Protalix BioTherapeutics, Inc.
Form 10-K
March 12, 2015

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)

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

For the fiscal year ended December 31, 2014

OR

.. 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	**(I.R.S. Employer**
of incorporation or organization	**Identification No.)**

2 Snunit Street

Science Park

POB 455

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 MKT**

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 ¨ 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 whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). 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. þ

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

Large accelerated filer ¨	Accelerated filer x
Non-accelerated filer ¨(Do not check if a smaller reporting company)	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 ¨ No x

The aggregate market value of the voting common equity held by non-affiliates of the Registrant, as of June 30, 2014 was approximately $179 million (based upon a per share price equal to $3.65, the closing price for shares of the Registrant's common stock reported by the NYSE MKT for such date). 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, 2015, approximately 93,603,819 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 meanings of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, including statements regarding expectations, beliefs, intentions or strategies for the future. When used in this report, the terms "anticipate," "believe," "estimate," "expect," "can," "continue," "could," "intend," "plan," "potential," "predict," "project," "should," "will," "would" and words or phrases of similar import, as they relate to our company or our subsidiaries 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 or revise, nor do we have a policy of updating or revising, 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:

- risks relating to the compliance by Fundação Oswaldo Cruz, or Fiocruz, an arm of the Brazilian Ministry of Health, or the Brazilian MOH, with its purchase obligations under our supply and technology transfer agreement which may result in the termination of such agreement which may have a material adverse effect on our company;

- risks related to the commercialization efforts for taliglucerase alfa in the United States, Israel, Brazil, Canada, Australia and other countries;

- risks related to the supply of drug product pursuant to our supply arrangement with Fiocruz;

- the risk of significant delays in the commercial introduction of taliglucerase alfa in the United States, Brazil, Israel, Canada, Australia and other markets as planned;

- risks related to the acceptance and use of taliglucerase alfa or any of our product candidates, if approved, by physicians, patients and third-party payors;

- the risk that we will not be able to develop a successful sales and marketing organization for taliglucerase alfa in Israel, or for any other product candidate, in a timely manner, if at all;

- failure or delay in the commencement or completion of our preclinical studies and clinical trials which may be caused by several factors, including: unforeseen safety issues; determination of dosing issues; lack of effectiveness during clinical trials; slower than expected rates of patient recruitment; inability to monitor patients adequately during or after treatment; inability or unwillingness of medical investigators and institutional review boards to follow our clinical protocols; or lack of sufficient funding to finance our clinical trials;

- the risk that the results of our clinical trials will not support the applicable claims of safety or efficacy, that our product candidates will not have the desired effects or include undesirable side effects or other unexpected characteristics;

- our dependence on performance by third party providers of services and supplies, including without limitation, clinical trial services;

- delays in the approval or the potential rejection of any application filed with or submitted to the regulatory authorities reviewing taliglucerase alfa outside of the United States, Israel, Brazil, Canada, Australia and other countries in which taliglucerase alfa is already approved;

- our ability to establish and maintain strategic license, collaboration and distribution arrangements, and to manage our relationships with Pfizer Inc., Fiocruz and any other collaborator, distributor or partner;

- risks relating to our ability to make scheduled payments of the principal of, to pay interest on or to refinance our 2018 convertible notes, or any other indebtedness;

- risks relating to our ability to finance our research programs, the expansion of our manufacturing capabilities and the ongoing costs in the case of delays in regulatory approvals for taliglucerase alfa outside of the United States, Israel, Brazil, Canada, Australia and other countries in which taliglucerase alfa is already approved;

- delays in our preparation and filing of applications for regulatory approval of our other product candidates in the United States, the European Union and elsewhere;

- our expectations with respect to the potential commercial value of our product and product candidates;

- the risk that products that are competitive to our product candidates may be granted orphan drug status in certain territories and, therefore, will be subject to potential marketing and commercialization restrictions;

- the impact of development of competing therapies and/or technologies by other companies;

- any lack of progress of our research and development activities and our clinical activities with respect to any product candidate;

- the inherent risks and uncertainties in developing the types of drug platforms and products we are developing;

- potential product liability risks, and risks of securing adequate levels of product liability and clinical trial insurance coverage;

- 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;

- risks relating to changes in healthcare laws, rule s and regulations in the United States or elsewhere; and

- 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 subsidiaries, our manufacturing facilities and our customers, suppliers, distributors, collaborative partners, licensees and clinical trial sites.

Companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in advanced or late-stage clinical trials, even after obtaining promising earlier trial results or preliminary findings for such clinical trials. Even if favorable testing data is generated from clinical trials of a drug product, the U.S. Food and Drug Administration or foreign regulatory authorities may not accept or approve a marketing application filed by a pharmaceutical or biotechnology company for the drug product.

These forward-looking statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. These and other risks and uncertainties are detailed under the heading “Risk Factors” in this Annual Report and are described from time to time in the reports we file with the U.S. Securities and Exchange Commission, or the Commission.

Item 1. Business

We are a biopharmaceutical company focused on the development and commercialization of recombinant therapeutic proteins based on our proprietary ProCellEx® protein expression system, or ProCellEx. Using our ProCellEx system, we are developing a pipeline of proprietary, clinically superior versions of recombinant therapeutic proteins that primarily target large, established pharmaceutical markets and that in most cases 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. With our experience, and having successfully developed Elelyso™, our first drug product, we believe ProCellEx will enable us to develop additional proprietary recombinant proteins that are therapeutically superior to existing recombinant proteins currently marketed for the same indications. We are now also applying the unique properties of our ProCellEx system for the oral delivery of therapeutic proteins.

The following table summarizes our current product candidates and our current projections regarding their respective stages of clinical development.

On May 1, 2012, the U.S. Food and Drug Administration, or the FDA, approved for sale our first commercial product, taliglucerase alfa for injection, which is being marketed in the United States and Israel under the brand name Elelyso, as an enzyme replacement therapy, or ERT, for the long-term treatment of adult patients with a confirmed diagnosis of type 1 Gaucher disease. Subsequently, taliglucerase alfa was approved by the Brazilian National Health Surveillance Agency (Agencia Nacional de Vigilancia Sanitaria, or ANVISA) in March 2013, and by the Israeli Ministry of Health, or the Israeli MOH, in September 2012. It has also been approved by other regulatory agencies for other countries. Taliglucerase alfa is being marketed under the name Uplyso™ in Brazil and certain other Latin American countries.

In August 2014, the FDA approved Elelyso for injection for pediatric patients and the Israeli MOH approved the pediatric indication in January 2015. Prior to the U.S. pediatric approval, Elelyso was approved for pediatric indications in Australia and Canada but in no other jurisdiction. In September 2014, CONITEC, the National Commission for Incorporation of Technologies in Brazil's Unified Healthcare System, announced that it had decided to give a positive funding recommendation for Uplyso in the treatment of adult patients with types 1 and 3 Gaucher disease, and established that Uplyso will be the first choice for treatment for new adult Gaucher patients in Brazil.

Since May 2012, taliglucerase alfa has been marketed in the United States by Pfizer Inc., or Pfizer, our commercialization partner, as provided in the exclusive license and supply agreement by and between Protalix Ltd., our wholly-owned subsidiary, and Pfizer, which we refer to as the Pfizer Agreement. We granted Pfizer an exclusive, worldwide license to develop and commercialize taliglucerase alfa under the Pfizer Agreement, but we retained those rights in Israel, and later in Brazil. We have agreed to a specific allocation between Protalix Ltd. and Pfizer of the responsibilities for the continued development efforts for taliglucerase alfa outside of Israel and Brazil. Protalix Ltd. has been marketing taliglucerase alfa in Israel since 2013 and in Brazil since January 2014.

On June 18, 2013, we entered into a Supply and Technology Transfer Agreement, or the Brazil Agreement, with Fiocruz, for taliglucerase alfa. The agreement became effective in January 2014. The technology transfer is designed to be completed in four stages and is intended to transfer to Fiocruz the capacity and skills required for the Brazilian government to construct its own manufacturing facility, at its sole expense, and to produce a sustainable, high-quality, and cost-effective supply of taliglucerase alfa. The initial term of the technology transfer is seven years. Under the agreement, Fiocruz committed to purchase at least approximately $40 million worth of taliglucerase alfa during the first two years of the term. Since the agreement went into effect, we have recorded revenues of approximately $3.5 million for sales of taliglucerase alfa to Fiocruz in 2014 and, during the first quarter of 2015, we received a purchase order for approximately $5.7 million of taliglucerase alfa out of which we have delivered approximately $1.7 million of the product. In subsequent years, Fiocruz is required to purchase at least approximately $40 million worth of taliglucerase alfa per year. We are not required to complete the final stage of the technology transfer until Fiocruz purchases at least approximately $280 million worth of taliglucerase alfa.

