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 (State or other jurisdiction of incorporation or organization)	87-0652870 (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.