Flexion Therapeutics Inc
Form 10-K
February 28, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(MARK ONE)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2018

or

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 001-36287

Flexion Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

| | |
|---|---|
| Delaware | 26-1388364 |
| (State or other jurisdiction of incorporation or organization) | (I.R.S. Employer Identification No.) |
| 10 Mall Road, Suite 301 | |
| Burlington, Massachusetts | 01803 |
| (Address of principal executive offices) | (Zip Code) |

(781) 305-7777

(Registrant's telephone number, including area code)

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

| Title of each class | Name of each exchange on which registered |
|---|---|
| Common Stock, par value $0.001 per share | 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 No .

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 .

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 No

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted 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 such files). Yes 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 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.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or 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 | Smaller reporting company |
| 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 by Rule 12b-2 of the Act). Yes No

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant based on the last reported sales price of the common stock on June 30, 2018 was approximately $859,717,982.

The number of outstanding shares of the registrant's common stock as of February 25, 2019 was 37,992,513 .

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's proxy statement to be filed with the Securities and Exchange Commission pursuant to Regulation 14A in connection with the registrant's 2019 Annual Meeting of Stockholders, which will be filed subsequent to the date hereof, are incorporated by reference into Part III of this Form 10-K. Such proxy statement will be filed with the Securities and Exchange Commission not later than 120 days following the end of the registrant's fiscal year ended December 31, 2018.

FLEXION THERAPEUTICS, INC.

FORM 10-K—ANNUAL REPORT

For the Fiscal Year Ended December 31, 2018

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PART I

Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K, or this Annual Report, contains "forward-looking statements"— that is, statements related to future, not past, events—as defined in Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, that reflect our current expectations regarding our future discovery, development and commercialization activities, results of operations, financial condition, cash flows, performance and business prospects, and opportunities, as well as assumptions made by, and information currently available to, our management. Forward-looking statements include any statement that does not directly relate to a current or historical fact. We have tried to identify forward-looking statements by using words such as "believe," "may," "could," "will," "estimate "continue," "anticipate," "intend," "seek," "plan," "expect," "should," or "would." Among the factors that could cause actual re differ materially from those indicated in the forward-looking statements are risks and uncertainties inherent in our business including, without limitation: we have incurred significant losses since our inception and we expect to incur substantial losses for the foreseeable future and may never achieve or maintain profitability; we have generated limited revenue from ZILRETTA®, and have not received regulatory approval for any other product candidates; we may require additional capital prior to completing development and commercializing any of our product candidates in development; we may be unable to successfully commercialize ZILRETTA or any of our other product candidates; we rely on third parties to manufacture and conduct the clinical trials of ZILRETTA and our development-stage product candidates, which could limit our commercialization efforts or delay or limit their future development or regulatory approval; we may be unable to adequately maintain and protect our proprietary intellectual property assets, which could impair our commercial opportunities; and other risks detailed below in "Item 1A. Risk Factors."

Although we believe that the expectations reflected in our forward-looking statements are reasonable, we cannot guarantee future results, events, levels of activity, performance or achievement. We undertake no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, unless required by law.

Item 1. Business

Unless the content requires otherwise, references to "Flexion," "Company," "we," "our," and "us," in this Annual Report refer
Flexion Therapeutics, Inc. and our subsidiary, Flexion Therapeutics Securities Corporation.

Overview

We are a biopharmaceutical company focused on the discovery, development and commercialization of novel, local therapies for the treatment of patients with musculoskeletal conditions, beginning with osteoarthritis, or OA, a type of degenerative arthritis. We have an approved product, ZILRETTA®, which we market in the United States. ZILRETTA is the first and only extended-release, intra-articular, or IA (meaning in the joint), injection indicated for the management of OA knee pain. ZILRETTA is a non-opioid therapy that employs our proprietary microsphere technology to provide effective pain relief. The pivotal Phase 3 trial, on which the approval of ZILRETTA was based, showed that ZILRETTA met the primary endpoint of pain reduction at Week 12, with statistically significant pain relief extending through Week 16.

ZILRETTA was approved by the U.S. Food & Drug Administration, or FDA, on October 6, 2017 and launched in the United States shortly thereafter. We market ZILRETTA to prescribing physicians through our own field sales force of approximately 100 Musculoskeletal Business Managers, or MBMs.

