Protalix BioTherapeutics, Inc.
Form 10-K
March 06, 2009

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

# FORM 10-K

**FOR ANNUAL AND TRANSITION REPORTS PURSUANT TO SECTIONS 13 OR 15(d)**
**OF THE SECURITIES EXCHANGE ACT OF 1934**

**(Mark One)**

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

**For the fiscal year ended December 31, 2008**

**OR**

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

**For the transition period from _____ to _____**

**001-33357**
**(Commission file number)**

**PROTALIX BIOTHERAPEUTICS, INC.**
**(Exact name of registrant as specified in its charter)**

| **Florida** | **65-0643773** |
|---|---|
| **State or other jurisdiction of incorporation or organization** | **(I.R.S. Employer Identification No.)** |
| **2 Snunit Street<br>Science Park<br>POB 455<br>Carmiel, Israel** | **20100** |
| **(Address of principal executive offices)** | **(Zip Code)** |

**972-4-988-9488**
**Registrant s telephone number, including area code**
**Securities registered pursuant to Section 12(b) of the Act:**

| **Title of each class** | **Name of each exchange on which registered** |
|---|---|
| **Common stock, par value $0.001 per share** | **NYSE Alternext US** |

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

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

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

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) 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. o

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

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

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

The aggregate market value of the voting stock held by non-affiliates of the Registrant, as of June 30, 2008 was approximately $93.6 million (based upon the closing price for shares of the Registrant s common stock as reported by the NYSE Alternext US (then known as the American Stock Exchange) as of June 30, 2008 of $2.71). Shares of common stock held by each officer, director and holder of 5% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

On March 1, 2009, approximately 75,943,392 shares of the Registrant s common stock, par value $0.001 per share, were outstanding.

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## PART I

*Except where the context otherwise requires, the terms, we, us, our or the Company, refer to the business of Protalix BioTherapeutics, Inc. and its consolidated subsidiaries, and Protalix or Protalix Ltd. refers to the business of Protalix Ltd., our wholly-owned subsidiary and sole operating unit.*

## CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

The statements set forth under the captions Business, Management s Discussion and Analysis of Financial Condition and Results of Operations and Risk Factors, and other statements included elsewhere in this Annual Report on Form 10-K, which are not historical, constitute forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, including statements regarding expectations, beliefs, intentions or strategies for the future. When used in this report, the terms anticipate, believe, estimate, expect and intend and words or phrases of similar import, as they relate to our or ou subsidiary or our management, are intended to identify forward-looking statements. We intend that all forward-looking statements be subject to the safe-harbor provisions of the Private Securities Litigation Reform Act of 1995. These forward-looking statements are only predictions and reflect our views as of the date they are made with respect to future events and financial performance, and we undertake no obligation to update any forward-looking statement to reflect events or circumstances after the date on which the statement is made or to reflect the occurrence of unanticipated events, except as may be required under applicable law. Forward-looking statements are subject to many risks and uncertainties that could cause our actual results to differ materially from any future results expressed or implied by the forward-looking statements.

Examples of the risks and uncertainties include, but are not limited to, the following:

- the inherent risks and uncertainties in developing drug platforms and products of the type we are developing;
- delays in our preparation and filing of applications for regulatory approval;
- delays in the approval or potential rejection of any applications we file with the United States Food and Drug Administration, or the FDA, or other regulatory authorities;
- any lack of progress of our research and development (including the results of clinical trials we are conducting);
- obtaining on a timely basis sufficient patient enrollment in our clinical trials;
- the impact of development of competing therapies and/or technologies by other companies;
- our ability to obtain additional financing required to fund our research programs;
- the risk that we will not be able to develop a successful sales and marketing organization in a timely manner, if at all;
- our ability to establish and maintain strategic license, collaboration and distribution arrangements and to manage our relationships with collaborators, distributors and partners;
- potential product liability risks and risks of securing adequate levels of product liability and clinical trial insurance coverage;
- the availability of reimbursement to patients from health care payors for any of our drug products, if approved;
- the possibility of infringing a third party s patents or other intellectual property rights;

the uncertainty of obtaining patents covering our products and processes and in successfully enforcing our intellectual property rights against third parties;

the possible disruption of our operations due to terrorist activities and armed conflict, including as a result of the disruption of the operations of regulatory authorities, our subsidiary, our manufacturing facilities and our customers, suppliers, distributors, collaborative partners, licensees and clinical trial sites; and

other risks and uncertainties detailed in Section 1A of this Annual Report on Form 10-K.

In addition, companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in advanced clinical trials, even after obtaining promising earlier trial results. These and other risks and uncertainties are detailed under the heading Risk Factors in this Annual Report on Form 10-K and are described from time to time in the reports we file with the Securities and Exchange Commission. We undertake no obligation to update, and we do not have a policy of updating or revising, these forward-looking statements.

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## Item 1. Business

We are a biopharmaceutical company focused on the development and commercialization of recombinant therapeutic proteins based on our proprietary ProCellEx[tm] protein expression system. Using our ProCellEx system, we are developing a pipeline of proprietary recombinant therapeutic proteins based on our plant cell-based expression technology that target large, established pharmaceutical markets and that rely upon known biological mechanisms of action. Our initial commercial focus has been on complex therapeutic proteins, including proteins for the treatment of genetic disorders, such as Gaucher disease and Fabry disease. We believe our ProCellEx protein expression system will enable us to develop proprietary recombinant proteins that are therapeutically equivalent or superior to existing recombinant proteins currently marketed for the same indications. In addition, we believe our ProCellEx protein expression system will enable us to express and produce bio similar or generic versions of other recombinant proteins not protected through patents in a cost effective manner. Because we are primarily targeting biologically equivalent versions of highly active, well-tolerated and commercially successful therapeutic proteins, we believe our development process is associated with relatively less risk compared to other biopharmaceutical development processes for completely novel therapeutic proteins.

Our lead product development candidate is prGCD for the treatment of Gaucher disease, which we are developing using our ProCellEx protein expression system. Gaucher disease is a rare and serious lysosomal storage disorder with severe and debilitating symptoms. prGCD is our proprietary recombinant form of Glucocerebrosidase (GCD), an enzyme naturally found in human cells that is mutated or deficient in patients with Gaucher disease. Lysosomal storage disorders are metabolic disorders in which the lysosomal enzyme, a protein that degrades cellular substrates in the lysosomes of cells, is mutated or deficient. In July 2007, we reached an agreement with the United States Food and Drug Administration, or the FDA, on the final design of our pivotal phase III clinical trial of prGCD, through the FDA s special protocol assessment (SPA) process. We completed enrollment of patients in the phase III clinical trial in December 2008 and expect to report results of the clinical trial in the second half of 2009. We anticipate submitting a New Drug Application (NDA) for prGCD to the FDA and other comparable regulatory agencies in other countries in the fourth quarter of 2009. In addition to our phase III clinical trial, we initiated, during the third quarter of 2008, a double-blind, follow-on extension study as part of our phase III clinical trial. In December 2009, we also initiated a clinical study evaluating the safety and efficacy of switching Gaucher patients currently treated under the current standard of care to treatment with prGCD. The switchover-study is not a prerequisite for approval of prGCD. The current standard of care for Gaucher patients is enzyme replacement therapy with Cerezyme which is produced by Genzyme Corporation and currently the only approved enzyme replacement therapy for Gaucher disease. Enzyme replacement therapy is a medical treatment in which recombinant enzymes are injected into patients in whom the enzyme is lacking or dysfunctional.

