such as rhIGF-1, is highly uncertain and involves issues relating to the scope of protection of claims to gene sequences and the production of their corresponding proteins.

There can be no assurance that our licensed patents will not be successfully circumvented by competitors. In particular, we do not have patent composition coverage on the rhIGF-1 protein alone, and we are aware that Chiron Corporation has developed a process to manufacture rhIGF-1 using yeast expression, rather than bacterial expression. In addition, the patent laws of foreign countries differ from those in the United States and the degree of protection afforded by foreign patents may be different from the protection offered by U.S. patents. Our competitors may obtain patents in the United States and Europe directed to methods for the manufacture or use of rhIGF-1 that may be necessary for us to conduct our business free from claims of patent infringement. We may not be able to license such patents on reasonable terms, if at all.

We may need additional intellectual property from other third parties to commercialize rhIGF-1 for diabetes. We cannot be sure that we will be able to obtain a license to any third party technology we may require to conduct our business.

In some cases, litigation or other proceedings may be necessary to defend against claims of infringement, to enforce patents licensed to us, to protect our know-how or other intellectual property rights or to determine the scope and validity of the proprietary rights of third parties. Any potential litigation could result in substantial cost to us and diversion of our resources. We cannot be sure that any of our licensed patents will ultimately be held valid. An adverse outcome in any litigation or proceeding could subject us to significant liability.

For example, we initiated patent infringement proceedings against Avecia Limited and Insmed in the United Kingdom and against Insmed in the United States to enforce patent rights we licensed from Genentech. We cannot predict the outcome of such litigation. Either or both of those actions could require a substantial diversion of financial and personnel resources in support of such actions and expose us to liability for costs or other awards of damages. Declaratory judgments of invalidity against the patents asserted in such actions could prevent us from using the affected patents to exclude others from competing with us.

We generally enter into confidentiality agreements with our employees and consultants. Our confidentiality agreements generally require our employees and consultants to hold in confidence and not disclose any of our proprietary information. Despite our efforts to protect our proprietary information, unauthorized parties may attempt to obtain and use our proprietary information. Policing unauthorized use of our proprietary information is difficult, and the steps we have taken might not prevent misappropriation, particularly in foreign countries where the laws may not protect our proprietary rights as fully as do the laws of the United States.

We have applied for registration of the trademarks Increlex, Tercica and the Tercica logo in the United States.

**Competition**

The biotechnology industry is intensely competitive and characterized by rapid technological progress. In each of our potential product areas, we face significant competition from large pharmaceutical, biotechnology and other companies. Most of these companies have substantially greater capital resources, research and development staffs, facilities and experience at conducting clinical trials and obtaining regulatory approvals. In addition, many of these companies have greater experience and expertise in developing and commercializing products.

We cannot at this time predict the relative competitive position of Increlex. However, we expect that the following factors, among others, will determine our ability to compete effectively:

- acceptance of Increlex by physicians and patients as a safe and effective treatment;
- reimbursement adoption;

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product price;

manufacturing costs;

the effectiveness of our sales and marketing efforts;

storage requirements and ease of administration;

dosing regimen;

safety and efficacy;

prevalence and severity of side effects; and

competitive products.

We believe that many of our competitors spend significantly more on research and development-related activities than we do. Our competitors may discover new treatments, drugs or therapies or develop existing technologies to compete with Increlex. Our commercial opportunities will be reduced or eliminated if these competing products are more effective, have fewer or less severe side effects, are more convenient or are less expensive than Increlex.

Insmed Incorporated s combination product, when launched commercially, will compete with Increlex for the treatment of patients with severe Primary IGFD. Insmed s combination product was recently approved by the FDA for the treatment of patients with severe Primary IGFD or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone.

Growth hormone products will likely compete with Increlex for the treatment of patients with Primary IGFD if Increlex is also approved for that indication. The major suppliers of commercially available growth hormone products in the United States are Genentech, Eli Lilly and Company, Teva Pharmaceutical Industries Ltd., Novo Nordisk A/S, Pfizer Inc and Serono S.A. Investigators from a Novo Nordisk clinical trial recently presented data that demonstrated growth hormone was effective in a population that included children with Primary IGFD. In addition, children with Primary IGFD may be diagnosed as having idiopathic short stature, or ISS. Eli Lilly and Company and Genentech have received FDA approval for their respective growth hormone products for the treatment of children with ISS. Accordingly, we expect that growth hormone products will compete directly with Increlex for the treatment of children with Primary IGFD who may be diagnosed as having ISS.

In addition, we are aware that Chiron Corporation has developed a process to manufacture rhIGF-1 using yeast expression and has intellectual property with respect to that process. We use bacterial expression, which differs from yeast expression, to manufacture Increlex.

We believe that Bristol-Meyers Squibb Company, Genentech, Merck & Co., Inc., Novo Nordisk and Pfizer Inc have conducted research and development of orally available small molecules that cause the release of growth hormone, known as growth hormone secretagogues. We believe that Rejuvenon Corporation has licensed certain rights to Novo Nordisk s growth hormone secretagogues and is actively developing one of these compounds for use in cancer cachexia, a wasting disorder affecting some cancer patients.

Many companies are seeking to develop products and therapies for the treatment of diabetes. These competitors include multinational pharmaceutical companies, specialized biotechnology firms, and universities and other research institutions. Insmed has also conducted clinical trials using a product that contains rhIGF-1 for the treatment of diabetes. It is possible that there are other products currently in development or that exist on the market that may compete directly with Increlex.

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**Government Regulation and Product Approval**

The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose substantial requirements upon the clinical development, manufacture and marketing of pharmaceutical products. These agencies and other federal, state and local entities regulate the testing, manufacture, quality control, safety, effectiveness, labeling, storage, record keeping, advertising and promotion of our products. Failure to comply with regulatory requirements may result in criminal prosecution, civil penalties, recall or seizure of products, total or partial suspension of production or injunction, as well as other actions that could affect our potential products or us. Any failure by us to comply with regulatory requirements, to obtain and maintain regulatory approvals, or any delay in obtaining regulatory approvals could materially adversely affect our business.

The process required by the FDA before drugs may be marketed in the United States generally involves the following:

- preclinical laboratory and animal tests;
- submission of an investigational new drug, or IND, application, which must become effective before human clinical trials may begin;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the proposed drug for its intended use; and
- FDA approval of an NDA.

The testing and approval process requires substantial time, effort, and financial resources, and we cannot be certain that any approvals for rhIGF-1 will be granted on a timely basis, if at all.

Once a pharmaceutical candidate is identified for development it enters the preclinical testing stage. During preclinical studies, laboratory and animal studies are conducted to show biological activity of the drug candidate in animals, both healthy and with the targeted disease. Also, preclinical tests evaluate the safety of drug candidates. Preclinical tests must be conducted in compliance with good laboratory practice regulations. In some cases, long-term preclinical studies are conducted while clinical studies are ongoing.

Prior to commencing a clinical trial, we must submit an IND application to the FDA. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Our submission of an IND may not result in FDA authorization to commence a clinical trial. All clinical trials must be conducted under the supervision of a qualified investigator in accordance with good clinical practice regulations. These regulations include the requirement that all subjects provide informed consent. Further, an independent institutional review board at the medical center proposing to conduct the clinical trial must review and approve the plan for any clinical trial before it commences. Reports detailing the results of the clinical trials must be submitted at least annually to the FDA, and more frequently, if adverse events occur.

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

- Phase I: The drug is initially introduced into healthy human subjects or patients and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion.
- Phase II: Involves studies in a limited patient population to identify possible adverse effects and safety risks, to determine 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

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establish the overall risk-benefit ratio of the product and provide, if appropriate, an adequate basis for product labeling.

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. Because these patients already have the target disease, these studies may provide initial evidence of efficacy traditionally obtained in Phase II trials, and thus these trials are frequently referred to as Phase I/II trials.

The FDA or an institutional review board or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk.

Concurrent with clinical trials and preclinical studies, companies also must develop 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 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 chemistry stability studies must be conducted to demonstrate that the product 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, and results of chemical studies are submitted to the FDA as part of an NDA requesting approval to market the product. The FDA reviews all NDAs submitted before it accepts them for filing. It may request additional information rather than accept an NDA for filing. In this event, the NDA 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 of the NDA. The submission of an NDA is subject to user fees, but a waiver of such fees may be obtained. The FDA may deny an NDA 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 does not satisfy the criteria for approval. Once issued, the FDA may withdraw product approval if compliance with regulatory standards is not maintained or if problems occur after the product reaches the market. In addition, the FDA may require testing and surveillance programs to monitor the effect of approved products, which 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.

The FDA has established priority and standard review classifications for original NDAs and efficacy supplements. Priority review applies to the time frame for FDA review of completed marketing applications and is separate from and independent of orphan drug status and the FDA s fast track and accelerated approval mechanisms. The classification system, which does not preclude the FDA from doing work on other projects, provides a way of prioritizing NDAs upon receipt and throughout the FDA application review process.

The classification system sets the target date for the completion of FDA review and for taking action to approve or not approve an NDA after its acceptance for filing. If the priority review designation criteria are not met, standard review procedures apply. Under the Prescription Drug User Fee Amendments of 2002, the FDA s performance goals for fiscal years 2003-2007 involve reviewing 90% of priority applications within six months of filing and 90% of standard applications within ten months of filing.