The Brazil Agreement may be extended for an additional five-year term, as needed, to complete the technology transfer. All of the terms of the arrangement, including the minimum annual purchases, will apply during the additional term. Upon completion of the technology transfer, and subject to Fiocruz receiving approval from ANVISA to manufacture taliglucerase alfa in its facility in Brazil, the agreement will enter into the final term and will remain in effect until our last patent in Brazil expires. During such period, Fiocruz will be the sole provider of this important treatment option for Gaucher patients in Brazil and shall pay us a single-digit royalty on net sales.

To facilitate the arrangement with Fiocruz, we and Pfizer agreed to an amendment of our exclusive license and supply agreement, which amendment provides for the transfer of the commercialization and other rights to taliglucerase alfa in Brazil back to us. As consideration for the transfer of the commercialization and supply rights, we agreed to pay Pfizer a maximum amount of approximately $12.5 million from its net profits (as defined in the license and supply agreement) per year. Pfizer has also agreed to perform certain transitional services in Brazil on our behalf in connection with the supply of taliglucerase alfa to Fiocruz.

We will pay a fee equal to 5% of the net proceeds generated in Brazil to our agent for services provided in assisting us complete the Brazil Agreement pursuant to an agency agreement between us and the agent. The agency agreement will remain in effect with respect to the Brazil Agreement until the termination thereof.

We are cooperating with Pfizer to obtain marketing approval for taliglucerase alfa in additional countries and jurisdictions. In addition to those countries in which taliglucerase alfa has been approved, marketing authorization applications have been filed in other countries.

Currently, patients are being treated with taliglucerase alfa on a commercial basis in the United States, Brazil, Israel and Chile.

In addition to taliglucerase alfa, we are developing an innovative product pipeline using our ProCellEx protein expression system. Our product pipeline currently includes, among other candidates:

(1) PRX-102, or alpha-GAL-A, a therapeutic protein candidate for the treatment of Fabry disease, a rare, genetic lysosomal disorder in humans, currently in an ongoing phase I/II clinical trial. We expect to report interim efficacy and safety results for the 1 mg/kg dose group of the trial during the third quarter of 2015 and to report final efficacy and safety results for the 0.2mg, 1 mg and 2mg/kg dose groups of the trial during the fourth quarter of 2015.

(2) PRX-106, our oral antiTNF product candidate which is being developed as an orally-delivered anti inflammatory treatment using plant cells as a natural capsule for the expressed protein. We expect to initiate a proof of concept efficacy study during 2015.

(3) PRX-110, a proprietary plant cell recombinant human Deoxyribonuclease 1, or DNase, under development for the treatment of cystic fibrosis, to be administered by inhalation. We expect to initiate a proof of concept efficacy study during 2015.

(4) PRX-112, an orally administered glucocerebrosidase enzyme for the treatment of Gaucher patients utilizing oral delivery of the recombinant GCD enzyme produced and encapsulated within carrot cells. PRX-102 has been the subject of successful proof of concept clinical trials, as described below, and we intend to focus our efforts on a new formulation of the treatment during 2015.

Except for the rights to commercialize taliglucerase alfa worldwide (other than Brazil and Israel), which we licensed to Pfizer, we hold the worldwide commercialization rights to all of our proprietary development candidates. We have built an internal marketing team designed to serve the Israeli and Brazilian market for taliglucerase alfa and we intend to establish internal commercialization and marketing teams for our other product candidates in North America, the European Union and in other significant markets, including Israel, subject to required marketing approvals, as the need arises. In addition, we continuously evaluate potential strategic marketing partnerships as well as collaboration programs with biotechnology and pharmaceutical companies and academic research institutes.

Our Strategy

In January 2015, we announced our newly implemented strategy for accelerated growth. The strategy centers around prioritizing existing and new pipeline candidates to focus on clinically superior products that offer a clear competitive advantage over existing treatments. The strategy was the culmination of two month of intensive review by our management of the company's internal resources and of the markets in which we think we can operate. The following highlights the details of the strategic plan.

PRX-102 for the Treatment of Fabry disease. PRX-102 is designed to be an improved enzyme replacement therapy product for the treatment of Fabry disease given its potential for clinically superior outcomes and enhanced safety when compared to currently marketed enzyme replacement therapies. The product candidate remains a key focus for our company, and we intend to aggressively push PRX-102 through clinical development. Interim efficacy and safety data from our ongoing phase I/II trial are described in this Annual Report.