ZILRETTA combines a commonly administered steroid, triamcinolone acetonide, or TA, with poly lactic-co-glycolic acid, referred to as PLGA, delivering a 32 mg dose of TA to provide extended therapeutic concentrations in the joint and persistent analgesic effect. Both the magnitude and duration of pain relief provided by ZILRETTA in clinical trials were clinically meaningful with the magnitude of pain relief amongst the largest seen to date in OA clinical trials. The overall frequency of treatment-related adverse events in these trials was similar to those observed with placebo and no drug-related serious adverse events were reported.

Based on the strength of our pivotal and other clinical trials, we believe that ZILRETTA represents an important treatment option for the millions of patients in the U.S. who are in need of safe and effective extended relief from OA knee pain. ZILRETTA is uniquely distinguished by the following attributes:

- in the Phase 3 trial,
  - statistically significant pain relief against placebo (saline) as measured by the weekly mean of the Average Daily Pain, or ADP, score:
    - demonstrated at week 12, the primary endpoint, a p-value of <0.0001, 2-sided, with benefits extending through week 16; and
    - at each week beginning at week 1 and continuing through week 12 nearly 60% of patients reported no pain or mild pain;
  - statistically significant change from baseline as compared to placebo in weekly ADP intensity score through week 12 as measured by the area under effect curve (p<0.0001) (demonstrating a 50% reduction from baseline);
  - numeric improvement when compared with placebo and immediate-release TA at each time point through 12 weeks on exploratory measures – WOMAC A (pain), WOMAC B (stiffness) and WOMAC C (function) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) quality of life subscale;
  - reduced rescue medicine consumption compared with placebo and immediate-release TA (exploratory endpoint); and
  - was superior to placebo, but the difference between ZILRETTA and immediate-release TA as measured by ADP was not statistically significant;
- an acceptable safety profile with side effects similar to placebo;

- statistically significant ($p<0.05$, 2-sided) reduction in the rise of blood glucose compared to that observed following immediate-release TA injection in patients with Type 2 diabetes who also have knee OA as measured by change in average blood glucose from baseline to 72 hours post injection; and
- persistent concentrations of drug in the joint.

In summary, ZILRETTA has demonstrated significant, durable relief for OA knee pain and, as such, can address an important unmet need among patients, physicians and healthcare payers. We believe that ZILRETTA has the potential to be prescribed as a first-line IA medicine for OA knee pain. In December 2018, we submitted a supplemental New Drug Application, or sNDA, with the FDA to revise the product label for ZILRETTA to allow for repeat administration. The sNDA includes the full data set from a Phase 3b single-arm, open-label clinical trial which evaluated the safety and tolerability of repeat administration of ZILRETTA. On February 26, 2019, the Company received a Day 74 letter from the FDA confirming the sNDA was accepted for filing. Under the Prescription Drug User Fee Act, or PDUFA, the Company anticipates FDA's decision on the sNDA by or on October 14, 2019.Also in December 2018, we initiated a Phase 3b pivotal study of ZILRETTA in hip OA which we anticipate completing in 2020.

OA is a type of degenerative arthritis that is caused by the progressive breakdown and eventual loss of cartilage in one or more joints. Arthritis is the most common cause of disability in the U.S. and OA is the most common joint disease, affecting more than 30 million adults in the U.S, and these numbers are expected to grow as a result of aging, obesity and sports injuries. OA commonly affects large weight-bearing joints like the knees and hips, but also occurs in the shoulders, hands, feet and spine. Patients with OA suffer from joint pain, tenderness, stiffness and limited movement. As the disease progresses, it becomes increasingly painful and debilitating, culminating, in many cases, in the need for total joint arthroplasty, or TJA.

Because there is no cure for OA, controlling pain and delaying surgery are the primary goals of prescribing clinicians. Oral drugs, such as non-steroidal anti-inflammatory drugs, or NSAIDs, including COX II inhibitors, and serotonin and norepinephrine reuptake inhibitors, or SNRIs, as well as topical NSAIDs, are used to treat early-stage OA pain but have limited effect and, given the amount and frequency of use in OA patients, are associated with serious side effects. For example, NSAIDs have shown increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke. Furthermore, this class of drugs can cause serious gastrointestinal adverse events including bleeding, ulceration and perforation of the stomach or intestines. These serious side effects are particularly worrisome because OA patients often have co-existing medical conditions, including diabetes and hypertension. For patients with moderate to severe OA pain, IA medicines, such as immediate-release steroids and hyaluronic acid, or HA, injected into the joint, are generally considered well-tolerated, but they leave the joint rapidly and often fail to produce or maintain clinically meaningful pain relief. Physicians may prescribe opioids, which in addition to the serious risk of addiction and abuse, have numerous serious side effects including respiratory depression, hypotension, constipation, cardiac events and, increasingly, deaths from unintentional overdose. As a result of these limitations, many OA patients experience persistent and worsening pain, which often culminates in the decision to have TJA, a painful and expensive procedure. Further, because the initial joint replacement wears out over time, the younger the patient is at the time of the joint replacement, the more likely it is that he or she will require repeat surgery in their lifetime.

