BIO-PATH HOLDINGS INC
Form 10-K
April 02, 2018

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

**FORM 10-K**

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

**For the fiscal year ended December 31, 2017**

OR

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

**Commission file number 001-36333**

BIO-PATH HOLDINGS, INC.

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

| | |
|---|---|
| Delaware<br>(State or other jurisdiction of incorporation or organization) | 87-0652870<br>(I.R.S. Employer Identification No.) |

4710 Bellaire Boulevard, Suite 210, Bellaire, Texas 77401
(Address of principal executive offices)

Registrant's telephone number, including area code: (832) 742-1357

Securities registered pursuant to Section 12(b) of the Act: Common Stock, par value $0.001 per share
Securities registered pursuant to Section 12(g) of the Act: None

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. x

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

| | |
|---|---|
| Large accelerated filer ¨ | Accelerated filer ¨ |
| Non-accelerated filer ¨ (Do not check if a smaller reporting company) | Smaller reporting company x |
| Emerging growth company ¨ | |

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ¨

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

As of March 22, 2018, there were 11,340,756 of the registrant's common stock issued and outstanding. The aggregate market value of the voting stock held by non-affiliates of the registrant was approximately $34,842,973 million as of June 30, 2017, the last business day of the registrant's most recently completed second fiscal quarter, based on the last sales price of the registrant's common stock as reported on The Nasdaq Capital Market on such date, after adjustment for the 1-for-10 reverse stock split that occurred effective as of 5:00 p.m. Eastern Time on February 8, 2018. For purposes of the preceding sentence only, all directors, executive officers and beneficial owners of 10% or more of the shares of the registrant's common stock are assumed to be affiliates.

DOCUMENTS INCORPORATED BY REFERENCE: NONE

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Unless the context requires otherwise, references in this Annual Report on Form 10-K to "we," "our," "us," "the Company" and "Bio-Path" refer to Bio-Path Holdings, Inc. and its subsidiary. Bio-Path Holdings, Inc.'s wholly-owned subsidiary, Bio-Path, Inc., is sometimes referred to herein as "Bio-Path Subsidiary."

**CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS**

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). Forward-looking statements can be identified by words such as "anticipate," "expect," "intend," "plan," "believe," "seek," "estimate," "project," "goal," "strategy," "future," "likely," "may," "should," "will" and va words and similar references to future periods, although not all forward-looking statements contain these identifying words. Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, projections, anticipated events and trends, the economy and other future conditions. Because forward-looking statements relate to the future, they are subject to inherent risks, uncertainties and changes in circumstances, including those discussed in "Item 1A. Risk Factors" of this Annual Report on Form 10-K. As a result, our actual results may differ materially from those expressed or forecasted in the forward-looking statements, and you should not rely on such forward-looking statements. Please refer to "Item 1A. Risk Factors" of this Annual Report on Form 10-K for a discussion of risks and factors that could cause our actual results and financial condition to differ materially from those expressed or forecasted in this Annual Report on Form 10-K.

Any forward-looking statement made by us in this Annual Report on Form 10-K is based only on information currently available to us and speaks only as of the date on which it is made. We undertake no obligation to publicly update any forward-looking statement, whether as a result of new information, future developments or otherwise. However, you should carefully review the risk factors set forth in other reports or documents we file from time to time with the U.S. Securities and Exchange Commission ("SEC").

**PART I**

**ITEM 1. BUSINESS**

**Overview**

We are a clinical and preclinical stage oncology focused RNAi nano particle drug development company utilizing a novel technology that achieves systemic delivery for target specific protein inhibition for any gene product that is over-expressed in disease. Our drug delivery and antisense technology, called DNAbilize®, is a platform that uses P-ethoxy, which is a deoxyribonucleic acid (DNA) backbone modification that is intended to protect the DNA from destruction by the body's enzymes when circulating *in vivo,* incorporated inside of a neutral charged lipid bilayer. We believe this combination allows for high efficiency loading of antisense DNA into non-toxic, cell-membrane-like structures for delivery of the antisense drug substance into cells. *In vivo,* the DNAbilize® delivered antisense drug substances are systemically distributed throughout the body to allow for reduction or elimination of proteins in blood diseases and solid tumors. DNAbilize® is a registered trademark of the Company.

Using DNAbilize® as a platform for drug development and manufacturing, we currently have three antisense drug candidates in development to treat a total of five different disease indications. Our lead drug candidate, prexigebersen (pronounced prex" i je ber' sen), is in the efficacy portion of a Phase II clinical trial for acute myeloid leukemia (AML), and a Phase IIa clinical trial, which is the safety segment of a Phase II clinical trial, for blast phase and accelerated phase chronic myelogenous leukemia (CML) is open for enrollment. Prexigebersen is also in preclinical studies for solid tumors, including breast cancer and ovarian cancer.

Our second drug candidate, Liposomal Bcl2 ("BP1002"), targets the protein Bcl-2, which is responsible for driving cell survival in up to 60% of all cancers. We are currently preparing an Investigational New Drug (IND) application for BP1002 in addition to completing additional IND enabling studies. We intend to initiate a Phase I clinical trial of BP1002 in refractory or relapsed lymphoma patients once we receive approval from the FDA.

Our third drug candidate, Liposomal Stat3 ("BP1003"), targets the Stat3 protein and is currently in preclinical development in a pancreatic patient-derived tumor model. Previous preclinical models have shown BP1003 to successfully penetrate pancreatic tumors and to significantly enhance the efficacy of standard frontline treatments. We intend to initiate IND enabling studies of BP1003 in 2018.