Although Gaucher disease is a relatively rare disease, it represents a large commercial market due to the severity of the symptoms and the chronic nature of the disease. The annual worldwide sales of Cerezyme were approximately $1.2 billion in 2008 according to public reports by Genzyme. prGCD is a plant cell expressed version of the GCD enzyme, developed through our ProCellEx protein expression system. prGCD has an amino acid, glycan and three-dimensional structure that is very similar to its naturally-produced counterpart as well as to Cerezyme, which is a mammalian cell expressed version of the same protein. We believe prGCD may prove more cost-effective than the currently marketed alternative due to the cost benefits of expression through our ProCellEx protein expression system. In addition, based on our laboratory testing, preclinical and clinical results, we believe that prGCD may have the potential for increased potency and efficacy compared to the existing enzyme replacement therapy for Gaucher disease, which may translate into lower dosages and/or less frequent treatments.

In addition to prGCD, we are developing an innovative product pipeline using our ProCellEx protein expression system. Our product pipeline currently includes, among other candidates, therapeutic protein candidates for the treatment of Fabry disease, a rare, genetic lysosomal disorder in humans, an acetylcholinesterase enzyme-based therapy for biodefense and intoxication treatments and an additional undisclosed therapeutic protein, all of which are currently being evaluated in animal studies. We plan to file an investigational new drug application (IND) with the FDA with respect to at least one additional product during 2009 and to initiate human clinical studies immediately thereafter. We believe that we may be able to reduce the development risks and time to market for our product

candidates as our product candidates are based on well-understood proteins with known biological mechanisms of actions. We hold the worldwide commercialization rights to our proprietary development candidates and we intend to establish an internal, commercial infrastructure and targeted sales force to market prGCD and our other products, if approved, in North America, the European Union and in other significant markets, including Israel. In addition we are continuously evaluating potential strategic marketing partnerships.

Our ProCellEx protein expression system consists of a comprehensive set of technologies and capabilities for the development of recombinant proteins, including advanced genetic engineering technology and plant cell-based protein expression methods. Through our ProCellEx protein expression system, we can develop highly complex recombinant

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therapeutic proteins all the way to the scale-up of a purified product produced in compliance with current good manufacturing practices, or cGMP. We believe that our plant cell-based expression technology will enable us, in certain cases, to develop and commercialize recombinant proteins without infringing upon the method-based patents or other intellectual property rights of third parties. The major elements of our ProCellEx system are patent protected in most major countries. Moreover, we expect to enjoy method-based patent protection for the proteins we develop using our proprietary ProCellEx protein expression technology, although there can be no assurance that any such patents will be granted. In some cases, we may be able to obtain patent protection for the compositions of the proteins themselves. We have filed for United States and international composition of matter patents for prGCD.

Our ProCellEx protein expression system is built on flexible custom-designed bioreactors made of polyethylene and optimized for the development of complex proteins in plant cell cultures. These bioreactors entail low initial capital investment, are rapidly scalable at a low cost and require less hands-on maintenance between cycles, compared to the highly complex, expensive, stainless steel bioreactors typically used in mammalian cell-based production systems. As a result, through our ProCellEx protein expression system, we believe that we can develop recombinant therapeutic proteins yielding substantial cost advantages, accelerated development and other competitive benefits as compared to mammalian cell-based protein expression systems.

We have successfully demonstrated the feasibility of our ProCellEx system by expressing, on an exploratory, research scale, many complex therapeutic proteins belonging to different drug classes, such as enzymes, hormones, monoclonal antibodies, cytokines and vaccines. The therapeutic proteins we have expressed to date in research models have produced the intended composition and similar biological activity compared to their respective human-equivalent proteins. Moreover, several of such proteins demonstrated advantageous biological activity when compared to the biotherapeutics currently available in the market to treat the applicable disease or disorder. We believe that clinical success of prGCD would be a strong proof-of-concept for our ProCellEx protein expression system and plant cell-based protein expression technology. We also believe that the significant benefits of our ProCellEx protein expression system, if further substantiated in clinical trials and commercialization of our product candidates, have the potential to transform the industry standard for the development of complex therapeutic proteins.

Our goal is to become a leading fully integrated biopharmaceutical company focused on the development and commercialization of proprietary and biosimilar or generic versions of recombinant therapeutic proteins. To that end, we are leveraging our ProCellEx protein expression system to develop a pipeline of proprietary and biosimilar versions of recombinant therapeutic proteins. In addition to the product candidates that we are developing internally, we have entered into agreements for additional compounds with academic institutions, including a licensing agreement with the technology transfer arm of Israel s Weizmann Institute of Science and an agreement with the technology transfer arm of the Hebrew University of Jerusalem. In addition, we are collaborating with other pharmaceutical companies to develop therapeutic proteins that can benefit from the significant cost, intellectual property and other competitive advantages of our ProCellEx protein expression system. We entered into an agreement with Teva Pharmaceutical Industries Ltd. in September 2006 under which we have agreed to collaborate on the research and development of two proteins to be developed using our ProCellEx protein expression system. We also continuously review and consider additional development and commercialization alliances with other pharmaceutical companies and academic institutions.

**Industry Overview**

Recombinant proteins have revolutionized the treatment of a variety of diseases and disorders. Recombinant proteins are forms of human proteins that are produced, or expressed, using a mammalian, plant, bacterial or yeast cell as a production engine. In the early 1970s, a number of key scientific breakthroughs, including, among others, the demonstration of genetic engineering and genetic sequencing techniques, as well as the synthesis of genes, led to the advancement of recombinant protein technology.

As a result, the market for pharmaceutical therapeutics has undergone a transformation as recombinant proteins and other biologic products have become an increasingly significant portion of the global drug market and the focus of research worldwide. Based upon data from the Biotechnology Industry Organization, an organization that provides information, advocacy and business support to the biotechnology industry, since the introduction in 1982 of recombinant human insulin, the world s first genetically engineered pharmaceutical product, over 254 biotechnology

drugs have been approved for over 392 indications. According to Datamonitor, a provider of business information to the pharmaceutical and other industries, the overall global biologics market size is expected to grow to $105.2 billion in 2010, from $56.1 billion in 2004, representing a compounded annual growth rate (CAGR) of 11.1%.

Mammalian cell-based systems are the current industry standard for expression of recombinant therapeutic glycoproteins (complex proteins that contain sugar residues), including catalytic enzymes and monoclonal antibodies. Mammalian cell-

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based systems were first introduced in the late 1980s and are currently used to produce many of the biotechnology industry s largest and most successful therapeutic proteins, including Epogen®, Neupogen®, Cerezyme, Rituxan®, Enbrel®, Neulasta® and Herceptin®. Mammalian cell-based expression technology is based on the introduction of a human gene encoding for a specific therapeutic protein into the genome of a mammalian cell. The cells most often used in connection with mammalian cell-based protein expression are Chinese hamster ovary (CHO) cells. Mammalian cell-based expression systems have become the dominant system for the expression of recombinant proteins due to their capacity for sophisticated, proper protein folding (which is necessary for proteins to carry out their intended biological activity), assembly and post-expression modification, such as glycosilation (the addition of sugar residues to a protein which is necessary to enable specific biological activity by the protein). While bacterial and yeast cell-based expression systems were the first protein expression systems developed by the biotechnology industry and remain cost-effective compared to mammalian cell-based production methodologies, proteins expressed in bacterial and yeast cell-based systems lack the capacity for sophisticated protein folding, assembly and post-expression modifications, which are key factors of mammalian cell-based systems. Accordingly, such systems cannot be used to produce glycoproteins or other complex proteins and, therefore, bacterial and yeast cell-based systems are limited to the expression of the most basic, simple proteins, such as insulin and growth hormones. Due to their significant advantages, mammalian cell-based expression systems can produce proteins with superior quality and efficacy compared to proteins expressed in bacteria and yeast cell-based systems. As a result, the majority of currently approved therapeutic proteins, as well as those under development, are produced in mammalian cell-based systems.