According to IQVIA, in 2017 approximately 5 million patients in the U.S. received an IA injection treatment for knee OA with approximately 4.5 million of these patients being treated with immediate-release steroids. Furthermore, despite guidance from prominent medical societies, including the American Academy of Orthopedic Surgeons and Osteoarthritis Research Society International that hyaluronic acid, or HA, is an ineffective treatment for knee OA, and the growing number of payers that no longer reimburse for the entire class of HA products, according to SmartTRAK, HA sales in the U.S. were approximately $1 billion in 2018, with a cost per course of treatment ranging from $421 to $1,425. Our market research indicates that, given the limitations of immediate-release steroids and HA, physicians are open to new treatment options which can provide their patients with extended pain relief.

Our pipeline program, FX201, is a gene therapy product candidate designed to stimulate the production of an anti-inflammatory protein, interleukin-1 receptor antagonist (IL-1Ra), with the goal of providing at least one year of pain relief from OA of the knee. Based on its mechanism of action, we believe FX201 also has the potential to

possibly arrest disease progression. FX201 is a preclinical stage program, and, subject to positive data and successful completion of our active Good Laboratory Practice, or GLP, toxicology studies, we plan to file an Investigational New Drug Application, or IND, and initiate clinical trials in the second half of 2019.

We have worldwide commercialization rights for ZILRETTA and our product candidate, FX201. We also have an exclusive worldwide license agreement with Southwest Research Institute, or SwRI®, with respect to the use of SwRI's proprietary microsphere manufacturing technologies for certain steroids formulated with PLGA, including ZILRETTA. Our PLGA formulation technology is protected through a combination of patents, trade secrets, and proprietary know-how, and we intend to seek marketing exclusivity for any approved products. In addition, we own or have rights to various trademarks, copyrights and trade names used in our business, including FLEXION®, ZILRETTA® and FLEXFORWARD®. Our logos and trademarks are the property of Flexion Therapeutics, Inc. All other brand names or trademarks appearing in this report are the property of their respective holders. Use or display by us of other parties' trademarks, trade dress, or products in this report is not intended to, and does not, imply a relationship with, or endorsement or sponsorship of us, by the trademark or trade dress owners.

Our Strategy

Our goal is to cost-effectively discover, develop and commercialize novel, locally administered medicines that can safely and effectively address significant unmet medical needs. The principal elements of our strategy include the following:

- Focus initially on novel biopharmaceutical candidates that provide long-lasting analgesia locally while minimizing the potential for systemic side effects. We are currently focusing on anti-inflammatory and analgesic therapies for the treatment of patients with musculoskeletal conditions, beginning with OA. Many OA patients will eventually require IA injection therapies to control their pain as the disease progresses. Immediate-release IA steroids leave the joint rapidly and typically fail to confer pain relief of sufficient magnitude or duration. Since, by medical practice, steroids are not injected more frequently than every three months, patients can experience a recurrence in, or increasing, pain during that time. While some patients may obtain benefit from HA injections, they are not recommended for OA pain by the American Academy of Orthopaedic Surgeons, or AAOS, based on a lack of efficacy. ZILRETTA was specifically designed to provide persistent and effective OA pain relief with an acceptable safety profile. It is formulated using our proprietary PLGA-based microsphere technology to slowly and continuously release drug in the joint for over 12 weeks, avoiding significant plasma concentrations of drug.
- Establish ZILRETTA as a first-line IA treatment for OA knee pain and maximize its value by expanding approved indications. Based on ZILRETTA's clinical profile, we believe that it can be a first-line IA therapy for OA knee pain, and in 2018 we initiated a comprehensive strategy to build physician awareness of ZILRETTA through a variety of targeted initiatives. In the second half of 2018, we initiated a variety of direct-to-patient marketing activities designed to increase patient awareness of the product. In December 2018, we filed an sNDA with the FDA to revise the product label for ZILRETTA to allow for repeat administration. While ZILRETTA is currently approved for the treatment of OA knee pain, we believe that it has the potential for broader use, specifically in large joints. Therefore, in December 2018 we initiated a Phase 3 pivotal trial of ZILRETTA in OA hip pain and we intend to start Phase 2 trials of ZILRETTA in OA shoulder pain and adhesive capsulitis in the second half of 2019.
- Build a robust pipeline of additional locally administered therapies to address musculoskeletal conditions. We seek to build a pipeline of additional product candidates and to mitigate development risk by selecting product candidates that have at least demonstrated efficacy in animal models of disease or have validated mechanisms of action. In 2017, we established the Flexion Innovation Lab in Woburn, Massachusetts to support our research and development activities. We aim to further build the pipeline through internal development and the selective addition of external opportunities.
- Retain commercial rights in the United States and selectively partner outside of the United States. Because IA therapies in the United States are administered by a relatively small number of specialists, particularly orthopedists