We have certain intellectual property as the basis for our current drug products in clinical development, prexigebersen and BP1002. We also currently maintain an exclusive license agreement (the "License Agreement") with The University of Texas, MD Anderson Cancer Center ("MD Anderson"), under which we license from MD Anderson certain technology relating to the original delivery technology platform. We are developing RNAi antisense nano particle drug candidates based on our own patented technology to treat cancer and autoimmune disorders where targeting a single protein may be advantageous and result in reduced adverse effects as compared to small molecule inhibitors with off-target and non-specific effects. We have composition of matter and method of use intellectual property for the manufacture of neutral charged DNA-liposome complexes. On July 19, 2017, we announced that the United States Patent and Trademark Office ("USPTO") issued a notice of allowance for claims related to DNAbilize®, including its use in the treatment of cancers, autoimmune diseases and infectious diseases. Our pipeline for development of antisense therapeutics is set forth in the table below:

**Figure 1. Bio-Path Pipeline for Development of Therapeutics**

* Received orphan drug designation from the U.S. FDA for AML and CML and from the European Medicines Agency (EMA) for AML

Ribonucleic acid (RNA) is a biologically significant type of molecule consisting of a chain of nucleotide units. Each nucleotide consists of a nitrogenous base, a ribose sugar and a phosphate. Although similar in some ways to DNA, RNA differs from DNA in a few important structural details. RNA is transcribed from DNA by enzymes called RNA polymerases and is generally further processed by other enzymes. RNA is central to protein synthesis. DNA carries the genetic information of a cell and consists of thousands of genes. Each gene serves as a recipe on how to build a protein molecule. Proteins perform important tasks for the cell functions or serve as building blocks. The flow of information from the genes determines the protein composition and thereby the functions of the cell.

The DNA is situated in the nucleus of the cell, organized into chromosomes. Every cell must contain the genetic information and the DNA is therefore duplicated before a cell divides (replication). When proteins are needed, the corresponding genes are transcribed into RNA (transcription). The RNA is first processed so that non-coding parts are removed (processing) and is then transported out of the nucleus (transport). Outside the nucleus, the proteins are built based upon the code in the RNA (translation).

Our basic drug development concept is to block expression of proteins that cause disease. RNA is essential in the process of creating proteins. We intend to develop drugs and drug delivery systems that work by delivering short strands of DNA material (antisense DNA) that block the production of proteins associated with disease (Figure 2).

**Figure 2.**

Antisense DNA therapeutics is the field of designing short DNA sequences that are complementary to an RNA for a protein of interest with the intention of inhibiting the production of the targeted protein. The DNA will find the matching RNA and form a complex. The complexed RNA will not have access to the protein-making machinery, which prevents the cell from translating it into a protein. Thus, protein production is turned off and levels of the targeted protein are reduced in the cell. This gene-specific process of controlling protein expression has led to great interest in using antisense DNA to shut off the production of proteins involved in disease. Antisense therapeutics have been in development for over 20 years; however, there have been many challenges to antisense therapeutics that have prevented or reduced the successful distribution and transfer of DNA into cells. Of all delivery methods in use today, we believe only DNAbilize® has the potential to overcome the most common challenges associated with antisense therapeutics.

Challenges associated with antisense therapeutics generally fall into two categories: (i) maintaining the stability of the DNA inside of the body as it is transported to the target cell and (ii) achieving efficient delivery and transfer of the DNA into the cell. DNA stability in the blood and lymphatic system is a challenge because of the abundance of enzymes present in human body fluids. Enzymes called nucleases will digest DNA into nonfunctional fragments making them too small to hybridize effectively to the correct RNA and block the protein machinery.

Efforts to overcome the stability challenges led to the development of DNA structural backbone chemistries that block nuclease digestion so that DNA can remain in circulation long enough to reach the target cell. The most popular modification employed is called phosphorothioate in which an oxygen atom in the DNA is replaced with a sulfur atom. This switch alters the DNA's structure so that enzymes can no longer break down the DNA. However, DNA that contains sulfur has two major drawbacks. First, it has been shown to cause liver toxicity because, as pure DNA that contains sulfur is circulated through the body, it is rapidly cleared by and accumulates in the liver. Second, sulfur also induces significant toxicity in the form of life threatening bleeding and clotting complications.

While the development and use of phosphorothioate was a step forward in allowing for progress of *in vivo* studies, the amount of antisense drug product that can be delivered is severely limited. Consequently, doses at the level needed for true therapeutic success are not possible. Accordingly, stabilizing the DNA backbone through the use of phosphorothioate has prevented the successful use of antisense therapeutics to treat patients at a therapeutic level without causing significant amounts of toxicity. Alternative approaches have since been developed that reduce the number of sulfur groups in the antisense molecule; however, these methods still contain sulfur, and toxicity will always remain a concern. The P-ethoxy modification used in our DNAbilize® technology is completely sulfur free.

The second category of challenges to the development of successful antisense therapeutics is achieving efficient delivery and transfer of a DNA molecule across a lipid based cell membrane. Cell membranes have a negative charge on the surface. DNA is also negatively charged. When the pure DNA is delivered to the cell surface, the similar charges repel each other, and uptake of the DNA into the cell is very inefficient. Accordingly, the DNA containing antisense drug products will not be delivered in an amount that will have a therapeutic effect.

