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Protalix BioTherapeutics, Inc. (PLX - NYSE)

FDA Approval To Start New Chapter

Based on our DCF model and a 15% discount rate, Protalix is valued at approximately $15.00 per share. Our model applies an 85% probability of ultimate approval and commercialization for PRX-102 in Fabry Disease. The model includes contributions from a global commercialization effort.

Current Price (12/4/2020)	$3.48
Valuation	**$15.00**

INITIATION

Protalix is a clinical and commercial pharmaceutical company using its proprietary ProCellEx plant-based expression system to produce therapeutic proteins for global markets. The company has one commercialized product, Elelyso, that is marketed by Fiocruz in Brazil & Pfizer in the rest of the world for Gaucher Disease. Other candidates include PRX-102 for Fabry Disease, now under consideration by the FDA with an anticipated target action date of April 27, 2021. If approved, Chiesi Rare Disease will commercialize the product globally.

Protalix has additional candidates in earlier stages of development including OPRX-106 for IBD and PRX-110 for Cystic Fibrosis. The company also has a partnership with SarcoMed for development of PRX-110 in Pulmonary Sarcoidosis.

We expect PRX-102 to be approved and sales related payments to be received in 2021. PRX-102 can fill an unmet need with several improvements over the market leader and is expected to command a premium to existing products. Elelyso is expected to show moderate growth over the next quarters as partners continue their commercialization efforts. Profits from revenue generating products are expected to be invested in new candidates in coming years.

SUMMARY DATA

52-Week High	**4.87**
52-Week Low	**2.04**
One-Year Return (%)	**12.2**
Beta	**2.88**
Average Daily Volume (sh)	**92,698**
Shares Outstanding (mil)	**33.3**
Market Capitalization ($mil)	**116**
Short Interest Ratio (days)	**2.1**
Institutional Ownership (%)	**15.9**
Insider Ownership (%)	**32.8**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2020 Estimate	**N/A**
P/E using 2021 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of USD)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2019	$10.4 A	$12.2 A	$14.2 A	$17.8 A	$54.7 A
2020	$21.6 A	$11.0 A	$10.8 A	$10.6 E	$53.8 E
2021					$48.9 E
2022					$78.4 E

Earnings per Share

	Q1	Q2	Q3	Q4	Year
2019	-$0.49 A	-$0.52 A	-$0.24 A	$0.02 A	-$1.23 A
2020	$0.10 A	-$0.13 A	-$0.14 A	-$0.13 E	-$0.39 E
2021					-$0.01 E
2022					$1.06 E

INITIATION

We are initiating coverage of Protalix BioTherapeutics, Inc. (NYSE: PLX) with a current valuation of $15.00 per share. This present value is based on our estimates for approval and commercialization of PRX-102 by Chiesi's Rare Disease division in 2021 and continued sales of Elelyso through partners Fiocruz and Pfizer. Both products are for rare diseases and command a premium price in part due to the small size of the target market. We estimate a sharp increase in sales for PRX-102 for Fabry Disease and modest revenue growth for the established Elelyso for Gaucher Disease. There are additional products in the pipeline that we anticipate will be advanced following successful launch of PRX-102.

Protalix uses a plant-based protein expression system to produce its biologics and successfully gained FDA approval for the first biologic expressed with a plant-based system. Following supply disruptions related to Genzyme's Cerezyme in 2009, the agency allowed taliglucerase alfa to be provided to Gaucher patients through an expanded access dispensation. The product was fully approved by the FDA for Gaucher disease in 2012, the first commercial enzyme produced in genetically engineered plant cells.

Plant-based expression systems offer several benefits over other expression systems. They do not harbor any known human pathogens including viruses, which increases safety and simplifies purification of therapeutic proteins. Among other benefits, plant-based systems require less expensive media as compared to mammalian systems as plant cell growth mainly requires minerals and sugars with no growth factors. This platform has been used to generate one approved product and another that is under consideration by the FDA. With potential approval of PRX-102 five months away, we are optimistic that we will see substantial near term revenues accruing to Protalix from milestones and royalties.

To date, Protalix has largely focused its efforts on rare diseases, including Fabry Disease. Pursuing a candidate in this category provides several benefits including the opportunity for a faster pathway to market and command of higher market prices in this limited population. Despite occurring in only one in 40,000 to one in 60,000 people, global revenues produced for Fabry treatment is near $1.8 billion. With the potential for improved efficacy and longer duration between infusions, PRX-102 may be able to take a commanding share.

We forecast modest growth of taliglucerase alfa revenues in the coming years. The primary driver for our valuation is a successful launch and commercialization of PRX-102, which will be conducted by Chiesi Rare Disease. Chiesi has made substantial investments in its rare disease effort and we believe they are highly motivated for success and can claim a material proportion of the market for Fabry in the coming years. Clinical trial results to date have been strong enough to justify expedited treatment of PRX-102 and if the head to head comparisons with Fabrazyme and Replagal are successful, PRX-102 may be able to command a dominant presence in the market. The enzyme may be even more desirable if it is able to provide four weeks of enzyme replacement per infusion compared to the two week periodicity required with standard of care.

Protalix has other candidates in its pipeline and with a successful launch of PRX-102, we see sufficient capital to support the advancement of additional candidates towards pivotal trials. While it is unclear which molecules will be advanced, the company has several candidates in its pipeline that have reached Phase II and may consider other options as well.

On September 30, 2020, Protalix held $41.3 million in cash on its balance sheet and convertible notes with a face value of $57.9 million which come due in November 2021. While the company is consuming cash and does not now have sufficient resources on its balance sheet to repay the debt, the company is eligible for a sizable milestone payment if PRX-102 is approved in April 2021. Protalix will also receive royalties on product sales, which will provide additional cash flow that can be used to refinance a portion of the debt if desired. If the approval and launch of PRX-102 is successful, we anticipate positive free cash flow by 2022.

Key reasons to own Protalix shares:

- **PRX-102 on cusp of commercialization**
  - **Target action date: April 27, 2021**
- **Potential for superiority vs market leader Fabrazyme**
  - **Improved efficacy**
  - **Longer duration between infusions**
- **Existing sales and royalty revenues from taliglucerase alfa**
  - **Pfizer, globally**
  - **Fiocruz, Brazil**
- **Maintain regulatory approved plant based expression system**
- **Orphan status granted for PRX-102**
- **Partnership with Chiesi for global commercialization of PRX-102 in Fabry Disease**
- **Rights to milestones and royalties**

In the following sections we provide a review of the types of protein expression systems that are in use and explain Protalix' own plant-based expression system, ProCellEx. We discuss the primary indications where the company has focused its efforts, Gaucher Disease and Fabry Disease, identifying the epidemiology, patho-physiology and standard of care for these rare diseases. We then detail the pipeline, focusing on taliglucerase alfa (Elelyso) and pegunigalsidase alfa (PRX-102), with an emphasis on the clinical trials conducted to support approval of the latter. We mention the other candidates lower down on the pipeline and the indications they are pursuing. A review of the competitive environment and the other products used to treat Gaucher and Fabry is provided along with an exhibit illustrating the therapeutic area where peers and competitors are working. We continue our analysis with a look at patents held and run through the major milestones and recent events for the company. Major risks are discussed and management team members are introduced. We wrap up our initiation with a valuation opinion which employs a discounted cash flow model to estimate the value of the company's portfolio. Our work generates a valuation of $15.00 per share.

Therapeutic Protein Manufacturing

In 1976 Genentech expressed the first recombinant protein in *Escherichia coli* (*E. coli*), producing Somatostatin, a growth hormone inhibitor. Two years later, the first human insulin was prepared with recombinant DNA, also using *E. coli*, launching the pharmaceutical world into the age of therapeutic protein manufacturing. Other expression systems were subsequently developed, such as insect, yeast and mammalian approaches, providing the mechanism for more complex protein production. Since the 1980s, when the first human recombinant enzyme Alteplase was manufactured in Chinese hamster ovary (CHO) cells, the biologics manufacturing world favored the use of CHO cells for human-use biologics. There are also other popular expression vectors which include fungal, insect, bacterial and plant. The selection of a specific expression system relies on the post-translational modifications (PTMs) desired and other factors including cost, productivity and time to production.

Mammalian systems such as CHO frequently use plasmid transfection and viral vector infection to introduce the instructions for protein creation. This process takes several weeks to months to create a stable cell line and the viral vector can be transfected in a few days. There are a few types of expression systems including transient, for research use, and stable, which is applicable for generating biologics-grade product. Stable expression allows the foreign DNA to replicate for an extended duration in the host cell but also requires a lengthy process to create.

Yeast systems have been used for thousands of years in beer and bread production and in the field of genetic engineering. Common use has led to their classification as GRAS (generally recognized as safe) by the FDA, with no production of toxins, reducing safety concerns and costs. This class may not be as suitable for high-density culture as it has low secretion efficiency, especially for large molecular weight proteins. There are a variety of yeast cells which can be used, and they vary in their PTMs, which makes selection of the proper host critical to the specific application needed.

Insect systems use the Baculovirus insect virus to insert the gene of interest into the cell. Baculoviruses are double stranded DNA viruses that naturally infect host insect cells and are able to express recombinant proteins. The system produces PTMs including proteolytic processing, phosphorylation and glycosylation, despite the glycosylation pattern not being a precise match for mammalian cells. High levels of expression and inherent safety during manufacture are other key benefits. The Baculovirus system can accommodate large inserts, which allows for the delivery of multiple genes. However, it does have some drawbacks including the time required for growth of the initial cell line and cell culture is only sustainable for a few days. Baculovirus has been used to produce alpha and beta interferon, erythropoietin, interleukin 2 and others.

Bacterial systems mostly use *E. coli* as the host cell, employing a plasmid vector to insert the proper DNA fragment. *E. coli* genetics are well known and the host is used broadly for the production of heterologous proteins, and is a less complex system than yeast, insect or mammalian cells. While it is simple and inexpensive to use, there are some disadvantages such as aggregation problems under high levels of overexpression and the lack of PTMs. The lack of sufficient PTMs, including protein glycosylation make it inappropriate for most human biologics use.

Plant systems are also used to express proteins of interest and use cells from a variety of sources including lettuce, tomato, carrot, rice and tobacco among others.[1] Tobacco plants have been favored due to the ease of delivering the biologic product sequence with *Agrobacterium*. Plant cells are effective as they are low cost, avoid many of the risks of contamination with mammalian pathogens and can present the appropriate post-translational modification. Other features of plant expression systems include ability to express in a wide variety of temperature, pH, and oxygen levels in contrast to other systems. Plant systems also avoid many of the viral contamination problems that are faced by the commonly used mammalian cells.

In 2009, Genzyme reported viral contamination in several of its key products including Cerezyme and Fabrazyme, raising questions about the safety of mammalian expression systems. This led to the loss of significant product for Genzyme and a shortage of the affected biologics. In response, the industry sought alternatives such as Protalix' carrot cell-based investigational product. Shortages of Cerezyme prompted the FDA to ask Protalix to provide its experimental therapy for Gaucher disease to patients under an expanded access protocol, allowing a plant-based protein to be used in humans outside of a clinical trial for the first time. Protalix' product, Elelyso, was eventually approved in 2012 using genetically engineered carrot cells based on its ProCellEx platform.

[1] Moon, K.B., *et al.* Development of Systems for the Production of Plant-Derived Biopharmaceuticals. Plants (Basel). 2020 Jan; 9(1): 30.