Oral Anti-TNF (PRX-106) Anti Inflammatory. Oral anti-TNF represents a novel mode of administering a recombinant anti-TNF protein. We plan to initiate clinical efficacy trials of Oral Anti-TNF during 2015. Upon reviewing the proof of concept (POC) data, expected in early 2016, we intend to collaborate with a well-suited partner for further development.

AIR DNase (PRX-110) for Cystic Fibrosis. AIR DNase has an actin inhibition resistance that is designed to improve lung function and lower the incidence of recurrent infections by enhancing the enzyme's efficacy in patients sputa. The product candidate has demonstrated improved disease parameters in animal models and human sputum testing when compared to the currently marketed product. We plan to initiate clinical efficacy trials of AIR DNase for the treatment

of Cystic Fibrosis (CF) during 2015. Upon reviewing the results of the trial, expected in early 2016, we intend to collaborate with a well-suited partner for further development.

Oral GCD (PRX-112) for Gaucher Disease. Oral GCD represents a novel mode of administrating taliglucerase alfa. The initial clinical data generated for this compound in pre-clinical and clinical trials is promising. In 2015, we intend to focus on improving the product candidate's formulation and delivery in order to transform it into a commercially viable product.

Potential Pipeline Candidates. We aim to expand our pipeline by leveraging the advantages of our proprietary ProCellEx® protein expression technology. The focus is expected to be on biologics with improved clinical profiles than the currently marketed proteins for these indications. Biosimilars will not be a market on which we focus, and will only be considered in the case of proteins that are highly difficult to express or that represent opportunities for early market entry arising from the intellectual property advantages arising from ProCellEx.

Elelyso™ for Gaucher Disease. We anticipate continuing to increase market share in Israel. Additionally, our management intends to continue to work closely with Pfizer, our collaboration partner, and with the Brazilian government, to increase sales globally.

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. The IMS Institute for Healthcare Informatics reports that global biologic spending was $169 billion in 2012 and anticipated to reach $221 billion in 2017 (Report by the IMS Institute for Healthcare Informatics, Nov. 2013).

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-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®, Humira®, Enbrel®, Neulasta®, Remicade® 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, and several cases of viral contamination have occurred recently. 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 and none of these technologies have been approved by the regulatory agencies with jurisdiction over any substantial market.

ProCellEx: Our Proprietary Protein Expression System

ProCellEx is our proprietary production system. We have developed ProCellEx based on our plant cell culture technology for the development, expression and manufacture of recombinant proteins. ProCellEx 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. This 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. 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 when compared to mammalian cell-based protein expression systems.

Our ProCellEx system is capable of producing proteins with an amino acid sequence and three dimensional structure practically equivalent to that of the desired human protein, and with a very similar, although not identical, glycan, or sugar, structure, as demonstrated in our internal research and external laboratory studies. In collaboration with the 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.

We believe that the ProCellEx system 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 taliglucerase alfa.

We have successfully demonstrated the feasibility of our ProCellEx system through: the FDA's approval of taliglucerase alfa; the clinical and preclinical studies we have performed to date, including the positive efficacy and safety data in our clinical trials for both Elelyso and PRX102 for the treatment of Fabry disease; preclinical results in well-known models in our enzyme for each of Fabry disease, DNase and antiTNF; and by expressing, on an exploratory, research scale, many additional 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 the FDA's approval of taliglucerase alfa represents a strong proof-of-concept of our ProCellEx system and plant cell-based protein expression technology. We also believe that the significant benefits of our ProCellEx system, if further substantiated in clinical trials and in the successful commercialization of taliglucerase alfa and our other product candidates, have the potential to transform the industry standard for the development of complex therapeutic proteins.

We are also using our ProCellEx system to produce active recombinant proteins through oral administration of plant cells expressing biotherapeutic proteins. In such method, an enzyme is naturally encapsulated within carrot cells genetically engineered to express the targeted enzyme. Plant cells have the unique attribute of a cellulose cell wall which makes them resistant to enzyme degradation when passing through the digestive tract. The plant cell itself serves as a delivery vehicle, once released and absorbed, to transport the enzyme in active form to the bloodstream. With initial proof of concept now demonstrated, this would be the first time an enzyme will be administered orally rather than through intravenous therapy. To date we have completed successful preclinical animal studies for oral GCD and oral antiTNF, and in early clinical trials of oral GCD in Gaucher patients.