Efforts to overcome the efficient delivery and transfer challenges led to the exploration of lipid-based carriers for transfer of DNA containing antisense drug products through the lipid bilayer to mimic the lipid cell membrane. Encapsulating the DNA inside a neutral charged lipid bilayer facilitates the delivery and transfer of DNA into the cell to be fluid and gentle. Research initially focused on cationic lipids because they have an overall positive charge, which would be attracted to the negative charge of the cell membrane. It was thought that this would enhance uptake and delivery of DNA.

Research did, in fact, confirm that cationic liposomes are capable of transferring DNA inside of cells at a higher efficiency than with no delivery liposomes; however, it was found that cationic lipids have major drawbacks in therapeutics. These include absorption of serum proteins while the complexes are circulating in the blood. Absorption of charged serum proteins leads to lipid reorganization, aggregation or disassociation, resulting in poor efficiency of transfer of DNA into cells and non-specific toxicity to cell membranes. DNAbilize® overcomes this challenge as well by encapsulating the DNA in a neutral lipid-based liposome, which is a lipid membrane without surface charge. The lipid particles can circulate through the blood without interacting with serum proteins, reaching target cells to transfer intact DNA without toxic effects.

We believe the DNAbilize® technology is a first in class approach that overcomes the challenges associated with both DNA stabilization and lipid-based delivery. We believe that the combination of the protected DNA using P-ethoxy to modify the DNA structure with the neutral lipid membrane is the ideal approach for antisense DNA therapeutics. While many companies have focused research on either the DNA stabilization problem or the lipid delivery problem, we are not aware of any company that has developed improvements in both areas. DNAbilize® is truly a stand-alone platform because, based on our current research, it allows for high doses of drug products to be delivered throughout the entire body while minimizing toxicity. This allows our research and development efforts to focus on drug targets rather than on indications because the DNAbilize® system should not be limited in what types of indications it can treat. As such, we believe that DNAbilize® represents the first ever antisense therapeutic approach that can successfully treat hematological and systemic diseases of the blood and lymph.

Because of our unique ability to address unmet needs in hematological malignancies, our lead drug candidates focus in this area. Our lead drug candidate, prexigebersen, targets the protein Grb2, a bridging protein between activated and mutated cellular kinases and the proteins involved in cell proliferation, and in particular, Ras protein. When mutations occur that activate these kinases, the cell proliferates uncontrollably, via Grb2, and this results in disease. Inhibition of Grb2 interrupts this pathway and shuts off growth signals.

Prexigebersen is in the efficacy portion of the Phase II clinical trial for AML in combination with frontline therapy low dose Ara C (LDAC) in elderly and induction therapy ineligible patients or patients who have decided to forego intensive induction therapy because of their age or fragile health. We completed the safety segment of Phase II clinical trials (the safety segment of Phase II clinical trials is also referred to as Phase Ib) in refractory AML patients demonstrating anti-leukemic benefit and no adverse events in two cohorts at two dose levels each with three evaluable patients. Patients in Cohort 7 received a 60 mg/m$^2$ dose of prexigebersen and patients in Cohort 8 received a 90 mg/m$^2$ dose of prexigebersen, each in combination with LDAC. Two of three patients in Cohort 7 achieved complete remission, despite having failed at least six other therapies prior to entering the trial. One patient in Cohort 8 achieved complete remission, while the remaining two patients in Cohort 8 had over 50% bone marrow blasts.

On November 2, 2016, we announced that the first patient in the efficacy portion of the Phase II trial for AML was dosed. The full trial design includes approximately 54 evaluable patients with an interim analysis to be performed after 19 patients are treated with the combination. In the event the interim results exceed the primary endpoint in the

number of patients that meet or exceed statistically determined thresholds, we may seek to convert the trial into a registration trial for accelerated approval. The multi-site trial is being conducted at leading cancer centers, among them are Weill Medical College of Cornell University, Baylor Scott &White Health, The University of Kansas, New Jersey Hematology Oncology Associates, West Virginia University/Mary Babb Randolph Cancer Center, and MD Anderson. To date, over 50 potential patients have been pre-screened for the efficacy portion of the Phase II trial, 26 patients have been screened, 23 patients have been enrolled and 17 patients have been deemed evaluable with six additional patients currently undergoing treatment. We expect the 19 patient pre-specified analysis to be completed in early 2018, at which time we will address the assessment of these patients.

In addition to the Phase II trial for AML, on December 29, 2017, we announced the initiation of our Phase Ib/IIa clinical trial, which is the safety portion of the Phase II clinical trial of prexigebersen for the treatment of CML in accelerated and blast phase patients. The trial is being conducted at MD Anderson as a potential salvage therapy for accelerated and blast phase CML patients. Two cohorts of three evaluable patients each will be enrolled to evaluate two doses (60 mg/ $m^2$ and 90 mg/ $m^2$) of prexigebersen in combination with the front-line treatment dasatinib.

Our second drug candidate, BP1002, targets the protein Bcl-2. Bcl-2 is an anti-apoptotic member of the Bcl-2 family of proteins that regulate cell death. Amplified expression of Bcl-2 protein is associated with numerous cancers due to the defining genetic hallmark of the disease, chromosomal translocation t(14;18). The t(14;18) moves the Bcl-2 gene from chromosome 18 into the heavy chain immunoglobin locus on chromosome 14, resulting in uncontrolled high level expression of Bcl-2 protein. Overexpression of Bcl-2 results in deregulated cell survival in affected cells. Initial IND enabling studies for BP1002 have been completed, although an additional second species study has been requested by the FDA. We anticipate being able to file an IND to open a Phase I clinical trial for refractory or relapsed lymphoma in 2018. The clinical trial would evaluate the safety of BP1002 in several dose escalating cohorts to determine a maximum tolerated dose and/or optimal biologically active dose.

