INVIVO THERAPEUTICS HOLDINGS CORP.
Form 10-K
March 04, 2016

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Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

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

FOR THE FISCAL YEAR ENDED DECEMBER 31, 2015

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

FOR THE TRANSITION PERIOD FROM TO
COMMISSION FILE NUMBER 000-52089

INVIVO THERAPEUTICS HOLDINGS CORP.

(Exact name of registrant as specified in its charter)

Nevada	**36-4528166**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
One Kendall Square, Suite B14402, Cambridge, Massachusetts	**02139**
(Address of principal executive offices)	(Zip Code)

(617) 863-5500
Registrant's telephone number, including area code

Securities registered pursuant to Section 12(b) of the Act:

Title of each class to be so registered	**Name of exchange on which registered**
Common Stock, $0.00001 par value	The Nasdaq Stock Market, LLC

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

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

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

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 ý No o

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§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 ý No o

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

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

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

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 30, 2015, the last business day of the registrant's most recently completed second fiscal quarter, was $433,011,482, based on a per share price of $16.15, which was the closing price of the registrant's common stock on the Nasdaq Capital Market on such date.

As of February 26, 2016, the number of shares outstanding of the registrant's common stock, $0.00001 par value per share, was 27,597,896.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2016 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein. Such proxy statement will be filed with the Securities and Exchange Commission within 120 days of the registrant's fiscal year ended December 31, 2015.

Table of Contents

INVIVO THERAPEUTICS HOLDINGS CORP.
ANNUAL REPORT ON FORM 10-K
FOR THE YEAR ENDED DECEMBER 31, 2015

TABLE OF CONTENTS

Table of Contents

PART I
SPECIAL 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"). Statements, other than statements of historical facts, contained in this Annual Report on Form 10-K regarding future events, our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "may," "might," "will," "should," "intends," "expects," "plans," "goals," "projects," "anticipates," "believes," "estimates," "predicts," "potential," or "continue" or the negative of these terms or other comparable terminology, and include statements about the market potential for treatment of acute and chronic spinal cord injury, the sufficiency of our existing capital resources for continuing operations in 2016, the safety, feasibility, and clinical effectiveness of our *Neuro-Spinal Scaffold* implant, the expected completion of our pivotal probable benefit study of the *Neuro-Spinal Scaffold* and its related clinical development, and our ability to develop collaborations and partnerships to support our business plan. These forward-looking statements are only predictions, are uncertain and involve substantial known and unknown risks, uncertainties and other factors which may cause our actual results, levels of activity or performance to be materially different from any future results, levels of activity or performance expressed or implied by these forward-looking statements. Such factors include, among others, the following:

- our limited operating history and history of net losses;
- our ability to raise substantial additional capital to finance our planned operations and to continue as a going concern;
- our ability to successfully commercialize our current and future product candidates, including our *Neuro-Spinal Scaffold*;
- our ability to successfully complete clinical trials and obtain and maintain regulatory approval of our product candidates;
- our ability to protect and maintain our intellectual property and licensing arrangements;
- our reliance on third parties to conduct testing and clinical trials;
- market acceptance of our technology and products;
- our ability to promote, manufacture and sell our products, either directly or through collaborative and other arrangements with third parties;
- our ability to attract and retain key personnel; and
- other factors set forth in the "Risk Factors" section of this Annual Report on Form 10-K and in subsequent filings we make with the Securities and Exchange Commission.

We cannot guarantee future results, levels of activity or performance. You should not place undue reliance on these forward-looking statements, which speak only as of the date of this Annual Report on Form 10-K. These cautionary statements should be considered with any written or oral forward-looking statements that we may issue in the future. Except as required by applicable law, including the securities laws of the United States, we do not intend to update any of the forward-looking statements to conform these statements to reflect actual results, later events or circumstances or to reflect the occurrence of unanticipated events.

As used herein, "we," "us," "our" or the "Company" means InVivo Therapeutics Holdings Corp., together with its consolidated subsidiaries, unless otherwise noted.

Table of Contents

Item 1. BUSINESS

Overview

We are a research and clinical-stage biomaterials and biotechnology company with a focus on treatment of spinal cord injuries (SCI). Our mission is to redefine the life of the SCI patient, and we are developing treatment options intended to provide meaningful improvement in patient outcomes following SCI. Our approach to treating acute SCIs is based on our investigational Neuro Spinal Scaffold implant, an investigational bioresorbable polymer scaffold that is designed for implantation at the site of injury within a spinal cord contusion and is intended to treat acute spinal cord injury. We believe the Neuro Spinal Scaffold implant is the only SCI therapy in development focused solely on treating acute SCI directly at the epicenter of the injury, and incorporates intellectual property licensed under an exclusive, world-wide license from Boston Children's Hospital ("BCH") and the Massachusetts Institute of Technology ("MIT"). We are continually evaluating other technologies and therapeutics that may be complementary to our development of the *Neuro-Spinal Scaffold* implant or offer the potential to bring us closer to our goal of redefining the life of the SCI patient. Recently we entered into exclusive license/assignment agreements with the University of California, San Diego and James Guest, M.D., Ph.D. covering delivery methods and devices for our pre-clinical Bioengineered Neural Trails injection program.