To date, our manufacturing facility, in which we utilize our ProCellEx system, was determined to be acceptable by each of the FDA, the European Medicines Agency, or the EMA, ANVISA, the Israeli MOH, the Australian Therapeutic Goods Administration, or the TGA, and Health Canada, after GMP inspections were performed as part of their respective reviews for marketing approval of taliglucerase alfa.

Competitive Advantages of Our ProCellEx Protein Expression System

We intend to continue to leverage the multiple unique advantages of our proprietary ProCellEx protein expression system, including our advanced genetic engineering technology and plant cell-based protein expression methods, to develop our pipeline. Significant advantages of ProCellEx over mammalian, bacterial, yeast and transgenic cell-based expression technologies, include the following:

Biologic Optimization. Our ProCellEx protein expression system has internal capabilities developed to improve the biologic dynamics of the expressed protein. For example, the proteins produced through our system 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. 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 expressed protein to bind to a target cell and subsequently be taken into the target cell for therapeutic benefit. 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. We believe this quality increases the potency and consistency of the expressed proteins, and thus, the effectiveness of the protein which presents an additional cost advantage of ProCellEx over competing protein expression methodologies.

Ability to Penetrate Certain Patent-Protected Markets. ProCellEx has the potential to provide workaround manufacturing that does not infringe the method-based patents or other intellectual property rights of third parties. Certain biotherapeutic proteins available for commercial sale are not protected by patents that cover the compound and are available for use in the public domain. Rather, 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 U.S. and international composition of matter patents for taliglucerase alfa, PRX-102 and certain of our other product candidates.

Broad Range of Expression Capabilities. Our ProCellEx protein expression system is able to produce a broad array of complex glycosilated proteins, which are difficult to produce in other systems, such as bacterial and yeast cell-based systems, as well as CHO (Chinese Hamster Ovary) systems. 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.

Significantly Lower Capital and Production Costs. Our ProCellEx system entails a lower cost of scale-up and of production. Plant cells grow rapidly under a variety of conditions and are not as sensitive as mammalian cells are to temperature, pH and oxygen levels. Our system, therefore, does not require the 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 can 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 associated with 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

proteins, plant cells require only simple and much less expensive solutions based on sugar, water and microelements at infrequent intervals to achieve target yields.

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 and product candidates to future patients, whether from known or unknown mammalian viruses, is eliminated. Because our products and product candidates do not bear the risk of mammalian 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 are required in mammalian cell-based production. In addition, the production process of our ProCellEx 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.

Potential ability to administer active therapeutic enzymes orally. We are using our ProCellEx system to produce active recombinant proteins through oral administration of plant cells expressing biotherapeutic proteins. Plant cells have the unique attribute of a cellulose cell wall which makes them resistant to enzyme degradation when passing through the digestive tract. The plant cell itself serves as a delivery vehicle, once released and absorbed, to transport the enzyme in active form to the bloodstream. If proven effective, this would be the first time an enzyme will be administered orally rather than through intravenous therapy. To date we have completed successful preclinical animal studies for oral GCD and oral anti TNF, and early clinical trials of oral GCD in Gaucher patients.

Elelyso, Our First Commercial Product

Elelyso (taliglucerase alfa), our first commercial product, is a plant cell expressed recombinant glucocerebrosidase enzyme (GCD) for the treatment of Gaucher disease. On May 1, 2012, the FDA approved Elelyso for injection as an enzyme replacement therapy (ERT) for the long-term treatment of adult patients with a confirmed diagnosis of type 1 Gaucher disease. It was subsequently approved by the Israeli MOH, ANVISA and the regulatory authorities of other countries. In August 2014, the FDA approved Elelyso for injection for pediatric patients and the Israeli MOH approved the pediatric indication in January 2015. Prior to the U.S. pediatric approval, Elelyso was approved for pediatric indications in Australia and Canada but in no other jurisdiction.

We believe that taliglucerase alfa has the potential to offer patients and healthcare payors an effective and cost efficient treatment of Gaucher disease compared to the currently available ERTs.

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. It is estimated that there are approximately 12,000 people suffering from Gaucher disease worldwide, but only approximately 6,000 patients are undergoing treatment. Enzyme replacement therapy is a medical treatment in which recombinant enzymes are injected into patients in whom the enzyme is

lacking or dysfunctional. Cerezyme and VPRIV®, enzyme replacement therapies commercialized by Genzyme Corporation (acquired by Sanofi), or Genzyme, and Shire plc, or Shire, respectively, are the only recombinant GCDs currently available on the market for the treatment of Gaucher disease. 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 patients generally receive the treatment over their entire lifetime. According to public reports by Sanofi, consolidated sales of Cerezyme during the year ended December 31, 2014 were €715 million (or approximately $865 million), a growth of approximately 8% compared to the same period in 2013. Shire reported annual worldwide sales of VPRIV of approximately $367 million in 2014, a growth of 7% compared to VPRIV's sales in 2013.