Our third drug candidate, BP1003, targets the Stat3 protein and is currently in preclinical development in a pancreatic patient-derived tumor model. Previous preclinical models have shown BP1003 to successfully penetrate pancreatic tumors and to significantly enhance the efficacy of standard frontline treatments. We intend to initiate IND enabling studies of BP1003 in 2018.

**Strategy**

Our strategy is to develop our lead candidates, prexigebersen, BP1002 and BP1003, for multiple indications where the pathways involving Grb2, Bcl-2 or Stat3, respectively, are utilized to promote cancer growth, proliferation and survival. Using DNAbilize® technology, we plan to develop therapeutics to a wide range of diseases and disorders independently and in partnership with others. The key elements of our strategy include:

(1) **Develop prexigebersen for treatment of AML and CML in combination with frontline therapies.** The Phase I clinical trial demonstrated an excellent safety profile of prexigebersen in patients with relapsed or refractory AML, CML and Myelodysplastic Syndrome (MDS). Moving forward with AML, the area of highest need, we announced on March 3, 2016 that we completed the Phase Ib trial for combination therapy of prexigebersen with the frontline therapy LDAC. On November 2, 2016, we announced that the first patient in the efficacy portion of the Phase II trial for AML was dosed. Eligible patients include de novo elderly patients ineligible for induction therapy or patients who have decided to forego intensive induction therapy because of their age or fragile health. The efficacy portion of the Phase II trial for AML is ongoing. On December 29, 2017, we announced the initiation of the Phase IIa clinical trial for blast and accelerated phase CML patients with prexigebersen in combination with dasatinib.

(2) **Develop prexigebersen for treatment of solid tumors.** Preclinical studies are underway to assess the efficacy of prexigebersen in solid tumors. Research using an ovarian cancer model and a breast cancer model are currently in development. Preclinical experiments are being performed in collaboration with leaders in the field of ovarian and breast cancer at MD Anderson. Results from these studies will be used to assess the ability of prexigebersen to work as a monotherapy and in combination therapies for solid tumors.

(3) **Develop BP1002 for lymphoma**. We have completed initial IND enabling studies and filed these in a briefing package with the FDA. The FDA requested an additional study be prepared for submission of an IND to start a Phase I trial in refractory or relapsed lymphoma that will include multiple types of lymphoma, such as Burkitt's lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT), and mantle cell lymphoma (MCL). It is expected that this will be a dual-site, open-label, dose-escalating trial involving between 15-30 patients. The filing of the IND to open the Phase I trial is expected in 2018.

(4) **Develop BP1003 for pancreatic cancer and solid tumors**. Our third drug candidate, BP1003, targets the Stat3 protein and is currently in preclinical development in a pancreatic patient-derived tumor model. Previous

preclinical models have shown BP1003 to successfully penetrate pancreatic tumors and to significantly enhance the efficacy of standard frontline treatments. Bio-Path intends to initiate IND enabling studies of BP1003 in 2018.

(5) **Expand DNAbilize® to evaluate targets beyond cancer.** We plan to apply the DNAbilize® delivery technology template to new protein targets that meet scientific, preclinical and commercial criteria and file new patents on these targets. We expect that these efforts will include collaboration with scientific key opinion leaders in the field of study and include developing drug candidates for diseases other than cancer. On July 19, 2017, we announced that the USPTO issued a notice of allowance for claims related to DNAbilize®, including its use in the treatment of cancers, autoimmune diseases and infectious diseases.

(6) **Establish DNAbilize® as the antisense drug delivery method of choice by forming partnerships with pharmaceutical and academic clinical research labs.** We plan to utilize our business and scientific expertise to identify potential partners and initiate a wide-ranging, proactive licensing program that will include co-development of specific liposomal antisense drug candidates, licensing the delivery template for outside development of one or more liposomal antisense drug candidates or an out-license of a partially developed drug for final development and marketing.

**Overview of Drug Candidates and Delivery Technology**

The historical perspective of cancer treatments has been the use of drugs that affect the entire body. Advances in the past decade have shifted to treating the tumor tissue itself. One of the main strategies in these developments has been targeted therapy, involving drugs that are targeted to block the expression of specific disease-causing proteins while having little or no effect on other healthy tissue. We believe that nucleic acid drug products, specifically antisense, are a promising field of targeted therapy. Development of antisense, however, has been limited by the lack of a suitable method to deliver antisense drugs to the diseased cells with high uptake into the cell without causing toxicity. Our currently licensed DNAbilize® neutral-lipid based liposome technology is designed to overcome these limitations. Studies conducted at MD Anderson have shown a 10-fold to 30-fold increase in tumor cell uptake with this technology compared to other delivery methods. In addition, to date, no adverse effects attributed to the study drug have been observed in our Phase I clinical trial for leukemia.

Antisense DNA therapeutics of the past have not adequately addressed the issues of toxicity and poor distribution and uptake. Without a lipid carrier, the majority of antisense DNA delivered intravenous is deposited in the liver and does not reach therapeutic levels in other organs in the body. Hence, antisense therapeutics have predominantly focused on diseases of the liver for which delivery of drugs is easy. Below is a table of antisense therapeutics we are aware of that are currently in clinical trials.