Market Opportunity

Our clinical program is intended to address the lack of successful treatments for SCIs. The current management of acute SCI is a surgical approach consisting of spine stabilization and an external decompression procedure of uncertain value. We believe the market opportunity for our *Neuro-Spinal Scaffold* implant is significant. It is estimated that approximately 276,000 people are currently living in the United States with paralysis due to spinal cord injury (chronic SCI), and approximately 12,500 individuals in the United States will become fully or partially paralyzed each year (acute SCI). The regulatory approval pathway for a Humanitarian Device Exemption (HDE) we are initially pursuing would, if U.S. Food and Drug Administration (FDA) approval is granted, cover a potential population of up to 4,000 acute SCI patients each year. This population includes patients afflicted with complete spinal cord injury, i.e., paraplegia or tetraplegia, and excludes gunshot or other penetrating wounds). SCI can lead to permanent paralysis, sensory impairment, and autonomic, bowel, bladder, and sexual dysfunction. Future products, which may include use of stem cells or drug ingredients may enable the treatment of a broader population such as patients with incomplete and/or chronic paralysis and would require separate regulatory approval.

Since 1973, the National Spinal Cord Injury Statistical Center ("NSCISC") at the University of Alabama has been commissioned by the U.S. government to maintain a national database of spinal cord injury statistics. The financial impact of spinal cord injuries, as reported by the NSCISC, is substantial. Direct costs, which include hospital and medical expenses, modification of the home, and personal assistance, are highest in the first year after injury. According to the fact sheet published by NSCISC titled "Spinal Cord Injury Facts and Figures at a Glance" in conjunction with its 2015 Annual Report, (i) during the first year, average "cost of care" ranges from $347,484 to $1,064,716, depending on the severity of the injury, (ii) the net present value ("NPV") to maintain a quadriplegic injured at age 25 for life is $4,724,181, and (iii) the NPV to maintain a paraplegic injured at age 25 for life is $2,310,104. These costs place a tremendous financial burden on families, insurance providers, and government agencies. Moreover, despite such a significant financial investment, the patient often remains disabled for life because current medical interventions address only the symptoms of SCI rather than the underlying neurological cause. We believe our approach could represent an important advance in the treatment of SCIs.

Table of Contents

The ASIA Impairment Scale: The American Spinal Injury Association (ASIA) in collaboration with the International Spinal Cord Society (ISCOS) has developed a neurologic examination tool for assessing spinal cord injury known as the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). Results of the ISNCSCI examination are used to determine the ASIA Impairment Scale (AIS) classification.

Patients with complete spinal cord injury are classified as AIS A. Patients with incomplete spinal cord injury have partial sensory and/or motor function below the level of injury and are classified as AIS B (partial sensory function), AIS C (partial sensory and motor function) or AIS D (partial sensory and increased motor function, i.e. can move at least half of the muscles against gravity). Patients who have a complete return of sensory and motor function are classified as AIS E.

These classifications are based upon the ISNCSCI examination in which the examiner performs a neurologic examination to assess sensory function of the entire body and motor function of the upper and lower extremities.

Our Clinical and Pre-Clinical Programs

We currently have a clinical development program for acute SCI and a pre-clinical development program for chronic SCI.

Neuro-Spinal Scaffold **implant for acute SCI**

Our leading product under development is our *Neuro-Spinal Scaffold* implant, an investigational bioresorbable polymer scaffold that is designed for implantation at the site of injury within a spinal cord contusion. The *Neuro-Spinal Scaffold* implant is intended to provide support to the surrounding tissue after injury, minimizing expansion areas of necrosis, and supporting endogenous healing/repair processes following injury. This form of appositional healing harbors the promise of sparing white matter, increasing neural sprouting, and diminishing post-traumatic cyst formation.

The *Neuro-Spinal Scaffold* implant is composed of two biocompatible and bioresorbable polymers that are cast to form a highly porous investigational product:

Poly lactic-*co*-glycolic acid (PLGA), a polymer that is widely used in resorbable sutures and provides the biocompatible support for *Neuro-Spinal Scaffold* implant; and

Poly-L-Lysine (PLL), a positively charged polymer commonly used to coat surfaces in order to promote cellular attachment.

Because of the complexity of spinal cord injuries, it is likely that multi- modal therapies will be required in order to maximize positive outcomes in SCI patients. In the future, we may attempt to further enhance the performance of our *Neuro-Spinal Scaffold* by multiple combination strategies involving electrostimulation devices, additional biomaterials, drugs approved by the U.S. Food & Drug Administration ("FDA"), or growth factors.

We expect the *Neuro-Spinal Scaffold* will be regulated by the FDA as a Class III medical device, please see below "Government Regulation" for additional information on the regulatory pathway for the *Neuro-Spinal Scaffold.*

Pre-Clinical and Non-Clinical Studies relating to the Neuro-Spinal Scaffold

SCI can result in permanent paralysis, sensory impairment, and autonomic, bowel, bladder, and sexual dysfunction. These functional deficits result from damage to or loss of cells (neurons and glia) in the affected region of the spinal cord, either from the initial mechanical trauma or through secondary mechanisms that persists for several weeks. The ability of potential treatments for SCI to mitigate loss of function or promote recovery can be evaluated with non- clinical models using different species and

Table of Contents

different methods of inducing SCI. In our pre-clinical studies, we utilized rat, non-human primate, and pig models because each exhibits a pattern of neuropathology following SCI that is similar to human SCI. Hemisection injury models, in which sections of spinal cord are surgically removed, are useful in the evaluation of treatment strategies that involve device implantation. Unilateral hemisection models preserve function on one side of the cord, resulting in improved recovery of bladder and bowel function. We, therefore, evaluated the bioresorbable polymer scaffold device in both rats and non-human primates with unilateral hemisection injury. Because most human SCIs are non-penetrating contusion injuries resulting from rapid compression of spinal tissue by intrusion of bone or disc material following mechanical disruption of the vertebral column, we also evaluated the bioresorbable polymer scaffold device in rat and pig models of spinal contusion injury.