In addition, Cerdelga® (eliglustat) is a substrate reduction therapy for Gaucher disease marketed by Sanofi. Cerdelga was approved for marketing by the FDA in August 2014 and by the European Commission in January 2015.

Cerezyme is produced through a mammalian cell-based protein expression process in CHO cells and VPRIV is produced using a human cancer cell line. There are no known severe side effects to the use of Cerezyme or VPRIV, and Cerezyme's approved use over the past decade suggests that it is an effective treatment of Gaucher disease. However, Cerezyme and VPRIV are both subject to the limitations of most mammalian cell-based therapeutic proteins, including lengthy and costly production processes and contamination risks.

Zavesca (miglustat), which is marketed by Actelion Ltd., or Actelion, is a small molecule drug for the treatment of Gaucher disease. 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 ERT, and, accordingly, have no other treatment alternative. As a result, Zavesca's use has been limited with respect to treating Gaucher disease. However, Zavesca is also used to treat other rare disorders. Actelion has reported total sales of Zavesca of approximately CHF 103 million (approximately $104 million) in 2014, an increase of approximately 8% compared to sales in 2013.

Our Pipeline Drug Candidates

PRX-102 for the Treatment of Fabry Disease

We are developing PRX-102, our proprietary plant cell expressed chemically modified version of the recombinant alpha-GAL-A protein, a therapeutic enzyme, for the treatment of Fabry disease, a rare genetic lysosomal storage disorder. We believe that PRX-102 has the potential to be an improved version of the currently marketed Fabry disease enzymes, Fabrazyme® and Replagal®, with improved activity in the Fabry disease target organs and significantly longer half-life due to higher stability, which together can potentially lead to improved substrate clearance. We believe that the treatment of Fabry disease is a specialty clinical niche with the potential for high growth.

Fabry Disease Background

Fabry disease is characterized by subnormal or absent enzymatic activity of alpha-GAL-A, a lysosomal enzyme which primarily catalyses the hydrolysis of terminal alpha-galactosyl groups of glycolipids, mainly the glycosphingolipid globotriaosylceramide (Gb3). The accumulation of Gb3 in body tissues results in Fabry disease. The ultimate consequence of glycosphingolipid deposition in the vasculature and other tissues is end-organ failure, particularly of the kidney, but also of the heart and cerebrovascular system. In addition, involvement of the central, peripheral and autonomic nervous systems results in episodes of pain and impaired peripheral sensation. Fabry disease affects approximately 8,000 people globally. In PRX-102, the prh-alpha-GALA, naturally occurring as a homodimer, is PEGylated and cross-linked to support and reinforce the homodimeric structure, which is crucial for the enzymatic activity of this enzyme. PRX-102 has been shown to be taken up by Fabry patients' cells where it localizes to the lysosome, in which Gb3 accumulates. PRX-102 is characterized by higher stability under physiologically relevant conditions, and extended circulation residence time as compared to current ERTs for Fabry disease.

Current Treatments for Fabry Disease

Currently there are two drugs available on the market to treat Fabry disease. Fabrazyme, marketed by Genzyme, is approved for the treatment of Fabry disease in the United States and the European Union. Sanofi reported €460 million (approximately $557 million) in worldwide sales of Fabrazyme in 2014, a growth of 23% compared to 2013. The other approved drug for the treatment of Fabry disease in the European Union is Replagal, which is marketed by Shire. Shire reported $500 million in sales of Replagal in 2014, an increase of 7% compared to 2013. According to public reports by Shire, during 2012 Shire withdrew its Biologics License Application (BLA) for Replagal with the FDA.

PRX-102 Development Program

In February 2015, we announced the completion of enrollment in our phase I/II clinical trial in adult Fabry patients. The phase I/II clinical trial is a worldwide, multi-center, open label, dose ranging study to evaluate the safety, tolerability, pharmacokinetics and exploratory efficacy parameters of PRX-102 in adult Fabry patients. There were 18 adult Fabry patients (11 male and 7 female) enrolled in the trial, each in one of three dosing groups, 0.2 mg/kg, 1mg/kg and 2mg/kg. Each patient receives intravenous infusions of PRX-102 every two weeks for 12 weeks, with a six-month efficacy follow up period. All patients that completed the trial have opted to continue to receive PRX-102 in an open-label extension trial.