Despite the utility and widespread use of mammalian cell-based systems, they are subject to a number of disadvantages. CHO cells and other mammalian cells are highly sensitive and can only be grown under near perfect conditions, requiring highly complex, expensive, stainless steel bioreactors which tightly regulate the required temperature, pH and oxygen levels. As a result, such bioreactor systems are very costly and complicated to operate. CHO cells and other mammalian cells are also susceptible to viral infections, including human viruses. The FDA and other regulatory authorities require viral inactivation and other rigorous and detailed procedures for mammalian cell-based manufacturing processes in order to address these potential hazards, thereby increasing the cost and time demands of such expression systems. Furthermore, the current FDA and other procedures only ensure screening for scientifically identified, known viruses. Accordingly, compliance with current FDA and other procedures does not fully guarantee that patients are protected against transmission of unknown or new potentially fatal viruses that may infect mammalian cells. In addition, mammalian cell-based expression systems require large quantities of sophisticated and expensive growth medium to accelerate the expression process.

Several companies and research institutions have explored alternatives to mammalian cell-based production technologies that overcome some of these disadvantages, focusing primarily on the expression of human proteins in genetically-modified organisms, or GMOs, such as transgenic field-grown, whole plants and transgenic animals. However, these alternate techniques may be restricted by regulatory and environmental risks regarding contamination of agricultural crops and by the difficulty in applying cGMP standards of the pharmaceutical industry to these expression technologies.

**ProCellEx: Our Proprietary Protein Expression System**

ProCellEx is our proprietary production system that we have developed based on our plant cell culture technology for the development, expression and manufacture of recombinant proteins. Our expression system consists of a comprehensive set of capabilities and proprietary technologies, including advanced genetic engineering and plant cell culture technology, which enables us to produce complex, proprietary and biologically equivalent proteins for a variety of human diseases. Our protein expression system facilitates the creation and selection of high expressing, genetically stable cell lines capable of expressing recombinant proteins. The entire protein expression process, from initial nucleotide cloning to large-scale production of the protein product, occurs under cGMP-compliant, controlled processes. Our plant cell culture technology uses plant cells, such as carrot and tobacco cells, which undergo advanced genetic engineering and are grown on an industrial scale in a flexible bioreactor system. Cell growth, from scale up through large-scale production, takes place in flexible, sterile, polyethylene bioreactors which are confined to a clean-room environment. Our bioreactors are well-suited for plant cell growth using a simple, inexpensive, chemically-defined growth medium as a catalyst for growth. The reactors are custom-designed and optimized for plant

cell cultures, easy to use, entail low initial capital investment, are rapidly scalable at a low cost and require less hands-on maintenance between cycles. Our protein expression system does not involve mammalian or animal components or transgenic field-grown, whole plants at any point in the production process.

Our ProCellEx system is capable of producing proteins with an amino acid structure practically equivalent to that of the desired human protein, and with a very similar, although not identical, glycan, or sugar, structure. Our internal research and external laboratory studies have demonstrated that ProCellEx is capable of producing recombinant proteins that

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exhibit a glycan and amino acid structure similar to their naturally-produced human counterparts. In collaboration with Israel s Weizmann Institute of Science, we have demonstrated that the three-dimensional structure of a protein expressed in our proprietary plant cell-based expression system retains the same three-dimensional structure as exhibited by the mammalian cell-based expressed version of the same protein. In addition, proteins produced by our ProCellEx system maintain the biological activity that characterize that of the naturally-produced proteins. Based on these results, we believe that proteins developed using our ProCellEx protein expression system have the intended composition and correct biological activity of their human equivalent proteins.

**Competitive Advantages of Our ProCellEx Protein Expression System**

We believe that our ProCellEx protein expression system, including our advanced genetic engineering technology and plant cell-based protein expression methods, affords us a number of significant advantages over mammalian, bacterial, yeast and transgenic cell-based expression technologies, including the following:

***Ability to Penetrate Certain Patent-Protected Markets.*** We seek to develop recombinant proteins that we believe we can produce and commercialize without infringing upon the method-based patents or other intellectual property rights of third parties. In several cases, a marketed biotherapeutic protein is not itself subject to patent protection and is available for use in the public domain; however, the process of expressing the protein product in mammalian or bacterial cell systems is protected by method-based patents. Using our plant cell-based protein expression technology, we are able to express an equivalent protein without infringing upon these method-based patents. Moreover, we expect to enjoy method-based patent protection for the proteins we develop using our proprietary ProCellEx protein expression technology, although there can be no assurance that any such patents will be granted. In some cases, we may be able to obtain patent protection for the compositions of the proteins themselves. We have filed for United States and international composition of matter patents for prGCD.

***Significantly Lower Capital and Production Costs.*** Plant cells have a number of dynamic qualities that make them well-suited for the production of therapeutic proteins. Plant cells grow rapidly under a variety of conditions and are not as sensitive to temperature, pH and oxygen levels as mammalian cells. Our ProCellEx protein expression system, therefore, requires significantly less upfront capital expenditures as it does not use highly complex, expensive, stainless steel bioreactors typically used in mammalian cell-based production systems to maintain very specific temperature, pH and oxygen levels. Instead, we use simple polyethylene bioreactors that are able to be maintained at the room temperature of the clean-room in which they are placed. This system also reduces ongoing production and monitoring costs typically incurred by companies using mammalian cell-based expression technologies. Furthermore, while mammalian cell-based systems require very costly growth media at various stages of the production process to achieve target yields of their proteins, plant cells require only simple and much less expensive solutions based on sugar, water and microelements at infrequent intervals to achieve target yields. We believe that these factors will potentially result in lower capital and production costs for the commercial scale production of proteins by our ProCellEx system thereby providing us with a competitive advantage over competing protein expression technologies.

***More Effective and Potent End Product Relative to Mammalian Based Systems.*** Our ProCellEx protein expression system produces enzymes which have uniform glycosilation patterns and therefore do not require the lengthy and expensive post-expression modifications that are required for certain proteins produced by mammalian cell-based systems, including the proteins for the treatment of Gaucher disease. Such post-expression modifications in mammalian cell-produced proteins are made in order to expose the terminal mannose sugar residues, which are structures on a protein that are key elements in allowing the produced protein to bind to a target cell and subsequently be taken into the target cell for therapeutic benefit. In the production of Cerezyme, exposing these terminal mannose sugar residues involves a multitude of highly technical steps which add time and cost to the production process. In addition, these steps do not guarantee the exposure of all of the required terminal mannose sugar residues, resulting in potentially lower effective yields and inconsistency in potency from batch to batch. Our ProCellEx protein expression system, by contrast, produces prGCD in a ready to use form that does not require additional glycosilation or other modifications to make prGCD suitable for use in enzyme replacement therapy for Gaucher disease. We believe this quality increases the potency and consistency of the expressed proteins, thereby further increasing the cost advantages of our ProCellEx protein expression system over competing protein expression methodologies.

***Elimination of the Risk of Viral Transmission or Infection by Mammalian Components.*** By nature, plant cells do not carry the risk of infection by human or other animal viruses. As a result, the risk of contamination of our products under development and the potential risk of viral transmission from our products under development to future patients, whether from known or unknown viruses, is eliminated. Because our product candidates do not bear the risk of viral transmission, we are not required by the FDA or other regulatory authorities to perform the constant monitoring procedures for mammalian viruses during the protein expression process that mammalian cell-based manufacturers are required to undertake. In

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addition, the production process of our ProCellEx protein expression system is void of any mammalian components which are susceptible to the transmission of prions, such as those related to bovine spongiform encephalopathy (commonly known as mad-cow disease ). These factors further reduce the risks and operating costs of our ProCellEx system compared to mammalian cell-based expression systems.

***Broad Range of Expression Capabilities.*** Unlike bacterial and yeast cell-based systems, which are unable to produce complex proteins, our ProCellEx protein expression system is able to produce a broad array of complex glycosilated proteins. We have successfully demonstrated the feasibility of our ProCellEx system by producing, on an exploratory, research scale, a variety of therapeutic proteins belonging to different classes of recombinant drugs, such as enzymes, hormones, monoclonal antibodies, cytokines and vaccines. We have demonstrated that the recombinant proteins we have expressed to date have the intended composition and correct biological activity of their human-equivalent protein, with several of such proteins demonstrating advantageous biological activity compared to the currently available biotherapeutics. In specific cases, we have been successful in expressing proteins that have not been successfully expressed in other production systems.