The first non-clinical study was conducted by founding scientists of our wholly-owned subsidiary in rats with surgically induced unilateral spinal cord hemisection injury. This study (see Teng, Y. D., Lavik, E. B., Qu, X., Park, K. I., Ourednik, J., Zurakowski, D., Langer, R., and Snyder, E. Y., *Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells*, Proceedings of the National Academy of Sciences 99, pg. 3024-3029, 2002) demonstrated the baseline safety and efficacy of porous, biodegradable scaffolds fabricated from PLGA-PLL polymer. Subsequently, the safety and efficacy of implantation of the bioresorbable polymer scaffold device was evaluated in rats with spinal cord contusion injury. Initial studies indicated that 24 hours after contusion injury was an appropriate time for device implantation based on both histological evaluation and ex vivo MRI techniques. Based on these results, larger rat contusion studies were performed in our laboratory. Functional recovery was evaluated with the 21-point Basso, Beattie, and Bresnahan (BBB) locomotor rating scale to assess open field locomotion. In this model, the BBB score was not improved by the scaffold device. However, implantation of the bioresorbable polymer scaffold device into the necrotic zone of the injured spinal cord resulted in appositional healing and tissue remodeling that preserved spinal cord architecture. Morphometric analysis of spinal sections stained with hematoxylin & eosin revealed that non-implanted rats with contusion injury developed large cavities surrounded by a thin rim of spared white matter. In contrast, rats treated with the implanted bioresorbable polymer scaffold device demonstrated decreased cavity volume along with increased amounts of spared and remodeled tissue at the lesion epicenter. Cavitation following spinal contusion injury, particularly if progressive, can impair recovery and result in serious clinical symptoms. These results indicate that implantation of the bioresorbable polymer scaffold device in the acutely injured rat spinal cord can provide the benefit of preserving spinal cord architecture through reduced cavitation, and promotion of white matter sparing and tissue remodeling.

The spinal cord anatomy of non-human primates is very similar to that of humans. We performed a series of studies in African green monkeys in order to evaluate the bioresorbable polymer scaffold device in a non-human primate. Our first study in African green monkeys established that unilateral thoracic hemisection SCI (a new model in this species) produced a consistent functional deficit, and we observed a consistently positive response to scaffold implantation (see Pritchard, C. D., Slotkin, J. R., Yu, D., Dai, H., Lawrence, M. S., Bronson, R. T., Reynolds, F. M., Teng, Y. D., Woodard, E. J., and Langer, R. S. *Establishing a model spinal cord injury in the African green monkey for the preclinical evaluation of biodegradable polymer scaffolds seeded with human neural stem cells*, Journal of Neuroscience Methods 188, pg. 258-269, 2010). We then conducted two larger studies evaluating the safety and efficacy of the bioresorbable polymer scaffold device in the African green monkey. The extent and time course of functional recovery in biopolymer implant treated primates was assessed with video capture and KinemaTracer evaluation of locomotor behavior with synchronous EMG recording along with locomotor observation rating. When the results of these two studies were combined and analyzed together, we found that implantation of the bioresorbable polymer scaffold device resulted in an increase in remodeled tissue in the region of the hemisection compared to non-implant controls, and improved recovery of locomotion in subjects with full unilateral hemisection lesions.

Table of Contents

The pig has been used as a large animal model of spinal cord contusion injury due to similarities in size and structure to the human spinal cord. We evaluated the surgical feasibility of implanting the bioresorbable polymer scaffold device in a spinal cord after a contusion injury in the pig model. Severe contusion injuries were created in Gottingen pigs with a weight drop apparatus. At approximately 4, 6, and 24 hours after contusion injury, pigs underwent the bioresorbable polymer scaffold device surgical implantation procedure. At each time point, a large volume of necro-hemorrhagic fluid and debris rapidly effluxed from the injury site, releasing built-up pressure and resulting in a substantial cavity in the center of the spinal cord. Increased spinal tissue pressure after contusion injury results in reduced blood perfusion and ischemia in damaged spinal tissue, and is an important contributor to the pathophysiology of spinal cord injury. As part of our study, we placed bioresorbable polymer scaffold devices into the resulting contusion-induced spinal cord cavity. We measured intraspinal pressure (using catheter pressure probes) at the contusion epicenter in the pigs before, during, and after the surgical procedure. As expected, contusion injury elevated intraspinal tissue pressure compared to normal values. Surgical implantation of the bioresorbable polymer scaffold device resulted in a return of intraspinal tissue pressure to physiologically normal levels.

Taken together, the results from these non-clinical studies in two rat spinal cord injury models, in the African green monkey unilateral hemisection injury model, and the pig contusion injury model, demonstrate that the bioresorbable polymer scaffold device, surgically implanted at the epicenter of the wound after an acute spinal cord injury, acts by appositional healing to spare spinal cord tissue, decrease post-traumatic cyst formation, and decrease spinal cord tissue pressure in preclinical models of spinal cord contusion injury.

Completed Pilot Study

We conducted an early feasibility human pilot study of our *Neuro-Spinal Scaffold* under our approved Investigational Device Exemption application (IDE) for the treatment of complete, traumatic acute spinal cord injury. The FDA approved the study, which was intended to capture the safety and feasibility of the *Neuro-Spinal Scaffold* for the treatment of complete functional spinal cord injury, as well as to gather preliminary evidence of the clinical effectiveness of the *Neuro-Spinal Scaffold*.