In January and February 2015, we announced positive interim efficacy and safety data from the study. PRX-102 demonstrated meaningful clinical benefits across the following key disease parameters already in the low dose of 0.2 mg/kg:

- Major reduction in Gb3 in Renal Peritubular Capillaries;
- Significant improvement in all pain parameters;
- Stabilization of cardiac and kidney function with favorable trends; and
- Low level of antibody formation.

The interim efficacy analysis includes six patients enrolled in the 0.2mg/kg dose group at six months of treatment (for Gb3 in renal peritubular capillaries n=5). The interim safety analysis includes 12 patients; six patients enrolled in the 0.2mg/kg dose group and six patients enrolled in the 1mg/kg dose group.

Based on an analysis of kidney biopsies with randomized blinded scoring, PRX-102 demonstrated a major reduction from baseline in renal peritubular capillary Gb3 using both the quantitative Barisoni Lipid Inclusion Scoring System (BLISS) and the semi quantitative method. Using the BLISS method, a reduction in the rate of 82.2% for males, 65.4% for females and 75.5% for males and females combined were observed. Absolute change from baseline was -4.5, -1.2 and -3.2, respectively. Applying the semi quantitative scoring method, commonly used by approved enzyme replacement therapies, PRX-102 demonstrated a reduction of 69.6% in abnormal capillary score.

Using the well-accepted Brief Pain Inventory scale, a 100% reduction in pain at its worst, a 60.0% reduction in mean severity, and 78.8% reduction on mean interference (which includes walking, working, sleeping, enjoyment of life and others) were observed. In addition to a 100% reduction in worst pain, all patients also reported a 100% reduction in mean interference, with the exception of one patient who experienced a 33.3% reduction. See Figure 1.

Figure 1. Improvement in Brief Pain Inventory (BPI)

Reductions of plasma Lyso-Gb3 and plasma Gb3 concentrations were also observed. Females (n=2) demonstrated a -2.4 ng/mL mean change in Lyso-Gb3 and a -0.4 µg/mL mean change in plasma Gb3. Males (n=4) demonstrated a -96.2 ng/mL and a -1.3 µg/mL change, respectively. All patients demonstrated a reduction in absolute Lyso-Gb3 concentration and all patients demonstrated a reduction in Gb3 except for one patient. See Figure 2.

Figure 2. Semi Quantitative Method

A meaningful reduction in the total score of Mainz Severity Score Index (MSSI), which looks at general, neurological, cardiovascular and renal parameters, was also demonstrated, with a reduction in all parameters included in MSSI.

The leading causes for death of Fabry patients include cardiovascular disease and renal failures. All patients that participated in the trial exhibited stable cardiac and kidney function, with favorable trends after only six months, as measured by left ventricular mass (LVM), left ventricular mass index (LVMI), ejection fraction (EF), estimated glomerular filtration rate (eGFR) and urine protein. See Figures 3 and 4.

Figure 3. Stability of Cardiac Parameters by MRI

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Figure 4. Stable Kidney Functions

The safety analysis for adverse events represents a total of 6.7 patient years. PRX-102 was well tolerated, with the majority of events being mild and moderate. Only one of the 12 patients evaluated for safety experienced hypersensitivity and discontinued per protocol. For this patient, anti PRX-102 IgG was negative and anti PRX-102 IgE was positive at baseline.

Six patients receiving the 0.2mg/kg dose and two patients receiving the 1m/kg dose were evaluated for antibody formation. Of these eight patients, only two patients, or 33% of the 0.2 mg/kg dose cohort, developed antibodies. All adverse events experienced by these patients were deemed by the investigators to be unrelated to PRX-102.

PRX-102 has a significantly longer circulatory half-life (T½) of approximately 60 hours, and a substantially higher area under the curve (AUC) of approximately 70,000 ng/mL*hour for the 0.2mg/kg dose, when compared to currently marketed enzyme replacement therapies. These enhanced pharmacokinetic benefits are believed to be the result of the chemical modifications made to PRX-102, including cross-linking and covalent bonding to make the enzyme a more stable homo-dimer. See Figures 5 and 6.