and rheumatologists, we believe that we can effectively commercialize

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ZILRETTA in the U.S. with our own sales and marketing organization, and thereby retain more of the commercial value of this product. While we believe that the U.S. represents the most attractive market for ZILRETTA, we continue to evaluate opportunities and potential partnerships to develop and commercialize ZILRETTA in territories outside the U.S. where we believe there is the potential for value-based pricing and reimbursement.

Osteoarthritis

Overview

OA, also referred to as degenerative joint disease, is the most common joint disease in the U.S. according to the U.S. Centers for Disease Control and Prevention, or CDC, affecting more than 30 million adults. These numbers are only expected to grow in the years ahead as a result of aging, obesity and sports injuries.

- With the U.S. population between the ages of 45 and 64 having grown 32% from 2000 through 2010 and accounting for 26% of the total population, we expect changing demographics will likely contribute to a growing number of OA patients.
- Approximately 35% of U.S. adults are obese, which increases the risk of developing OA.
- Knee injury is common, particularly amongst young athletes, and increases the risk of developing OA later in life by more than five-fold.
- OA accounts for over $185 billion of annual healthcare expenditures, which does not include loss of productivity costs.
- As reported in an Osteoarthritis Research Society International white paper (Nov 2016), “subjects in the US with symptomatic radiographic knee OA were 23% more likely to die prematurely than people free from OA independent of age, sex, and race.”

According to the CDC, one of every two people in the U.S. is expected to develop symptomatic knee OA, the most common form of OA during their lifetime. Recent research estimates that the average age of physician-diagnosed knee OA has fallen by 16 years, from age 72 in the 1990s to age 56 in the 2010s. According to the same research, U.S. adults between the ages of 35 and 84 in the early 2010s will account for approximately 6.5 million new cases of knee OA over the next decade.

OA is a progressive disease for which there is no cure. As a result, current treatments are intended to address the symptoms of OA, in particular, relief of pain and improvement in functional status. The therapeutic regimen for OA becomes increasingly invasive with progression of the disease, culminating, in many cases, in TJA. In addition, because patients are being diagnosed with OA earlier in their lives, many patients require repeat TJAs. Because the decision to have TJA is based in large part on intractable pain and functional impairment, we believe that therapies which can meaningfully and durably relieve pain and improve function could potentially delay TJA.

Common Treatments for OA

In early-stage disease, treatment begins with non-pharmacologic therapy including exercise, weight control and physical therapy. As the disease progresses, physicians prescribe pharmacologic therapy, beginning with acetaminophen and progressing to oral NSAIDs, including COX II inhibitors, topical NSAIDs or SNRIs. Physicians may also treat OA pain with opioids; however, these drugs have serious drawbacks and are generally considered to be a suboptimal therapy for chronic non-cancer pain, like that associated with OA.

When non-pharmacologic therapy and oral pain medications prove inadequate, physicians typically transition patients to IA injections. Immediate-release steroids have historically served as the first line IA therapy, and when these no longer provide sufficiently durable pain relief, patients may progress to IA HA, a significantly more expensive therapy with only marginally greater effect than placebo. TA, the corticosteroid used in ZILRETTA, is amongst the most commonly prescribed IA corticosteroid injections.

Due to severe pain that can no longer be controlled therapeutically, many patients opt to have TJA, which is costly and painful. One of the most prevalent TJA procedures in the U.S. is total knee arthroplasty. Compared to

existing drug therapy, total knee arthroplasty is very expensive, with average costs ranging between $25,000 and $60,000, and many patients (~20%) are dissatisfied with the outcome of this procedure. The earlier a patient receives TJA, the more likely it is that the patient will need repeat replacement surgery in following years. In 2014, inpatient costs were nearly $12 billion in the U.S. for total knee arthroplasty alone and, based on some estimates, the number of total knee arthroplasties is expected to reach approximately 3.5 million procedures per year by 2030.