Priority designation applies to new drugs that have the potential for providing significant improvement compared to marketed products in the treatment, diagnosis or prevention of a disease. Hence, even if an NDA is initially classified as a priority application, this status can change during the FDA review process, such as in the situation where another product is approved for the same disease for which previously there was no available therapy.

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We cannot guarantee that the FDA will grant a request for priority review designation or will permit expedited development, accelerated approval, or treatment use of any product. We also cannot guarantee that if such statutory or regulatory provisions apply to our products, that they will necessarily affect the time period for FDA review or the requirements for approval. Additionally, the FDA s approval of drugs can include restrictions on the product s use or distribution, such as permitting use only for specified medical procedures, limiting distribution to physicians or facilities with special training or experience, or requiring presubmission of advertising and promotional materials.

Satisfaction of FDA requirements or similar requirements of state, local and foreign regulatory agencies typically takes several years and the actual time required may vary substantially, based upon the type, complexity and novelty of the product or disease. Government regulation may delay or prevent marketing of potential products or new diseases 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. Even if a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages. 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 rhIGF-1 could harm our business. In addition, we cannot predict what adverse governmental regulations may arise from future United States or foreign governmental action.

Any drug products manufactured or distributed by us pursuant to FDA approvals are subject to continuing regulation by the FDA, including record-keeping requirements, reporting of adverse experiences with the drug, drug sampling and distribution requirements, notifying the FDA and gaining its approval of certain 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 establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP, which impose certain procedural and documentation requirements upon us and our third party manufacturers. We cannot be certain that we or our present or future suppliers will be able to comply with the pharmaceutical cGMP regulations and other FDA regulatory requirements.

The FDA s policies may change and additional government regulations may be enacted which could prevent or delay regulatory approval of Increlex for other indications, including Primary IGFD. We cannot predict the likelihood, nature or extent of adverse governmental regulation, which might arise from future legislative or administrative action, either in the United States or abroad.

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat rare diseases or conditions, which are generally diseases or conditions that affect fewer than 200,000 individuals in the United States. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process. If a product that has orphan drug designation subsequently receives FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication, except in limited circumstances, for seven years. The FDA may, however, approve applications to market the same drug for different indications, and applications to market different drugs for the same indication as the drug that has orphan exclusivity.

The FDA granted Increlex seven years of orphan exclusivity for the long-term treatment of growth failure in children with severe Primary IGFD or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to growth hormone. In addition, we intend to file for orphan drug designation for other

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rhIGF-1 diseases that meet the criteria for orphan exclusivity. There is no guarantee that we will be awarded orphan exclusivity for any other indications, including Primary IGFD, or other products that we may develop. Obtaining FDA approval to market a product with orphan exclusivity may not provide us with a material commercial advantage, also. For example, the FDA recently approved Insmed Incorporated s combination product for the treatment of severe Primary IGFD and granted Insmed s product orphan drug designation. Accordingly, notwithstanding our orphan drug designation for rhIGF-1, Insmed s combination product for rhIGF-1 and BP-3 was deemed by the FDA to be a different drug than ours, and therefore, it will compete with Increlex for the treatment of patients with severe Primary IGFD, when it is launched commercially.

Under the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, Congress created an abbreviated FDA review process for generic versions of pioneer (brand name) drug products like Increlex. The law also provides incentives by awarding, in certain circumstances, non-patent marketing exclusivities to pioneer drug manufacturers. For example, the Hatch-Waxman Act provides five years of new chemical entity exclusivity to the first applicant to gain approval of an NDA for a product that does not contain an active ingredient found in any other approved product. The FDA granted Increlex new chemical entity exclusivity, which expires on August 30, 2010.

During this period, the FDA is prohibited from accepting any abbreviated New Drug Application (ANDA) for a generic version of Increlex. An ANDA is a type of application in which approval is based on a showing of sameness to an already approved drug product. An ANDA does not contain full reports of safety and effectiveness, as do NDAs, but rather demonstrates that the proposed product is the same as a reference product in terms of conditions of use, active ingredient, route of administration, dosage form, strength, and labeling. ANDA applicants are also required to demonstrate the bioequivalence of their products to reference products. Bioequivalence generally means that there is no significant difference in the rate and extent to which the active ingredient in the products becomes available at the site of drug action. ANDAs also must contain data relating to formulation, raw materials, stability, manufacturing, packaging, labeling, and quality control, among other information.

During this exclusivity period, the FDA is also prohibited from accepting any NDA for a modified version of Increlex where the applicant does not own or have a legal right of reference to all of the data required for approval, otherwise known as a 505(b)(2) application. The FDA has determined that 505(b)(2) applications may be submitted for products that represent changes to approved products like Increlex. Such changes may be to the approved product s conditions of use, active ingredient, route of administration, dosage form, strength, labeling, or bioavailability. A 505(b)(2) applicant also may reference more than one approved product. It is the FDA s position that such an applicant must only submit the pre-clinical and clinical data necessary to demonstrate the safety and effectiveness of the changes made to the approved product.

This new chemical entity exclusivity protects the entire new chemical entity franchise, including all products containing Increlex s active ingredient for any use and in any strength or dosage form. This exclusivity will not, however, prevent the submission or approval of a full NDA, as opposed to an ANDA or 505(b)(2) application, for any drug, including a drug with the same conditions of use, active ingredient, route of administration, dosage form, and strength as Increlex. In addition, an ANDA or a 505(b)(2) application may be submitted after four years, rather than five years, if that ANDA or 505(b)(2) application contains a certification (known as a Paragraph IV certification ) that one of the patents listed with the Increlex NDA is invalid or will not be infringed by the manufacture, use, or sale of the product described in that ANDA or 505(b)(2) application.

The Hatch-Waxman Act also provides three years of new use exclusivity for the approval of NDAs, 505(b)(2) applications, and NDA supplements, where those applications contain the results of new clinical investigations (other than bioavailability studies) essential to the FDA s approval of the applications. Such applications may be submitted for new indications, new dosage forms, new strengths, or new conditions of use of already approved products like Increlex. So long as the new clinical investigations are essential to the FDA s approval of the change, this new use exclusivity prohibits the approval of ANDAs or 505(b)(2) applications for

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products with the specific changes associated with those clinical investigations. Should Increlex receive this exclusivity, however, it will not prevent the submission or approval of a full NDA for any drug, including a drug with the same changes as are protected by the exclusivity. It also would not prohibit the FDA from accepting or approving ANDAs or 505(b)(2) applications for other products containing the same active ingredient. It would only protect against the approval of ANDAs and 505(b)(2) applications for products with the specific changes to Increlex that were approved based on the new clinical investigations.

The Hatch-Waxman Act also requires an ANDA or 505(b)(2) applicant that has submitted an ANDA or a 505(b)(2) application with a Paragraph IV certification to notify the owner of the patent that is the subject of the Paragraph IV certification and the holder of the approved NDA of the factual and legal basis for the applicant s opinion that that patent is invalid or will not be infringed by the manufacture, use, or sale of the product described in that ANDA or 505(b)(2) application. The NDA holder or patent owner may then sue such an ANDA or 505(b)(2) applicant for infringement. If the NDA holder or patent owner files suit within 45 days of receiving notice of the Paragraph IV certification, a one-time 30-month stay of the FDA s ability to approve the ANDA or 505(b)(2) application is triggered. However, the FDA may approve the ANDA or 505(b)(2) application before the expiration of the 30-month stay if a court finds the patent invalid or not infringed, or if the court shortens the 30-month period because a party failed to cooperate in expediting the litigation. In addition, if the NDA holder or patent owner chooses not to sue such an ANDA or 505(b)(2) applicant after receiving notification of the Paragraph IV certification, or sues outside of the 45-day window, the FDA may approve the ANDA or 505(b)(2) application whenever all of the other requirements for approval are met.

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 to conduct research about the safety and effectiveness 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 Federal Food, Drug, and Cosmetic Act, the extra 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 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 a pediatric population, may 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 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 or commonly accepted scientific principles. There is no guarantee that the FDA will issue a Written Request for such studies or accept the reports of the studies. We believe that Increlex may become eligible for pediatric exclusivity, although there can be no assurances that FDA will grant such exclusivity. The current pediatric exclusivity provision is scheduled to expire on October 1, 2007, and there can be no assurances that it will be reauthorized.

**Reimbursement**

Sales of biopharmaceutical products depend in significant part on the availability of third-party reimbursement. We anticipate third-party payors will provide reimbursement for Increlex. It is time consuming and expensive for us to seek reimbursement from third-party payors. Reimbursement may not be available or sufficient to allow us to sell our products on a competitive and profitable basis.

The passage of the Medicare Prescription Drug and Modernization Act of 2003, or the MMA, imposes new requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries, which may affect the marketing of our products. The MMA also introduced a new reimbursement methodology, part of which went into effect in 2004. At this point, it is not clear what effect the MMA will have on the prices paid for currently approved drugs and the pricing options for new drugs approved after January 1, 2006. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy

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and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

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 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.

We expect that there will continue to be a number of federal and state proposals to implement governmental pricing controls. While we cannot predict whether such 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.

**Employees**

As of December 31, 2005, we had 89 full-time employees. Of the full-time employees, 39 were engaged in product development and 50 were engaged in selling, general and administrative positions. We believe that our employee base will need to grow in order to execute our development and commercialization plans for rhIGF-1. We believe our relations with our employees are good.