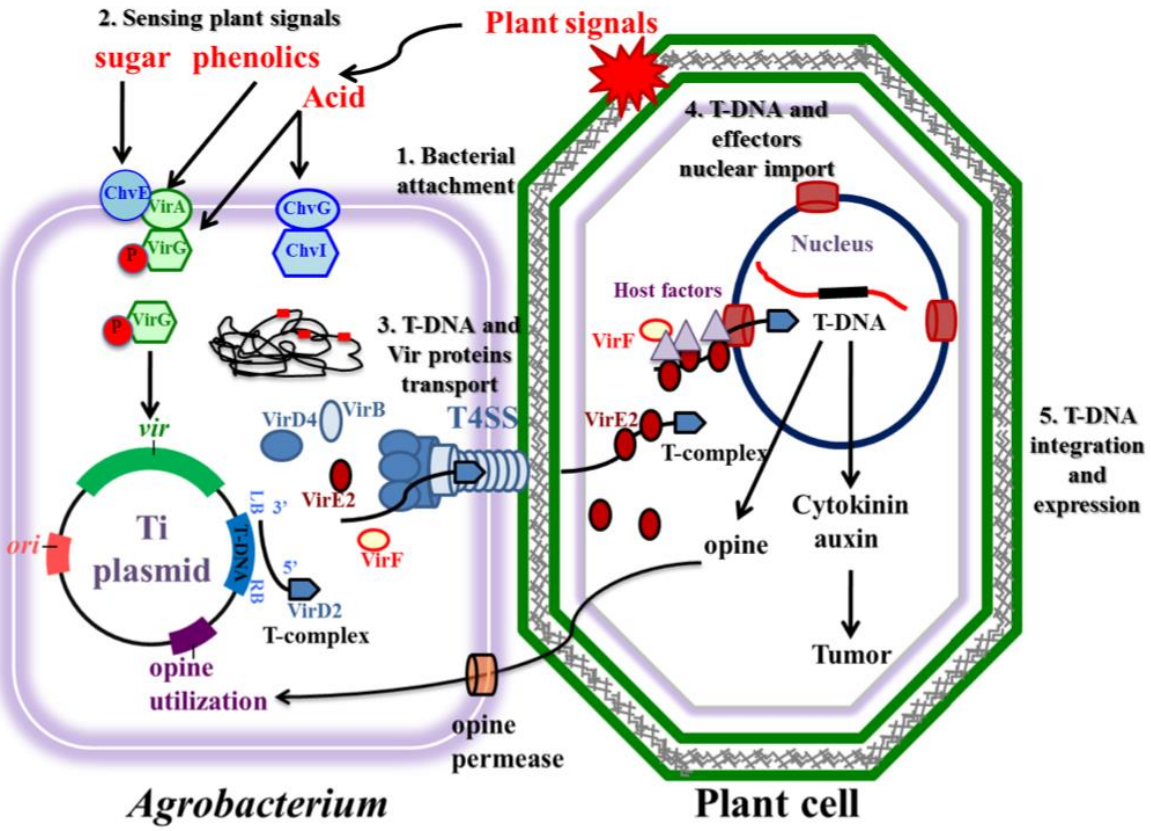
Plant Cell Protein Expression

Agrobacterium tumefaciens Plant Cell Transformation

The most common method for plant genetic engineering today is transformation via *Agrobacterium tumefaciens*. Discovery of *Agrobacteria* began in 1907 when plant pathologists Erwin Smith and Charles Townsend identified *Bacterium tumefaciens* as the cause of the plant disease called crown gall.[2] It wasn't until 1974, when researcher Ivo Zaenen[3] discovered the plasmid responsible for the abnormal growth. The discovery would spark a decade of progress to understand the genes, signals and evolutionary incentive behind tumor formation. The bacterium infection causing the gall inhabits the soil and enters the open wounds of plants to deliver its DNA.[4] The bacterium's tumor-inducing plasmid is delivered to the plant nucleus and integrated into the plant's genome.

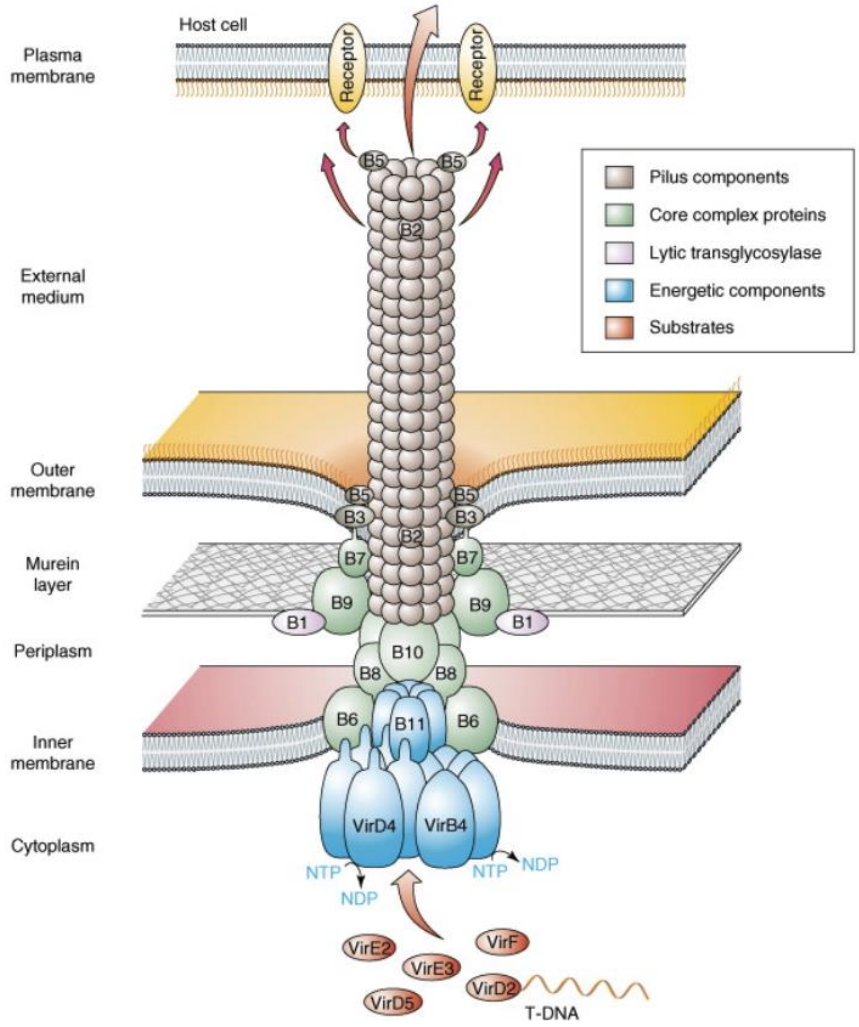
Bacterium tumefaciens' effectiveness in inserting its foreign DNA provided the important tool to genetically modify plants. The *Agrobacterium* presented several beneficial characteristics including the ability to grow rapidly in simple medium and be genetically modified.

Exhibit I – Transformation of Plant Cell via *Agrobacterium*[5]



[2] Nester EW (2015) Agrobacterium: nature's genetic engineer. *Front. Plant Sci.* **5**:730. doi: 10.3389/fpls.2014.00730
[3] Zaenen, I., *et al.* Supercoiled circular DNA in crown-gall inducing Agrobacterium strains. Journal of Molecular Biology. 15 June 1974, Pages 109-116, IN19, 117-127
[4] Hau-Hsuan Hwang, Manda Yu, Erh-Min Lai "*Agrobacterium*-Mediated Plant Transformation: Biology and Applications," The Arabidopsis Book, 2017(15), (20 October 2017)
[5] Hau-Hsuan Hwang, Manda Yu, Erh-Min Lai "*Agrobacterium*-Mediated Plant Transformation: Biology and Applications," The Arabidopsis Book, 2017(15), (20 October 2017)

Exhibit II – Model of *Agrobacterium* T4SS[6]



The mechanism of transformation begins with *A. tumefaciens* attachment to the plant cell. Via membrane receptors, various plant-cell compounds are sensed. The compounds are unique to and secreted by damaged plant cells, such as sap and phenolic compounds and lead to the phosphorylation of specific genes that then proceeds to activate transcription of the Agrobacterium's internal Tumor inducing (Ti)-plasmid to express the other virulence region proteins. Genes are transferred to the plant cells using Transfer (T)-DNA, which identifies the sequence to be transferred into the plant genome. Virulence genes are also required to transfer the foreign DNA to the plant genome but they remain in place. The sequence of T-DNA that contains the crown gall instructions is replaced with the genes of interest.

[6] Steffen Backert, Remi Fronzes, Gabriel Waksman, VirB2 and VirB5 proteins: specialized adhesins in bacterial type-IV secretion systems?, Trends in Microbiology, Volume 16, Issue 9, 2008, Pages 409-413, ISSN 0966-842X, https://doi.org/10.1016/j.tim.2008.07.001.

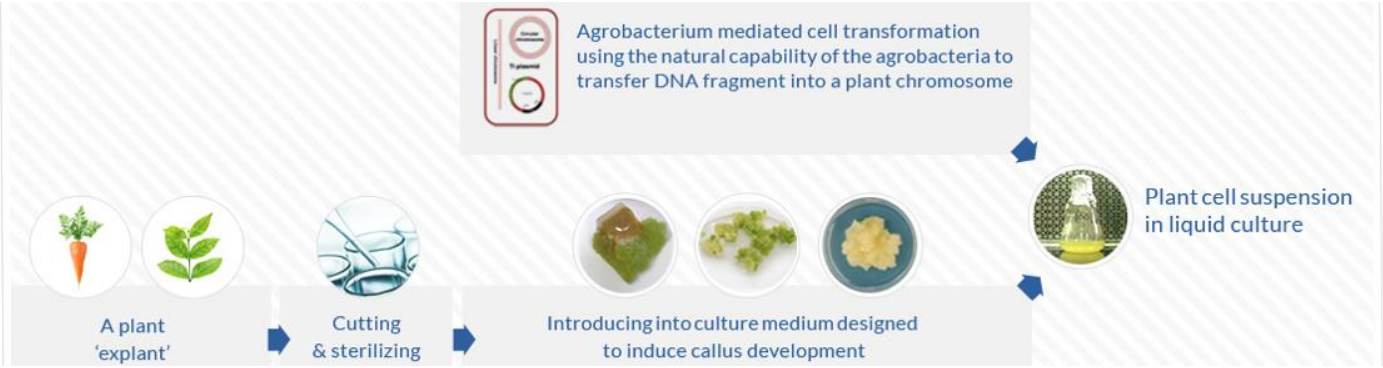
ProCellEx

Since the discovery of *A. tumefaciens,* the bacterium's abilities have been adapted to work on algae, fungi and even human cells. ProCellEx is based on *Agrobacterium* transformation of highly engineered plant cells. The specific cell type is proprietary. Plant-based expression system confer several benefits which we enumerate below.[7]

In comparison with other expression systems, ProCellEx:

1. Can tolerate a wider range of culturing conditions and is not susceptible to infections by human or animal pathogens;
2. Does not require a complex culture medium in contrast to the special supplements that mammalian cells require to grow;
3. Can be grown in polyethylene disposable bioreactors which require less investment, lower maintenance and are scalable versus stainless steel bioreactors;
4. May be able to express certain proteins with post translational modification that are difficult to express in other systems, even mammalian systems, while maintaining the advantages of a plant-based system;
5. Can side-step protocol-specific patents or other intellectual property rights of third parties for the production of recombinant proteins;
6. Allows for more rapid platform speed, enabling rapid batch testing of clinical material.

Exhibit III – *Agrobacterium* Transformation of Plant Cell for Expression.[8]



Scale production on the ProCellEx platform begins with the selection of an already transformed strain from the cell bank. Growth is performed in cell culture amplification and once a critical level has been reached, the cells' production of the therapeutic proteins occurs in the bioreactors' production phase. Harvesting the production begins with separation and crude processing and ends with column purification. While initial production of taliglucerase alfa was done with carrot cells, Protalix' ProCellEx manufacturing system now uses the *Nicotiana tabacum* bright yellow 2 (BY2) cell line.

[7] https://www.thermofisher.com/us/en/home/life-science/protein-biology/protein-biology-learning-center/protein-biology-resource-library/pierce-protein-methods/overview-protein-expression-systems.html
[8] Source: Protalix website, http://protalix.com/technology/procellex-platform/

Indications

Gaucher Disease

Gaucher Disease (GD) results from deficiency of glucocerebrosidase enzyme, driven by glucocerebrosidase (GBA) gene mutation, resulting in the pathological accumulation of cells in various organs in the body. Type 1 GD is the most common and is treated with enzyme replacement. GD type 2 and 3 have early onset brain involvement that progressively worsens over time; these types are sometimes known as neuronopathic Gaucher Disease.[9] GD is an autosomal recessive disease meaning both parents must be carriers of the gene creating a 50% chance that the child will be an asymptomatic carrier and a 25% chance that the child will have the disease. Diagnosis requires measuring the enzyme activity of glucocerebrosidase and can also involve genetic testing.