Limitations of Common Treatments for OA

Oral therapies, such as NSAIDs, may offer adequate analgesia for early-stage OA pain, but they may be associated with serious side effects such as gastrointestinal bleeding, cardiovascular events and other adverse events. For example, SNRIs may have a role in worsening depression and the emergence of suicidality in certain patients. In addition to their serious side effects, oral drugs may provide limited pain relief and eventually can become insufficient to control OA pain for many patients as the disease progresses.

IA therapies, including immediate-release steroids and HA therapies, are generally well-tolerated but provide pain relief that is often insufficient or inadequate in duration. Historically, all IA steroid therapies approved for OA are immediate-release suspensions or solutions that leave the joint within hours to days, and they are rapidly absorbed systemically, which may result in undesirable side effects. For example, IA immediate-release steroid injections are associated with a rapid elevation of blood glucose in diabetics, which can be of clinical concern. While IA steroids demonstrate large initial analgesic effects relative to other therapies, as a result of leaving the joint quickly, IA steroids typically fail to confer pain relief of sufficient magnitude or duration. In addition, current clinical practice dictates that IA steroid suspensions not be administered more frequently than once every three months. Based on internal analysis, we believe approximately 50% of patients receiving IA immediate-release steroids are unsatisfied with the duration of benefit.

Despite estimated U.S. sales of approximately $1 billion in both 2017 and 2018, IA HA therapies, which are approved only for treatment in the knee, produce only marginally more effective pain relief than placebo and may have no discernible effect on a patient’s ability to carry out their daily activities. In treatment guidelines for non-operative management of knee OA published in May 2013, the AAOS concluded that data from then-current published studies did not show clinically meaningful effectiveness for HA injections. As a result, the guidelines do not recommend HA treatment for symptomatic knee OA due to lack of efficacy and, most recently, certain insurance carriers are no longer providing policy coverage of HA.

While the consequences from the overuse and abuse of opioids are well-known, these powerful medicines are still commonly prescribed for OA related pain, despite the fact that they are not an effective treatment for this chronic condition. A recent study estimated that as many as 70% of patients who are prescribed a medicine for OA pain will receive an opioid because physicians have so few effective treatment options. We further believe that the growing societal awareness of the risks posed by opioids may make new treatment options attractive for patients and physicians seeking non-opioid alternatives. Beyond the significant concerns related to the potential for overuse, abuse and unintentional overdose, opioid use is also associated with a host of other serious side effects including, respiratory depression, hypotension, constipation, cardiac events and, increasingly, death.

The Flexion Extended-Release Technology

Our extended-release technology allows us to incorporate active pharmaceutical ingredients in PLGA microspheres. We believe we are the first company to administer PLGA microspheres into a human joint. PLGA is a proven extended-release delivery vehicle that is metabolized to carbon dioxide and water as it releases drug in the IA space and is used in other approved drug products and surgical devices. The technology is designed to enable novel formulations of pharmaceuticals by providing extended-release of drugs over time and the physical properties of the

polymer-drug matrix can be varied to achieve specified drug loads and release rates. Key to the success of our IA therapies is the ability to maintain persistent concentrations of drug in the joint, while minimizing systemic exposure. Utilizing our PLGA microsphere technology, ZILRETTA is the first and only approved extended-release, IA therapy for patients confronting OA-related knee pain.

We believe ZILRETTA and our technology will be protected primarily through a combination of patents, trade secrets and proprietary know-how, and we intend to seek marketing exclusivity for any approved products. A composition of matter patent has been issued by the United States Patent and Trademark Office, or U.S. PTO, for

ZILRETTA, with a patent term into 2031. The U.S. PTO has also issued two patents directed at the methods of manufacturing and using ZILRETTA with patent terms into 2031. Considerable expertise and effort were required to carry out the large body of original work underlying the formulation of ZILRETTA, including experimenting with, and observing the effects of over 50 steroid and PLGA formulations. We believe our extensive know-how and trade secrets relating to the manufacturing process for ZILRETTA, including those that relate to precise pharmaceutical release profiles, represent a meaningful entry barrier.

The Flexion Pipeline

Our pipeline strategy is to continue to study ZILRETTA in other areas and, if feasible, expand ZILRETTA's product label to include additional indications and broaden its scope of administration, and build a robust pipeline of additional locally administered therapies to address musculoskeletal conditions, with an initial focus on OA.