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**Executive Officers of the Registrant**

Our executive officers, their ages and their positions as of March 15, 2006, are as follows:

| Name | Age | Position(s) |
|---|---|---|
| John A. Scarlett, M.D. | 55 | President, Chief Executive Officer and Director |
| Ross G. Clark, Ph.D. | 55 | Chief Technical Officer and Director |
| Susan Wong | 43 | Acting Chief Financial Officer, Vice President, Finance and Chief Accounting Officer |
| Stephen N. Rosenfield | 56 | Executive Vice President of Legal Affairs, General Counsel and Secretary |
| Andrew Grethlein, Ph.D. | 41 | Senior Vice President, Pharmaceutical Operations |
| Chris E. Rivera | 44 | Senior Vice President, Commercial Operations |
| Thorsten von Stein, M.D., Ph.D. | 44 | Chief Medical Officer and Senior Vice President of Clinical and Regulatory Affairs |

*John A. Scarlett* has served as our President and Chief Executive Officer and as a member of our board of directors since February 2002. From March 1993 to May 2001, Dr. Scarlett served as President and Chief Executive Officer of Sensus Drug Development Corporation, a development stage pharmaceutical company. In 1995, he co-founded Covance Biotechnology Services, Inc., a biotechnology contract manufacturing company, and served as a member of its board of directors from inception to 2000. From 1991 to 1993, Dr. Scarlett headed the North American Clinical Development Center and served as Senior Vice President of Medical and Scientific Affairs at Novo Nordisk Pharmaceuticals, Inc., a wholly owned subsidiary of Novo Nordisk A/S, a pharmaceutical company. From 1985 to 1990, Dr. Scarlett served as Vice President, Clinical Affairs and headed the clinical development group at Greenwich Pharmaceuticals, Inc., a pharmaceutical company. From 1982 to 1985, Dr. Scarlett served as Associate Director and, subsequently, as Director, of Medical Research and Services at Ortho-McNeil Pharmaceuticals, a wholly owned subsidiary of Johnson & Johnson. Dr. Scarlett received his B.A. degree in chemistry from Earlham College and his M.D. from the University of Chicago, Pritzker School of Medicine.

*Ross G. Clark* has served as our Chief Technical Officer since May 2002 and as a member of our board of directors since December 2001. From December 2001 to August 2003, Dr. Clark served as Chairman of our board of directors. From December 2001 to February 2002, Dr. Clark served as our Chief Executive Officer and President. Dr. Clark founded Tercica Limited, our predecessor company in New Zealand, in September 2000. Since September 1997, Dr. Clark has served as Professor of Endocrinology at the University of Auckland. From October 1997 to January 2000, Dr. Clark served as Chief Scientist for NeuronZ Limited, a New Zealand biotechnology company. In July 1999, Dr. Clark served as a board member of ViaLactia Biosciences (NZ) Ltd, a biotechnology subsidiary of the New Zealand Dairy Board. From 1990 to 1997, Dr. Clark served as a senior scientist for Genentech, Inc., a biotechnology company. Dr. Clark received his B.Sc., Dip.Sci. and Ph.D. degrees in veterinary physiology from Massey University, New Zealand.

*Susan Wong* has served as our Vice President of Finance and Chief Accounting Officer since March 2006 and Acting Chief Financial Officer since June 2005; and Vice President, Finance and Controller from January 2004 to March 2006. From November 2001 to December 2003, Ms. Wong was an independent financial services consultant. From August 2000 to October 2001, she served as Senior Vice President and Corporate Controller at innoVentry Corp., a privately-held provider of fee-based financial services. From September 1993 to July 2000, Ms. Wong served as Vice President and Corporate Controller at Ocular Sciences, Inc., a publicly-held manufacturer and distributor of soft contact lenses. From September 1989 to 1993, Ms. Wong served as Director of Corporate Accounting and Financial Reporting, Planning & Analysis at Vanstar, Inc., a computer reseller. Ms. Wong held various positions in the audit group at Coopers & Lybrand from August 1985 to August 1989. Ms. Wong is a Certified Public Accountant, and received her B.S. degree in finance and accounting from University of California, Berkeley.

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*Stephen N. Rosenfield* has served as our Executive Vice President of Legal Affairs, General Counsel and Secretary since March 2006; and Senior Vice President of Legal Affairs, General Counsel and Secretary since July 2004. From February 2003 to May 2004, Mr. Rosenfield served as Executive Vice President of Legal Affairs, General Counsel and Secretary of InterMune, Inc., a biopharmaceutical company. From February 2000 to February 2003, Mr. Rosenfield served as Senior Vice President of Legal Affairs, General Counsel and Secretary of InterMune, Inc. From February 1996 to March 2000, Mr. Rosenfield was as an attorney at Cooley Godward LLP and served as outside counsel for biotechnology and technology clients. Mr. Rosenfield received his B.S. degree from Hofstra University and his J.D. degree from Northeastern University School of Law.

*Andrew Grethlein* has served as our Senior Vice President, Pharmaceutical Operations since August 2005 and Vice President, Manufacturing from April 2003 to August 2005. From December 2000 to April 2003, Dr. Grethlein served as Senior Director, South San Francisco Operations for Elan Corporation, plc, a pharmaceutical company. From November 1998 to December 2000, he served as Director, Biopharmaceutical Operations for Elan Corporation, plc. From 1997 to November 1998, Dr. Grethlein served as Associate Director, Neurotoxin Production for Elan Corporation, plc. From 1995 to 1997, Dr. Grethlein served as Manager, Biologics Development and Manufacturing for Athena Neurosciences, Inc., a biotechnology company. From 1991 to 1995, Dr. Grethlein served in various engineering positions for Michigan Biotechnology Institute, a non-profit technology research and business development corporation, and its wholly-owned subsidiary, Grand River Technologies, Inc. Dr. Grethlein received his B.S. degree in biology from Bates College and his Ph.D. in chemical engineering from Michigan State University.

*Chris E. Rivera* has served as our Senior Vice President of Commercial Operations since April 2005. From September 2003 through December 2004, Mr. Rivera served as Vice President, Sales, at Corixa Corporation, a biopharmaceutical company. From April 2003 until September 2003, Mr. Rivera served as Vice President, Business Development for GeneCraft, Inc. (currently Trubion), also a biopharmaceutical company. From June 1998 until April 2003, Mr. Rivera served at Genzyme Corporation in various commercial positions with increasing responsibilities, the most recent as Senior Vice President, Therapeutics, where he was responsible for the U.S. commercialization of Genzyme Corporation s renal division. From April 1996 until May 1998, Mr. Rivera served as Vice President, Sales for Genzyme Tissue Repair. Prior to serving at Genzyme Corporation, Mr. Rivera helped to build the original commercial organizations at Cephalon, Inc. from 1993 through 1995 and at Centocor, Inc. from 1991 through 1993. Mr. Rivera began his career at E.R. Squibb and Sons (currently known as Bristol Myers-Squibb) in 1986 in a sales capacity, and was promoted to Seattle District Manager in 1989. Mr. Rivera received his B.S. degree in Business Administration at Northwestern Oklahoma State University and his M.S. degree in Audiology at the University of Oklahoma Health Sciences Centery. Mr. Rivera also attended the M.B.A. program at Seattle University s Albers School of Business and Economics, where he studied marketing and management.

*Thorsten von Stein* has served as our Chief Medical Officer and Senior Vice President of Clinical and Regulatory Affairs since January 2005. From August 2003 to January 2005, Dr. von Stein served as Chief Medical Officer at NeurogesX, Inc., a pharmaceutical company. From December 2001 to July 2003, Dr. von Stein served as Vice President, Clinical Development at Neurogesx. From 1994 to 2001, Dr. von Stein held positions of increasing responsibility in medical research, global clinical development and project management for Roche Palo Alto and F. Hoffman-La Roche AG in Basel, Switzerland. Dr. von Stein served as Director of Medical Research at Roche Palo Alto from 1998 to December 2001. Dr. von Stein received his M.D. degree from Munich University, Germany, and his Ph.D. degree in computer science from the University of Hamburg, Germany.

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**Corporate Information**

Tercica, Inc. was formed in December 2001 as a Delaware corporation. In early 2002, Tercica, Inc. acquired all the intellectual property rights and assumed specified liabilities of Tercica Limited, which was formed in October 2000 as a New Zealand company. Tercica Limited was subsequently liquidated.

**Available Information**

We file electronically with the U.S. Securities and Exchange Commission, or SEC, our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934. We make available on our website at http://www.tercica.com, free of charge, copies of these reports as soon as reasonably practicable after filing these reports with, or furnishing them to, the SEC.

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**Item 1A. Risk Factors.**

*We have identified the following additional risks and uncertainties that may have a material adverse effect on our business, financial condition or results of operations. Investors should carefully consider the risks described below before making an investment decision. The risks described below are not the only ones we face. Additional risks not presently known to us or that we currently believe are immaterial may also significantly impair our business operations. Our business could be harmed by any of these risks. The trading price of our common stock could decline due to any of these risks, and investors may lose all or part of their investment.*

**Risks Related to Our Business**

***We are a development stage company with a limited operating history and may not be able to successfully market and sell any products, generate significant revenues or attain profitability.***

We are a development stage company focused on the development and commercialization of Increlex for the treatment of short stature and other endocrine disorders. From our inception in October 2000 through December 31, 2005, we have accumulated a deficit of $165.7 million. We have not generated and may not be able to generate significant revenues from operations and may not be able to attain profitability. We incurred a net loss of $46.2 million during the year ended December 31, 2005. We expect to incur substantial net losses, in the aggregate and on a per share basis, for the foreseeable future as we attempt to develop, market and sell Increlex for severe Primary IGFD and Primary IGFD. We are unable to predict the extent of these future net losses, or when we may attain profitability, if at all. These net losses, among other things, have had and will continue to have an adverse effect on our stockholders equity and net current assets.