Type 1 GD (GD1) is the most common form of the disease in western countries where approximately 95% of GD patients have type 1 and some are asymptomatic. GD1 is limited to peripheral maladies and the brain is unaffected. The disease is treated with enzyme replacement therapy (ERT) or substrate reduction therapy (SRT). Primary symptoms include liver and spleen enlargement. Other symptoms include bone marrow fibrosis, which negatively impacts the production of red blood cells leading to anemia and fatigue and white blood cells causing leukopenia. People of Ashkenazi Jewish descent are especially prone to GD1 with an estimated prevalence of 118 per 100,000 people.

Type 2 GD (GD2), which is also known as acute infantile neuronopathic GD, has the earliest onset and is characterized by buildup of glucocerebroside in the brain. Symptoms appear within the first three to six months of life. This type is fatal within two years. In addition to the symptoms associated with type 1, those with type two also suffer from loss of motor skills, decrease in muscle tone, muscle spasms and trouble swallowing. The symptoms can lead to severe feeding and breathing difficulties which may lead to death in the first few years of life.

Type 3 GD (GD3) is known as chronic neuronopathic GD and has later and more gradual onset compared with GD2. People with this type can survive into adulthood. GD3 is more common than GD1 in the Middle East, India, China and other Asian countries. The symptoms for GD3 are varied and include seizures, eye movement disorders, cognitive and coordination issues, enlarged liver and spleen, respiratory problems and blood disorders. Due to the prolonged duration of GD3, skeletal irregularities are present that do not appear in GD2.

Neurologic pathology dominates GD2 and GD3. There is no effective treatment available for GD2. Only non-neurological symptoms can be treated with enzyme replacement therapy for GD3 patients; the enzymes do not penetrate into the brain.

Epidemiology

According to Nalysnyk *et al.*, GD2 and GD3 incidence is between one in 100,000 and one in 300,000, with studies varying in their estimates. Combined, standardized prevalence rates for GD2 and GD3 were 0.34 in the Czech Republic, 0.26 in the Netherlands and 0.55 in Portugal, per 100,000, respectively. At the lower end of this estimate, and assuming global total births of approximately 140.7 million in 2020,[10] approximately 470 births per year will have neuronopathic GD. Assuming average life expectancy of one year, prevalence of GD2 is, again, approximately 470 infants.[11] Estimates do not distinguish between GD2 and GD3. The ICGG Gaucher Registry reports 6%[12] worldwide prevalence of neuronopathic GD, the majority of whom are, based on the analysis above, likely GD3. Gaucher disease is a $1.6 billion[13] global annual therapeutic market that includes Sanofi's Cerezyme, Shire's (acquired by Takeda) Vpriv, Sanofi's Cerdelga and Protalix' Elelyso/Uplyso.

[9] https://www.gaucherdisease.org/about-gaucher-disease/what-is/type-2-3/
[10] https://ourworldindata.org/births-and-deaths
[11] https://www.gaucherdisease.org/about-gaucher-disease/what-is/type-2-3/
[12] Nalysnyk finds this an underestimate as prevalence of GD3 is higher than GD1 in the Middle East and Asia.
[13] Source: Evaluate Pharma including 2020 estimated revenues for Cerezyme, Vpriv, Cerdelga and Elelyso.

Pathophysiology
Gaucher Disease is an inherited lysosomal storage disorder (LSD). It results from deficiency of lysosomal enzyme acid β-glucosidase, driven by GBA gene mutation. Due to the lack of the enzyme, sphingolipid glucosylceramide accumulates in the lysosomes of macrophages; these engorged cells are known as Gaucher cells.[14,15] The accumulation of these Gaucher cells is the root of the symptomology and morbidity of the condition. Gaucher cells will concentrate in the liver, spleen, bone and bone marrow and, depending on the type of GD, the brain, causing organ inflammation and dysfunction.

Standard of Care
The most common treatment for Gaucher Disease is enzyme replacement therapy. The enzyme typically supplemented is imiglucerase (Cerezyme), which makes up over half the market. Substrate reduction therapy (SRT) is another method to control Gaucher Disease that reduces the amount of GL-1 produced. The two SRT available for Gaucher Disease are miglustat (Zavesca) and eliglustat (Cerdelga), which are small molecules marketed by Actelion and Genzyme, respectively.

Exhibit IV – Gaucher Sales (in Millions)[16]

Gaucher sales	2020	% of Total	Company
Cerezyme	$824.0	48%	Sanofi
Vpriv	$357.0	21%	Shire
Cerdelga	$271.0	16%	Sanofi
Zavesca	$129.0	8%	JNJ
Elelyso	$126.0	7%	Protalix

Fabry Disease

Fabry disease is a rare genetic disorder driven by a defective gene. It is also an X-linked inherited disease, characterized by deficient activity of the lysosomal α–Galactosidase–A enzyme.[17] The enzyme is responsible for metabolizing globotriaosylceramide (GL-3) and without the enzyme, the result is a progressive accumulation of GL-3 throughout the body. Symptoms are wide ranging, from mild to severe, and can include potentially life-threatening consequences such as kidney failure, heart attacks and strokes.

Epidemiology
Fabry disease prevalence has been estimated to be 1 in 40,000 people, with prevalence in Caucasians as high as 1 in 17,000.[18] Because Fabry disease is a sex-linked disease located on the X chromosome, men, who lack a second X chromosome, are more likely to have the disease (hemizygote). Interestingly, heterozygous females can also present with features of Fabry disease.[19] Mean age of stroke onset in hemizygotic men is between 29-38 years of age while heterozygotic females present strokes around the age of 40-43. Other symptoms present in males and females as young as nine and 13, respectively.

Pathophysiology
Fabry disease is driven by gene mutation of the GLA gene located on the X-chromosome making the disease not only hereditary, but sex-linked. Heterozygous females will typically have milder symptoms and later age of onset compared to males. The GLA gene is located at Xq21.3-q22.[20] Mutation of the GLA gene causes deficient activity of the alpha-galactosidase A (α-GAL A). This enzyme metabolizes the cerebroside trihexoside globotriaosylceramide (GL-3). Without properly functioning alpha-galactosidase A, GL-3 accumulates in cells and tissues throughout the body. As it accumulates, tissues swell and endothelial cells proliferate. Specifically, within the cell, GL-3 accumulates in lysosomes where α-GAL A typically works: organelles that are responsible for digesting and recycling cellular waste and debris, hence Fabry disease's classification as a Lysosomal Storage Disease. As the lysosomes accumulate GL-3, they grow, interfering with cell function, until entire tissues and organs stop

[14] Nalysnyk L, Rotella P, Simeone JC, Hamed A, Weinreb N. Gaucher disease epidemiology and natural history: a comprehensive review of the literature. *Hematology*. 2017;22(2):65-73. doi:10.1080/10245332.2016.1240391
[15] https://www.gaucherdisease.org/about-gaucher-disease/what-is/
[16] Source: Evaluate Pharma, accessed November 2020 and Zacks SCR.
[17] https://www.fabrydisease.org/index.php/about-fabry-disease/what-is-fabry-disease
[18] https://emedicine.medscape.com/article/1952086-overview#a3
[19] https://emedicine.medscape.com/article/1952086-overview#a6
[20] https://emedicine.medscape.com/article/1952086-overview#a2

functioning. The changes in endothelial cells, blood flow in the brain and peripheral vessels has been documented using MRI, PET, transcranial Doppler imaging (TCD) and plethysmography.[21]

The swelling creates variation in pressure and the properties of blood vessels, causing them to dilate and elongate, with the vertebrobasilar arteries at highest risk of dilation-based arteriopathy; small penetrating arteries commonly become narrowed and blocked and cerebral infarcts result from the blockage of the blood vessels.[22] Decreased levels of thrombomodulin and increased plasminogen activator inhibitor appear to create a prothrombotic state increasing coagulation, contributing to the 10-24% of stroke occurrence in Fabry patients. Non-ischemic, pressure-related complications of dilated intracranial arteries include hydrocephalus, trigeminal neuralgia, cranial nerve palsies and optic atrophy.[23]

Morbidity and mortality in Fabry disease are driven primarily by renal and heart failure, and stroke. Stroke presents in many Fabry cases. Cerebrovascular complications are common and the lesions increase with age. Heart failure, left ventricular hypertrophy, conduction and valve issues and myocardial infarctions can be manifested as well. Proteinuria and progressive renal failure result from GL-3 accumulation in the kidneys' glomeruli and tubules. CNS issues include hemiparesis, vertigo, diplopia, dysarthria, hemianopia and sensory loss. Death, as a result of the aforementioned complications, typically occurs between the ages of 40 and 50.

Standard of Care

There is no cure for Fabry Disease. The condition is managed with the supplementation of functioning enzymes, or Enzyme Replacement Therapy (ERT), similar to other lysosomal storage disorders. The leading ERT for Fabry is agalsidase beta (Fabrazyme), administered intravenously, biweekly. Male patients may be placed on ERT very early on in the diagnosis to avoid damage to the kidneys that begins asymptomatically.[24] In 2018, the FDA approved migalastat (Galafold) that is orally administered which is used in patients that present misfolded enzyme. The drug assists the body's mutant α-GAL A to function by shifting the folding towards the proper conformation and is effective in fewer than half of Fabry patients. Despite only working in a subset of the Fabry population, efficacy of migalastat can be predicted through genetic analysis. Symptom management includes prescription of anti-seizure medications, ACE inhibitors, gastrointestinal medication, skin treatments and hearing aids to address the wide variety of symptoms that present with Fabry.

Exhibit V – Fabry Sales (in Millions)[25]

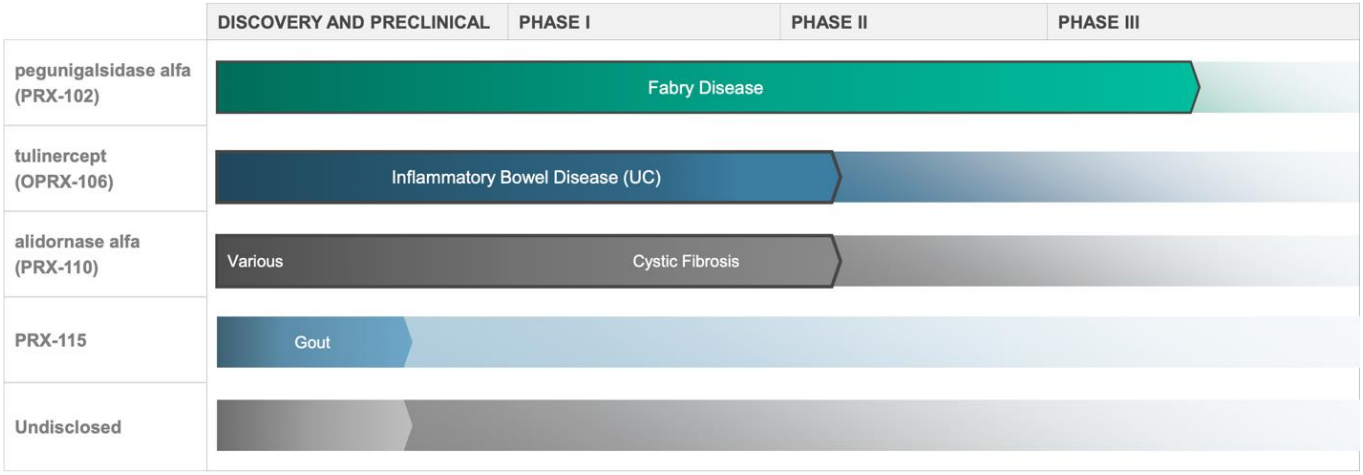
Drug	2020 Sales (MM)	Market Share	Company
Fabrazyme	$934.0	52%	Sanofi
Galafold	$255.0	14%	Amicus
Replagal	$605.0	34%	Shire/Takeda

[21] Wilcox WR, Banikazemi M, Guffon N, Waldek S, Lee P, Linthorst GE, et al. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am J Hum Genet. 2004 Jul. 75(1):65-74.
[22] https://emedicine.medscape.com/article/1952086-overview#a2
[23] https://emedicine.medscape.com/article/1952086-overview#a2
[24] https://www.webmd.com/a-to-z-guides/fabry-disease-treat#1
[25] Source: Evaluate Pharma, accessed November 2020 and Zacks SCR.