FX201

FX201 is an IA gene therapy candidate which is designed to induce the local production of interleukin-1 receptor antagonist (IL-1Ra), an anti-inflammatory protein. Following injection of FX201, its genetic material is incorporated into local cells, and IL-1Ra is expressed in response to inflammation in the joint tissues. Inflammation is a known cause of pain, and chronic inflammation is thought to play a major role in the progression of OA. By persistently suppressing inflammation, we believe FX201 has the potential to both reduce pain and possibly arrest disease progression. Based on preclinical data, we believe a single injection of FX201 could enable expression of IL-1Ra in an osteoarthritic joint for at least a year. Pending successful results from our active GLP toxicology studies, we intend to file an IND and initiate a first-in-human clinical trial in the second half 2019. We acquired the rights to FX201 via a definitive agreement with GeneQuine Biotherapeutics GmbH, or GeneQuine, and have an exclusive license to the underlying intellectual property rights for human use of FX201 from Baylor College of Medicine.

ZILRETTA – FDA Approved Product for the Management of OA Knee Pain

Key Regulatory Developments

On October 6, 2017, ZILRETTA received approval from the FDA for the management of OA pain of the knee. ZILRETTA is the first and only approved extended-release, IA therapy for OA knee pain. It is a non-opioid medicine that employs our proprietary microsphere technology to provide proven pain relief. The approval was based upon data from the pivotal Phase 3 clinical trial, a randomized, double-blind study which evaluated 484 patients at 37 centers worldwide. The pivotal Phase 3 trial showed that ZILRETTA met the primary endpoint of pain reduction at Week 12, with statistically significant pain relief extending through Week 16. ZILRETTA's label reflects its strong safety profile and states the most commonly reported adverse reactions (incidence ≥1%) in clinical studies included sinusitis, cough and contusions.

In December 2018, we submitted a supplemental new drug application, or sNDA, to the U.S. FDA to revise the product label for ZILRETTA to allow for repeat administration. The sNDA is based on data from a Phase 3b single-arm, open-label clinical trial, which indicated that repeat administration of ZILRETTA for treatment of OA knee pain was safe and well tolerated with no deleterious impact on cartilage or joint structure observed through X-ray analysis conducted at baseline and Week 52. The primary endpoint of the study was the safety and tolerability of repeat administration of ZILRETTA in patients with symptomatic OA of the knee. The patients enrolled in the study generally had longstanding and extensive disease, with more than two-thirds of the participants presenting with Kellgren-Lawrence Grade 3 (37.5%) or Grade 4 (30.3%), the most radiographically severe form of OA.

Participants received an initial intra-articular injection of ZILRETTA followed by evaluation at Weeks 12, 16, 20 and 24 to determine their eligibility for a second injection. A second dose was administered only when patients reported they were ready for additional treatment (based on pain levels) and their physician agreed it was clinically indicated. The median time to a second injection was 16.6 weeks, with 25.1%, 33.5%, 20.7% or 20.1% of patients receiving their second injection at Week 12, 16, 20 or 24, respectively. Among those who received two injections, the magnitude and duration of clinical benefit after the 1st and 2nd injections were similar with marked improvements from baseline in pain scores observed when first assessed at four weeks. Clinical benefit was measured through validated OA-specific instruments including the WOMAC questionnaire that evaluates a patient's pain, stiffness and function, and the Knee Injury and Osteoarthritis Outcome Score, or KOOS, Quality of Life scale. There were no serious adverse events related to ZILRETTA reported during the trial, and the patterns of treatment emergent adverse events were consistent with those reported in previous clinical studies of ZILRETTA. No participants discontinued the trial due to drug-related adverse events. The results from this trial were published in the journal Rheumatology and Therapy in February 2019.

In July 2018, we had discussions with FDA regarding our objections to wording on the ZILRETTA product label, including a sentence which states the product "is not intended" for repeat administration. We have disagreed with certain ZILRETTA label language since the time of FDA approval of ZILRETTA as we believe it is unwarranted and confusing to patients, prescribers and payers. As a result of the July 2018 discussions, the FDA advised us to make a formal request for changes to the ZILRETTA label, and, in August 2018, we filed a supplemental label revision with our proposed modifications. In February 2019, the FDA informed us that they will subsume the August 2018 labeling supplement into the review of the December 2018 sNDA which was accepted for filing on February 26, 2019. We now have an sNDA PDUFA date of October 14, 2019 at which time we expect FDA's decision on any ZILRETTA label changes.

Summary of Active and Key Completed Clinical Trials

Prior to FDA approval, we completed seven clinical trials evaluating ZILRETTA (also known as FX006) against either immediate release triamcinolone acetonide crystalline suspension, or TAcs, placebo (saline), or both in patients with OA of the knee. In total, 424 patients were treated with a single IA injection (32mg) of ZILRETTA in those trials.