We anticipate that for the foreseeable future our ability to generate revenues and achieve profitability will be solely dependent on the successful commercialization of Increlex for the treatment of severe Primary IGFD and Primary IGFD. There is no assurance that we will be able to obtain or maintain governmental regulatory approvals to market Increlex in the United States or rest of the world for these indications or any other indication. If we are unable to generate significant revenue from Increlex or attain profitability, we will not be able to sustain our operations.

***If there are fewer children with severe Primary IGFD or Primary IGFD than we estimate, we may not generate sufficient revenues to continue development of other products or to continue operations, or we may not be able to complete our clinical trials.***

If there are fewer children with severe Primary IGFD or Primary IGFD than we estimate, we may not generate sufficient revenues to continue development of other indications or products and may cease operations. We estimate that the number of children in the United States with short stature is approximately one million, of which approximately 380,000 are referred to pediatric endocrinologists for evaluation. We believe that approximately 30,000 of these children have Primary IGFD, of which approximately 6,000 have severe Primary IGFD. Our estimate of the size of the patient population is based on published studies as well as internal data, including our interpretation of a study conducted as part of Genentech s National Cooperative Growth Study program. This study reported results of the evaluation of the hormonal basis of short stature in approximately 6,450 children referred to pediatric endocrinologists over a four-year period. We believe that the aggregate numbers of children in Western Europe with Primary IGFD and severe Primary IGFD are substantially equivalent to the numbers in the United States. If the results of Genentech s study or our interpretation and extrapolation of data from the study do not accurately reflect the number of children with Primary IGFD or severe Primary IGFD, our assessment of the market may be incorrect, making it difficult or impossible for us to meet our revenue goals or to enroll a sufficient number of patients in our clinical trials on a timely basis, or at all.

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***Increlex may fail to achieve market acceptance, which could harm our business.***

Prior to our January 2006 commercial launch of Increlex in the United States for the treatment of severe Primary IGFD, rhIGF-1 had never been commercialized in the United States or Europe for any indication. Even though the FDA has approved Increlex for sale in the United States, physicians may choose not to prescribe it, in which event we may be unable to generate significant revenue or become profitable.

Acceptance of Increlex will depend on a number of factors including:

- acceptance of Increlex by physicians and patients as a safe and effective treatment;
- reimbursement adoption;
- product price;
- the effectiveness of our sales and marketing efforts;
- storage requirements and ease of administration;
- dosing regimen;
- safety and efficacy;
- prevalence and severity of side effects; and
- competitive products.

***Reimbursement may not be available for Increlex, which could diminish our sales and impact our ability to achieve profitability.***

Market acceptance, our sales of Increlex and our profitability will depend on reimbursement policies and health care reform measures. The levels at which government authorities and third-party payors, such as private health insurers and health maintenance organizations, reimburse the price patients pay for Increlex, and the timing of reimbursement decisions by these payors, will affect the commercialization of Increlex. We believe that Increlex will be reimbursed to a similar extent that growth hormone therapy is reimbursed. If our assumptions regarding the timing of reimbursement decisions or the level of reimbursement for Increlex are incorrect, our expected revenues may be delayed or substantially reduced. Since the FDA approved Increlex for severe Primary IGFD, only prescriptions for that indication may be reimbursable. Also, we cannot be sure that reimbursement amounts will not reduce the demand for, or the price of, Increlex. If reimbursement is not available or is available only to limited levels, we may not be able to market and sell Increlex.

We believe that the annual wholesale acquisition cost of Increlex therapy for the treatment of severe Primary IGFD for a 24 kilogram child would be approximately $23,000 per year. The actual cost per year per patient for Increlex will depend on the weight of the child, the treatment dose prescribed and compliance. In addition, it is possible that the children receiving Increlex therapy during the first few years of our launch are younger and/or smaller than those children receiving the drug in ensuing years, and the price per patient could be less than in subsequent years. If our assumptions regarding the price per patient of Increlex therapy for the treatment of severe Primary IGFD and Primary IGFD are incorrect, the market opportunity for Increlex therapy for the treatment of severe Primary IGFD and Primary IGFD may be substantially reduced.

In recent years, officials have made numerous proposals to change the health care system in the United States. These proposals include measures that would limit or prohibit payments for certain medical treatments or subject the pricing of drugs to government control. In addition, in many foreign countries, particularly the countries of the European Union, the pricing of prescription drugs is subject to government control. If our product becomes subject to government legislation that limits or prohibits payment for Increlex, or that subjects the price of our product to governmental control, we may not be able to generate revenues, attain profitability or

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market and sell our product. Because these initiatives are subject to substantial political debate, which we cannot predict, the trading price of biotechnology stocks, including ours, may become more volatile as this debate proceeds.

As a result of legislative proposals and the trend towards managed health care in the United States, third-party payors are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement of new drugs. They may also refuse to provide any coverage of uses of approved products for medical indications other than those for which the FDA has granted market approvals. As a result, significant uncertainty exists as to whether and how much third-party payors will reimburse patients for their use of newly approved drugs, which, in turn, will put pressure on the pricing of drugs.

***We face significant competition from large pharmaceutical, biotechnology and other companies that could harm our business.***

The biotechnology industry is intensely competitive and characterized by rapid technological progress. In each of our potential product areas, we face significant competition from large pharmaceutical, biotechnology and other companies. Most of these companies have substantially greater capital resources, research and development staffs, facilities and experience at conducting clinical trials and obtaining regulatory approvals. In addition, many of these companies have greater experience and expertise in developing and commercializing products.

We cannot predict the relative competitive position of Increlex. However, we expect that the following factors, among others, will determine our ability to compete effectively:

- acceptance of Increlex by physicians and patients as a safe and effective treatment;
- reimbursement adoption;
- product price;
- manufacturing costs;
- the effectiveness of our sales and marketing efforts;
- storage requirements and ease of administration;
- dosing regimen;
- safety and efficacy;
- prevalence and severity of side effects; and
- competitive products.

We believe that many of our competitors spend significantly more on research and development-related activities than we do. Our competitors may discover new treatments, drugs or therapies or develop existing technologies to compete with Increlex. Our commercial opportunities will be reduced or eliminated if these competing products are more effective, have fewer or less severe side effects, are more convenient or are less expensive than Increlex.

Insmed Incorporated s combination product, when launched commercially, will compete with Increlex for the treatment of patients with severe Primary IGFD. Insmed s combination product was recently approved by the FDA for the treatment of patients with severe Primary IGFD or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone.

Growth hormone products will likely compete with Increlex for the treatment of patients with Primary IGFD if Increlex is also approved for that indication. The major suppliers of commercially available growth hormone

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products in the United States are Genentech, Eli Lilly and Company, Teva Pharmaceutical Industries Ltd., Novo Nordisk A/S, Pfizer Inc and Serono S.A. Investigators from a Novo Nordisk clinical trial recently presented data that demonstrated growth hormone was effective in a population that included children with Primary IGFD. In addition, children with Primary IGFD may be diagnosed as having idiopathic short stature, or ISS. Eli Lilly and Company and Genentech have received FDA approval for their respective growth hormone products for the treatment of children with ISS. Accordingly, we expect that growth hormone products will compete directly with Increlex for the treatment of children with Primary IGFD who may be diagnosed as having ISS.

In addition, we are aware that Chiron Corporation has developed a process to manufacture rhIGF-1 using yeast expression and has intellectual property with respect to that process. We use bacterial expression, which differs from yeast expression, to manufacture Increlex.

We believe that Bristol-Meyers Squibb Company, Genentech, Merck & Co., Inc., Novo Nordisk and Pfizer Inc have conducted research and development of orally available small molecules that cause the release of growth hormone, known as growth hormone secretagogues. We believe that Rejuvenon Corporation has licensed certain rights to Novo Nordisk s growth hormone secretagogues and is actively developing one of these compounds for use in cancer cachexia, a wasting disorder affecting some cancer patients.

Many companies are seeking to develop products and therapies for the treatment of diabetes. These competitors include multinational pharmaceutical companies, specialized biotechnology firms, and universities and other research institutions. Insmed has also conducted clinical trials using a product that contains rhIGF-1 for the treatment of diabetes. It is possible that there are other products currently in development or that exist on the market that may compete directly with Increlex.

***If we do not receive additional regulatory marketing approvals of Increlex, our business will be harmed.***

We are currently developing Increlex in clinical trials for the treatment of Primary IGFD, which has substantially more patients than severe Primary IGFD. The FDA has substantial discretion in the approval process and may decide that our data is insufficient to allow approval of Increlex for Primary IGFD. If we do not receive regulatory marketing approval in the United States for Primary IGFD, our business will be harmed. We will also need to file applications with regulatory authorities in foreign countries to market Increlex for Primary IGFD in foreign countries. Although we have submitted a marketing authorization application in Europe for severe Primary IGFD, there is no assurance that we will receive marketing approval in Europe for either severe Primary IGFD or Primary IGFD. If we fail to obtain European marketing approval for Increlex, the geographic market for Increlex would be limited. If such approvals are delayed, it would postpone our ability to generate revenues in Europe.