The pilot study was initially approved for five subjects in up to six clinical sites across the United States, and was later modified to increase the number of allowable clinical sites to up to 20 and to permit enrollment of up to 10 subjects. The pilot study was initially staggered such that each patient that met the eligibility criteria would be followed for three months prior to enrolling the next patient in the study. In December 2014, barring significant safety issues, the FDA approved an expedited enrollment plan. We enrolled five subjects in the pilot study between October 2014 and September 2015. As discussed below, the FDA has approved a pivotal probable benefit study, the INSPIRE study, that includes data from the patients enrolled in the pilot study.

The INSPIRE Study

Our *Neuro-Spinal Scaffold* implant is currently being studied in a pivotal probable benefit study formally known as The **INSPIRE** Study: **In**Vivo Study of Probable Benefit of the *Neuro-**Spi**nal Scaffold* for Safety and Neurologic **Re**covery in Subjects with Complete Thoracic AIS A Spinal Cord Injury. The FDA approved converting the pilot study into the INSPIRE study in January 2016. The purpose of the study is to evaluate whether the *Neuro-Spinal Scaffold* implant is safe and demonstrates probable benefit for the treatment of complete T2-T12/L1 spinal cord injury. The primary endpoint is defined as the proportion of patients achieving an improvement of at least one AIS grade by 6 months post-implantation.

The INSPIRE study is currently approved to enroll up to 12 patients, but we expect that the FDA will approve the full 20 patients, inclusive of the five pilot patients, following the review of the

Table of Contents

complete 6-month data package for the first five patients. The FDA has requested this data package to include complete and objective comparisons of post-operative and pre-implants magnetic (MRI) findings for each patient to assess the possibility of cyst formation in certain patients. We plan to submit this five-patient, 6-month data package in the second quarter of 2016. We anticipate this will be the only study required for marketing approval under the HDE regulatory pathway. We are targeting completion of the study, which includes completion of enrollment, follow-up, and submission of the HDE application, in 2017.

We have seen promising neurologic outcomes and a favorable profile in the five enrolled pilot study subjects.

Patient	Date of Implantation	Neurologic Level of Injury	Neurologic Outcome to Date
1	Oct. 2014	T11	Converted from AIS A to AIS C at Month 1 with substantial ongoing lower limb motor and sensory improvement through Month 12
2	Jan. 2015	T7	Remains AIS A but with marked bowel and bladder improvement through Month 12
3	June 2015	T4	Converted from AIS A to AIS B at Month 1 with additional sensory improvement (from mid-chest to mid-abdomen) through Month 6
4	Aug. 2015	T3	Remains AIS A at Month 6
5	Sept. 2015	T8	Remains AIS A at Month 3
6	Feb. 2016	T10	In follow up

In February 2016, we received approval of a protocol amendment for The INSPIRE Study. The amended protocol establishes the Objective Performance Criterion (OPC), which is a measure of study success used in clinical studies designed to demonstrate safety and probable benefit in support of a Humanitarian Device Exemption approval. The OPC for The INSPIRE Study is defined as 25% or more of the patients in the study demonstrating an improvement of at least one AIS grade by six months post-implantation. Since The INSPIRE Study is designed to enroll 20 patients with complete (AIS A) spinal cord injuries (inclusive of the 5 patients enrolled in the company's pilot trial), the OPC equates to having five patients convert to any other AIS grade by six months post-implantation.

Bioengineered Neural Trails injection program for chronic SCI

In December 2015, we announced our preclinical Bioengineered Neural Trails injection program for the treatment of chronic spinal cord injury. Bioengineered Neural Trails are injectable combinations of biomaterials and neural stem cells (NSCs) delivered using minimally-invasive surgical instrumentation and techniques to create trails across the chronic injury site. To support this program, we recently entered into an exclusive license agreement with University of California, San Diego and an assignment agreement with James Guest, M.D., Ph.D., for issued patents covering technology related to the Bioengineered Neural Trails program, and we also have filed a provisional application in support of the Bioengineered Neural Trails injection program. We expect that our Bioengineered Neural Trails injection investigational product will be regulated by the FDA as a combination product, and we are targeting a pre-Investigational New Drug meeting with the FDA by the end of 2016. For further information on the regulatory pathway for the Bioengineered Neural Trails injection product, please see "Government Regulation" below.

Intellectual Property

We rely on a combination of patents, licenses, trade secrets and non-disclosure agreements to develop, protect and maintain our intellectual property. Our patent portfolio includes patents and

Table of Contents

patent applications. We seek to develop or obtain intellectual property that we believe might be useful or complementary with our products and technologies, including by way of licenses or acquisitions of other companies or intellectual property from third parties.

We hold an exclusive worldwide license to a broad suite of patents co-owned by BCH and MIT covering the use of a wide range of polymers to treat SCI, and to promote the survival and proliferation of human stem cells in the spinal cord (the "BCH License"). Issued patents and pending patent applications licensed under the BCH License cover the technology underlying our *Neuro-Spinal Scaffold* implant and the use of a wide range of biomaterial scaffolding for treating SCI by itself or in combination with drugs, growth factors or human stem cells. The BCH License covers seven issued United States patents and four issued international patents expiring between 2018 and 2027, and one pending United States patent and 10 pending international patents.

The BCH License has a 15-year term, or as long as the life of the last expiring patent right under the license, whichever is longer, unless terminated earlier by BCH. In connection with our acquisition of the BCH License, we submitted to a 5-year development plan to BCH and MIT that includes certain targets and projections related to the timing of product development and regulatory approvals. We are required to either meet the stated targets and projections in the plan, or notify BCH and revise the plan. BCH has the right to terminate the BCH License for failure by us to either meet the targets and projections in the plan or our failure submit an acceptable revision to the plan within a 60-day cure period after notification by BCH that we are not in compliance with the plan. We are currently in compliance with our plan.