Commercialized Products and Candidates

Protalix has one product that is being marketed by partners Fiocruz and Pfizer and another in development that will be commercialized by Chiesi Rare Disease once approved. Its most advanced in-development candidate, PRX-102, is the subject of a biological license application (BLA) that has been submitted to the FDA with a target action date of April 27, 2021. Protalix has additional programs that we believe will be pursued either through the efforts of partners or internally once PRX-102 generates revenues.

Exhibit VI – Protalix Clinical Development Pipeline[26]



Taliglucerase alfa (Elelyso/Uplyso)

Taliglucerase alfa was Protalix' first commercialized product. It was approved by the FDA in 2012 as injectable enzyme replacement therapy (ERT) for the long-term treatment of adults with type 1 Gaucher disease. In August 2014, taliglucerase alfa was approved for injection for pediatric patients. The therapy is now approved in over 20 markets.

Commercialization

Protalix has licensed global rights for taliglucerase alfa to Pfizer in all markets except Brazil. Under the terms of the license, Protalix manufactures taliglucerase alfa for Pfizer while Pfizer retains 100% of revenue and reimburses 100% of direct costs. The license agreement is set for 10 years and Pfizer retains the right to extend the supply period for two additional 30-month periods.

Protalix maintains distribution rights in Brazil where taliglucerase alfa is marketed as Uplyso. Distribution in Brazil is via supply and technology transfer agreement with Fiocruz, an arm of the Brazilian Ministry of Health (MoH). In 2019, Brazilian MoH sales amounted to $9.1 million.

Pegunigalsidase alfa (PRX-102)

Pegunigalsidase alfa (PRX–102) is a recombinant α-Galactosidase-A enzyme. Protalix uses its ProCellEx platform to express the enzyme and then chemically modifies the enzyme via unique pegylation. Protein sub-units are co-valently bound via chemical cross-linking using short PEG moieties, resulting in a molecule with unique pharmaco-kinetic parameters. In clinical studies, PRX–102 has demonstrated a circulatory half-life of approximately 80 hours. Protalix designed PRX–102 to address the continued unmet clinical need in Fabry patients. Due to the chronic nature of Fabry, patients must receive IV infusion of enzyme replacement therapy every two weeks, which is a significant burden. PRX-102, with its extended half-life, aims not only to be more effective, but also to reduce the frequency of doctors' visits by Fabry patients. PRX-102 is currently in a head-to-head study against current standard of care Fabrazyme. While this type of trial entails risks, if PRX-102 demonstrates superiority, it may gain additional market share and command a premium price.

[26] Source: Protalix Corporate Presentation September 2020

Clinical & Regulatory

Phase III clinical evaluation of PRX-102 has been accomplished via the studies designated BALANCE, BRIDGE and BRIGHT. In 2015, a Phase I/II trial set the foundation for the aforementioned, Phase III trials; patients that completed the Phase I/II clinical trial were allowed to continue treatment as part of a long-term study. The current lineup of Phase III studies evaluates two additional dosing configurations, 1 mg/kg biweekly, and 2 mg/kg monthly. The alternate dosing regimens examine the potential for better efficacy and safety and lower treatment burden compared with current standard of care, respectively.

BALANCE and BRIGHT studies have completed enrollment. Topline results from the BRIDGE study were released in May 2020 while the last patient's final visit in the BRIGHT study was in July 2020. On May 27, 2020, the BLA for PRX-102 was submitted under the Accelerated Approval pathway and on August 11 it was announced that the FDA had accepted the BLA and granted Priority Review designation with a target action date of January 27, 2021. The FDA expressed that due to COVID-19 related travel restrictions, it may not be able to conduct facility inspections prior to the announced Prescription Drug User Fee Act (PDUFA) date. In response, Protalix has requested a Type A meeting to seek resolution on this issue, with response expected November 2020.

Management reports only minimal impact from the pandemic on the Phase III trials of PRX-102; protocols were conducted in the patients' homes and many patients had already been treated. A few patients that completed the initial stage of the trial were not able to transfer into the study extension due to the pandemic restrictions; as a result the main trial was prolonged to allow for the continuation of treatment.

Phase I/II (2015) and Extension Study

Clinical evaluation of PRX-102 began in 2012 with a Phase I/II trial. It was a worldwide, multi-center, first-in-human, open label study designed to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics and efficacy across doses. Doses were administered via intravenous (IV) infusion biweekly for 12 weeks to symptomatic adults with Fabry disease who had not previously received enzyme replacement therapy (ERT) and then another nine months in the Phase II. The trial measured renal GL-3 inclusions, assessed by Barisoni Lipid Inclusion Scoring System (BLISS), plasma GL-3 and globotriaosylsphingosine (lyso-GL-3) and supportive clinical data. Sixteen patients (9 male and 7 female) completed the trial. The patients were enrolled into one of three dosing groups, 0.2 mg/kg, 1 mg/kg and 2 mg/kg in a dose ascending manner. An efficacy follow-up was conducted after six-month and twelve-month periods. The majority of the patients who completed the trial opted to continue receiving PRX-102 in an open-label, extension study, under which all patients receive 1 mg/kg of the drug.

Kidney biopsies, used to evaluate GL-3 accumulation, were available from 14 patients. 11 of 14 (78.6%) of the patients had ≥ 50% reduction in the average number of GL-3 inclusions per kidney proximal tubule cell (PTC) from baseline to six months. PRX-102 reduced kidney GL-3 inclusions burden and lyso-GL-3 in circulation. The overall results demonstrated a strong correlation between reduction of kidney GL-3 inclusions and the reduction of plasma lyso-GL-3 over six months of treatment.

Results showed that lyso-GL-3 levels decreased almost 90% from baseline for male patients and over 70% in female patients. Renal function remained stable with mean estimated glomerular filtration rate (eGFR) levels of 108.02 and 106.90 at baseline and 24 months, respectively, with annual eGFR slope of -1.8. Gastrointestinal symptoms including severity and frequency of abdominal pain and frequency of diarrhea showed improvement. Cardiac parameters evaluated included left ventricular mass, mass index and ejection fraction (EF), which remained stable with no cardiac fibrosis progression detected. Disease severity, as measured by the Mainz Severity Score Index (MSSI)[27] showed 40% improvement with an improvement in each of the individual MSSI parameters. The majority of adverse events were mild or moderate, and temporary. Within the first year of treatment, only 3 of 16 patients (<19%) produced antibodies against the enzyme, two of which had neutralizing antibodies. Production of anti-drug antibodies ceased after 12 months and were inconsequential when produced.

BALANCE

BALANCE is a Phase III clinical trial of PRX-102 in treated Fabry disease patients with ongoing renal failure. The trial is randomized, double blind against the active control, agalsidase beta (Fabrazyme). It is intended to evaluate renal function in Fabry patients with progressing kidney disease, previously treated with biweekly Fabrazyme infusion. Study duration is targeted to be 24-months. The 78 patients that enrolled in the trial had previously been treated with Fabrazyme for approximately one year, were on a stable dose of the medication for at least six months and presented an important kidney function deterioration. Patients were stratified by urinary protein to creatinine

[27] The Mainz Severity Score Index (MSSI) is a metric combining neurological, renal and cardiovascular parameters.

ratio (UPCR) of < or ≥ 1 g/g by spot urine sample. Then they were randomized 2:1 into arms of 1 mg/kg of PRX-102 and 1 mg/kg Fabrazyme arms ensuring that no more than 50% of the patients enrolled were female.

The primary endpoint is annualized rate of decline of eGFR slope, compared between PRX-102 and Fabrazyme. Cardiac assessment, lyso-GL-3 levels, pain, quality of life, immunogenicity, Fabry clinical events, pharmacokinetics and other parameters are also evaluated.

Protalix intends to conduct an interim analysis when the last enrolled patient reaches 12 months of treatment in order to test for non-inferiority, supporting anticipated regulatory filings with the European Medicines Agency (EMA). Patients will continue to be treated for a total of 24 months, after which the data will be analyzed to test for superiority in a final analysis of the study data. This final analysis will be used to support converting the accelerated approval into a traditional approval, if the May 2020 PRX-102 BLA submission results in an approval from the FDA under the Accelerated Approval pathway. The next data readout for BALANCE will be disclosure of interim results, expected in 1H:21.

BRIDGE

BRIDGE was an open label, switch-over study designed to evaluate the safety and efficacy of 1 mg/kg of PRX-102 infused every two weeks in Fabry patients. The 22 enrolled Fabry patients were previously treated with agalsidase alfa (Replagal) for at least two years and on a stable dose for at least six months prior to enrollment. Top line results were announced in May 2020.

Topline results showed significant improvement in renal function as measured by mean eGFR slope and disease course improvement in both male and female patients. PRX-102 was found to be well tolerated, with all adverse events transient. Two of the 22 enrolled withdrew early due to hypersensitivity reaction, and 20 of the patients successfully completed the 12-month treatment duration. Eighteen of the patients who completed the study opted to roll over to a long-term extension study and continue to be treated with PRX-102.

In the BRIDGE study, the mean annualized eGFR slope[28] of the study participants improved from -5.90 while on Replagal to -1.19 on PRX-102 in all patients. Male patients improved from -6.36 to -1.73 and female patients improved from -5.03 to -0.21. Baseline characteristics of the patients, ranging from ages 24 to 60 years, were as follows: mean eGFR 75.87 in males and 86.14 in females; mean residual leucocytes enzymatic activity was 4.8% of lab normal mean in males and 27.9% in females. Plasma lyso-GL-3 mean levels were elevated at baseline despite previous treatment 51.81 nM and 13.8 nM in males and females, respectively, with expected higher values in male patients. A continuous mean reduction in plasma Lyso Gb3 concentrations was observed until month 12.

Data from the interim analysis of the BRIDGE Study was included in the PRX-102 BLA submission to the FDA under the Accelerated Approval pathway. Management anticipates that the final analysis will be used to support a Marketing Authorization Application (MAA) with the EMA. Final results are expected in 4Q:20.

BRIGHT

BRIGHT is the third Phase III clinical trial of PRX-102 for the treatment of Fabry disease. The trial was completed in July 2020 and is in final stages of analysis and expected to read out in 2Q:21.[29] BRIGHT was a 12-month, open-label switch-over study designed to assess the safety, efficacy and pharmacokinetics of PRX-102 via intravenous infusions of 2 mg/kg administered every four weeks in up to 30 patients with Fabry disease. The patients had been previously treated with ERT (Fabrazyme or Replagal). The rationale for this open-label switch-over study was based on the pharmacokinetic profile of PRX-102. Phase I/II study data suggested that 2.0 mg/kg every four weeks would be effective in mild to moderate Fabry patients. The dosing regimen served as maintenance ERT for mild to moderate Fabry patients without severe clinical symptoms and with relatively slow disease progression, with opportunity to manage. To determine eligibility for participation in the study, candidates were screened to identify and select Fabry patients with a relatively stable clinical presentation and a slow disease progression. Patients who matched the criteria were enrolled in the study and switched from their current treatment of biweekly intravenous infusions to monthly 2 mg/kg of PRX-102 for 12 months.

[28] Units are mL/min/1.73m^2/year
[29] Protalix October 2020 corporate presentation.