***If our contract manufacturers facilities and operations do not maintain satisfactory cGMP compliance, we may be unable to market and sell Increlex.***

The facilities used by and operations of our contract manufacturers to manufacture and test Increlex must undergo continuing inspections by the FDA for compliance with cGMP regulations in order to maintain our Increlex approval for the treatment of severe Primary IGFD. As an example, Cambrex Bio Science Baltimore, Inc. is our sole provider of bulk rhIGF-1. We have no alternative manufacturing facilities or plans for additional facilities at this time. We do not know if the Cambrex Baltimore facilities or their operations required for the commercial manufacture of Increlex will continue to receive satisfactory cGMP inspections. In the event these facilities or operations do not continue to receive satisfactory cGMP inspections for the manufacture of our product, or for the operation of their facilities in general, we may need to invest in significant compliance improvement programs, fund additional modifications to our manufacturing processes, conduct additional validation studies, or find alternative manufacturing facilities, any of which would result in significant cost to us as well as result in a delay or prevention of commercialization, and may result in our failure to maintain approval. In addition, Cambrex Baltimore, and any alternative contract manufacturer we may utilize, will be

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subject to ongoing periodic inspection by the FDA and corresponding state and foreign agencies for compliance with cGMP regulations and similar foreign standards. We do not have direct control over our contract manufacturers compliance with these regulations and standards. Any of these factors could delay or suspend clinical trials, regulatory submissions or regulatory approvals, entail higher costs and result in our being unable to effectively market and sell Increlex or maintain Increlex in the marketplace, which would adversely affect our ability to generate revenues.

***Our inability to enter into a commercial agreement on commercially reasonable terms with a single-source manufacturer to fill-finish our approved product could adversely affect our commercial supply and ability to grow revenues.***

We currently source all of our fill-finish manufacturing and portions of release testing through a single-source third-party supplier. This single-source supplier is the only approved supplier currently available to us, and could only be replaced by qualification of a new site for the same operations. We are currently negotiating a commercial agreement with this fill-finish manufacturer, which has agreed to provide commercial product under an existing agreement. However, if we are unable to enter into such a commercial agreement with this single-source third-party supplier, we may be unable to fill-finish our commercial product until we could move our process to another fill-finish manufacturer. It would take a significant amount of time and expense to arrange for an alternative manufacturer. If we need to change to another commercial fill-finish manufacturer, this manufacturer s facilities and processes, prior to our use, would have to undergo pre-approval and/or cGMP compliance inspections. In addition, we would need to transfer and validate the processes and certain analytical methods necessary for the production and testing of rhIGF-1 to this new manufacturer. Such a transfer may result in a shortage of our commercial product and a loss of revenues.

***We rely solely on single-source third parties in the manufacture, testing, storage and distribution of our products.***

We source all of our fill-finish manufacturing and testing and final product storage and distribution operations, as well as our all of our bulk manufacturing, testing, and shipping operations, through single-source third-party suppliers and contractors. Single-source suppliers are the only approved suppliers currently available to us, and could only be replaced by qualification of new sites for the same operations.

If our contract facilities, contractors or suppliers become unavailable to us for any reason, including as a result of the failure to comply with cGMP regulations, manufacturing problems or other operational failures, such as equipment failures or unplanned facility shutdowns required to comply with cGMP, damage from any event, including fire, flood, earthquake or terrorism, business restructuring or insolvency, or if they fail to perform under our agreements with them, such as failing to deliver commercial quantities of bulk drug substance or finished product on a timely basis and at commercially reasonable prices, we may be delayed in manufacturing Increlex or may be unable to maintain validation of Increlex. This could delay or prevent the supply of commercial and clinical product, or delay or otherwise adversely affect revenues. If the damage to any of these facilities is extensive, or, for any reason, they do not operate in compliance with cGMP or are unable or refuse to perform under our licenses and/or agreements, we will need to find alternative facilities. The number of contract manufacturers with the expertise and facilities to manufacture rhIGF-1 bulk drug substance on a commercial scale in accordance with cGMP regulations is extremely limited, and it would take a significant amount of time and expense to arrange for alternative manufacturers. If we need to change to other commercial manufacturers, these manufacturers facilities and processes, prior to our use, would likely have to undergo pre-approval and/or cGMP compliance inspections. In addition, we would need to transfer and validate the processes and analytical methods necessary for the production and testing of rhIGF-1 to these new manufacturers.

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***We rely in certain cases on single-source and sole-source materials suppliers to manufacture Increlex.***

Certain specific components and raw materials used to manufacture Increlex at our third-party manufacturers are obtained and made available through either single-source or sole-source suppliers. Single-source suppliers are the only approved suppliers currently available to us, and could only be supplemented by qualification of new sources for the material required. Sole-source suppliers are the only source of supply available to us, and could only be replaced through qualification of an alternate material after demonstrating suitability. Supply interruption of these materials could result in a significant delay to our manufacturing schedules and ability to supply product, and would likely be required to undergo lengthy regulatory approval procedures prior to product distribution. Limits or termination of supply of these materials could significantly impact our ability to manufacture Increlex, cause significant supply delays while we qualified, at significant expense, new suppliers or new materials, and would consequently cause harm to our business.

***Difficulties or delays in product manufacturing due to advance scheduling requirements and/or capacity constraints at our third-party manufacturers could harm our operating results and financial performance.***

The manufacture of Increlex requires successful coordination between us and all of our suppliers, contractors, service-providers, and manufacturers. Coordination failures with these different elements of our supply chain could require us to delay shipments and/or impair our ability to supply product. Furthermore, uncertainties in estimating future demand for new products such as Increlex may result in manufacture of surplus inventory requiring us to record charges for any expired, unused product, or may result in inadequate manufacturing of product inventory, causing delays to shipments or no shipments at all. Additionally, our reliance on third-party manufacturing requires long lead times from order to delivery of product, and may be hampered by available capacity at those manufacturers, making our ability to supply product supplies in excess of our forecast extremely difficult. As a consequence, we may have inadequate capacity to meet unexpected demand, which could negatively affect our operating results.

***Claims and concerns may arise regarding the safety and efficacy of Increlex, which could require us to perform additional clinical trials, could slow introduction into the marketplace, or cause reduced sales or product withdrawal after introduction.***

Increlex was approved in the United States for the treatment of severe Primary IGFD based on long-term and extensive studies and clinical trials conducted to demonstrate product safety and efficacy. Discovery of previously unknown problems with the raw materials, product or manufacturing processes, such as loss of sterility, contamination, new data suggesting an unacceptable safety risk or previously unidentified side effects for the product, could result in a voluntary or mandated withdrawal of the product from the marketplace, either temporarily or permanently. Studies may result in data or evidence suggesting another product is safer, better tolerated, or more efficacious than Increlex, which could lead to reduced sales. Additionally, discovery of unknown problems with our product or manufacturing processes for our product could negatively impact the established safety and efficacy profile and result in possible reduced sales or product withdrawal. Such outcomes could negatively and materially affect our product sales, operating results, and financial condition.

***If other companies overcome our U.S. orphan drug marketing exclusivity or obtain marketing exclusivity in Europe, they will be able to compete with us, and our revenues will be diminished.***

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States. The company that obtains the first FDA approval for a designated orphan drug for a rare disease receives marketing exclusivity for use of that drug for the designated condition for a period of seven years. Increlex has received from the FDA orphan drug marketing exclusivity for the long-term treatment of patients with severe Primary IGFD. However, more than one product may be approved by the FDA for the same orphan indication or disease. As a result, even though our product has been approved and has received marketing

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exclusivity for severe Primary IGFD, the FDA can still approve other drugs for use in treating the same indication or disease covered by our product, which would create a more competitive market for us. For example, the FDA recently approved Insmed Incorporated s combination product for the treatment of severe Primary IGFD and granted Insmed s product orphan drug designation. Accordingly, notwithstanding our orphan drug designation for rhIGF- 1, Insmed s combination product for rhIGF-1 and BP-3 was deemed by the FDA to be a different drug than ours, and therefore, it will compete with Increlex for the treatment of patients with severe Primary IGFD, when it is launched commercially.

Furthermore, drugs considered to be the same as Increlex that are clinically superior or provide a major contribution to patient care may be approved for marketing by the FDA despite our initial orphan drug marketing exclusivity. If other companies are able to overcome our U.S. orphan drug exclusivity, they will be able to compete with us, and our revenues will be diminished.

We believe that Insmed s drug has also received an orphan drug designation in Europe from the European Medicines Agency, or EMEA, that covers the treatment of severe Primary IGFD. If Insmed s or another company s drug product is granted orphan drug marketing exclusivity for severe Primary IGFD in Europe before ours and is considered to be the same drug as ours, we would not be able to market or sell Increlex for severe Primary IGFD in Europe, and our revenues would be diminished.