We have the right to sublicense the patents covered by the BCH License, and have full control and authority over the development and commercialization of any products that use the licensed technology, including clinical trial design, manufacturing, marketing, and regulatory filings,. We also own the rights to the data generated pursuant to the BCH License, whether generated by us or a sublicensee. We have the first right of negotiation with BCH and MIT for a 30-day period to any improvements to the intellectual property covered by the BCH License.

We are required to pay certain fees and royalties under the BCH License. We paid an initial fee upon execution of the BCH License and are required to pay an amendment fee if we expand the field of use under the BCH License. We are also required to make milestone payments upon completing various phases of product development, including upon (i) filing with the FDA of the first investigational new drug application and IDE application for a product that uses the licensed technology; (ii) enrollment of the first patient in Phase II testing for a product that uses the licensed technology; (iii) enrollment of the first patient in Phase III testing for a product that uses the licensed technology; (iv) FDA approval of first new drug application or related application for a product that uses the licensed technology, and (v) first market approval in any country outside the United States for a product that uses the licensed technology. Each year prior to the release of a licensed product, we are also required to pay a maintenance fee for the BCH License. Further, we are required to make ongoing payments based on any sublicenses we grant to manufacturers and distributors. Following commercialization, we are required to make ongoing royalty payments equal to a percentage of net sales of any product that uses the licensed technology.

In addition to the rights it licensed under the BCH license, InVivo has additional rights relating to the *Neuro-Spinal Scaffold.* InVivo and MIT co-own patent application No. U.S. 14/232,525 ("Poly((lactic-co-glycolic acid)-b-lysine) and process for synthesizing a block copolymer of PLGA and PLL- (poly-e-cbz-l-lysine)"). InVivo also owns patent application No. U.S. 13/793,231 ("Protective packaging with product preparation features incorporated") and US patent application No. U.S. 13/930,829 ("cupped forceps").

To support our Bioengineered Neural Trails injection program, we recently entered into agreements with the University of California, San Diego (UC San Diego) and

Table of Contents

James Guest, M.D., Ph.D., to expand our intellectual property portfolio. We entered into an exclusive license agreement with UC San Diego for an issued patent and into an assignment agreement with Dr. Guest for an issued patent. We also have filed a provisional application in support of the Bioengineered Neural Trails injection program with the USPTO.

Government Regulation

The testing, manufacturing, and potential labeling, advertising, promotion, distribution, import and marketing of our products are subject to extensive regulation by governmental authorities in the U.S. and in other countries. In the U.S., the FDA, under the Public Health Service Act, the Federal Food, Drug and Cosmetic Act (FDCA), and their implementing regulations, regulates biologics and medical device products. In addition, our products under development are subject to extensive regulation by other U.S. federal and state regulatory bodies and comparable authorities in other countries. To ensure that medical products distributed domestically are safe and effective for their intended use, the FDA and comparable authorities in other countries have imposed regulations that govern, among other things, the following activities that we or our partners perform or will perform:

- product design and development;
- product testing;
- product manufacturing;
- product labeling;
- product storage;
- premarket clearance, approval or CE marking of products;
- advertising and promotion;
- product marketing, sales and distribution; and
- post-market surveillance reporting, including reporting of death or serious injuries.

The labeling, advertising, promotion, marketing and distribution of biopharmaceuticals, or biologics and medical devices also must be in compliance with the FDA requirements which include, among others, standards and regulations for off-label promotion, industry sponsored scientific and educational activities, promotional activities involving the internet, and direct-to-consumer advertising. In addition, the Federal Trade Commission, or FTC, also regulates the advertising of many medical devices. The FDA and FTC have very broad enforcement authority, and failure to abide by these regulations can result in penalties, including the issuance of a warning letter directing us to correct deviations from regulatory standards and enforcement actions that can include seizures, injunctions and criminal prosecution. . In addition, under the federal Lanham Act and similar state laws, competitors and others can initiate litigation relating to advertising claims.

The FDA has broad post-market and regulatory enforcement powers. As with medical devices, manufacturers of biologics and combination products are subject to unannounced inspections by the FDA to determine compliance with applicable regulations, and these inspections may include the manufacturing facilities of some of our subcontractors. Failure by manufacturers or their suppliers to comply with applicable regulatory requirements can result in enforcement action by the FDA or other regulatory authorities. Potential FDA enforcement actions include:

- warning letters, fines, injunctions, consent decrees and civil penalties;

unanticipated expenditures to address or defend such actions

customer notifications for repair, replacement, refunds;

Table of Contents

recall, detention or seizure of our products;

operating restrictions or partial suspension or total shutdown of production;

refusing or delaying our requests for 510(k) clearance or premarket approval of new products or modified products;

operating restrictions;

withdrawing 510(k) clearances on PMA approvals that have already been granted;

refusal to grant export approval for our products; or

criminal prosecution.

FDA Regulation Medical Device Products

FDA's Premarket Clearance and Approval Requirements

Unless an exemption applies, each medical device we wish to commercially distribute in the U.S. will require either prior 510(k) clearance or prior premarket approval from the FDA. The FDA classifies medical devices into one of three classes. Devices deemed to pose lower risk are placed in either Class I or II, which requires the manufacturer to submit to the FDA a premarket notification which must be cleared by the FDA before the medical device may be distributed commercially. This process is known as 510(k) clearance. Most Class I devices are exempt from this requirement. Devices deemed by the FDA to pose the greatest risk, such as life-sustaining, life-supporting or implantable devices, or devices deemed not substantially equivalent to a previously cleared 510(k) device, are placed in Class III, requiring premarket approval or approval of a humanitarian device exemption. We expect the *Neuro-Spinal Scaffold* implant will be regulated by the FDA as a Class III medical device.