Patients participating in the study were evaluated for various disease-related clinical symptoms and biomarkers, including rate of deterioration of the kidneys, while being treated with the once-monthly dosing regimen as measured by eGFR. Safety and tolerability of PRX-102 was also assessed. In February 2019, Protalix presented preliminary pharmacokinetic data from BRIGHT. The results demonstrated that PRX-102 was present and remained active in the plasma over the every 4 weeks infusion intervals. **The mean concentration of PRX-102 at day 28 was 138 ng/mL, showing that it was still present in the blood. In comparison, published data on Fabrazyme (1 mg/kg every 2 weeks) shows a mean concentration of 20 ng/mL at 10 hours post infusion.** In addition, the area under the curve (AUC) for PRX-102 was measured to be approximately 2,000,000 ng hr/mL over 28 days. Based on published data, the AUC of Fabrazyme is approximately 10,000 ng hr/mL. The AUC is a measure of both the duration and magnitude that a patient is exposed to a therapy. A preliminary safety analysis of 19 patients enrolled in the BRIGHT study was also conducted, and indicated that PRX-102 was well tolerated. Most of the patients who completed the study opted, with the advice of the treating physician, to continue in the follow on long-term extension study.

Partnerships

Protalix has entered into two exclusive global licensing and supply agreements for PRX-102 for the treatment of Fabry disease with Chiesi. The agreements have significant revenue potential for Protalix. Under the agreements, Protalix Ltd. has received $50.0 million in upfront payments and was entitled to development cost reimbursements of up to $45.0 million, up to more than $1.0 billion in potential milestone payments and tiered royalties of 15% - 40% inside the United States and 15% - 35% outside the United States.

On October 19, 2017, Protalix Ltd. and Chiesi entered into the Chiesi Ex-US Agreement pursuant to which Chiesi was granted an exclusive license for all markets outside of the United States to commercialize PRX-102. Under the Chiesi Ex-US Agreement, Chiesi made an upfront payment to Protalix Ltd. of $25.0 million in connection with the execution of the agreement and Protalix Ltd. was entitled to additional payments of up to $25.0 million in development costs in the aggregate, capped at $10.0 million per year. Protalix Ltd. is also eligible to receive additional payments of up to a maximum of $320.0 million in regulatory and commercial milestone payments. Protalix will manufacture all of the PRX-102 needed for all purposes under the agreement, subject to certain exceptions, and Chiesi will purchase PRX-102 from Protalix subject to certain terms and conditions. Chiesi is required to make tiered payments of 15% to 35% of its net sales, depending on the amount of annual sales, as consideration for the supply of PRX-102.

On July 23, 2018, Protalix Ltd. entered into the Chiesi US Agreement with respect to the development and commercialization of PRX-102 in the United States. Protalix Ltd. received an upfront, non-refundable, non-creditable payment of $25.0 million from Chiesi and was entitled to additional payments of up to a maximum of $20.0 million to cover development costs for PRX-102, subject to a maximum of $7.5 million per year. Protalix is also eligible to receive additional payments of up to a maximum of $760.0 million, in the aggregate, in regulatory and commercial milestone payments. Chiesi will also make tiered payments of 15% to 40% of its net sales under the Chiesi US Agreement to Protalix Ltd., depending on the amount of annual sales, subject to certain terms and conditions, as consideration for product supply.

Tulinercept (OPRX-106)

Tulinercept is expressed via the ProCellEx platform. It is a recombinant human tumor necrosis factor receptor II fused to an IgG1 Fc domain (TNFRII-Fc). TNF-alpha is an inflammatory cytokine produced by macrophages during acute inflammation. By joining the TNF receptor and the Fc domain, OPRX-106 can bind TNF-alpha and activate the immune system.

When administered orally and while passing through the digestive tract, the plant cells function as a natural delivery vehicle, protected by the cellulose of the cell wall, making them resistant to degradation. Oral administration has the added benefit of localized administration in the gut, avoiding the systemic exposure that occurs when TNF-α inhibitors are injected or intravenously infused. Tulinercept may be safer with less immunogenicity, avoiding the activation of anti-drug antibodies, which has led to the loss of response in competing TNF-α treatments.

Clinical
Positive results from Phase II clinical trial of OPRX-106 in ulcerative colitis were announced in March and June of 2018. The trial was randomized, open label and had two arms.

A total of 24 patients with active mild to moderate ulcerative colitis were enrolled in the study with 18 patients completing it. Individuals were randomized to receive 2 mg or 8 mg of OPRX-106, administered orally, once daily, for 8 weeks. The average baseline Mayo score was 7.1 (from a scale of 0-12) and the average baseline mucosal endoscopy sub score was 2.1 (from a scale of 0-3). Of the 18 patients, 89% had a baseline Mayo score between 6 and 9, meeting the criteria of moderate disease activity and 84% had a baseline mucosal endoscopy sub score of 2 and above, indicating moderate to severe disease based on mucosal appearance. Following 8 weeks treatment, 67% of patients experienced a clinical response in each of the 2 mg dose and 8 mg dose cohorts, 44% of patients experienced a clinical remission in the 8 mg dose and 11% in the 2 mg dose for an overall average of 28%.

Efficacy was also observed in mucosal healing as measured by endoscopy. 61% of patients experienced mucosal improvement and 33% of patients experienced mucosal healing with consistent trends between both arms. 89% of patients showed an improvement in Mayo score in both dosing groups, with an average decrease of 46% at week 8 in the 8 mg dose and 40% in the 2 mg dose. In addition, all of the patients also showed an improvement in at least one of the other efficacy parameters. In terms of immunogenicity, no anti-drug antibodies were detected, nor was systemic absorption evident. Overall, OPRX-106 was safe and well tolerated with only temporary mild to moderate adverse events, and no serious adverse events.

Alidornase alfa (PRX-110)

Alidornase alfa is recombinant human deoxyribonuclease I (DNase I) expressed via the ProCellEx platform. Administration is via inhalation for direct application to the congested lung. DNase I therapy can act as a mucus thinning agent (mucolytic) to help with clearance from the airways to improve lung function and reduce the chances of infection. Disintegrating inflammatory cells, namely neutrophils, release DNA into the sputum, which polymerizes and is present at high concentrations contributing to the viscosity of the sputum. DNase I degrades the DNA, thus reducing the viscosity of the mucus.[30] Alidornase alfa is in development for the treatment of Cystic Fibrosis.

PRX-115

PRX-115 is a uricase that Protalix can express using the ProCellEx platform. The candidate is among the earliest stages in Protalix' portfolio, and is targeting gouty arthritis.

[30] Pressler T. (2008). Review of recombinant human deoxyribonuclease (rhDNase) in the management of patients with cystic fibrosis. *Biologics : targets & therapy*, *2*(4), 611–617. https://doi.org/10.2147/btt.s3052

Peers, Competitors & Competing Technologies

Protalix' peers, competitors and competing technologies are defined in terms of candidates and indications.

Gaucher Disease
Elelyso is marketed globally through partnerships with Fiocruz Brazil and Pfizer Inc. as treatment for Gaucher Disease. The most common treatment for Gaucher Disease is enzyme replacement therapy (ERT) and includes Cerezyme (imiglucerase), which is a recombinant analogue of β-glucocerebrosidase and is produced by Sanofi Genzyme. Another commercially available glucocerebrosidase derivative is Vpriv (velaglucerase alfa), manufactured by Shire. Cerezyme holds a dominant market share in the US and around the world. Substrate reduction therapy (SRT) is another way to control Gaucher Disease that reduces the amount of glucosylceramide (GL-1) produced. The two SRT available for Gaucher Disease are miglustat (Zavesca) and eliglustat (Cerdelga), which are small molecules marketed by Actelion and Sanofi Genzyme, respectively.

Fabry Disease
Fabry Disease is managed with the supplementation of functioning enzymes, or ERT, similar to treatment for other storage disorders. The leading ERT for Fabry is Sanofi's agalsidase beta (Fabrazyme). If PRX-102 is approved for market, it will contend directly with Fabrazyme. Preliminary clinical data suggests superiority of PRX-102 to Replagal[31] and Fabrazyme, as evidenced by improvement in mean annualized eGFR slope in BRIDGE, and orders of magnitude higher AUC[32] in BRIGHT. The PEGylation that is unique to PRX-102 appears to extend the half-life of the enzyme supplement, potentially enabling better efficacy and less frequent dosing.

Recently, in 2018, the FDA approved Galafold (migalastat), an orally administered product. The drug is a chaperone for mutant alpha galactosidase A (α-GAL A) that also helps the enzyme to fold into the correct conformation, enhancing function, but is only effective in fewer than half of Fabry patients who have the specific, amenable mutation.

Symptom-addressing medication is not in direct contest with PRX-102, and may be used concurrently if and as the disease progresses. If efficacy is proven in the clinic and the candidate approved, PRX-102 stands to challenge standard of care and would provide patients with an option for less frequent, more effective dosing, alleviating significant patient burden.

Inflammatory Bowel Disease (IBD)
IBD is a complex pathology without cure which has a myriad of treatments that both alleviate the condition and address symptoms. Standard of care for IBD typically begins with the use of anti-inflammatory medications, including corticosteroids, aminosalicylates (5-ASA), such as mesalamine, balsalazide and olsalazine and janus kinase (JAK) inhibitors, such as tofacitinib. Immune system suppressors are sometimes prescribed, including azathioprine, mercaptopurine, cyclosporine and methotrexate. With increasing severity, patients are treated with biologics, the most notable of which are tumor necrosis factor (TNF)-alpha inhibitors. The leading TNF-alpha inhibitor is infliximab (Remicade), with next generation TNF antagonists including adalimumab (Humira), golimumab (Simponi) and certolizumab pegol (Cimzia).[33,34] A Remicade biosimilar has also been approved, infliximab-dyyb (Inflectra). Unfortunately, some patients develop resistance to the therapy and produce antibodies against the anti-TNF inhibitor. As TNF-alpha inhibitors suppress the immune system, serious conditions may arise such as tuberculosis (TB), hepatitis B, pneumonia, herpes zoster, as well as skin cancer, malignant lymphoma, psoriasis, lupus-like syndrome, demyelinating disease, congestive heart failure, and hepatotoxicity.[35] Medications that address symptoms or complications include antibiotics like ciprofloxacin and metronidazole, and anti-diarrhea medications, pain relievers, iron supplements, and calcium and vitamin D supplements.

OPRX-106 is administered orally in contrast to other approved products in the market. Infliximab, adalimumab, golimumab and certolizumab pegol are administered via either IV infusion or subcutaneous injection. While effective, there are immunogenic risks, and a burden on the patient with many clinical visits for dosing. By circumventing much of the circulatory system, OPRX-106 is less likely to be immunogenic. An oral option could provide significant

[31] Replagal is marketed by Shire/Takeda
[32] Area under the curve, a measure of dosing exposure over time
[33] https://www.mayoclinic.org/diseases-conditions/inflammatory-bowel-disease/diagnosis-treatment/drc-20353320
[34] Park, S. C., & Jeen, Y. T. (2018). Anti-integrin therapy for inflammatory bowel disease. World journal of gastroenterology, 24(17), 1868–1880. https://doi.org/10.3748/wjg.v24.i17.1868
[35] Park, S. C., & Jeen, Y. T. (2018). Anti-integrin therapy for inflammatory bowel disease. World journal of gastroenterology, 24(17), 1868–1880. https://doi.org/10.3748/wjg.v24.i17.1868

patient relief in those who require monthly physician visits for dosing. Biologics include interleukin (IL) inhibitors, TNF inhibitors and anti-integrin. As research continues into the underlying mechanisms of inflammatory bowel disease (IBD), it is likely novel drug mechanisms will surface and compete with OPRX-106.

Alidornase alfa (PRX-110) for Cystic Fibrosis

Currently there is no cure for Cystic Fibrosis (CF), only the management of the condition. Close monitoring and early intervention are key to slowing the progression of the disease. The primary goals of managing CF include lung infections, removing and loosening mucus from lungs, treating and preventing intestinal blockage. Medications can include antibiotics to fight infection, anti-inflammatory medications to reduce pulmonary edema, and mucus thinning drugs or bronchodilators. To aid with digestion, pancreatic enzyme supplementation may better help nutrition absorption. Finally, stool softeners can help prevent bowel obstruction and constipation. As a DNase, PRX-110 may be used concurrently with other drugs that address the symptoms of CF, although, if PRX-110 is effective, the need to fight infection may be decreased.