***We will not be able to sell our products if we are not able to maintain our regulatory approval due to changes to existing regulatory requirements.***

Although we have obtained regulatory approval for Increlex in the United States for the treatment of severe Primary IGFD, this product and our manufacturing processes are subject to continued review and ongoing regulation by the FDA post approval, including, for example, changes to manufacturing process standards or good manufacturing practices, changes to product labeling, revisions to existing requirements or new requirements for manufacturing practices, or changing interpretations regarding regulatory guidance. Such changes in the regulatory environment and requirements could occur at any time during the commercialization of Increlex. This could adversely affect our ability to maintain our approval or require us to expend significant resources to maintain our approval, which could result in the possible withdrawal of Increlex from the marketplace, which would harm our business and negatively impact our financial performance.

***Competitors could develop and gain FDA approval of products containing rhIGF-1, which could adversely affect our competitive position.***

Although we are not aware of any other company currently marketing rhIGF-1 in the United States for any human therapeutic indication, rhIGF-1 manufactured by other parties may be approved for use in the United States in the future. For example, we are aware that Chiron Corporation has developed a process to manufacture rhIGF-1 using yeast expression and has intellectual property with respect to that process. In the event there are other rhIGF-1 products approved by the FDA to treat indications other than those covered by Increlex, physicians may elect to prescribe a competitor s product containing rhIGF-1 to treat the indications for which Increlex has received and may receive approval. This is commonly referred to as off-label use. While under FDA regulations a competitor is not allowed to promote off-label use of its product, the FDA does not regulate the practice of medicine and as a result cannot direct physicians as to what product containing rhIGF-1 to prescribe to their patients. As a result, we would have limited ability to prevent off-label use of a competitor s product containing rhIGF-1 to treat any diseases for which we have received FDA approval even if it violates our method of use patents and/or we have orphan drug exclusivity for the use of rhIGF-1 to treat such diseases.

***Competitors could challenge our patents and file an Abbreviated New Drug Application (ANDA) or a 505(b)(2) new drug application for an IGF-1 product and adversely affect the competitive position of Increlex.***

Products approved for commercial marketing by the FDA are subject to the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Act. The Hatch-Waxman Act

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provides companies with marketing exclusivity for varying time periods during which generic or modified versions of a drug may not be marketed and allows companies to apply to extend patent protection for up to five additional years. It also provides a means for approving generic versions of a drug once the marketing exclusivity period has ended and all relevant patents have expired. The period of exclusive marketing, however, may be shortened if a patent is successfully challenged and defeated. Competitors with a generic IGF-1 product or a modified version of IGF-1 may attempt to file an ANDA or a 505(b)(2) NDA and challenge our patents and marketing exclusivity. Such applications would have to certify that one of the patents in the Increlex NDA is invalid or not infringed by the manufacture, use, or sale of the product described in that ANDA or 505(b)(2) application under the Hatch-Waxman Act. If successful, a competitor could come to market at an earlier time than expected. We can provide no assurances that we can prevail in a challenge or litigation related to our patents or exclusivity.

***If we fail to protect our intellectual property rights, competitors may develop competing products, and our business will suffer.***

lf we are not able to protect our proprietary technology, trade secrets and know-how, our competitors may use our inventions to develop competing products. We have licensed intellectual property rights, including patent rights, relating to rhIGF-1 technologies from Genentech. However, these patents may not protect us against our competitors. Patent litigation is very expensive, and we therefore may be unable to pursue patent litigation to its conclusion because currently we do not generate revenues.

We do not have patent composition coverage on the rhIGF-1 protein alone. Although we have licensed from Genentech its rights to its methods of use and manufacturing patents, it may be more difficult to establish infringement of such patents as compared to a patent directed to the rhIGF-1 protein composition alone. Our licensed patents may not be sufficient to prevent others from competing with us. We cannot rely solely on our patents to be successful. The standards that the U.S. Patent and Trademark Office and foreign patent offices use to grant patents, and the standards that United States and foreign courts use to interpret patents, are not the same and are not always applied predictably or uniformly and can change, particularly as new technologies develop. As such, the degree of patent protection obtained in the United States may differ substantially from that obtained in various foreign countries. In some instances, patents have issued in the United States while substantially less or no protection has been obtained in Europe or other countries. Our United States Patent No. 6,331,414 B1 licensed from Genentech is directed to methods for bacterial expression of rhIGF-1 and expires in 2018. We have no equivalent European patent. The European Patent Office has determined that the claims of Genentech s corresponding European patent application are not patentable under European patent law in view of public disclosures made before the application was filed.

We are uncertain of the level of protection, if any, that will be provided by our licensed patents if we attempt to enforce them, and they are challenged in court where our competitors may raise defenses such as invalidity, unenforceability or possession of a valid license. For example, we initiated patent infringement proceedings against Avecia Limited and Insmed Incorporated in the United Kingdom and against Insmed Incorporated in the United States to enforce patent rights we licensed from Genentech. The United States action, among other things, alleges infringement of United States Patent No. 6,311,414 B1 identified above. If the court finds any of the patents at issue in those litigations, including United States Patent No. 6,311,414 B1, to be invalid or unenforceable, we would be prevented from enforcing such patents against third parties in the future, thus preventing us from using the affected patents to exclude others from competing with us. In addition, the type and extent of patent claims that will be issued to us in the future are uncertain. Any patents that are issued may not contain claims that will permit us to stop competitors from using similar technology.

In addition to the patented technology licensed from Genentech, we also rely on unpatented technology, trade secrets and confidential information, such as the proprietary information we use to manufacture Increlex. We may not be able to effectively protect our rights to this technology or information. Other parties may independently develop substantially equivalent information and techniques or otherwise gain access to or disclose this

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technology. We generally require each of our employees, consultants, collaborators, and certain contractors to execute a confidentiality agreement at the commencement of an employment, consulting or collaborative relationship with us. However, these agreements may not provide effective protection of this technology or information or, in the event of unauthorized use or disclosure, they may not provide adequate remedies.

***We may incur substantial costs as a result of patent infringement litigation or other proceedings relating to patent and other intellectual property rights, and we may be unable to protect our intellectual property rights.***

In December 2004, we initiated patent infringement proceedings against Avecia Limited and Insmed Incorporated in the United Kingdom and against Insmed in the United States to enforce patent rights we licensed from Genentech. We cannot predict the outcome of such litigation. These actions have required a substantial diversion of financial and personnel resources and could expose us to liability for costs or other awards of damages. Declaratory judgments of invalidity against our patents asserted in such actions could prevent us from using the affected patents to exclude others from competing with us.

In addition, a third party may claim that we are using its inventions covered by its patents and may initiate litigation to stop us from engaging in our operations and activities. Although no third party has claimed that we are infringing on their patents, patent lawsuits are costly and could affect our results of operations and divert the attention of managerial and technical personnel. There is a risk that a court would decide that we are infringing the third party s patents and would order us to stop the activities covered by the patents. In addition, there is a risk that a court will order us to pay the other party damages for having infringed the other party s patents. The biotechnology industry has produced a proliferation of patents, and it is not always clear to industry participants, including us, which patents cover various types of products or methods of use. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we are sued for patent infringement, we would need to demonstrate that our products or methods of use do not infringe the patent claims of the relevant patent and/or that the patent claims are invalid, and we may not be able to do so. Proving invalidity, in particular, is difficult since it requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents.

We are aware of a U.S. patent of Chiron Corporation related to processes of manufacturing rhIGF-1 in yeast host cells, to fusion proteins, DNA, and yeast host cells useful in such processes of manufacturing rhIGF-1 in yeast host cells, and to rhIGF-1 made as a product of such processes. While we use bacterial expression, not yeast expression, in our process for manufacturing Increlex, we cannot predict whether our activities relating to the development and commercialization of Increlex in the United States will be found to infringe Chiron s patent in the event Chiron brings patent infringement proceedings against us. We may not be able to obtain a license to Chiron s patent under commercially reasonable terms, if at all. If we are unable to obtain a license to Chiron s patent, and if in any patent infringement proceeding Chiron brings against us the court decides that our activities relating to the development and commercialization of Increlex in the United States infringe Chiron s patent, the court may award damages and/or injunctive relief to Chiron. Any such damages, injunctive relief and/or other remedies the court may award could render any further development and commercialization of Increlex commercially infeasible for us or otherwise curtail or cease any further development and commercialization of Increlex.

We cannot be certain that others have not filed patent applications for technology covered by our licensor s issued patents or our pending applications or our licensor s pending applications or that we or our licensors were the first to invent the technology because:

- some patent applications in the United States may be maintained in secrecy until the patents are issued,
- patent applications in the United States and many foreign jurisdictions are typically not published until 18 months after filing, and
- publications in the scientific literature often lag behind actual discoveries and the filing of patents relating to those discoveries.

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Patent applications may have been filed and may be filed in the future covering technology similar to ours. Any such patent application may have priority over our patent applications and could further require us to obtain rights to issued patents covering such technologies. In the event that another party has filed a U.S. patent application on inventions similar to ours, we may have to participate in an interference proceeding declared by the U.S. Patent and Trademark Office to determine priority of invention in the United States. The costs of these proceedings could be substantial, and it is possible that such efforts would be unsuccessful, resulting in a loss of our United States patent position with respect to such inventions.

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 harm our business.

***If we lose our licenses from Genentech, we may be unable to continue our business.***

We have licensed intellectual property rights and technology from Genentech, under our U.S. and International License and Collaboration agreements with Genentech. Under each agreement, Genentech has the right to terminate our license if we are in material breach of our obligations under that agreement and fail to cure that breach. Under the terms of the agreements, we are obligated, among other things, to use reasonable business efforts to meet specified milestones, including filing for regulatory approval in the United States for either a diabetes indication or a substitute indication by December 31, 2008. If we fail to use reasonable business efforts to meet our development milestones for either agreement, Genentech may terminate that agreement. If either agreement were terminated, then we would lose our rights to utilize the technology and intellectual property covered by that agreement to develop, manufacture, market and sell Increlex for any indication. This may prevent us from continuing our business.