Premarket Approval Pathway

A premarket approval application must be submitted if the device cannot be cleared through the 510(k) process. A premarket approval application, or PMA, must be supported by extensive data including, but not limited to, technical, preclinical and other nonclinical, clinical, and manufacturing and labeling information to demonstrate to the FDA's satisfaction the safety and effectiveness of the device for its intended use.

If the FDA determines that a PMA submission is sufficiently complete, the FDA will accept the application for filing and begin an in-depth review of the submitted information. By statute, the FDA has 180 days to review the "accepted application," although, generally, review of the application can take between one and three years, and it may take significantly longer. During this review period, the FDA may request additional information or clarification of information already provided. Also during the review period, an advisory panel of experts from outside the FDA may be convened to review and evaluate the application and provide recommendations to the FDA as to the approvability of the device. In addition, the FDA will conduct a preapproval inspection of the manufacturing facility to ensure compliance with quality system regulations. New PMAs or PMA supplements are required for modifications that affect the safety or effectiveness of the device, including, for example, certain types of modifications to the device's indication for use, manufacturing process, labeling and design. Premarket approval supplements often require submission of the same type of information as a PMA, except that the supplement is limited to information needed to support any changes from the device covered by the original PMA, and may not require as extensive clinical data or the convening of an advisory panel.

Table of Contents

Humanitarian Device Exemption

Alternatively, a Class III device may qualify for FDA approval to be distributed under a Humanitarian Device Exemption (HDE) rather than a PMA. For a device to be eligible for an HDE, it must be first designated by the FDA as a Humanitarian Use Device (HUD) intended to benefit patients in the treatment or diagnosis of a disease or condition that affects fewer than 4,000 individuals in the United States per year. The HDE also requires that there must be no other comparable device available to provide therapy for this condition. An HDE application is similar in form and content to a PMA application and, although exempt from the effectiveness requirements of a PMA, an HDE does require sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use. In addition, a HUD may only be used in facilities that have established a local institutional review board, or IRB, to supervise clinical testing of devices, and after an IRB has approved the use of the device to treat or diagnose the specific disease.

In addition, except in certain circumstances, products approved under an HDE cannot be sold for an amount that exceeds the costs of research and development, fabrication, and distribution of the device (i.e., for profit). Currently, a product is only eligible to be sold for profit after receiving HDE approval if the device (1) is intended for the treatment or diagnosis of a disease or condition that occurs in pediatric patients or in a pediatric subpopulation, and such device is labeled for use in pediatric patients or in a pediatric subpopulation in which the disease or condition occurs; or (2) is intended for the treatment or diagnosis of a disease or condition that does not occur in pediatric patients or that occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe. If an HDE-approved device does not meet either of the eligibility criteria, the device cannot be sold for profit. We expect our *Neuro-Spinal Scaffold* will meet the eligibility criteria to be sold for a profit.

Clinical Trials

Clinical trials are almost always required to support a PMA or HDE application. If the device presents a "significant risk" to human health as defined by the FDA, the FDA requires the device sponsor to submit an investigational device exemption application, or IDE, to the FDA and obtain IDE approval prior to commencing the human clinical trials. The IDE must be supported by appropriate data, such as animal and laboratory testing results, showing that it is safe to test the device in humans and that the testing protocol is scientifically sound. The IDE must be approved in advance by the FDA for a specified number of patients, unless the product is deemed a "non-significant risk" device in which case, and IDE will not be required, although the clinical trial must meet other requirements including IRB approval. Clinical trials for a significant risk device may begin once the IDE is approved by the FDA and the appropriate IRB at each clinical trial sites. Future clinical trials may require that we obtain an IDE from the FDA prior to commencing clinical trials and that the trial be conducted with the oversight of an IRB at the clinical trial site. Our clinical trials must be conducted in accordance with FDA regulations and federal and state regulations concerning human subject protection, including informed consent and healthcare privacy. A clinical trial may be suspended by FDA or at a specific site by the relevant IRB at any time for various reasons, including a belief that the risks to the trial participants outweigh the benefits of participation in the clinical trial. Even if a clinical trial is completed, the results of our clinical testing may not demonstrate the safety and efficacy of the device, or may be equivocal or otherwise not be sufficient to obtain approval of our product.

Table of Contents

Pervasive and Continuing FDA Regulation

After a device is placed on the market, numerous regulatory requirements continue to apply. These include:

- product listing and establishment registration, which helps facilitate FDA inspections and other regulatory action;
- Quality System Regulation, or QSR, which requires manufacturers, including third-party manufacturers, to follow stringent design, testing, control, documentation and other quality assurance procedures during all aspects of the manufacturing process;
- labeling regulations and FDA prohibitions against the promotion of products for uncleared or unapproved indications or other off-label uses;
- clearance of product modifications that could significantly affect safety or efficacy or that would constitute a major change in intended use of one of our cleared devices;
- approval of product modifications that affect the safety or effectiveness of one of our approved devices;
- medical device reporting regulations, which require that manufacturers comply with FDA requirements to report if their device may have caused or contributed to a death or serious injury, or has malfunctioned in a way that would likely cause or contribute to a death or serious injury if the malfunction of the device or a similar device were to recur;
- post-approval restrictions or conditions, including post-approval study commitments;
- post-market surveillance regulations, which apply when necessary to protect the public health or to provide additional safety and effectiveness data for the device;
- the FDA's recall authority, whereby it can ask, or under certain conditions order, device manufacturers to recall from the market a product that is in violation of governing laws and regulations;
- regulations pertaining to voluntary recalls; and
- notices of corrections or removals.