Recently, medications that target cystic fibrosis transmembrane conductance regulator (CFTR) function have been approved. Various combinations of elexacaftor, ivacaftor, tezacaftor and lumacaftor exist on the market for various patient ages, with combination elexacaftor-ivacaftor-tezacaftor (Trikafta) regarded as a breakthrough therapy for CF.[36] There are over 2,000 known CFTR mutations and many patients have mutations that are currently ineligible for the offerings in this drug class.[37]

CFTR-targeting agents are available for treatment; however, the medications do not resolve existing viscous mucus and only act to improve CFTR function. Thus, PRX-110, if clinically tested and approved, may find its place in the routine management of symptoms with physical therapy in addition to drugs that directly target the condition.

Gout

Treatment of gout typically is medication-based. Nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine and corticosteroids can help treat and prevent attacks. NSAIDs and colchicine can both be used for the acute and prophylactic treatment of gout attacks. Corticosteroids address the inflammation associated with the condition. Medications also exist to inhibit the production of uric acid. The two top revenue generating drugs in the space, Krystexxa and Uloric, both have black box warnings. Krystexxa by Horizon Therapeutics is an enzyme that breaks down the uric acid associated with gout, allowing it to be passed through the urine. Uloric (febuxostat) and allopurinol are xanthine oxidase inhibitors which limit the amount of uric acid produced, reducing the chances for uric acid to crystallize. Uloric is intended for gout patients that cannot tolerate allopurinol. Other medications, called uricosurics, improve the kidneys' ability to remove uric acid from the blood and include Probalan and Zurampic (discontinued). Because PRX-115 differs in its mechanism of action, it is not necessarily in direct competition with these drugs, and could work synergistically with them.

Exogenous uricase can catalyze the conversion of uric acid into allantoin, which is more soluble in blood, preventing crystallization. Humans do not produce uricase; however, supplementation with uricase is an option.[38] Uricase supplementation is administered twice weekly by intravenous injection in a healthcare setting and can be immunogenic. Via PEGylation, Protalix hopes to augment the efficacy and hopefully reduce the frequency of dosing needed, alleviating both patient and clinical burden. If approved, PRX-115 would likely compete directly with Pegloticase, a porcine uricase approved by the FDA in September 2010.[39]

[36] Ridley, K., & Condren, M. (2020). Elexacaftor-Tezacaftor-Ivacaftor: The First Triple-Combination Cystic Fibrosis Transmembrane Conductance Regulator Modulating Therapy. *The journal of pediatric pharmacology and therapeutics: JPPT: the official journal of PPAG*, *25*(3), 192–197. https://doi.org/10.5863/1551-6776-25.3.192

[37] https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis

[38] BMJ 2018;362:k2893

[39] https://www.hopkinsarthritis.org/arthritis-info/gout/gout-treatment/

Exhibit VII – Peers and Competitors[40]

Ticker	Company	Price	MktCap (MM)	EV (MM)	Therapeutic Area
ABBV	AbbVie	$107.28	$189,400	$263,732	Humira (IBD),
FOLD	Amicus	$23.18	$6,040	$5,920	Galafold (migalastat)
068270	Celltrion	$350.60	$42,440	$42,311	Remsima for ulcerative colitis, Crohn's
COPN	Cosmo	$93.71	$1,378	$1,289	Colonoscopic lesion detection
RHHBY	Genentech	$42.68	$292,294	$312,580	Pulmozyme for CF
GILD	Gilead Sciences	$61.56	$77,167	$82,070	Cayston for CF
GSK	GSK	$37.50	$94,070	$118,306	CF respiratory disorder products
HZNP	Horizon Pharma	$71.72	$15,829	$15,103	Krystexxa
IBIO	iBio	$1.49	$271	$220	Plant based expression systems
JNJ	Johnson&Johnson	$150.27	$395,592	$397,491	Remicade, Simpoint & Stelara
MYL	Viatris	$16.27	$21,118	$32,817	TOBI Podhaler & Liquid for CF
PFE	Pfizer	$40.34	$224,226	$252,099	Xeljanz
PXS	Pharmaxis	$0.98	$21	$76	Bronchitol for CF
PTGX	Protagonist Tx	$22.41	$857	$663	Janssen collab for PTG-200 for Crohn's
SNY	Sanofi Genzyme	$51.03	$127,786	$127,786	Cerezyme, Cerdelga, Fabrazyme
TAK	Takeda Shire	$18.75	$59,114	$96,575	Vpriv, Replagal, Amicus, Entyvio
UCB.BR	UCB	$107.51	$21,045	$23,094	Cimzia
VRTX	Vertex Pharma	$228.32	$59,372	$53,767	CF portfolio:Trikafta,symdeko,orkambi,kalydeco+R&D
pvt	Actelion				Zavesca or miglustat for GD
pvt	Greenovation Bio				Biologics from plant based expression systems
pvt	Medicago				Plant expressed vaccines
PLX	Protalix	$3.48	$116.0	$128.2	Plant cell-based expression, ERT

[40] Price and market capitalization data in USD and is as of December 4, 2020. Source: Zacks Research System.

Intellectual Property

Protalix holds a broad intellectual property portfolio with more than 85 patents granted and 40 patents pending globally as of June 30, 2020. In 2016 the company received patents in the family "Large Scale Disposable Bioreactor," which adds to the ten patents already granted under this heading. Other patent families that were built upon include "Stabilized Alpha- Galactosidase and Uses Thereof" adding to the 18 patents previously granted and "Nucleic Acid Construct for Expression of Alpha-Galactosidase in Plants and Plant Cells," adding to the seven previously granted. Protalix' strategy is to pursue patents on methods of production, compositions of matter and methods of use. In addition to the intellectual property protections, the company also relies on internal knowledge, continuing technological innovation, licensing and partnership opportunities to develop and maintain its competitive position. Below we summarize the key Protalix patents relied upon for the company's commercialized and development portfolio.

Exhibit VIII – Key Protalix Patents[41]

Title
Production of High Mannose Proteins in Plant Culture
Cell-Tissue Culturing Device, System and Method
System and Method for Production of Antibodies in Plant Cell Culture
Mucosal or Enteral Administration of Biologically Active Macromolecules
Saccharide-containing Protein Conjugates and uses thereof
Saccharide-containing Protein Conjugates and uses thereof
Large Scale Disposable Bioreactor
Stabilized Alpha-galactosidase and uses thereof
Nucleic Acid Construct for Expression of Alphagalactosidase in Plants and Plant Cells
Therapeutic Regimen For The Treatment of Fabry Using Stabilized Alpha-galactosidase
Dry Powder Formulations of Dnase 1
DNase I Polypeptides, Polynucleotides Encoding Same, Methods of Producing DNase I and uses thereof in Therapy
Inhalable Liquid Formulations of Dnase I
Modified DNase and uses thereof
Chimeric Polypeptides, Polynucleotides Encoding Same, Cells Expressing Same and Methods of Producing Same
TNF Alpha Inhibitor Polypeptides, Polynucleotides Encoding Same, Cells Expressing Same and Methods of Producing Same
Use of Plant Cells Expressing a TNF Alpha Polypeptide Inhibitor in Therapy
Chimeric Polypeptides, Polynucleotides Encoding Same, Cells Expressing Same and Methods of Producing Same

[41] Source: Protalix Corporate Filings.

Operational and Financial Results

Corporate Milestones

During 2020 Protalix achieved a number of milestones including a topline readout from the BRIDGE study, the raise of additional capital, and submission of a BLA to the FDA for PRX-102. Below we highlight these and other important recent and future milestones.

- Closing of $43.7 million private placement – March 2020
- Topline results from BRIDGE study and FDA submission – May 2020
- Appointment of Yael Hayon, Ph.D. as Vice President, Research and Development - June 2020
- Promotion of Einat Brill Almon, Ph.D. to Sr. Vice President and Chief Development Officer- June 2020
- Collaboration with SarcoMed for PRX-110 in Pulmonary Sarcoidosis - July 2020
- FDA: BLA for PRX-102 accepted – August 2020
- Completion of BRIGHT trial – August 2020
- Expanded access program launched for PRX-102 – October 2020
- ATM Equity Offering Sales Agreement with BofA Securities – October 2020
- BRIDGE final results – 4Q:20
- PRX-102 PDUFA date – April 2021
- BALANCE interim results – 1H:21
- Launch of PRX-102 – 3Q:21
- BRIGHT readout – 2Q:21
- Marketing Authorization Submission (EU) for PRX-102 – 4Q:21

Protalix' first operational announcement in 2020 shared the receipt of an agreement letter for an Initial Pediatric Study Plan (iPSP) for PRX-102 on February 6, 2020. Later in the month, Dr. David G. Warnock, principal investigator in the BALANCE Phase III clinical trial, presented topics related to PRX-102 at the 16th Annual WORLDSymposium 2020. Company representatives also participated in the 2020 BIO CEO & Investor Conference and Noble Capital Markets' Small & Microcap Investor Conference.

On March 12th, 2020, Protalix reported fiscal year 2019 results and announced the raise of $43.7 million through a private equity investment. On March 16th, Protalix announced a feasibility study with Kirin Holdings to produce a novel complex protein using the ProCellEx platform. Kirin agreed to provide research funding while Protalix scientists conduct cell line engineering and protein expression studies.

Protalix began May with a readout of positive topline results from BRIDGE Phase III trial for PRX-102 in Fabry Disease. At the end of May, Protalix and partner Chiesi Global Rare Diseases announced the submission of a Biologics License Application (BLA) for PRX-102 for treatment of adults with Fabry Disease via the FDA's Accelerated Approval pathway.

Protalix reported 1Q:20 results on June 1, 2020. On June 8th, the company announced the appointment of Yael Hayon, Ph.D. as Vice President of Research and Development bringing over a decade of pharma R&D experience in both scientific and administrative functions. At the end of July, Protalix and SarcoMed USA entered into a non-binding term sheet to potentially develop, produce and commercialize PRX-110, alidornase alfa for Pulmonary Sarcoidosis and related diseases.

2Q:20 financial results were published on August 10, 2020 followed two weeks later by the completion of the treatment phase of the BRIGHT clinical trial. In August, the FDA accepted the BLA for PRX-102. In early October Protalix and partner Chiesi Global Rare Diseases announced the launch of an expanded access program in the US for PRX-102 in Fabry disease. On October 29, Protalix reported 3Q:20 financials and provided a corporate update.

In the quarter ending September 30, 2020, Protalix recorded total revenues of $10.8 million. Sales of goods were $3.3 million, a decrease of $1.8 million (36%) from the same quarter last year. The contraction resulted from a timing difference in sales to Brazil, partially offset by an increase in Pfizer sales. Revenues from licensing and R&D services totaled $7.5 million for the period, declining 18% from 3Q:19 due to the completion of two of the three PRX-102 trials that were being funded by Chiesi. Cost of goods sold decreased 11% to $2.9 million versus 3Q:19, driven by change in cost structure as well as lower royalties paid to Israeli Innovation Authority. This produced a gross margin of 13.0%, compared to 2Q:20 gross margin of 49.9% and 3Q:19 gross margin of 37.5%. R&D expenses totaled $7.7 million, down $2.3 million from the prior year period. Completion of two of the PRX-102 trials reduced costs, as did a decrease in manufacturing expenditures. SG&A expense was $2.8 million, up 9% from 3Q:19. Financial expenses were $1.9 million declining 8% compared to the prior year period.

On September 30, 2020, Protalix held $13.5 million in cash and equivalents and $27.8 million in bank deposits. Cash burn was ($3.3) million in 3Q:20 and ($18.6) million for the first nine months of 2020. This compares to ($3.7) million in 3Q:19 and ($16.3) million in the first nine months of 2019. Management expects financial reserves to be sufficient to sustain the company for at least 12 months.

Risk Considerations

All investments contain an element of risk which reflects business uncertainty and opportunity. Some investments exhibit higher predictability, with current cash flows and established sales. These enterprises will have a lower level of perceived risk while other companies that are developing an undefined, new technology have a much higher level of perceived risk.