**Table 1. Antisense or Anti-MiR drugs FDA Approved or in Clinical Trials**

| **Nucleic Acid Modification** | **Drug** | **Targeted Gene** | **Clinical Status** | **Indications** |
|---|---|---|---|---|
| *Backbone Modifications* | | | | |
| Phosphorothioate | Vitravene | Cytomegalovirus | Approved | CMV retinitis |
| P-ethoxy | Prexigebersen | Grb2 | Phase II | Leukemia |
| *Sugar Modifications* | | | | |
| Morpholino | Eteplirsen | Dystrophin exon 51 | Approved | Duchenne Myotonic dystrophy |
| Morpholino | AVI-7100 | Influenza virus | Phase I | Influenza |
| Locked Nucleic Acid | SPC2968 | Hypoxia Inducing Factor | Phase II | Hepatocellular carcinoma |
| Locked Nucleic Acid | Miravirsen | miR-122 | Phase II | Hepatitis C |
| 2’-O-methyl | Drisapersen | Dystrophin exon 51 | Phase III | Duchenne Myotonic dystrophy |
| 2’- methoxy-O-ethyl | Mipomersen | Apolipoprotein B | Approved | Famial hypercholesterolemia |

| | | | | |
|---|---|---|---|---|
| | Nusinersen | SMN1 | Approved | Spinal muscular atrophy |

| **Lipid System** | **Natural Components** | **Potential toxicity** |
|---|---|---|
| SNALP | Cholesterol, Phosphatidylcholine | Cationic lipid, PEG |
| Lipidoid | Cholesterol | PEG |
| LPH | Cholesterol, hyaluronic acid | DOTAP, PEG |
| Neutral lipid particle | DOPC lipid | None |

Lipid delivery approaches using cationic lipids, which enhance the uptake of charged antisense DNA molecules into cells as compared to no lipid, still do not efficiently transfer antisense DNA into cells due to serum protein interactions and subsequent cell toxicity. The antisense field has attempted to work around these issues by either avoiding a delivery method completely, or by utilizing polyethylene glycol (PEG) as a positive charged based carrier of DNA into cells. PEG showed promise in extending the time of circulation of antisense DNA *in vivo* and avoiding clearance by the liver. However, adverse effects have been demonstrated by PEG carriers, including hypersensitivity, activation of blood clotting, embolism and anaphylaxis. To date, the only known lipid delivery method that has not shown any adverse effects in clinical trials is the neutral lipid method utilized by DNAbilize®.

***PREXIGEBERSEN***

Prexigebersen is targeted at the protein Grb2. Antisense inhibition of Grb2 interrupts the signals between mutated and activated receptors that connect to a well-known cancer associated switch called Ras protein. Inhibition of Grb2 does not cause cell death and thus does not result in adverse events typically observed with receptor inhibitors or Ras pathway inhibitors. We believe that prexigebersen has the potential to be an ideal combination for any number of cancer therapeutics where the Ras pathway is aberrantly activated and patient fitness is a major concern.

We have completed our Phase I clinical trials for prexigebersen for indications of AML, CML, MDS and Acute Lymphoblastic Leukemia (ALL). We are currently prioritizing our efforts on AML and CML and have begun the Phase II/Phase IIa, respectively, clinical trials for these indications. Priorities for additional indications, including MDS or ALL, are expected to be addressed in the future as the results of our Phase II and work in solid tumors progresses.

*Indications for Acute Myeloid Leukemia (AML) and Chronic Myelogenous Leukemia (CML)*

*AML – Background and Common Treatments*. AML is the rapid accumulation of immature myeloid cells in the blood, resulting in a drop of the other cell types such as red blood cells and platelets. The expansion of immature monocytes leaves the patient unable to fight infection. If AML is left untreated, it usually results in death within three months. AML incidence increases with age, with more than 50% of the cases in people age 60 or older. AML is the most common acute leukemia in adults, and the National Cancer Institute estimates that approximately 20,000 new cases occur each year (Figure 3). The cure rate is between 5 to 15% in older adults, and those who cannot receive the standard course of chemotherapy have an average survival rate of five to ten months. The standard induction therapy for AML is Cytarabine with anthracycline. In April of 2017, the U.S. Food and Drug Administration (FDA) approved the first targeted-therapy to treat adults with AML. Rydapt (midostaurin) is used in combination with chemotherapy to treat newly diagnosed adults who have a mutation in a gene called FLT3. In August of 2017, the FDA approved Vyxeos (liposomal daunorubicin and cytarabine) for the treatment of newly diagnosed adults with therapy related AML (t-AML) or AML with myelodysplasia related changes (AML-MRC). In September of 2017, the FDA approved Mylotarg (gemtuzumab ozogamicin) for the treatment of adults with newly diagnosed AML whose tumors express the CD33 antigen (CD33-positive AML). Finally, the FDA also approved Mylotarg for the treatment of relapsed or refractory patients aged 2 years and older with CD33-positive AML. Despite this unusually high number of approvals for AML treatments in one year, these therapies target small sub-populations within the AML patient community, leaving the majority of newly diagnosed and relapsed and refractory elderly patients without new options. The 5-year survival rate for people with AML is approximately 27%**.** AML remains an area of high unmet need for both the relapsed and the de novo elderly population who are typically ineligible for induction therapy.

**Figure 3. Basic Statistics for AML**

*CML – Background and Common Treatments*. CML is characterized by expansion in the blood and bone marrow of mature myeloid cells and their precursors. It can show no symptoms and is often detected during a routine blood test. If left untreated, after several years it will progress to an accelerated phase and eventually blast crisis where it becomes an acute leukemia. With the introduction of drugs such as Gleevec, the life expectancy of patients treated in the chronic phase has been significantly improved, and only 1 to 1.5% of patients ever go into blast crisis. However, for those patients who do progress into blast crisis, there are currently few treatment options. Myeloid cells in blast crisis have accumulated genetic abnormalities that resist traditional treatment methods that kill leukemic cells. Patients in blast crisis have an average survival rate of seven to eleven months. New treatments for this critical population are necessary.