Active Clinical Trials

- We believe ZILRETTA's extended-release profile may also provide effective treatment for OA pain of the hip and OA pain of the shoulder, and in December 2018, we initiated a double-blind, placebo-controlled Phase 3 registration trial to evaluate the safety and efficacy of ZILRETTA in 440 patients with hip OA. The initiation of

this trial was supported by findings from a Phase 2, randomized, open-label, pharmacokinetic, or PK, study in the shoulder and hip joints, known as the SHIP study. The results from the SHIP study demonstrated that ZILRETTA was generally safe and well tolerated, and the PK profile of ZILRETTA observed in both joints was consistent with previous PK studies in the knee. Results also showed that an injection of ZILRETTA into the hip resulted in 6-fold lower peak plasma levels and reduced systemic exposure compared to TAcs.

The primary endpoint of the Phase 3 hip trial is the magnitude of pain relief versus placebo as measured on the WOMAC A (pain) subscale at Week 12. Patients will undergo index hip X-rays at screening and again at Week 12. Following initial injection of ZILRETTA or placebo, participants will be evaluated at Weeks 12, 16, 20 and 24 to determine if a second IA injection for hip OA pain is clinically indicated. If eligible for a second injection, patients will receive open-label ZILRETTA at the time of recurrent symptoms and will be followed for 12 weeks after that injection. Patients who do not receive a second injection will be followed for up to 24 weeks after their first injection. The trial is expected to be completed in 2020.

With respect to shoulder, in the second half of 2019, we plan to initiate additional Phase 2 studies of ZILRETTA in both OA and adhesive capsulitis, commonly referred to as “frozen shoulder.”

- In May 2018, we initiated an open-label Phase 3b trial assessing the effect of a single administration of ZILRETTA on synovitis (inflammation of the synovial membrane) in patients with OA of the knee. Patients will undergo initial ultrasound examination and MRI scans with contrast of the index knee at baseline and then return to the clinic at Weeks 6 and 24 for MRI scans and other assessments. Topline results are anticipated in 2020.

Additional Key Completed Studies

- In April 2018, we announced that the data from our pivotal Phase 3 clinical trial of ZILRETTA in patients with moderate to severe OA knee pain were published in the Journal of Bone and Joint Surgery. This trial evaluated 484 patients who were randomized 1:1:1 to ZILRETTA 32 mg, immediate release TA 40 mg or placebo (saline) injection. The trial successfully met its primary endpoint, demonstrating highly statistically significant ($p<0.0001$) pain relief against placebo (saline) at Week 12. In addition, ZILRETTA achieved a statistically significant change from baseline as compared to placebo in weekly ADP intensity score through Week 12 as measured by the area under effect curve ($p<0.0001$) (demonstrating a 50% reduction in pain from baseline). In clinical trials, the “p-value” is the probability that the result was obtained by chance. For example, a “p-value” of less than 0.10 (or $p<0.10$) would indicate that there is a less than 10% likelihood that the observed results could have happened at random. By convention, a “p-value” that is less than 0.05 is considered statistically significant.

ZILRETTA also delivered persistent analgesia against placebo in this trial at each of Weeks 1 through 16. Results showed it was superior to placebo on ADP; however, a secondary exploratory analysis showed a numeric but not statistically significant difference between ZILRETTA and immediate-release TA for the change from baseline at Week 12 in weekly mean ADP.

In pre-specified exploratory analyses, compared to placebo and immediate-release TA, ZILRETTA also demonstrated numeric improvement at each measured time point through 12 weeks on the Western Ontario and McMaster Universities Osteoarthritis Index, commonly referred to as WOMAC®, subscales for WOMAC A (pain), WOMAC B (stiffness) and WOMAC C (function) and the validated Knee injury and Osteoarthritis Outcome Score, commonly

referred to as KOOS, quality of life, or QOL, subscale. WOMAC is a validated, widely accepted questionnaire (in our surveys over 90% of treating orthopedists are familiar with WOMAC whereas only approximately 10% are familiar with the Numeric Rating Scale which forms the basis for the ADP determination) used by healthcare professionals to specifically evaluate the condition of patients with OA of the knee and hip, including pain, stiffness, and physical function of the joints and the KOOS QOL subscale is a validated questionnaire used by healthcare professionals to evaluate the extent to which knee symptoms compromise a patient's quality of life.

The frequency of treatment-related side effects in this study was comparable across all treatment arms. No drug-related serious adverse events were observed and no patients treated with ZILRETTA were discontinued from the study due to a treatment-related side effect.