The biotechnology space includes companies at both ends of the spectrum, from mega-cap powerhouses that have multiple drugs currently generating revenues, to small operations with a handful of employees conducting pre-clinical studies. Many of the risks faced by the large and small biotechnology firms are similar; however, there are some hazards that are particular to smaller companies that have not yet established themselves or their products. Protalix falls in the middle of this spectrum with a platform validated by an FDA approved product and additional drug candidates in development. We review the principal risk categories faced by Protalix including pandemic, regulatory, commercialization, partnerships and access to capital.

Pandemic Risk

The pandemic has disrupted economic activity around the globe. Protalix management has identified impacts to the company's operations and a potential delay of inspections at manufacturing facilities which may affect the approval timeline for pegunigalsidase alfa. Active trials have not been materially impacted although some adjustments have been made to accommodate FDA guidance issued in March 2020 and additional adjustments may be necessary in the future. The pandemic has delayed the last monitoring visits for the BRIGHT Phase III clinical necessary for final analysis but topline results remain expected in 4Q:20. Protalix facilities now operate in two shifts, reducing the number of employees present at the facilities at any time. The FDA notified the company that its original assigned PDUFA date in January would be extended by three months. Additionally, the FDA may not be able to inspect Protalix' facilities in Israel and France prior to the PDUFA date. Consequently, Protalix management has filed for a Type A meeting with the FDA to address this issue.

Liquidity, Financing & Trading

Securing funding may be difficult especially during a period of economic volatility. During periods of confidence, capital may be easy to obtain; however, during a liquidity crisis or a period of heightened risk perception, even companies with bright prospects may be in trouble if they are dependent on the financial markets to fund their work. Pre-revenue firms or those with in-development technologies rely heavily on equity issuance to fund their operations. The timeline for drug and device development is considerable and long periods can pass before a product is sold. Funds can be sourced through debt or equity issuances; however, these sources may reduce the flexibility of the company and can dilute existing shareholders.

If capital is required to sustain operations and it is not readily available, a company may be forced to suspend research and development, sell equity at a substantial discount to previous valuations and dilute earlier shareholders. A lack of funding may leave potentially promising therapies without a viable route forward or force a company to accept onerous terms.

Trading volumes are frequently low for smaller firms, creating liquidity risk where large transactions may have a material impact on share price. In periods of crisis or heightened risk perception, share price may be volatile. Companies with smaller capitalizations are typically riskier and changes in sentiment may adversely affect their trading prices and volumes. Smaller firms may also have less visibility, compete for investor dollars in a shallow market and be excluded from market indices. Price volatility and periodic equity issuance may lead to difficulty meeting exchange listing requirements for smaller companies. Inability to comply with listing standards may result in delisting, which could severely impact trading volumes.

As of September 30, 2020, Protalix held $41.3 million in cash, equivalents and short term deposits on its balance sheet, which management estimates will be sufficient to sustain the company over the next year. Protalix also holds $57.9 million in 7.5% convertible secured promissory notes which are due November 15, 2021. While this amount exceeds current cash resources, we anticipate several favorable events to take place in the near term that will enable repayment and/or refinancing. Pegunigalsidase alfa is in front of the FDA with a late April target action date. Once approved, we anticipate payment of milestones by Chiesi, that while likely insufficient to repay the complete $57.9 million balance in full, will be enough to reduce it materially. If approved, Protalix is eligible for

royalty revenues from the sale of pegunigalsidase alfa which will provide the necessary cash flows to secure and support new debt financing or allow for additional equity issuance at favorable prices.

Market Risk

Once granted marketing authorization, the commercialization of a candidate relies on an experienced salesforce, key opinion leaders and supportive clinical data. Success relies on product acceptance, adoption and continued safety during the post-marketing period. Lack of marketing effort, exclusion from formularies and lack of product acceptance by the medical community may prevent material penetration of an approved product. New and improved competing therapies may siphon off market share.

While Elelyso has already been approved, it still bears the risk of a competitive response from others in the same indication, intellectual property protection expiration, continued safety surveillance and regulation and maintaining an adequate supply chain with quality control. Elelyso is marketed internationally, including in Brazil where Fiocruz, an arm of the Brazilian Ministry of Health, has purchase obligations under supply and technology transfer agreement. Failure to meet purchase obligations could have negative financial impacts on Protalix and result in termination of the agreement.

Clinical Trials

For smaller, early-stage companies, investing in product development is a lengthy process. The timeframe for conducting pre-clinical research to eventually commercializing a medical device can take from 3 to 7 years[42] or longer given market and company-specific conditions. Patient recruitment, especially for smaller disease populations can be challenging, especially in rare diseases where there is a smaller pool of individuals. Third party contractors manage multiple trials and may not provide the required effort to produce a successful effort. Clinical trials must be designed to meet specific endpoints and generate statistically significant results in order to be considered by the FDA.

Protalix has three candidates in its clinical pipeline with PRX-102 currently under consideration by the FDA for approval. Should PRX-102 receive a complete response letter and not be granted approval from the FDA or other regulatory agency, Protalix may have to assume additional expense and conduct additional studies to address the identified concerns. If the deficiencies cannot be addressed, the candidate may never be approved, requiring a write-down of the asset's value. Other candidates such as OPRX-106 and PRX-115 may not advance further in the development process if resources are re-allocated to PRX-102.

Partner Risks

Protalix is a biotechnology research and development company and relies on partners to commercialize its products. Taliglucerase alfa is commercialized by Fiocruz in Brazil and Pfizer in other regions around the globe. Partners may have insufficient incentive or lack the ability to effectively sell the product which may not achieve its potential. Assuming approval is granted to pegunigalsidase alfa, Protalix' partner Chiesi Rare Disease will commercialize the product. Chiesi has made substantial investments in its rare disease effort in the United States and launched a new division in Boston last February that will market its portfolio of rare disease medicines including PRX-102.

[42] Gail Van Norman, "Drugs, Devices, and the FDA: Part 2: An Overview of Approval Processes: FDA Approval of Medical Devices," *JACC: Basic to Translational Science* 01/04 June 2016, 277-287

Management Profiles

Dror Bashan, President & Chief Executive Officer, Director

Mr. Bashan joined Protalix in June 2019, bringing over two decades worth of experience in the pharmaceutical industry. He has held roles in business development, marketing, sales and finance across regions and has deep knowledge of global pharmaceutical and health industries. Between 1998 and 2018, Bashan served in a number of senior roles at Teva Pharmaceutical Industries. In his most recent role at Teva, he served as Senior Vice President, Global Business Development where he was involved in strategic alliances, cross-company projects and the acquisition and divestiture of assets. Bashan received a Bachelor of Arts in economics and business management and a Master of Business Administration with focus on finance and marketing from Tel Aviv University.

Eyal Rubin, Senior Vice President & Chief Financial Officer

Mr. Rubin joined the company in September 2019 and brings over 20 years of finance and capital markets experience with an extensive background in financial planning and operations, management and strategy. Before joining, he served at BrainStorm Cell Therapeutics Inc. as Executive Vice President and Chief Financial Officer where he was responsible for finance, accounting and investor relations. Prior to his role at BrainStorm, Rubin held several roles at Teva Pharmaceutical Industries including, most recently, Vice President, Head of Corporate Treasury, where he oversaw Teva's cash operations and management as well as equity and debt capital market transactions. He holds a BA in financing and IT systems from the College of Management, Israel and an MBA from Bar-Ilan University, Israel.

Einat Brill Almon, Ph.D., Sr. Vice President & Chief Development Officer

Dr. Almon joined Protalix Ltd. in December 2004 and has held roles at Protalix as Senior Director, Vice President and Senior Vice President, Product Development in 2006. Almon has years of experience in bio- and agrobiotech, with direct experience in clinical, device and scientific software development as well as intellectual property. Prior to joining Protalix, she served as Director of R&D and IP of Medgenics Medical Ltd. Dr. Almon has also trained as a biotechnology patent agent at leading IP firms. Dr. Almon holds both a doctorate and masters in molecular biology from the Weizmann Institute of Science with a focus in cancer and bachelors from Hebrew University. Dr. Almon also conducted post-doctoral research at the Hebrew University in the area of plant molecular biology.

Yaron Naos, Senior Vice President, Operations

Mr. Naos joined Protalix in 2004, originally as a Senior Director for Operations and later as Vice President for Production, and became our Senior Vice President, Operations in 2018. He has a wealth of hands-on experience and knowledge in the field of pharmaceutical development. Prior to joining Protalix, he served for a decade as R&D Product Manager at Dexxon Pharmaceutical Co., one of Israel's largest pharmaceutical companies, where he was responsible for technology transfer from R&D to production, and in charge of R&D activities that led to the commercialization of many products. Later, Mr. Naos was plant manager of Medibrands Pharmaceutical Company, as well as logistics manager of Mediline for a period of four years, where he was responsible for all operational activities, from procurement to distribution. Mr. Naos holds a B.Sc. in Food Engineering and Biotechnology from the Technion-Israel Technology Institute and an MBA from Haifa University.

Yael Hayon, Ph.D., Vice President, Research and Development

Dr. Hayon joined Protalix as its Vice President, Research & Development in July 2020. She brings to Protalix over a decade of experience in pharmaceutical research in development, both in the scientific operations and the administrative functions. She most recently served as Vice President of Clinical Affairs of Syqe Medical Ltd., Tel-Aviv, where she, among other things, established the clinical and medical global strategy, and was responsible for providing strategic input on the regulatory development plan. Prior to her role at Syqe Medical, Dr. Hayon served as the Head of R&D Israeli Site of LogicBio Therapeutics, Inc., Cambridge, Massachusetts, where she managed LogicBio's Israeli-based Research and Development facility and was involved in strategic decision-making. From 2014 through 2016 she served as the R&D Manager, Stem Cell Medicine Ltd., Jerusalem, Israel. Dr. Hayon holds a Ph.D. in Neurobiology/Hematology, and an M.Sc. in Neurobiology, both from the Hebrew University Faculty of Medicine, Jerusalem, Israel.

Valuation

Protalix has one approved product and one product under review by the FDA which we consider in our valuation. The company holds other candidates in its pipeline which are not evaluated.

Protalix' taliglucerase alfa is marketed by Fiocruz in Brazil and Pfizer in the rest of the world. The product generated $15.9 million in revenues in royalties for Protalix in 2019 and $15.8 million in revenues in the trailing four quarters ending 3Q:20. Gross margins have been in the low 30% range representing the cost to manufacture product and royalties paid to the Israeli Innovation Authority. Our forecasts assume a modest low single digit level of growth for this product and improving margins based on a favorable price change with Pfizer.

The primary driver of value in our assessment is the commercialization of pegunigalsidase alfa (PRX-102), which has been assigned a Prescription Drug User Fee Act (PDUFA) date of April 27, 2021.[43] We estimate an 85% likelihood of approval based on historical success rates as provided in Clinical Development Success Rates.[44] PRX-102 will be commercialized in the US and rest of world by Chiesi for Fabry Disease patients. We estimate the size of the Fabry population to be approximately 6,600 persons in the United States and about 26,000 persons in the rest of the developed world.

Pricing for biologics in rare disease is strong. We estimate annual revenues per patient of $382,000 per year of treatment in the United States and half this level or $191,000 in the rest of the world.[45] Penetration into the Fabry population is expected to initially be 1.5% in 2021 reflecting a partial year of sales. In year two, we anticipate this will increase to 5% and rise to 12% of the market by the sixth year of commercialization. We anticipate a slow move into other markets, beginning the submission of a marketing authorization application (MAA) in the EU next year. Assuming one year to obtain approval and one year to negotiate pricing, we model European sales starting in 2023. Work to obtain approval in other regions will advance in parallel with EU efforts. Penetration into the ex-US Fabry population is modelled at 1.5% in year one rising to 6% by year five. If PRX-102 is able to demonstrate superiority to Fabrazyme and successfully communicate this to providers, higher penetration estimates are justified.

Protalix signed agreements with Chiesi that grant marketing rights to the latter in return for upfronts, milestones and royalties. Although specific details are not provided, the agreements identify milestones of $760 million and tiered royalties ranging from 15% to 40% inside the US and milestones of $320 million and tiered royalties ranging from 15% to 35% outside of the US. We simplify this arrangement and assume milestones and royalties are represented by a fixed 44% royalty in the US and a 40% royalty in other regions.