**Our Strategy**

Our goal is to become a leading fully integrated biopharmaceutical company focused on the development and commercialization of proprietary and biosimilar recombinant therapeutic proteins. To achieve our goal, we intend to:

**Obtain Regulatory Approval for prGCD for the Treatment of Gaucher Disease.** We completed enrollment of all the patients required for our phase III pivotal clinical trial of prGCD on December 2008 and expect to announce the initial study results in the second half of 2009. We anticipate submitting a New Drug Application (NDA) to the FDA and other comparable regulatory agencies in the fourth quarter of 2009. We are currently conducting the phase III clinical trial in selected leading medical centers worldwide in North America, South America, Israel, Europe and South Africa. In the third quarter of 2008, we initiated a double blind, follow-on extension study as part of the phase III clinical trial in which patients that successfully completed treatment in the trial were given the opportunity to continue to be treated with prGCD at the same dose that they received in the trial. We are compiling additional information relating to the long term safety and efficacy of prGCD through the follow-on study. In addition, in the fourth quarter of 2008 we announced the enrollment of the first patient in a worldwide, multi-center, open-label, switch-over trial to assess the safety and efficacy of prGCD. The switch-over trial, which is not a pre requisite for approval, is designed to include 15 patients with Gaucher disease that are currently undergoing enzyme replacement therapy with imiglucerase (Cerezyme). We believe that prGCD may have cost, efficacy and potency advantages over the currently available enzyme replacement therapy for Gaucher disease and we intend to pursue post-marketing studies to confirm these advantages. Although Gaucher disease is a relatively rare disease, it represents a substantial commercial market due to the severity of the symptoms and the chronic nature of the disease. We believe that the approval of prGCD as a treatment for Gaucher disease, if at all, with its potentially longer acting profile and more cost-effective development process, may lead to increase the number of patients who will be able to have access and afford such treatment, thereby expanding the market for Gaucher disease treatments.

**Develop a Pipeline of Innovative or Biosimilar Versions of Recombinant Therapeutic Proteins.** We are leveraging our ProCellEx protein expression system to develop a pipeline of innovative or biosimilar versions of recombinant proteins, with an emphasis on therapeutic treatments with large market opportunities. We select additional therapeutic candidates for development through in-house testing, licensing agreements with academic institutions and collaborations with pharmaceutical partners. We have currently identified several product candidates that are mainly oriented towards the specialty disease and therapeutic market segments, including treatments for Fabry disease and an acetylcholinesterase enzyme based therapy for biodefense and intoxication treatments. We believe that the clinical and regulatory pathway for many of our pipeline product programs candidates is already established, and that this may reduce the risks and costs associated with our clinical development programs. Furthermore, established markets already exist for the development of most of our current product candidates. We plan to apply the manufacturing, clinical and regulatory experience we have gained from the development of our lead product candidate to advance a number of our preclinical product candidates into clinical trials over the next few years.

**Build a Targeted Sales and Marketing Infrastructure.** We plan to establish our own, internal sales and marketing capabilities in North America, the European Union and in other significant markets, including Israel. We believe that

the focus of our current clinical pipeline on relatively rare genetic disorders with small patient populations and a highly concentrated group of physicians focused on treating patients with such disorders will facilitate our creation of a targeted internal sales force. In addition we are continuously evaluating potential strategic marketing partnerships.

**Establish Development and Commercialization Alliances with Corporate Partners.** We believe that our technology and know-how has broad applicability to many classes of proteins and can be used to develop and potentially enhance numerous existing marketed protein therapeutics. We intend to leverage our technology and know-how by pursuing development and

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commercialization alliances with corporate partners for specific products and territories in order to enable us to optimize our resources and effectively penetrate a wider range of target diseases and therapeutic markets. We entered into an agreement with Teva in September 2006 for the development of two proteins. We are in various stages of discussions with a number of multinational pharmaceutical companies regarding additional collaboration agreements.

**Acquire or In-License New Technologies, Products or Companies.** We continuously seek attractive product candidates and innovative technologies to in-license or acquire. We intend to focus on product candidates that would be synergistic with our ProCellEx protein expression system and expertise and that represent large potential market opportunities. In August 8, 2007, we entered into an agreement with the Yissum Research and Development Company, the technology transfer arm of the Hebrew University of Jerusalem, Israel, and the Boyce Thompson Institute for Plant Research, at Cornell University, Ithaca, New York, to develop a proprietary plant cell-based acetylcholinestrase (AChE) and its molecular variants for the use in several therapeutic indications, including a biodefense program and an organophosphate-based pesticide treatment program. The scope of this program was expanded in January 2008. See Acetylcholineterase. We believe that by pursuing selective acquisitions of technologies in businesses that complement our own, we will be able to enhance our competitiveness and strengthen our market position.

**Leverage Strength and Experience of Our Management Team and Board of Directors.** Our management team has extensive experience in the biotechnology and pharmaceutical industry. The Chairman of our Board of Directors, Mr. Eli Hurvitz, is an experienced pharmaceutical industry veteran and the current Chairman of the Board and former President and Chief Executive Officer of Teva. In February 2008, we appointed Professor Roger D. Kornberg, a renowned biochemist and laureate of the Nobel Prize in Chemistry, to our Board of Directors. We will continue to leverage their experience and established track record as well as their relationships across the biotechnology and pharmaceutical industries.

**Our Pipeline Drug Candidates**

**Our Lead Product Candidate, prGCD**

prGCD, our lead proprietary product candidate, is a plant cell expressed recombinant Glucocerebrosidase enzyme (GCD) for the treatment of Gaucher disease. In July 2007, we reached an agreement with the United States Food and Drug Administration, or the FDA, on the final design of our pivotal phase III clinical trial of prGCD, through the FDA s special protocol assessment (SPA) process. We completed enrollment of all the patients required for our phase III pivotal clinical trial of prGCD in December 2008 and expect to announce results of the clinical trial in the second half of 2009. We anticipate submitting a New Drug Application (NDA) to the FDA and comparable regulatory agencies in other countries in the fourth quarter of 2009. During the third quarter of 2008, we initiated a double blind, follow-on extension study as part of the phase III clinical trial in which patients that successfully completed treatment in the trial were given the opportunity to continue to be treated with prGCD at the same dose that they received in the trial. We are compiling additional information relating to the long term safety and efficacy of prGCD through the follow-on study. In addition, in the fourth quarter of 2008 we announced the enrollment of the first patient in a worldwide, multi-center, open-label, switch-over trial which has been reviewed by the FDA and is designed to assess the safety and efficacy of prGCD. The switch-over trial, which is not a pre requisite for approval, is designed to include 15 patients with Gaucher disease that are currently undergoing enzyme replacement therapy with imiglucerase (Cerezyme). In clinical trials in healthy subjects and in vivo primate studies, prGCD has demonstrated an increased half-life and prolonged presence of the enzyme in the blood serum of the subjects as compared to Cerezyme, the only enzyme replacement therapy currently marketed to treat Gaucher disease. We believe that prGCD, if approved, has the potential to offer patients and healthcare payors a more effective and cost efficient treatment of Gaucher disease because of the following features:

***Increased Glycan Efficacy and Consistency.*** We believe that our ProCellEx protein expression system produces recombinant proteins that exhibit consistent enzymatic activity from batch to batch. This results in a highly active product that may achieve a desired therapeutic effect more effectively than the activity demonstrated in proteins produced through mammalian cell-based expression systems due to its greater glycan efficacy and consistency. This quality increases the effective consistency in potency and further increases the cost advantages from using our plant cell-based expression technology compared to competing protein expression methodologies.

***Longer Half-Life*.** The data generated in preclinical and human clinical trials relating to the half-life of prGCD in the subjects blood serum after infusion showed that the half-life of prGCD is significantly longer than that of Cerezyme when measured and compared to publicly available data on Cerezyme.