We and any third-party manufacturers that we use must register with the FDA as medical device manufacturers and must obtain all necessary state permits or licenses to operate our business. As manufacturers, we and any third-party manufacturers that we use are subject to announced and unannounced inspections by the FDA to determine our compliance with quality system regulation and other regulations. We have not yet been inspected by the FDA. We believe that we are in substantial compliance with quality system regulation and other regulations.

Failure to comply with applicable regulatory requirements can result in enforcement action by the FDA, which may include any of the following sanctions:

- warning letters, fines, injunctions, consent decrees and civil penalties;

unanticipated expenditures to address or defend such actions

customer notifications for repair, replacement, refunds;

recall, detention or seizure of our products;

operating restrictions or partial suspension or total shutdown of production;

refusing or delaying our requests for 510(k) clearance or premarket approval of new products or modified products;

Table of Contents

operating restrictions;

withdrawing 510(k) clearances on PMA approvals that have already been granted;

refusal to grant export approval for our products; or

criminal prosecution.

Regulatory Pathway for Neuro-Spinal Scaffold implant

We expect the *Neuro-Spinal Scaffold* will be regulated by the FDA as a Class III medical device. A Class III medical device typically will require FDA approval of a Pre-Market Approval (PMA) Application before we can begin selling the product in the United States. A PMA application must be supported by extensive data including, but not limited to, technical information regarding device design and development, preclinical and clinical trials, data and manufacturing and labeling to support the FDA's determination that there is reasonable assurance that the device is safe and effective for its intended use.

Alternatively, a Class III device may qualify for FDA approval to be distributed under a Humanitarian Device Exemption (HDE) rather than a PMA. For a device to be eligible for an HDE, it must be first designated by the FDA as a Humanitarian Use Device (HUD) intended to benefit patients in the treatment or diagnosis of a disease or condition that affects fewer than 4,000 individuals in the United States per year. The FDA granted HUD designation for our *Neuro-Spinal Scaffold* implant in 2013. In 2015, we received conditional approval from the FDA to convert our ongoing pilot study into a pivotal probable benefit study, which condition to approval was lifted, and for which full approval subsequently granted, in January 2016.

In the future, if our *Neuro-Spinal Scaffold* is approved via either the PMA or HDE pathway, modifications or enhancements that could significantly affect the safety or effectiveness of the device or that constitute a major change to the intended use of the device will require new PMA or HDE application and approval. Other changes may require a supplement or other change notification that must be reviewed and approved by the FDA. Modified devices for which a new PMA or HDE application, supplement or notification is required cannot be distributed until the application is approved by the FDA. An adverse determination or a request for additional information could delay the market introduction of new products, which could have a material adverse effect on our business, financial condition and results of operations. We may not be able to obtain PMA or HDE approval in a timely manner, if at all, for the *Neuro-Spinal Scaffold* implant or any future devices or modifications to *Neuro-Spinal Scaffold* implant or such devices for which we may submit a PMA or HDE application.

European Economic Area (EEA)

Sales of medical devices are subject to foreign government regulations, which vary substantially from country to country. In order to market our products outside the United States, we must obtain regulatory approvals or CE Certificates of Conformity and comply with extensive safety and quality regulations. The time required to obtain approval by a foreign country or to obtain a CE Certificate of Conformity may be longer or shorter than that required for FDA clearance or approval, and the requirements may differ. In the EEA, we are required to obtain Certificates of Conformity before drawing up an EC Declaration of Conformity and affixing the CE mark to our medical devices. Many other countries, such as Australia, India, New Zealand, Pakistan and Sri Lanka, accept CE Certificates of Conformity or FDA clearance or approval although others, such as Brazil, Canada and Japan require separate regulatory filings.

In the EEA, our devices are required to comply with the Essential Requirements laid down in Annex I to the Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, known as the Medical Devices Directive. Compliance with these requirements entitles us to affix the CE mark to our

Table of Contents

medical devices, without which they cannot be commercialized in the EEA. To demonstrate compliance with the Essential Requirements laid down in Annex I to the Medical Devices Directive and obtain the right to affix the CE mark to our medical devices, we must undergo a conformity assessment procedure, which varies according to the type of medical device and its classification. Except for low risk medical devices (Class I with no measuring function and which are not sterile), where the manufacturer can issue an EC Declaration of Conformity based on a self-assessment of the conformity of its products with the Essential Requirements laid down in the Medical Devices Directive, a conformity assessment procedure requires the intervention of a Notified Body. This is an organization designated by the competent authorities of a EEA country to conduct conformity assessments. The Notified Body would typically audit and examine products' Technical File and the quality system for the manufacture, design and final inspection of our devices before issuing a CE Certificate of Conformity demonstrating compliance with the relevant Essential Requirements laid down in Annex I to the Medical Devices Directive. Following the issuance of this CE Certificate of Conformity, we can draw up an EC Declaration of Conformity and affix the CE mark to the products covered by this CE Certificate of Conformity and the EC Declaration of Conformity. We have not applied for CE Mark for the *Neuro-Spinal Scaffold*.

After the product has been CE marked and placed on the market in the EEA, we must comply with a number of regulatory requirements relating to:

registration/notification of medical devices in individual EEA countries;

pricing and reimbursement of medical devices;

establishment of post-marketing surveillance and adverse event reporting procedures;

Field Safety Corrective Actions, including product recalls and withdrawals;

marketing and promotion of medical devices; and

interactions with physicians.