As part of the agreement with Chiesi, Protalix was provided reimbursement for its research and development activities. We forecast these revenues to taper off in 2021 and 2022 as PRX-102 research activities wind down and the focus shifts to commercialization.

Protalix will manufacture PRX-102 and receive royalties paid by Chiesi. We assume a high 90% gross margin for product sold based on gross revenues and estimated manufacture cost, growing at inflation. For taliglucerase alfa sales, we assume an 11 percentage point improvement in gross margin over the next three years.

R&D costs are forecast at $19.4 million in 2021, falling to $15 million in 2022 and declining to $10 million in 2023 and 2024. SG&A is modeled at $11.5 million in 2021, falling slightly to $10.5 million in 2022, to reflect continued cost cutting, then rising at normal inflationary rates.

As an Israeli company granted Approved Enterprise status and located in a special tax preferred zone, Protalix is exempt from income tax in Israel for a ten-year period following the generation of taxable income. Combined with the anticipated consumption of over $225 million in net operating losses, we do not anticipate cash taxes to be paid over the duration of our discounted cash flow forecasts.

We use a discounted cash flow (DCF) model to generate our valuation. DCF assumptions include a 15% discount rate and a -10% terminal growth rate. All warrants and options are assumed to be exercised, resulting cash is added to the balance sheet and related shares are added to the share balance. Net debt is subtracted from the enterprise value to generate our unadjusted NPV of equity. We apply a weighted probability of success to our valuation of 87%,[46] which produces a valuation of $15.00 per equity share.

[43] Extended from the original PDUFA date of January 27, 2021.
[44] Clinical Development Success Rates 2006-2015. Biotechnology Innovation Organization, Biomedtracker, Amplion.
[45] Based on our review, pricing for Fabrazyme, which is off-patent, commands a price of $350 to $360 thousand per year in the US.
[46] We take the relative revenue weight of PRX-102 (85% rate) and taliglucerase alfa (100% rate) to generate our overall probability of success.

CONCLUSION

Protalix has distinguished itself by developing the first plant-cell culture expressed protein approved by the FDA for human use, which was subsequently approved by other regulatory agencies around the globe. Its ProCellEx platform offers several advantages compared to other expression systems. The company has carved out a niche in the orphan space, focused on Gaucher Disease and Fabry Disease and is looking to expand its product set into other areas with its earlier stage pipeline. One product is being commercialized, taliglucerase alfa, by Fiocruz and Pfizer, and another, PRX-102, is close to its FDA target action date. If approved, PRX-102 will be commercialized by Chiesi, which has secured global rights. In 2021, we expect an application will be made for approval in the EU and in other regions around the globe.

Chiesi established a rare disease group in Boston earlier this year that will develop treatments in lysosomal storage, hematological and ophthalmological disorders. The company has made a commitment to launching and growing this unit in coming years and its most important product is expected to be PRX-102.

Companies such as Sanofi and Shire have dominated the space occupied by Protalix' leading products, but have not produced any recent innovations. PRX-102 may provide several benefits over Fabrazyme and Replagal and are respectively being compared to PRX-102 in the BALANCE and BRIDGE clinical trials. Due to pegylation, the enzyme provides a longer half-life and may provide superior efficacy compared to standard of care and require fewer doctor visits for administration, providing additional benefits to patients.

PRX-102 has undergone several trials including a Phase II, which was used to support the BLA submission to the FDA, and three Phase III studies evaluating PRX-102 against standard of care with infusion of the enzyme extended to every four-weeks rather than every two. The BRIDGE study has provided topline data and demonstrated an improvement in renal function and was well tolerated. The results were included in the BLA submission to the FDA under the Accelerated Approval pathway. BALANCE and BRIGHT results will be combined with existing studies for the marketing authorization application (MAA) submission to the EMA in late 2021.

Protalix has several other candidates in the pipeline including OPRX-106 for IBD, PRX-110 for cystic fibrosis, PRX-115 for Gout and other undisclosed assets that are in the discovery and preclinical stage. Protalix management will decide which prospects will advance following the successful commercialization of PRX-102.

Fabry Disease is classified as rare and, by our estimate guided by available data, falls well below the threshold with fewer than 7,000 cases per year in the United States. Despite the small size of the population, the disease is severe and successful treatment can extend healthy life. This justifies a premium for the drug and 2020 estimated revenues for existing Fabry drugs are almost $1.8 billion, providing a large market for a potentially improved treatment. We anticipate a steady ramp up of penetration into the existing market with upside to our estimates if superiority and increased ease of use compared to standard of care is shown. We also believe Chiesi is strongly motivated to succeed following their material investment into the Boston rare disease unit.

While there may be concerns regarding the balance sheet given cash burn and net debt that is due in late 2021, we see these dissipating following approval of PRX-102. A successful approval will provide milestone payments and royalty payments that will bring the security and capital necessary to pay down and refinance the debt.

Key reasons to own Protalix shares:

- **PRX-102 on cusp of commercialization**
  - **Target action date: April 27, 2021**
- **Potential for superiority vs market leader Fabrazyme**
  - **Improved efficacy**
  - **Longer duration between infusions**
- **Existing sales and royalty revenues from taliglucerase alfa**
  - **Pfizer, globally**
  - **Fiocruz, Brazil**
- **Maintain regulatory approved plant based expression system**
- **Orphan status granted for PRX-102**
- **Partnership with Chiesi for global commercialization of PRX-102 in Fabry Disease**
- **Rights to milestones and royalties**

Based on our analysis of Protalix' existing and development assets, we see the shares as undervalued relative to existing opportunities. Our valuation work forecasts continued contributions from taliglucerase alfa and layers on Chiesi's global commercialization of PRX-102 to generate our target price. The opportunity for Protalix extends into other critical diseases which we anticipate will be vigorously pursued following the successful launch of PRX-102. We initiate on Protalix with a valuation of $15.00 per share.

PROJECTED FINANCIALS

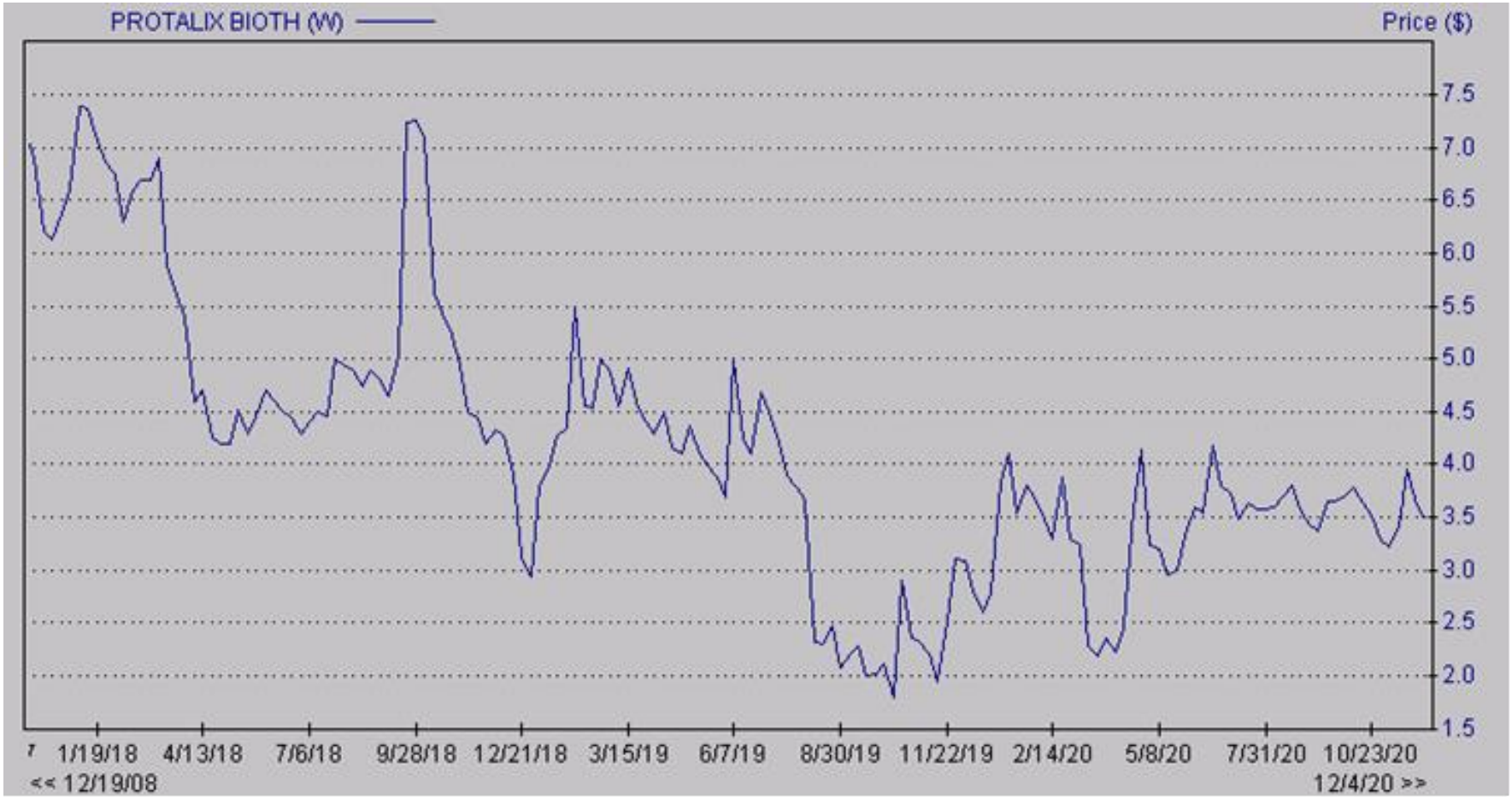
Protalix Biotherapeutics, Inc. - Income Statement

Protalix Biotherapeutics	2019 A	Q1 A	Q2 A	Q3 A	Q4 E	2020 E	2021 E	2022 E
Total Revenues ($US '000)	**$54,693**	**$21,646**	**$10,967**	**$10,790**	**$10,556**	**$53,828**	**$48,939**	**$78,417**
YOY Growth	60%	107%	-10%	-24%	-41%	-2%	-9%	60%
Cost of Revenues	$10,895	$3,426	$1,827	$2,868	$2,919	$11,040	$11,339	$12,638
Product Gross Margin	31.3%	31.9%	49.9%	13.0%	33%	32%		
Research & Development	$44,616	$10,340	$9,186	$7,688	$7,500	$34,714	$19,400	$15,000
Selling, General & Admin	$9,899	$3,187	$2,194	$2,816	$2,560	$10,757	$11,457	$10,510
Income from operations	($10,717)	$4,693	($2,240)	($2,582)	($2,423)	($2,683)	$6,743	$40,269
Operating Margin	-20%	22%	-20%	-24%	-23%	-5%	14%	51%
Financial Expenses	$7,966	$3,229	$1,948	$1,973	$1,950	$9,100	$7,350	$0
Financial Income	($407)	($203)	($38)	($118)	($100)	($459)	($400)	($200)
Pre-Tax Income	($18,276)	$1,667	($4,150)	($4,437)	($4,273)	($11,324)	($207)	$40,469
Net Income	**($18,276)**	**$1,667**	**($4,150)**	**($4,437)**	**($4,273)**	**($11,324)**	**($207)**	**$40,469**
Net Margin	-33%	8%	-38%	-41%	-40%	-21%	0%	52%
Reported EPS	**($1.23)**	**$0.10**	**($0.13)**	**($0.14)**	**($0.13)**	**($0.39)**	**($0.01)**	**$1.06**
Basic Shares Outstanding	14,838	17,381	32,443	32,864	33,300	28,997	34,850	38,200

Source: Company Filing // Zacks Investment Research, Inc. Estimates

HISTORICAL STOCK PRICE

Protalix Biotherapeutics, Inc. – Share Price Chart[47]



[47] Source: Zacks Research System

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