**Figure 4. Basic Statistics for CML**

*Prexigebersen Development and Treatment for AML and CML.* Our lead liposome delivered antisense drug candidate, prexigebersen, has been clinically tested in patients having AML, CML, MDS and ALL in a Phase I trial. During the Phase I trial, 80% of the evaluable patients had refractory or relapsed AML, having failed at least 6 prior therapies. In our study, 83% of patients showed decreased circulating blasts and anti-leukemic activity and eight patients stabilized for extended treatments.

*Phase I Clinical Trials*

The Phase I clinical trial was a dose-escalating study to determine the safety and tolerance of escalating doses of prexigebersen. The study determined an optimal biologically active dose for further development. The pharmacokinetics of prexigebersen in patients from the study are being evaluated. In addition, patient blood samples from the trial were tested using a new assay developed by us to measure down-regulation of the target protein, the critical scientific data that demonstrated the delivery technology does in fact successfully deliver the antisense drug substance to the cell and across the cell membrane into the interior of the cell where expression of the target protein is blocked. The clinical trial was conducted at MD Anderson.

The original IND granted by the FDA in March 2010 allowed us to proceed with a Phase I clinical trial having five cohorts culminating in a maximum dose of 50 mg/m$^2$. However, in November 2012, we announced that since there had been no evidence of significant toxicity from treatment of patients with prexigebersen, we requested the FDA to allow higher dosing in patients. The principal investigator for the clinical trial, in consultation with our management team, advised us that with the absence of any real toxicity barriers, we should continue to evaluate higher doses of prexigebersen. The absence of significant toxicity provided a significant opportunity for us to test higher doses in patients in order to find a dose that provides maximum potential benefit and duration of anti-leukemia effect. These actions were approved and a revised protocol was submitted allowing higher dosing. We announced in October 2014 that we completed Cohort 6, successfully treating three patients at a dose 90 mg/m$^2$. There has been no evidence of significant toxicity from treatment of patients with prexigebersen in our Phase I clinical trial.

An important outcome for the Phase I clinical trial is the ability to assess for the first time the performance of our delivery technology platform in human patients. We have developed two new assays to be able to provide scientific proof of concept of the delivery technology. The first involves a novel detection method for the drug substance in blood samples that will be used to assess the pharmacokinetics of the drug. The second involves a method to measure down-regulation of the target protein in a patient blood sample that was achieved. The latter measurement will provide

critical proof that DNAbilize® neutral liposome delivery technology delivered the drug substance to the cell and was able to transport it across the cell membrane into the interior to block cellular production of the Grb2 protein.

In this regard, in August 2013 we announced that our DNAbilize® liposomal delivery technology achieved a major milestone in the development of antisense therapeutics based on a scientific assay confirming that treating patients with our drug candidate prexigebersen inhibits the Grb2 disease-causing target protein in patients with blood cancers (Figure 7). Inhibition of the disease-causing protein has the effect of down regulating the disease. This will allow for prexigebersen to be used potentially in combination with current frontline treatments. This discovery also points to the potential use of a liposomal antisense treatment as a standalone treatment to transform and manage a disease that has a disease-causing protein as a chronic disorder. This accomplishment is a potentially significant breakthrough for antisense therapeutics, whose development, to date, as a class of therapeutics has been severely limited by a lack of a systemic delivery mechanism that can safely distribute the drug throughout the body and deliver the antisense drug substance across the cell membrane into the interior of the cell. Further, we expect that scientific proof of principle for DNAbilize® may lead to licensing and business development opportunities, supporting our business model.

The principal investigator for the Phase I clinical trial is a leading expert in the treatment of CML, AML, MDS and ALL. Because the results of the first trial produced unexpected and clinically interesting results in some patients, the principal investigator prepared an abstract of the results of the first cohort that was accepted for presentation at the American Society of Hematology (ASH) annual meeting in December 2011. Results that demonstrated potential anti-leukemia benefits in treated patients were included in the presentation. Subsequently, in fall 2013 the principal investigator prepared an abstract of updated information on the results of the clinical trial through Cohort 5, which was accepted for presentation at the ASH annual meeting in December 2013. Highlights (which have been updated to include patients from Cohort 6) of the presentation prepared by the principal investigator for the meeting included:

*Data from the Phase I Clinical Trial*

- Among 20 evaluable patients, 15 demonstrated anti-leukemia activity with reduction in peripheral or bone marrow blasts from baseline.
- Five patients demonstrated transient improvement and/or stable disease, three of whom received a total of five cycles each.
- Two patients, in addition to achieving market blast percentage declines, also experienced transient improvements in leukemia cutis lesions.

*Disease Stabilization in MDS and AML*

- Two patients with MDS, a 53-year-old male and a 72-year-old female, both achieved disease stabilization and continued therapy for five cycles before disease progression.
- A 54-year-old HIV positive male with AML achieved stable disease and marked reduction in peripheral blasts, continuing therapy for five cycles before disease progression (Figure 5).

**Figure 5. AML Patient with HIV Demonstrated Reduction of Peripheral Blasts and Sustained Improvement Over 5 Cycles of Treatment**

**End of C = end of the cycle of treatment**

*Experience in CML-Blast Phase*

- Patient with myeloid blast crisis of CML.
- Prior therapies consisted of: imatinib, dasatinib, nilotinib, DCC-2036, cytarabine + fludarabine + dasatinib + gemtuzumab, PHA-739358, clofarabine + dasatinib.
- Upon start of prexigebersen, patient showed a significant reduction in white blood cell (WBC) blasts from 81 percent to 5 percent, but due to leptomeningeal disease progression discontinued therapy before full cycle (Figure 6).