***We are subject to Genentech s option rights with respect to the commercialization of Increlex for all diabetes and non-orphan indications in the United States.***

Under our U.S. License and Collaboration Agreement with Genentech, Genentech has the option to elect to jointly commercialize rhIGF-1 for all diabetes and non-orphan indications in the United States. Orphan indications are designated by the FDA under the Orphan Drug Act, and are generally rare diseases or conditions that affect fewer than 200,000 individuals in the United States. With respect to those non-orphan and diabetes indications in the United States, once Genentech has exercised its option to jointly develop and commercialize, Genentech has the final decision on disputes relating to development and commercialization of such indications. Our ability to sublicense the development and commercialization of such products requires the consent of Genentech.

***We do not know whether our planned clinical trials will begin on time, or at all, or will be completed on schedule, or at all.***

The commencement or completion of any of our clinical trials may be delayed or halted for numerous reasons, including, but not limited to, the following:

- the FDA or other regulatory authorities either do not approve a clinical trial protocol or place a clinical trial on clinical hold;
- patients do not enroll in clinical trials at the rate we expect (for example, in one of our current Phase III clinical trials of rhIGF-1 in Primary IGFD, patients have not enrolled at the rate we expected);
- patients experience adverse side effects;
- patients develop medical problems that are not related to our products or product candidates;

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- third-party clinical investigators do not perform our clinical trials on our anticipated schedule or consistent with the clinical trial protocol and good clinical practices, or other third-party organizations do not perform data collection and analysis in a timely or accurate manner;
- contract laboratories fail to follow good laboratory practices;
- interim results of the clinical trial are inconclusive or negative;
- sufficient quantities of the trial drug may not be available, or available drug may become unusable;
- our trial design, although approved, is inadequate to demonstrate safety and/or efficacy;
- re-evaluation of our corporate strategies and priorities; and
- limited financial resources.

In addition, we may choose to cancel, change or delay certain planned clinical trials, or replace one or more planned clinical trials with alternative clinical trials. Our clinical trials or intended clinical trials may be subject to further change from time to time as we evaluate our research and development priorities and available resources. Our development costs will increase if we need to perform more or larger clinical trials than planned. Significant delays for our current or planned clinical trials may harm the commercial prospects for Increlex and our prospects for profitability.

***Clinical development is a long, expensive and uncertain process, and delay or failure can occur at any stage of any of our clinical trials.***

To gain approval to market a product for treatment of a specific disease, we must provide the FDA and foreign regulatory authorities with clinical data that demonstrate the safety and statistically significant efficacy of that product for the treatment of the disease. Clinical development is a long, expensive and uncertain process, and delay or failure can occur at any stage of any of our clinical trials. A number of companies in the pharmaceutical industry, including biotechnology companies, have suffered significant setbacks in advanced clinical trials, even after promising results in earlier trials. Success in preclinical testing and early clinical trials does not ensure that later clinical trials will be successful. If a clinical trial failed to demonstrate safety and statistically significant efficacy, we would likely abandon the development of that product, which could harm our business and may result in a precipitous decline in our stock price.

***If third-party clinical research organizations do not perform in an acceptable and timely manner, our clinical trials could be delayed or unsuccessful.***

We do not have the ability to conduct all of our clinical trials independently. We rely on clinical investigators, third-party clinical research organizations and consultants to perform a substantial portion of these functions. If we cannot locate acceptable contractors to run our clinical trials or enter into favorable agreements with them, or if these contractors do not successfully carry out their contractual duties, satisfy FDA requirements for the conduct of clinical trials, or meet expected deadlines, we may be unable to obtain or maintain required approvals and may be unable to market and sell Increlex on a timely basis, if at all.

***We may need others to market and sell Increlex in Europe.***

We may need others to market and sell Increlex in Europe. If we receive marketing approval for Increlex in Europe and decide to sell Increlex in Europe through one or more third parties, we will need to enter into marketing arrangements with them. We may not be able to enter into marketing arrangements with third parties on favorable terms, or at all. In addition, these arrangements could result in lower levels of income to us than if we marketed Increlex entirely on our own. In the event that we are unable to enter into a marketing arrangement for Increlex in Europe, we may not be able to develop an effective sales force to successfully market and sell our product in Europe. If we fail to enter into marketing arrangements for our product and are unable to develop an effective international sales force, our revenues could be limited.

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***If we fail to identify and in-license other patent rights, products or product candidates, we may be unable to grow our revenues.***

We do not conduct any preclinical laboratory research. Our strategy is to in-license products or product candidates and further develop them for commercialization. The market for acquiring and in-licensing patent rights, products and product candidates is intensely competitive. If we are not successful in identifying and in-licensing other patent rights, products or product candidates, we may be unable to grow our revenues with sales from new products.

In addition, we may need additional intellectual property from other third parties to market and sell Increlex for indications other than severe Primary IGFD or Primary IGFD. We cannot be certain that we will be able to obtain a license to any third-party technology we may require to conduct our business.

***The committed equity financing facility that we entered into with Kingsbridge Capital Limited may not be available to us if we elect to make a draw down, and may require us to pay certain liquidated damages.***

In October 2005, we entered into a committed equity financing facility, or CEFF, with Kingsbridge Capital Limited, or Kingsbridge, which entitles us to sell and obligates Kingsbridge to purchase, from time to time over a period of three years, newly issued shares of our common stock for cash consideration of up to an aggregate of $75.0 million, subject to certain conditions and restrictions. Kingsbridge will not be obligated to purchase shares under the CEFF unless certain conditions are met, which include:

- a minimum price for our common stock;
- the accuracy of representations and warranties made to Kingsbridge;
- compliance with laws;
- effectiveness of the registration statement, filed by us with the U.S. Securities and Exchange Commission, or SEC, for the resale of the shares of common stock issuable in connection with the CEFF and the shares of common stock underlying the warrant we issued to Kingsbridge in connection with the entering into of the CEFF; and
- the continued listing of our stock on the Nasdaq Stock Market.

In addition, Kingsbridge is permitted to terminate the CEFF if it determines that a material and adverse event has occurred affecting our business, operations, properties or financial condition. If we are unable to access funds through the CEFF, or if the CEFF is terminated by Kingsbridge, we may be unable to access capital on favorable terms or at all.

The terms of the CEFF require us to pay certain liquidated damages in the event that the registration statement filed by us with the SEC is not available for the resale of securities purchased by Kingsbridge under the CEFF or upon exercise of the warrant we issued to Kingsbridge. Except for certain periods of ineffectiveness permitted under the CEFF, we are obligated to pay to Kingsbridge an amount equal to the number of shares purchased under the CEFF and held by Kingsbridge at the date the registration statement becomes unavailable, multiplied by any positive difference in price between the volume weighted average price on the trading day prior to such period of unavailability and the volume weighted average price on the first trading day after the period of unavailability. In addition, we are entitled in certain circumstances to deliver a blackout notice to Kingsbridge to suspend the use of the registration statement and prohibit Kingsbridge from selling shares under the registration statement. If we deliver a blackout notice in the 15 trading days following a settlement of a draw down, then we must make a blackout payment to Kingsbridge as liquidated damages, or issue Kingsbridge additional shares in lieu of this payment, calculated by means of a varying percentage of an amount based on the number of shares purchased and held by Kingsbridge and the change in the market price of our common stock during the period in which the use of the registration statement is suspended. If the trading price of our common stock declines during a suspension of the registration statement, the blackout payment could be significant and could adversely affect our liquidity and our ability to raise capital.

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***If we fail to obtain the capital necessary to fund our operations, we will be unable to execute our business plan.***

We believe that our existing cash, cash equivalents and short-term investments as of December 31, 2005, together with the net proceeds from our public offering of common stock in January 2006 and our CEFF, will be sufficient to meet our projected operating and capital expenditure requirements through at least the end of 2007 based on our current business plan. We expect capital outlays and operating expenditures to increase over the next several years as we expand our operations.

Our future capital needs and the adequacy of our available funds will depend on many factors, including:

- our ability to market and sell sufficient quantities of Increlex;
- the status of competing products;
- the commercial status of the Increlex bulk drug manufacturing operations at Cambrex Baltimore, including the success of our cGMP production activities;
- the success of Increlex final drug product manufacturing;
- the costs, timing and scope of additional regulatory approvals for Increlex;
- the rate of progress and cost of our future clinical trials and other research and development activities; and
- the pace of expansion of administrative expenses.

We expect that we will require and attempt to raise additional funds through equity or debt financings, collaborative arrangements with corporate partners or from other sources, and the CEFF. However, there can be no assurance that additional financing will be available when needed, or, if available, that the terms will be favorable. If additional funds are not available, we may be forced to curtail or cease operations.

***If we are unable to manage our expected growth, we may not be able to implement our business plan.***

Our ability to implement our business plan requires an effective planning and management process. As of December 31, 2005, we had 89 full-time employees, and we expect to hire additional employees in the near term. Our offices are located in the San Francisco Bay area where competition for personnel with biopharmaceutical skills is intense. If we fail to identify, attract, retain and motivate these highly skilled personnel, we may be unable to continue our development and commercialization activities.