Figure 5. Improved Pharmacokinetics

Figure 6. Area under the Curve (AUC)

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We expect to report interim results from the 1mg/kg cohort in the third quarter of 2015, and full top-line results from all dosing cohorts in the fourth quarter of 2015. We intend to request an end of phase II meeting with the FDA in the fourth quarter of 2015, and anticipate initiating a phase III pivotal trial in early 2016.

PRX-106; Oral antiTNF as an Anti Inflammatory

Our oral antiTNF product candidate is a recombinant antiTNF (Tumor, Necrosis Factor) protein that we are expressing through ProCellEx. AntiTNF drugs represent the biggest category of biological drugs in the world today with combined sales of over $20 billion a year.

Oral antiTNF is a plant cell-expressed form of the fused protein that is naturally encapsulated within carrot cells genetically engineered to express the enzyme. Plant cells have the unique attribute of a cellulose cell wall which makes them resistant to enzyme degradation when passing through the digestive tract. The plant cell itself serves as a delivery vehicle, once released and absorbed, to transport the enzyme in active form to the bloodstream. If proven effective, our experimental oral antiTNF would be the first protein to be administered orally rather than through injectable therapy. We believe that our oral delivery mechanism could be applied to additional proteins and has the potential to change the method of protein administration in certain indications.

We are currently developing oral antiTNF an orally-administered anti inflammatory using plant cells as a natural capsule for the expressed protein. In preclinical studies, oral PRX-106 alleviated immune-mediated hepatitis and reduced interferon gamma levels in a concanavalin A (ConA) inflammatory mouse model. Additionally, oral administration of PRX-106 alleviated immune mediated colitis in a well-established mouse model, promoting serum levels of anti-inflammatory IL-10 and regulatory T-cells.

pr-antiTNF is a plant cell-expressed recombinant fusion protein made from the binding domain of the human TNF receptor (TNFR), fused to the Fc component of a human antibody domain. It has an identical amino acid sequence to Enbrel and our in vitro and preclinical animal studies have demonstrated that pr-antiTNF exhibits similar or better activity to Enbrel. See Figure 7.

Figure 7. IBD Animal Model

We are now conducting additional preclinical studies on oral antiTNF for several attractive indications, and we plan to initiate clinical efficacy trials of oral anti TNF during 2015. Upon reviewing the proof of concept (POC) data, expected in early 2016, we intend to collaborate with a well-suited partner for further development.

PRX-110; AIR DNase for the Treatment of Cystic Fibrosis

PRX-110, or AIR DNase, is our plant cell recombinant form of human deoxyribonuclease I (DNase I) that we are developing for the treatment of Cystic Fibrosis, to be administered by inhalation. DNase I cleaves extracellular DNA and thins the thick mucus that accumulates in the lungs of Cystic Fibrosis patients. Currently, Pulmozyme® is the only DNase I commercially available, with annual sales of approximately $626 million in sales for 2014, according to public reports by F. Hoffman-La Roche Ltd.

In vitro studies with PRX-110 demonstrated improved enzyme kinetics, less sensitivity to inhibition by actin and improved ex vivo efficacy when compared to Pulmozyme. Preclinical studies of PRX-110 administered by inhalation showed substantial enzymatic activity in lungs.

AIR DNase has an actin inhibition resistance that is designed to improve lung function and lower the incidence of recurrent infections by enhancing the enzyme's efficacy in patients' sputa. The product candidate has demonstrated improved disease parameters in animal and human models sputum testing when compared to the currently marketed product. See Figure 8.

Figure 8. Rheology Data Analysis in in human sputum samples

We plan to initiate clinical efficacy trials of AIR DNase for the treatment of Cystic Fibrosis during 2015. Upon reviewing the results of the trial, expected in early 2016, we intend to collaborate with a well-suited partner for further development.

PRX-112; Orally Administered GCD for the Treatment of Gaucher Disease

We are developing PRX-112, an orally-delivered glucocerebrosidase (GCD) enzyme for the enzyme replacement therapy treatment of Gaucher disease. In 2015, our focus with respect to oral GCD, will be on improving oral GCD's formulation and delivery in order to transform the product candidate into a commercially viable product.

Oral GCD Development Program

In February 2015, the last Gaucher patient was treated in our phase IIa clinical trial of oral GCD. The phase IIa clinical trial was a 28-day open-label, sequential dose escalation study to evaluate the safety of PRX-112, and study the dose dependent pharmacokinetics of PRX-112 in naïve adult Gaucher patients. The primary objective of the trial was to measure the safety of oral GCD in Gaucher patients. Additional objectives included an evaluation of oral GCD's pharmacokinetic profile and exploratory endpo