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**Figure 6. Prexigebersen Monotherapy Reversed Blast Phase Crisis in a Patient in the Phase I Clinical Trial for Prexigebersen**

*Inhibition of Target Grb2 Protein*

- Grb2 levels were compared to baseline prior to treatment.
- By end of treatment, prexigebersen decreased Grb2 in 10 out of 12 samples (83%) tested (average reduction 50%).
- Phosphorylated ERK (pERK, extracellular signal related kinase), a protein downstream of the Ras protein, was decreased in 58% of samples.

**Figure 7. Grb2 Protein and Downstream pERK are Downregulated in Prexigebersen Treated Patient's Cells**

**Grb2 levels decreased in 10 out of 12 patient samples by end of treatment (EOT)**

**pErk levels decreased in 7 of 12 patient samples by EOT**

The Phase I clinical trial is typically ended when a maximum tolerated dose (MTD) is encountered. However, due to the lack of toxicity of the drug, a MTD was not observed. As a result, an optimal biological dose was determined and we completed Cohort 6 of our Phase I clinical trial. It is noted, however, that the lack of toxicity is a major advantage for the drug candidate prexigebersen since it allows higher levels of drug to be administered to the patient, increasing the potential therapeutic benefit.

In April 2015, we received orphan drug designation by the FDA for prexigebersen in AML. Orphan drug status provides Bio-Path with seven years of exclusivity after receiving formal marketing approval, as well as additional development incentives. The FDA grants this designation to certain drugs that target diseases affecting fewer than 200,000 people in the United States ("U.S."). In October 2016, prexigebersen received orphan drug designation for AML in the European Union ("E.U.") from the European Medicines Agency ("EMA"). To receive orphan drug designation from the EMA, a therapy must be intended for the treatment of a life-threatening or chronically debilitating rare condition with a prevalence of less than five in 10,000 in the E.U. Orphan drug designation provides incentives designed to facilitate development, including fee reductions for protocol assistance, scientific advice and importantly, may provide up to ten years of market exclusivity in the E.U. following product approval.

*Phase II Clinical Trials*

On February 9, 2015, we announced that we began enrollment into the combination therapy Phase Ib clinical trial for prexigebersen in patients with AML. The combination therapy Phase Ib clinical trial consisted of two dosing cohorts of prexigebersen (60 mg/m$^2$ and 90 mg/m$^2$) to test the safety profile of treating AML patients with prexigebersen in combination with LDAC. Patients ineligible for intensive induction therapy are currently treated only with LDAC.

On October 9, 2015, we announced the completion of Cohort 7, the first dosing cohort of the Phase Ib clinical trial, consisting of a 60 mg/m$^2$ dose of prexigebersen in combination with LDAC. On March 3, 2016, we announced the completion of Cohort 8, the second dosing cohort of the Phase Ib clinical trial, consisting of a 90 mg/m$^2$ dose of prexigebersen in combination with LDAC. On June 6, 2016, we announced that data from Cohort 7 and Cohort 8 of the Phase Ib clinical trial combination therapy of prexigebersen and LDAC showed no dose limiting toxicities. Of the six evaluable patients from the Phase Ib clinical trial, four patients completed more than two cycles of treatment, three patients achieved complete remission and two patients had over 50% decrease in bone marrow blast counts (Figure 8). Pharmacokinetics of prexigebersen demonstrated a half-life at 60 mg/m$^2$ of 30 hours, significantly better than the 90 mg/m$^2$ dose. The final analysis of these data, along with the demonstrated reductions in bone marrow blasts, suggested that 60 mg/m$^2$ is the appropriate dose for use in the Phase II trial. Administratively, this required Bio-Path to substantially revise documents for the Phase II trial with the 60 mg/m$^2$ dose and resubmit for approvals with the FDA and site Institutional Review Boards, which delayed the commencement of the Phase II trial.

**Figure 8. Five out of six patients in cohorts 7 and 8 receiving the combination prexigebersen + LDAC have greater than 50% decrease in bone marrow blasts**

A summary of the clinical trial results for the Phase I monotherapy for indications of AML, CML, MDS and ALL, and Phase Ib combination therapy for prexigebersen for indications of AML is shown in Table 2 below. The first six cohorts, patients 001 to 034, were treated in the Phase I clinical trial using prexigebersen as a monotherapy. The seventh cohort, patients 035, 037 and 038, were treated in our Phase Ib clinical trial evaluating the combination therapy of 60 mg/$m^2$ prexigebersen. The eighth cohort, patients 039, 040 and 041, were treated with combination therapy of 90 mg/$m^2$.