Failure to comply with these requirements may result in enforcement measures being taken against us by the competent authorities of the EEA countries. These can include fines, administrative penalties, compulsory product withdraws, injunctions and criminal prosecution. Such enforcement measures would have an adverse effect on our capacity to market our products in the EEA and, consequently, on our business and financial position. Such failures may also lead to cancelation, suspension, or variation of our CE Certificates of Conformity by our Notified Body.

Further, the advertising and promotion of our products in the EEA is subject to the provisions of the Medical Devices Directive, Directive 2006/114/EC concerning misleading and comparative advertising, and Directive 2005/29/EC on unfair commercial practices, as well as other national legislation in the individual EEA countries governing the advertising and promotion of medical devices. These laws may limit or restrict the advertising and promotion of our products to the general public and may impose limitations on our promotional activities with healthcare professionals.

FDA Regulation Combination Products/Biologics

We believe that our Bioengineered Neural Trails under development may be defined as combination products consisting of two or more regulated components, that is, a biologic and a medical device. In the U.S., a combination product is assigned by the FDA to one of the agency's centers, such as the Center for Biologics Evaluation and Research (CBER) or Center for Devices and Radiological Health (CDRH) with the chosen center to take the lead in pre-marketing review and approval of the combination product. Other FDA centers also may review the product in regard to matters that are within their expertise. The FDA selects the lead center based on an assessment of the combination

Table of Contents

product's "primary mode of action." Some products also may require approval or clearance from more than one FDA center.

To determine which FDA center or centers will review a combination product submission, companies may submit a request for assignment to the FDA. Those requests may be handled formally or informally. In some cases, jurisdiction may be determined informally based on FDA experience with similar products. However, informal jurisdictional determinations are not binding on the FDA. Companies also may submit a formal Request for Designation to the FDA Office of Combination Products. The Office of Combination Products will review the request and make its jurisdictional determination within 60 days of receiving a Request for Designation. Stem cell-based therapies are typically regulated under the jurisdiction of CBER typically requiring an Investigational New Drug (IND) application and a biologic license application, or BLA, for marketing approval.

The IND and BLA Approval Process

Biological products must satisfy the requirements of the Public Health Services Act and its implementing regulations. In order for a biologic product to be legally marketed in the U.S., the product must have a BLA approved by the FDA.

The steps for obtaining FDA approval of a BLA to market a biopharmaceutical, or biologic product in the U.S. include:

- completion of preclinical laboratory tests, animal studies and formulation studies under the FDA's GLP regulations;
- submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials may begin and which must include IRB approval at each clinical site before the trials may be initiated;
- performance of adequate and well-controlled clinical trials in accordance with good clinical practices, or GCPs, to establish the safety, purity, and potency of the product for each indication;
- submission to the FDA of a BLA, which contains detailed information about the chemistry, manufacturing and controls for the product, reports of the outcomes of the clinical trials, and proposed labeling and packaging for the product;
- the FDA's acceptance of the BLA for filing;
- for any biological product containing an active ingredient not previously approved, automatic referral to an appropriate advisory committee for review prior to approval, unless the FDA decides otherwise;
- satisfactory review of the contents of the BLA by the FDA, including the satisfactory resolution of any questions raised during the review or by the advisory committee, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP requirements, to assure that the facilities, methods and controls are adequate to ensure the product's identity, strength, quality and purity; and
- FDA approval of the BLA.

Preclinical or nonclinical studies include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies, and may be conducted before or after an IND is submitted.

An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about issues such as the conduct of the trials as outlined in

16

Table of Contents

the IND. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials can proceed.

Clinical trials are subject to extensive monitoring, recordkeeping and reporting requirements. Clinical trials must be conducted under the oversight of an IRB for the relevant clinical trial sites and must comply with FDA requirements, including but not limited to those relating to GCP. Clinical trials involving drugs and biologics are typically conducted in three sequential phases. The phases may overlap or be combined. A fourth, or post-approval, phase may include additional clinical trials. These phases are described generally below.

Phase I. Phase I clinical trials involve the initial introduction of the drug into healthy human subjects to test for safety, dosage tolerance, absorption, metabolism, distribution and excretion. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

Phase II. Phase II clinical trials usually involve studies in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific, targeted indications, to determine dosage tolerance and optimal dosage, and to identify possible adverse effects and safety risks.

Phase III. Phase III involves studies undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical sites. These studies are intended to establish the overall risk-benefit ratio of the product and provide an adequate basis for product labeling.

Post-Approval (Phase IV). Post-approval clinical trials are required of or agreed to by a sponsor as a condition of, or subsequent to marketing approval. Further, if the FDA becomes aware of new safety information about an approved product, it is authorized to require post-approval trials of the biological product. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication and to document a clinical benefit in the case of biologics approved under accelerated approval regulations. Failure to promptly conduct Phase IV clinical trials could result in withdrawal of approval for products approved under accelerated approval regulations.

Clinical testing may not be completed successfully within any specified time period, if at all. The FDA closely monitors the progress of each of the three phases of clinical trials that are conducted under an IND and may, at its discretion, reevaluate, alter, suspend, or terminate the testing based upon the data accumulated to that point and the FDA's assessment of the risk/benefit ratio to the patient. The FDA or the sponsor may suspend or terminate clinical trials at any time for various reasons, including a finding that the subjects or patients are being exposed to an unacceptable health risk. The FDA can also request that additional preclinical studies or clinical trials be conducted as a condition to product approval. Additionally, new government requirements may be established that could delay or prevent regulatory approval of our products under development. Furthermore, IRBs have the authority to suspend clinical trials in their respective institutions at any time for a variety of