We expect that our anticipated future growth will place a significant strain on our management, systems and resources. In particular, to fulfill our strategy to market and sell Increlex in the United States, we may need to hire a significant number of additional employees. To manage the anticipated growth of our operations, we will need to increase management resources and implement new financial and management controls, reporting systems and procedures. If we are unable to manage our growth, we could be unable to execute our business strategy.

***If product liability lawsuits are brought against us, we may incur substantial liabilities.***

One potential risk of using growth factors like rhIGF-1 is that it may increase the likelihood of developing cancer or, if patients already have cancer, that the cancer may develop more rapidly. Increlex may also increase the risk that diabetic patients may develop or worsen an existing retinopathy, which could lead to the need for additional therapy such as laser treatment of the eyes or result in blindness. We have Phase III study results from the treatment of 76 children with severe Primary IGFD with Increlex for an average of 4.4 years, with some patients being treated for over 12 years. None of the children withdrew from the study due to adverse events.

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However, some patients experienced hypoglycemia, or low blood glucose levels. Other side effects noted in some patients include hearing deficits, enlargement of the tonsils and intracranial hypertension.

There may also be other adverse events associated with the use of Increlex, which may result in product liability suits being brought against us. While we have licensed the rights to develop, market and sell Increlex in certain indications, we are not indemnified by any third party, including our contract manufacturers, for any liabilities arising out of the development or use of rhIGF-1.

Whether or not we are ultimately successful in defending product liability litigation, such litigation would consume substantial amounts of our financial and managerial resources, and might result in adverse publicity or reduced acceptance of Increlex in the market, all of which would impair our business. We have obtained clinical trial insurance and product liability insurance; however, we may not be able to maintain our clinical trial insurance or product liability insurance at an acceptable cost, if at all, and this insurance may not provide adequate coverage against potential claims or losses.

***Budgetary or cash constraints may force us to delay our efforts to develop certain research and development programs in favor of developing others, which may prevent us from meeting our stated timetables and completing these projects through to product commercialization.***

Because we are an emerging company with limited resources, and because research and development is an expensive process, we must regularly assess the most efficient allocation of our research and development resources. Accordingly, we may choose to delay or abandon our research and development efforts for the treatment of a particular indication or project to allocate those resources to another indication or project, which could cause us to fall behind our initial timetables for development. As a result, we may not be able to fully realize the value of some of our product candidates in a timely manner, since they will be delayed in reaching the market, or may not reach the market at all.

***We must implement additional finance and accounting systems, procedures and controls as we grow our business and organization and to satisfy new reporting requirements.***

As a public reporting company, we must comply with the Sarbanes-Oxley Act of 2002 and the related rules and regulations of the Securities and Exchange Commission, including expanded disclosures and accelerated reporting requirements and more complex accounting rules. Compliance with Section 404 of the Sarbanes-Oxley Act of 2002 and other requirements will increase our costs and require additional management resources. We have upgraded our finance and accounting systems, procedures and controls and will need to continue to implement additional procedures and controls as we grow our business and organization and to satisfy new reporting requirements. Section 404 requires annual management assessments of the effectiveness of our internal control over financial reporting and a report by our independent registered public accountants attesting to and reporting on these assessments. If we are unable to complete the required assessment as to the adequacy of our internal control reporting or if our independent registered public accounting firm is unable to provide us with an unqualified report as to the effectiveness of our internal controls over financial reporting, investors could lose confidence in the reliability of our internal control over financial reporting, which could adversely affect our stock price.

***If we are unable to attract and retain additional qualified personnel, our ability to market and sell Increlex and develop other product candidates will be harmed.***

Our success depends on our continued ability to attract and retain highly qualified management and scientific personnel and on our ability to develop relationships with leading academic scientists and clinicians. We are highly dependent on our current management and key medical, scientific and technical personnel, including: Dr. John A. Scarlett, our President and Chief Executive Officer and Dr. Ross G. Clark, our Chief Technical Officer, whose knowledge of our industry and technical expertise would be extremely difficult to

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replace. We have at will employment contracts with all of our executive officers. They may terminate their employment without cause or good reason and without notice to us.

**Risks Related to Our Common Stock**

***If our results do not meet analysts forecasts and expectations, our stock price could decline.***

While research analysts and others have published forecasts as to the amount and timing of our future revenues and earnings, we have stated that we will not be providing any forecasts of the amount and timing of our future revenues and earnings until after the assessment of two quarters of product sales. Analysts who cover our business and operations provide valuations regarding our stock price and make recommendations whether to buy, hold or sell our stock. Our stock price may be dependent upon such valuations and recommendations. Analysts valuations and recommendations are based primarily on our reported results and their forecasts and expectations concerning our future results regarding, for example, expenses, revenues, clinical trials, regulatory marketing approvals and competition. Our future results are subject to substantial uncertainty, and we may fail to meet or exceed analysts forecasts and expectations as a result of a number of factors, including those discussed under the section entitled Risks Related to Our Business above. If our results do not meet analysts forecasts and expectations, our stock price could decline as a result of analysts lowering their valuations and recommendations or otherwise.

***If our officers, directors and largest stockholders choose to act together, they are able to control our management and operations, acting in their best interests and not necessarily those of other stockholders.***

As of December 31, 2005, our directors, executive officers and principal stockholders and their affiliates beneficially owned approximately 66.7% of our common stock. Our greater than five percent beneficial owners include entities affiliated with MPM Capital, which beneficially owned 21.7%; entities affiliated with Prospect Management Co. II, LLC, which beneficially owned 9.7%; MedImmune, Inc., which beneficially owned 9.5%; entities affiliated with Rho Ventures, which beneficially owned 9.5%; The Bank of New York, which beneficially owned 5.9%; and State of Wisconsin Investment Board, which beneficially owned 5.6%. Our directors, executive officers and principal stockholders and their affiliates collectively have the ability to determine the election of all of our directors and to determine the outcome of most corporate actions requiring stockholder approval. They may exercise this ability in a manner that advances their best interests and not necessarily those of other stockholders.

***Anti-takeover provisions in our charter documents and under Delaware law may make an acquisition of us, which may be beneficial to our stockholders, more difficult.***

Provisions of our amended and restated certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us, even if doing so would benefit our stockholders. These provisions:

- establish a classified board of directors so that not all members of our board may be elected at one time;
- authorize the issuance of blank check preferred stock that could be issued by our board of directors to increase the number of outstanding shares and hinder a takeover attempt;
- limit who may call a special meeting of stockholders;
- prohibit stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders; and
- establish advance notice requirements for nominations for election to our board of directors or for proposing matters that can be acted upon at stockholder meetings.

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In addition, Section 203 of the Delaware General Corporation Law, which prohibits business combinations between us and one or more significant stockholders unless specified conditions are met, may discourage, delay or prevent a third party from acquiring us.

***The committed equity financing facility that we entered into with Kingsbridge may result in dilution to our stockholders.***

Pursuant to the CEFF, Kingsbridge committed to purchase, subject to certain conditions and at our election, up to $75.0 million of our common stock. Should we sell shares to Kingsbridge under the CEFF, or issue shares in lieu of any blackout payment, it will have a dilutive effect on the holdings of our current stockholders, and may result in downward pressure on the price of our common stock. If we draw down amounts under the CEFF, we will issue shares to Kingsbridge at a discount of up to ten percent from the volume weighted average price of our common stock. If we draw down amounts under the CEFF when our share price is decreasing, we will need to issue more shares to raise the same amount than if our stock price was higher. Issuances in the face of a declining share price will have an even greater dilutive effect than if our share price were stable or increasing, and may further decrease our share price.

***Our stock price may be volatile, and an investment in our stock could decline in value.***

The trading price of our common stock has fluctuated significantly since our initial public offering in March 2004, and is likely to remain volatile in the future. The trading price of our common stock could be subject to wide fluctuations in response to many events or factors, including the following:

- announcements by us or our competitors of regulatory developments, clinical trial results, clinical trial enrollment, regulatory filings, new products and product launches, significant acquisitions, strategic partnerships or joint ventures;
- estimates of our business potential and earnings prospects;
- deviations from analysts projections regarding business potential, costs and/or earnings prospects;
- quarterly variations in our operating results;
- significant developments in the businesses of biotechnology companies;
- changes in financial estimates by securities analysts;
- changes in market valuations or financial results of biotechnology companies;
- additions or departures of key personnel;
- changes in the structure of healthcare payment or reimbursement systems, regulations or policies;
- activities of short sellers and risk arbitrageurs;

future sales of our common stock;

general economic, industry and market conditions; and

volume fluctuations, which are particularly common among highly volatile securities of biotechnology companies.

In addition, the stock market has experienced volatility that has particularly affected the market prices of equity securities of many biotechnology companies, which often has been unrelated or disproportionate to the operating performance of these companies. These broad market fluctuations may adversely affect the market price of our common stock. If the market price of our common stock declines in value, you may not realize any return on your investment in us and may lose some or all of your investment.

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***We are at risk of securities class action litigation.***

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology companies have experienced greater than average stock price volatility in recent years. If we faced such litigation, it could result in substantial costs and a diversion of management s attention and resources, which could harm our business.

***Substantial sales of shares may impact the market price of our common stock.***

If our stockholders sell substantial amounts of our common stock, including shares issued upon the exercise