***Cost-Effective.*** prGCD is potentially less expensive to produce as the manufacturing process does not require the large initial set-up investments involved in mammalian cell-based protein production, the extensive ongoing costs associated with growth

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media and monitoring throughout the production process nor any of the post-expression modification costs in order to modify the glycosilation of the proteins produced through the mammalian cell-based methodologies.

As such, we believe that prGCD s potential advantages may lead prGCD to become a highly efficacious and cost-effective treatment alternative for Gaucher disease patients.

In addition, we are developing a new method for delivering active recombinant proteins systemically through oral administration of transgenic plant cells expressing biotherapeutic proteins. If proven effective, we intend to apply this breakthrough technology to prGCD before we apply it to any other product candidates. If proven effective, our experimental oral prGCD would be the first protein to be administered orally rather than through intravenous therapy. We are developing our oral prGCD product candidate to be used in enzyme replacement therapy, not as a small molecule. This differentiates our oral product candidate from other early clinical stage, experimental, small molecule, oral drugs which are being developed for the treatment of Gaucher disease by Amicus Therapeutics, Inc. and Genzyme. Small molecule based treatments for Gaucher disease, such as Zavesca, are different in their mechanism of action from treatments through enzyme replacement therapy, and may be associated with a number of side effects. In connection with such new method for protein delivery, we have filed patent applications in other countries with commercially significant markets.

**Gaucher Disease Background**

Gaucher disease, a hereditary, genetic disorder with severe and debilitating symptoms, is the most prevalent lysosomal storage disorder in humans. Lysosomal storage disorders are metabolic disorders in which a lysosomal enzyme, a protein that degrades cellular substrates in the lysosomes of cells, is mutated or deficient. Lysosomes are small membrane-bound cellular structures within cells that contain enzymes necessary for intracellular digestion. Gaucher disease is caused by mutations or deficiencies in the gene encoding GCD, a lysosomal enzyme that catalyzes the degradation of the fatty substrate, glucosylceramide (GlcCer). The normal degradation products of GlcCer are glucose and ceramide, which are easily excreted by the cells through normal biological processes. Patients with Gaucher disease lack or otherwise have dysfunctional GCD and, accordingly, are not able to break down GlcCer. The absence of an active GCD enzyme leads to the accumulation of GlcCer in lysosomes of certain white blood cells called macrophages. Macrophages affected by the disease become highly enlarged due to the accumulation of GlcCer and are referred to as Gaucher cells. Gaucher cells accumulate in the spleen, liver, lungs, bone marrow and brain. Signs and symptoms of Gaucher disease may include enlarged liver and spleen, abnormally low levels of red blood cells and platelets and skeletal complications. In some cases, the patient may suffer an impairment of the central nervous system.

**Current Treatments for Gaucher Disease**

The standard of care for Gaucher disease is enzyme replacement therapy using recombinant GCD to replace the mutated or deficient natural GCD enzyme. The latest studies estimate that there are approximately 10,000 patients suffering from Gaucher disease worldwide. Enzyme replacement therapy is a medical treatment in which recombinant enzymes are injected into patients in whom the enzyme is lacking or dysfunctional. Cerezyme, an enzyme replacement therapy commercialized by Genzyme Corporation, is the only recombinant GCD currently available on the market and approved worldwide for the treatment of Gaucher disease. According to public reports issued by Genzyme, Cerezyme was used to treat over 5,000 patients and had annual sales of approximately $1.2 billion in 2008. Cerezyme is produced through a mammalian cell-based protein expression process in CHO cells. There are no known severe side effects to the use of Cerezyme and its approved use over the past decade suggests that it is an effective treatment of Gaucher disease. However, Cerezyme is subject to the limitations of most mammalian cell-based therapeutic proteins, including lengthy and costly production processes. As enzyme replacement therapy does not cure the genetic disorder, but rather provides an external source for transfusion of the missing or mutated enzyme, Gaucher disease patients generally receive the treatment over their entire lifetime. The current average annual cost for enzyme replacement therapy for an adult Gaucher disease patient in the United States is in excess of $200,000.

The only other approved drug for the treatment of Gaucher disease is Zavesca (miglustat), marketed by Actelion Ltd. Zavesca has been approved by the FDA for use in the United States as an oral treatment. However, it has many side effects and the FDA has approved it only for administration to those patients who cannot be treated through enzyme replacement therapy, and, accordingly, have no other treatment alternative. As a result, Zavesca s use has been

extremely limited. Actelion has reported sales of Zavesca of approximately CHF 40.1 million (approximately $34.2 million) in 2008.

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**prGCD Development Program**

We believe the clinical development path for prGCD will be similar to that followed by the existing enzyme replacement therapy currently on the market. The primary efficacy endpoint for our pivotal study is the reduction in size of spleen and the secondary endpoints for our pivotal study include increase in platelet and hemoglobin counts and reduction in liver size, all of which are generally well-established and accepted by regulatory agencies and specifically agreed to by the FDA in the special protocol assessment (SPA) of the final design of our pivotal phase III clinical trial for prGCD. See Phase III Clinical Trial. The primary end point for our switch-over study, which is not a prerequisite for approval, is non deterioration in the patient s clinical condition as measured through significant, well established end points such as platelet and hemoglobin counts and spleen and liver size.

**Laboratory Testing and Preclinical Studies of prGCD**

We have conducted several in vitro tests and in vivo preclinical studies of prGCD. Our preclinical rodent and primate trials generated extensive toxicological and safety data that demonstrated no adverse effects, even with very high doses of prGCD being administered via intravenous infusions. In short term repeat dose studies in rodents and primates and nine month repeat dose studies in primates, no toxicity was observed at dosage levels of up to 10 times the current dose recommended for GCD in clinical use. Furthermore, no neutralizing antibodies were detected in any of the primates treated in the studies. The presence of neutralizing antibodies would have implied a likelihood of the host rejecting the therapeutic enzyme or reacting to it in a less efficient manner.

Our laboratory and preclinical data demonstrate that prGCD has the potential to be an efficacious enzyme replacement therapy for the treatment of Gaucher disease. Data produced from these preliminary development studies show that, relative to Cerezyme, prGCD has:

an equivalent to superior level of enzymatic activity (see Figure 1);

enhanced uptake based on observed GlcCer substrate degradation (see Figure 2); and

a prolonged half-life (see Figure 3).

As shown in Figure 1, we compared the enzymatic activity of prGCD and Cerezyme using an in vitro assay where increasing amounts of GlcCer substrate (S), provided in millimolar, were degraded by a fixed amount of prGCD and Cerezyme, measured in milligrams. Enzymatic activity was measured by the rate of degradation of GlcCer into glucose and ceramide (its normal degradation products), measured by millimoles of product produced per minute per fixed amount of enzyme. In the study assays performed, one demonstrated that prGCD had enzymatic activity that was equivalent to Cerezyme; the other studies demonstrated superior activity by prGCD. Figure 1 demonstrates that the enzymatic activity of prGCD was superior to Cerezyme.

**Figure 1: prGCD and Cerezyme Enzymatic Activity**

As shown in Figure 2, we compared the uptake of increasing amounts of Cerezyme and prGCD into the target cell, using an ex vivo mouse macrophage cell model. Cellular uptake was measured in cell lysates, solutions containing the contents of burst cells, by comparing enzymatic activity at various enzyme concentrations of Cerezyme and prGCD based on the

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amount of GlcCer substrate degradation into glucose and ceramide, measured in a microplate absorbance reader, a flat plate with multiple wells used as small test tubes, at an optical density of 405 nanometers. The results in Figure 2 demonstrate that the uptake into the macrophage cells of prGCD was greater than the uptake of Cerezyme at higher enzyme concentrations, as measured by the resulting enzymatic activity in the cells. We believe that the ability of the plant cells to directly generate the required terminal mannose structures for efficient glycosilation of prGCD, results in the enhanced uptake of prGCD into the Gaucher cells. In contrast, Cerezyme requires post-expression and purification modifications to expose the terminal mannose structures, which modification process can yield enzymes with less consistent glycosilation patterns and could reduce cellular uptake of Cerezyme.