**Table 2. Summary Cohorts 1-8 Prexigebersen Clinical Trial Phase I and IB**

Nadir: the lowest point, Off-TX: off treatment, DLT: dose limiting toxicity, PD: progressive disease, SD: stable disease, WD: withdraw, CR: complete remission, NE: not enough sample to evaluate, ND: not done, NA: not available

With the completion of Cohort 8, the Phase Ib trial has been completed. Results from the Phase Ib clinical trial demonstrated it is safe to add prexigebersen, which appears to yield better response rates in this AML patient population. On November 2, 2016, we announced that the first patient in the efficacy portion of the Phase II trial was dosed. The full trial design includes approximately 54 evaluable patients with an interim analysis to be performed after 19 patients are treated with the combination. In the event the interim results exceed the primary endpoint in the number of patients that meet or exceed statistically determined thresholds, we may seek to convert the trial into a registration trial for accelerated approval (Figure 9). The multi-site trial is being conducted at leading cancer centers, among them are Weill Medical College of Cornell University, Baylor Scott & White Health, The University of Kansas, New Jersey Hematology Oncology Associates, West Virginia University/Mary Babb Randolph Cancer Center, and MD Anderson. To date, over 50 potential patients have been pre-screened for the efficacy portion of the Phase II trial, 26 patients have been screened, 23 patients have been enrolled and 17 patients have been deemed evaluable with six additional patients currently undergoing treatment. We expect the 19 patient pre-specified analysis to be completed in early 2018, at which time we will address the assessment of these patients.

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**Figure 9. Trial Design**

In addition to the Phase II trial for AML, on December 29, 2017, we announced the initiation of our Phase Ib/IIa clinical trial, which is the safety portion of the Phase II clinical trial, of prexigebersen for the treatment of CML in accelerated and blast phase patients. The trial is being conducted at MD Anderson as a potential salvage therapy for accelerated and blast phase CML patients. Two cohorts of three evaluable patients each will be enrolled to evaluate two doses (60 mg/ $m^2$ and 90 mg/ $m^2$) of prexigebersen in combination with the front-line treatment dasatinib.

Development of new therapeutics for AML and CML in blast crisis can meet currently unmet needs for patients who have very few treatment options due to age, fitness or treatment-resistance of advanced genetically unstable cells. Elderly patients unfit to receive a stem cell transplant or induction therapy face a likelihood of relapse to a more resistant leukemia for which current drug products are not effective. prexigebersen and DNAbilize® technology offer new hope for achieving remission for fragile populations. We believe that the combination of prexigebersen with frontline chemotherapy can provide a way to treat cancer without added toxicity so that the patient can remain under treatment long enough to reach complete remission.

*Indications for Triple Negative Breast Cancer (TNBC) and Inflammatory Breast Cancer (IBC)*

*TNBC and IBC – Background and Common Treatments*. Approximately 15 to 20 percent of breast cancers fall into the category of triple-negative. TNBC tumors do not express estrogen receptors, progesterone receptors, and low human epidermal growth factor receptor 2 (HER2). These negative results mean that the growth of the cancer is not supported by the hormones estrogen and progesterone, or by the presence of HER2 receptors. Therefore, TNBC does not respond to hormonal therapy or therapies that target HER2 receptors. In addition, TNBC tumors are very aggressive. IBC often presents as TNBC and is a rare and very aggressive disease in which cancer cells block lymph vessels in the skin of the breast. This type of breast cancer is called “inflammatory” because the breast often looks swollen and red, or “inflamed.” IBC accounts for 2 to 5% of all breast cancers. IBC tumors are very aggressive and are frequently hormone receptor negative, which means hormone therapies may not be effective. The five-year survival rate for IBC is approximately 40% versus approximately 87% for all breast cancers combined, making IBC a priority area for development of new treatments. The current treatment regimen includes radiation, chemotherapy and surgery. A lack of targeted treatments for these types of breast cancer has led to development of new therapeutics currently in clinical trials. Because of the aggressiveness of these cancers, a systemic treatment is needed. Prexigebersen represents a systemic treatment that targets an important pathway for TNBC and IBC cell growth and has potential to be integral for the treatment of these diseases.

*Prexigebersen Development and Treatment for TNBC and IBC*. In July 2013, we announced that we were initiating preclinical testing of prexigebersen for TNBC and IBC. Our plan is to develop prexigebersen as a targeted therapy against TNBC and IBC. Our treatment goals are two-pronged: the first is to develop prexigebersen as a tumor reduction agent in combination with other approved drugs in preoperative settings for TNBC and IBC patients, and the second is to develop prexigebersen as a drug to treat and control or eliminate cancer metastasis in TNBC and IBC patients. Both of these treatment goals address high need situations for patients. Once the preclinical studies are completed, we believe that the observations that we learned from the original Phase I trial will help us increase the speed of progress for such Phase I trial in TNBC and IBC, as the toxicity profile of prexigebersen is currently well-established.

*Indications for Other Solid Tumors (e.g., Lymphoma, Colon, Thyroid, and Head and Neck Cancers)*

Cancers of colon, thyroid, head and neck, and lymphoma are solid tumors which utilize the same signaling pathway as TNBC and IBC, which involve the Grb2 protein. It has been proposed that prexigebersen may have clinical efficacy in these indications due to the overlapping similarity of the mechanisms of their growth and proliferation. As our program for prexigebersen continues to develop, it is anticipated that these indications will be assessed in preclinical research.

In recently completed preclinical models, prexigebersen effectively penetrated ovarian tumors and has demonstrated clinical benefit both as a monotherapy and in combination with standard frontline therapies. Bio-Path plans to initiate a Phase I clinical trial of prexigebersen targeting several solid tumors types in 2018.

***BP1002***

BP1002, also known by its scientific name as Liposomal Bcl-2, is our second liposome delivered antisense drug candidate. BP1002 is intended to target the lymphoma and certain solid tumor markets. Clinical targets for BP1002 include lymphoma, breast cancer, colon cancer, prostate cancer and leukemia. We believe that BP1002 has the potential to treat 40% to 60% of solid tumors.

Bcl-2 is a protein that is involved in regulating apoptosis, or programmed cell death. Apoptosis is a physiologic mechanism of cell turnover by which cells actively commit suicide in response to aberrant external