**Figure 2: prGCD and Cerezyme Cellular Uptake**

Furthermore, the data generated in preclinical trials relating to pharmacokinetic parameters, specifically the half-life of enzyme in the subjects blood serum after infusion, showed that the half-life of prGCD is significantly longer than that of Cerezyme based upon data disclosed publicly by Genzyme. We believe the extended half-life of prGCD relative to Cerezyme is attributable to the different glycoside profile, thereby resulting in the enhanced uptake of prGCD into the Gaucher cells.

**Figure 3: prGCD and Cerezyme Half-Life Data**

| | **prGCD** | **Cerezyme** |
|---|---|---|
| **Primates** | ~13.0-20.0 minutes | ~ 6.8-8.0 minutes (1) |
| **Humans** | ~10.5-14.5 minutes | ~3.6-10.4 minutes (2) |

(1) Source: Cerezyme NDA PharmTox review

(2) Source: Cerezyme labeling approved by FDA for package insert

Prior to submitting an NDA for prGCD, if at all, we intend to conduct further, standard preclinical studies of prGCD.

**Phase I Clinical Trial**

We completed a phase I clinical trial of prGCD in June 2006 which was performed under an FDA Investigational New Drug (IND) approval. The phase I clinical trial was a single-center, non-randomized, open label, dose ranging study designed to evaluate the safety and pharmacokinetics of prGCD in healthy subjects. The trial was conducted on healthy subjects over a four-week period in which subjects received three single escalating doses of prGCD administered as intravenous infusions.

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All doses administered to subjects in the phase I clinical trial, including the highest dose, which was the same dosage currently suggested with respect to the treatment by Cerezyme, demonstrated a strong safety profile. The data from our phase I clinical trial showed that prGCD was safe and well tolerated at all doses. See Figure 4.

**Figure 4: Adverse Events presented by: Dose Group, Severity and Relation to Study Treatment (Incidents; Subjects (% of Subjects))**

| Relation between Event to Drug | 15 U/kg | 30 U/kg | 60 U/kg | Placebo | Events Severity | Total |
|---|---|---|---|---|---|---|
| Unrelated to drug (1) | 0; 0 (0%) | 0; 0 (0%) | 2; 1 (17%) | 0; 0 (0%) | Moderate | 2 |
| Remotely related to drug (2) | 4; 2 (33%) | 1; 1 (17%) | 2; 1 (17%) | 1; 1 (17%) | Mild | 8 |
| Possibly related to drug (3) | 0; 0 (0%) | 0; 0 (0%) | 0; 0 (0%) | 0; 0 (0%) | | 0 |
| Probably related to drug (4) | 0; 0 (0%) | 0; 0 (0%) | 0; 0 (0%) | 0; 0 (0%) | | 0 |
| Related to drug (5) | 0; 0 (0%) | 0; 0 (0%) | 0; 0 (0%) | 0; 0 (0%) | | 0 |

(1) The event is clearly related to other factors, such as a subject s clinical state, therapeutic interventions or concomitant medications.

(2) The event was most likely produced by other factors, such as a subject s clinical state, therapeutic interventions or concomitant medications, and does not follow a known response pattern to the study drug.

(3) The event has a reasonable temporal relationship to the study drug administration and follows a

known response pattern to the study drug. However, a potential alternate etiology may be responsible for the event. The effect of drug withdrawal is unclear. Rechallenge information is unclear or lacking.

(4) The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug and cannot be reasonably explained by other factors. There is a reasonable response to withdrawal of the drug. Rechallenge information is not available or advisable.

(5) The event follows a temporal sequence from the time of drug administration and follows a known response pattern to the

study drug. The event either occurs immediately following the study drug administration, improves on stopping the drug or reappears on repeated exposure.

There were no serious adverse events and no subjects withdrew from the trial or discontinued treatment due to an adverse event.

In addition, as illustrated in Figure 3 above, the half-life of prGCD was found to be significantly longer than that of Cerezyme, based upon data disclosed publicly by Genzyme, which was consistent with our preclinical data.

Further, no neutralizing antibodies or adverse immunological responses were detected in any of the subjects treated in the phase I clinical trial. The presence of neutralizing antibodies would imply that the human body may reject the therapeutic enzyme.

We believe the results of our biochemical, biological and preclinical studies and pharmacokinetic data from our phase I clinical trial may support claims for less frequent treatment and lower dosages of prGCD for Gaucher disease patients, as compared to the current standard of care. This would represent a substantial improvement over currently marketed enzyme replacement therapies. However, further clinical evaluation will still be required to support these claims. We will explore the potential for lower dosages in our phase III clinical trial.

**Phase III Clinical Trial**

After the conclusion of the phase I clinical trial and discussions with the FDA, we applied to commence a pivotal phase III clinical trial of prGCD, without the requirement to first complete a phase II clinical trial. In April 2007, we received approval from the FDA to initiate a pivotal phase III clinical trial. We submitted to the FDA a request for a special protocol assessment (SPA) of the final design of our pivotal phase III clinical trial for prGCD. In July 2007, we reached an agreement with the FDA on the design that we submitted in the SPA request and in the third quarter of 2007 we initiated enrollment and treatment of patients in the phase III clinical trial. According to the SPA, the phase III clinical

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trial is to include at least 30 naive patients in a randomized, double-blind, dose ranging study, with two parallel groups, one receiving a dosage equivalent to the prevalent standard of care for enzyme replacement therapy and one receiving a dosage equal to one half of that amount. We commenced enrollment and treatment of patients in our phase III clinical trial in the third quarter of 2007 and completed enrollment in the fourth quarter of 2008. During the third quarter of 2008, we initiated a double blind, follow-on extension study as part of our phase III clinical trial in which patients that successfully completed treatment in the trial were given the opportunity to continue to be treated with prGCD at the same dose that they received in the trial. We are compiling additional information relating to the long term safety and efficacy of prGCD through the follow-on study. In addition, in the fourth quarter of 2008, we announced the enrollment of the first patient in a worldwide, multi-center, open-label, switch-over trial to assess the safety and efficacy of prGCD. The switch-over trial, which is not a pre requisite for approval, is designed to include 15 patients with Gaucher disease that are currently undergoing enzyme replacement therapy with imiglucerase (Cerezyme). We are currently conducting the phase III clinical trial in selected medical centers worldwide, in North America, South America, Israel, Europe and South Africa.

**Other Drug Candidates in Our Pipeline**

We are developing other recombinant therapeutic proteins to be expressed by our ProCellEx protein expression system, with an emphasis on treatments for which there are large, established pharmaceutical markets and where our proprietary protein expression system enables us to develop and commercialize recombinant proteins that are patent-protected and therapeutically equivalent or superior to the existing treatments. We select additional therapeutic candidates for development by testing candidates in-house and through collaborations with academic partners. We have identified several product candidates oriented towards specialty disease and therapeutic market segments, including treatments for Fabry disease. In the past, we were developing variants of Follicle Stimulating Hormone (FSH), a human fertility hormone targeted at the female infertility market but have since determined not to expend additional resources for those projects. We are also conducting initial research to evaluate potential programs in the fields of monoclonal antibodies, cytokines and vaccines. We plan to file an investigational new drug application (IND) with the FDA with respect to at least one additional product during 2009. Last, we are developing a new method for delivering active recombinant proteins systemically through oral administration of transgenic plant cells expressing such biotherapeutic proteins.

**PRX-102**

We are developing a proprietary alpha Galactosidase enzyme, currently titled PRX-102, which is a therapeutic enzyme for the treatment of Fabry disease, a rare genetic lysosomal storage disorder in humans, the symptoms of which involve the accumulation of lipids in the cells of the kidneys, heart and other organs. These symptoms may lead to kidney failure and increased risk of heart attack and stroke. Fabry disease affects more than 8,000 people globally. We believe that the treatment of Fabry disease is a specialty clinical niche with the potential for high growth. Currently there are two drugs available on the market to treat Fabry disease. Fabrazyme, made by Genzyme, was approved for the treatment of Fabry disease in the European Union in 2001 and the United States in 2003. Genzyme reported $494 million in worldwide sales of Fabrazyme in 2008. The other approved drug for the treatment of Fabry disease in the European Union is Replagal, which is sold by Shire plc. Shire reported $176.1 million in sales of Replagal in 2008.

We are currently in the animal evaluation testing phase of the development of PRX-102, which tests are based on a well established mouse model for Fabry disease. We expect to file an IND with the FDA for PRX-102 following the completion of the animal studies. As was the case in our development of prGCD, our development of PRX-102 involves the expression by our proprietary protein expression system of a naturally occurring enzyme to be used in enzyme replacement therapy for the treatment of Fabry disease. Based on our experience with prGCD and the experience of other companies developing enzyme replacement therapies for Fabry disease, we have reason to believe that, if favorable data is accumulated in preclinical and phase I clinical trials, the FDA may allow us to proceed directly with a pivotal phase III clinical trial without the need to complete a phase II clinical trial. However, there can be no assurance that we will initiate phase I clinical trials and if we do, that such trials will result in favorable data. In addition, there can be no assurance that the FDA will allow us to proceed directly with a phase III clinical trial after completion of a phase I clinical trial.

**Acetylcholinesterase**

In August 2007, we entered into an agreement with the Yissum Research and Development Company and the Boyce Thompson Institute, Inc. pursuant to which we are developing a proprietary plant cell-based acetylcholinesterase (AChE) and its molecular variants for the use in several therapeutic and prophylactic indications, as well as in a biodefense program and an organophosphate-based pesticide treatment program. Pursuant to the terms of the agreement, we have received an exclusive, worldwide right and license to certain technology, including patents and certain patent applications relating to AChE for the therapeutic and prophylactic indications as well as an exclusive license not limited to such indications with

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respect to certain of those patents and patent applications. In consideration for those licenses, we have agreed to make certain regulatory milestone payments, a sales-based milestone payment, a license maintenance fee and a royalty on net sales of any products developed with the licensed technology.

In January 2008, we expanded the scope of our acetylcholinesterase program with Yissum after we achieved proof of concept results in an animal study conducted as part of the program. In our animal study, the plant cell expressed form of the acetylcholinesterase protein demonstrated full protection from organophosphate poisoning, stimulating the capacity of the plant cell expressed acetylcholinesterase protein to treat nerve gas and pesticide poisoning. Under our agreement with Yissum, we intend to conduct a collaborative research program in the laboratory of Professor Hermona Soreq, a world leader in the field of acetylcholinesterase research and Dean of the Faculty of Science at the Hebrew University.

To date, our in vitro experiments have shown that the acetylcholinesterase expressed in our ProCellEx protein expression system demonstrates promising biological activity on biochemical and cellular levels. In addition, early animal studies demonstrated that the acetylcholinesterase expressed in our ProCellEx protein expression system was able to treat successfully animals exposed to the nerve gas agent analogs, both when injected with our acetylcholinesterase product candidate immediately before exposure or when injected after exposure. We recently held a pre-IND meeting with the FDA to clarify the requirements and scope of the clinical studies required for regulatory approval of our acetylcholinesterase product candidate. We plan to submit an IND application for acetylcholinesterase during 2009, and to initiate a clinical study immediately after our IND is accepted, if at all.

**PRX-111**

In the past were developing variants of Follicle Stimulating Hormone (FSH), a human fertility hormone targeted at the female infertility market. Although we believe that our in vitro experiments with these hormones demonstrated equivalent to superior biochemical and cellular results when compared to the currently marketed biotherapeutic hormones used in approved female infertility treatments, we have determined not to proceed with this project due to the current, general market conditions.

**Strategic Collaborations**

***Teva Pharmaceutical Industries***

In September 2006, we entered into a Collaboration and Licensing Agreement with Teva for the development and manufacture of two proteins, to be identified by Teva and us using our ProCellEx protein expression system. These proteins are not part of our current product development pipeline. We have launched preliminary animal studies with respect to one protein under the agreement and we expect to launch feasibility studies with respect to the second protein during 2009. Pursuant to the agreement, we have agreed to collaborate on the research and development of the two proteins utilizing our ProCellEx protein expression system. If the research and preclinical development efforts for either protein are successful and if Teva elects to pursue clinical trials for the development of either protein through our ProCellEx protein expression system, we have agreed to grant to Teva an exclusive license to commercialize the products developed based on the protein in return for royalty and milestone payments payable upon the achievement of certain pre-defined goals. We will retain certain exclusive manufacturing rights with respect to the active pharmaceutical ingredient of the proteins following the first commercial sale of a licensed product under the agreement and other rights. See Risk Factors Our strategy, in many cases, is to enter into collaboration agreements with third parties to leverage our ProCellEx system to develop product candidates. If we fail to enter into these agreements or if we or the third parties do not perform under such agreements or terminate or elect to discontinue the collaboration, it could have a material adverse affect on our revenues.

***Weizmann Institute of Science***

In March 2006, we entered into a Research and License Agreement with the Yeda Research and Development Company Limited, the technology transfer arm of the Weizmann Institute of Science, pursuant to which Yeda is using its technology to design a next generation of GCD for the treatment of Gaucher disease that can be expressed using our ProCellEx protein expression system and that may have certain benefits over the first generation treatments used today. The technology licensed from Yeda provides a methodology for the rational design of an improved drug for the treatment of Gaucher disease by enzyme replacement therapy, based on the three-dimensional crystal structure of GCD that was solved by scientists from the Weizmann Institute of Science. In consideration for Yeda s research, we

agreed to pay a fixed research budget amount. Yeda has granted us a license to use their technology and discoveries for the development, production and sale of enzymatically active mutations of GCD and derivatives thereof for the treatment of Gaucher disease. We are responsible for commercializing the products developed under the license. Under the agreement, we are obligated to pay certain minimum royalty amounts and varying fixed royalty amounts on net sales of products developed using the licensed technology for the

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treatment of Gaucher disease and other indications as well as for sublicensing revenues. Accordingly, we will have certain payment obligations to Yeda even if we were to fail to generate any revenue from the licensed technology. See Risk Factors If we cannot meet requirements under our license agreements, we could lose the rights to our products, which could have a material adverse effect on our business.

**Intellectual Property**

We maintain a proactive intellectual property strategy which includes patent filings in multiple jurisdictions, including the United States and other commercially significant markets. We hold 14 granted patents and 56 patent applications currently pending with respect to various compositions, methods of production and methods of use relating to our ProCellEx protein expression system and our proprietary product pipeline. Of such patent applications, two are expected to reach the national phase during 2009. We also have one joint patent with a third party and hold licensed rights to four patents and 21 patent applications.

Our competitive position and future success depend in part on our ability, and that of our licensees, to obtain and leverage the intellectual property covering our product candidates, know-how, methods, processes and other technologies, to protect our trade secrets, to prevent others from using our intellectual property and to operate without infringing the intellectual property of third parties. We seek to protect our competitive position by filing United States, European Union, Israeli and other foreign patent applications covering our technology, including both new technology and improvements to existing technology. Our patent strategy includes obtaining patents, where possible, on methods of production, compositions of matter and methods of use. We also rely on know-how, continuing technological innovation, licensing and partnership opportunities to develop and maintain our competitive position. Lastly, we monitor third parties for activities that may infringe our intellectual property, as well as the progression of third party patent applications that may cover our product candidates or expression methods and thus, potentially, interfere with the development of our business. We are aware, for example, of United States patents, and corresponding international counterparts of such patents, owned by third parties that contain claims covering methods of producing GCD. We do not believe that, if any claim of infringement were to be asserted against us based upon such patents, prGCD would be found to infringe any valid claim under such patents. However, there can be no assurance that a court would find in our favor or that, if we choose or are required to seek a license to any one or more of such patents, a license would be available to us on acceptable terms or at all.

Our patent portfolio consists of several patent families (consisting of patents and/or patent applications) covering our technology, protein expression methodologies and system and product candidates. We have been issued, and hold licensed rights to, patents in the United States, the European Union, Israel, Canada, the Czech Republic, Hungary, Japan, Poland, Mexico, Hong Kong and India that cover our ProCellEx protein expression system, including the methods that we use for culturing and harvesting plant cells and/or tissues in consecutive cycles. Another patent family in our patent portfolio contains patent applications relating to our method for producing glycosilated proteins in a plant culture, particularly proteins having a terminal mannose glycosilation, including prGCD. An additional patent family contains patent applications relating to a system and method for production of antibodies in a plant cell culture, and antibodies produced in such a system. In addition, our patent portfolio includes a patent family for a new method for delivering active recombinant proteins systemically through oral administration of transgenic plant cells. Lastly, our patent portfolio includes a patent family containing patent applications that we co-own and that covers human glycoprotein hormone and chain splice variants, including isolated nucleic acids encoding these variants. More specifically, this patent portfolio covers a new splice variant of human FSH.

In April 2004, we entered into a Collaborative Research Agreement with Icon Genetics AG (which was subsequently acquired by Bayer Corporation) regarding an option to license Icon s amplification technology for utilization in the expression of our products under development in order to improve our yield. In connection with such option, we entered into a license agreement with Icon in April 2005, pursuant to which we received an exclusive worldwide license to develop, test, use and commercialize Icon s technology to express certain proteins in our ProCellEx protein expression system. In addition, we are entitled to a non-exclusive worldwide license to make and have made other proteins expressed by using Icon s technology in our technology. In consideration for the licenses, we are obligated to pay to Icon development milestone payments and royalties. See Risk Factors If we fail to adequately protect or enforce our intellectual property rights or secure rights to third party patents, the value of our intellectual property rights

would diminish and our business, competitive position and results of operations would suffer.

**Manufacturing**

Our drug product candidates, including prGCD, must be manufactured in a sterile environment and in compliance with cGMPs set by the FDA and other relevant foreign regulatory authorities. We use our current facility, which has approximately 9,000 sq/ft of clean rooms built according to industry standards, to develop, process and manufacture prGCD

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and other recombinant proteins. In January 2008, we signed a lease agreement for additional space as part of the expansion of our manufacturing and research facility. The expanded space, located in our existing facility, provides us with approximately three times our current manufacturing space. In January 2009 we commenced the final upgrade of the manufacturing space within our facility to ensure that the manufacturing space will be able to comply with the good laboratory, clinical and manufacturing practices required by the FDA and other comparable regulatory authorities for production of pharmaceutical products on a commercial scale. We intend to use our current manufacturing space to produce all of the prGCD we need in the near future. In addition, we recently held a design review meeting with the FDA to obtain the FDA s input on the facility design. We intend to use our expanded facility to house the laboratory space necessary for further development of other product candidates in our pipeline. Total expected cost for such expansion is estimated to be approximately $5 million and the process is expected to be completed by the end of 2009.

We have entered into a contract with Teva pursuant to which Teva has agreed to perform the final filling and freeze drying steps for prGCD. Upon the approval of prGCD, if at all, we are planning to expand our existing manufacturing space further to satisfy our entire production needs for the product worldwide. Although this will result in a significant increase in our capital expenditures, we expect these expenditures to be substantially lower than those associated with the construction of mammalian cell-based systems. We have begun to prepare conceptual designs of a new manufacturing facility and are currently evaluating potential locations for such facility.

Our current facility in Israel has been granted Approved Enterprise status, and we have elected to participate in the alternative benefits program. Our facility is located in a Zone A location, and, therefore, our income from the Approved Enterprise will be tax exempt in Israel for a period of 10 years, commencing with the year in which we first generate taxable income from the relevant Approved Enterprise. To remain eligible for these tax benefits, we must continue to meet certain conditions, and if we increase our activities outside of Israel, for example, by future acquisitions, such increased activities generally may not be eligible for inclusion in Israeli tax benefit programs. In addition, our technology is subject to certain restrictions with respect to the transfer of technology and manufacturing rights. See Risk Factors The manufacture of our products is an exacting and complex process, and if we or one of our materials suppliers encounter problems manufacturing our products, it will have a material adverse effect on our business and results of operations.

**Raw Materials and Suppliers**

We believe that the raw materials that we require throughout the manufacturing process of our current and potential drug product candidates are widely available from numerous suppliers and are generally considered to be generic industrial biological supplies. We do not rely on a single or unique supplier for any materials relating to the current production of any biotherapeutic proteins in our pipeline.

Development and regulatory approval of our pharmaceutical products are dependent upon our ability to procure active ingredients and certain packaging materials from sources approved by the FDA and other regulatory authorities. Since the FDA and other regulatory approval processes require manufacturers to specify their proposed suppliers of active ingredients and certain packaging materials in their applications, FDA approval of a supplemental application to use a new supplier in connection with any drug candidate or approved product, if any, would be required if active ingredients or such packaging materials were no longer available from the specified supplier, which could result in manufacturing delays. From time to time, we intend to identify alternative FDA-approved suppliers to ensure the continued supply of necessary raw materials.

**Competition**

The biotechnology and pharmaceutical industries are characterized by rapidly evolving technology and significant competition. Competition from numerous existing companies and others entering the fields in which we operate is intense and expected to increase. Most of these companies have substantially greater research and development, manufacturing, marketing, financial, technological personnel and managerial resources than we do. In addition, many specialized biotechnology companies have formed collaborations with large, established companies to support research, development and commercialization of products that may be competitive with our current and future product candidates and technologies. Acquisitions of competing companies by large pharmaceutical or biotechnology companies could enhance such competitors financial, marketing and other resources. Academic institutions,

governmental agencies and other public and private research organizations are also conducting research activities and seeking patent protection and may commercialize competitive products or technologies on their own or through collaborations with pharmaceutical and biotechnology companies.

We specifically face competition from companies with approved treatments of Gaucher disease, including Genzyme and to a much lesser extent, Actelion Ltd. Shire plc is currently developing a gene-activated GCD enzyme expressed in human cancer cells to treat Gaucher disease. In addition, we are aware of other early clinical stage, experimental, small molecule, oral drugs which are being developed for the treatment of Gaucher disease by Amicus Therapeutics, Inc. and Genzyme. We also

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face competition from companies with approved enzyme treatments of Fabry disease, including Genzyme and Shire, and we are aware of other early stage drugs which are being developed for the treatment of Fabry disease, including a drug being developed by Amicus Therapeutics.

We also face competition from companies that are developing other platforms for the expression of recombinant therapeutic pharmaceuticals. We are aware of companies that are developing alternative technologies to develop and produce therapeutic protein in anticipation of the expiration of certain patent claims covering marketed proteins. Competitors developing alternative expression technologies include Crucell N.V., Shire and GlycoFi, Inc. (which was acquired by Merck & Co. Inc.). Other companies are developing alternate plant-based technologies, include Biolex, Inc., Chlorogen, Inc., Greenovation Biotech GmbH, and Symbiosys, none of which are cell-based. Rather, such companies base their product development on transgenic plants or whole plants.

Several biogeneric companies are pursuing the opportunity to develop and commercialize follow-on versions of other currently marketed biologic products, including growth factors, hormones, enzymes, cytokines and monoclonal antibodies, which are areas that interest us. These companies include, among others, Novartis AG/Sandoz Pharmaceuticals, BioGeneriX AG, Barr Pharmaceuticals, Stada Arzneimittel AG, BioPartners G