- In September 2018, we announced that the data from the double-blind, randomized Phase 2 study evaluating blood glucose levels in patients with OA knee pain and controlled Type 2 diabetes were published in the peer-reviewed journal, Rheumatology. The paper shows that the study met its primary endpoint, demonstrating that the change in blood glucose levels was significantly lower following ZILRETTA injection than immediate-release TAcs injection in people with OA knee pain and controlled Type 2 diabetes.

Investigators from seven study sites enrolled 33 patients, randomized 1:1 to receive a single IA injection of 32 mg ZILRETTA or 40 mg immediate-release TA. Blood glucose levels were evaluated for a total of three weeks (one week prior to injection and two weeks post injection) using a continuous glucose monitoring device. Patients returned for follow-up visits at Day 8, day 15 and day 43 (Week 6). The primary endpoint compared the change in average glucose values from the period of 72 hours before to the period of 72 hours after injection with ZILRETTA versus immediate-release TA. The data demonstrate that ZILRETTA is associated with a statistically significant (p-value of <0.05, 2-sided) and clinically relevant reduction in the rise of blood glucose compared to that observed following TA injection in patients who also have knee OA.

- In October 2018, results from the Phase 2 clinical trial evaluating the safety and PK of concurrent administration of ZILRETTA in bilateral knee OA compared to immediate-release TAcs were presented at the American College of Rheumatology Annual Meeting. The results show that exposure to triamcinolone acetonide was significantly lower in patients given ZILRETTA compared to those given TAcs, with maximum plasma concentrations nearly 10-fold lower (2,577.8 pg/mL compared to 24,289.4 pg/mL). Safety profiles were similar for the ZILRETTA and TAcs treatment groups.

Manufacturing

We believe that the multifaceted nature of PLGA drug product manufacturing and the limited number of capable contract manufacturing companies that offer PLGA drug product manufacturing creates an entry barrier. The technology is designed to enable novel formulations of pharmaceuticals by providing extended-release of drugs over time and the physical properties of the polymer-drug matrix can be varied to achieve specified drug loads and release rates.

We utilize contract manufacturers to produce the drug substances and drug products used in ZILRETTA. Manufacture of PLGA microspheres is a complex process and there are a limited number of contract manufacturing sites with PLGA experience. Our proprietary injectable IA extended-release technology allows us to incorporate pharmaceuticals in PLGA microspheres, such as TA, in the case of ZILRETTA, as well as potentially other product candidates. Following extensive development programs, we have established that a single injection of ZILRETTA sustains local concentrations of TA in the joint for several months. The ZILRETTA microsphere PLGA formulation has gone through numerous iterations and has been optimized to release the drug over an extended period of time. In developing this unique combination of manufacturing process and formulation, we have established numerous trade secrets that relate to precise pharmaceutical release profiles.

The active pharmaceutical ingredient in ZILRETTA, TA, is manufactured and supplied by Farmabios SpA in accordance with current Good Manufacturing Practice, or cGMP, standards. This supplier is subject to regular inspections by the FDA. The PLGA material used in the manufacture of ZILRETTA is supplied by Evonik

Corporation, or Evonik. In November 2016, we entered into a Supply Agreement with Evonik for the purchase of PLGA for clinical and commercial supply of ZILRETTA. The initial term of the Supply Agreement is until July 2021 and will renew for two successive two-year terms upon mutual written consent by both parties. Under the Supply Agreement, we are bound to purchase PLGA from Evonik at certain minimum purchase amounts, which decrease over time, and at a specified price per gram, subject to adjustment from time to time, including due to changes in price indices and in the event the initial term of the Supply Agreement is extended. Upon termination of the Supply Agreement (other than termination due to the bankruptcy of either Evonik or us) we are obligated to pay the costs associated with the binding supply forecast provided to Evonik.

In August 2015, we entered into a Manufacturing Agreement with Patheon U.K. Limited, or Patheon, for the manufacture of clinical and commercial supplies of ZILRETTA finished drug product. In connection with the agreement, Patheon undertook certain technical transfer activities and construction services to prepare its United Kingdom facility for the manufacture of ZILRETTA in dedicated manufacturing suites. The initial term of our Manufacturing Agreement with Patheon is until October 2027. We may terminate this agreement upon one month's notice if a regulatory authority causes the withdrawal from, or halts development of, ZILRETTA (in either case for reasons outside our reasonable control) in the United States or any other market that represents 80% of our overall sales. We may also terminate this agreement at any time for convenience by providing 24 months' notice. Either we or Patheon may terminate this Agreement in the event of (a) an unremedied material breach or bankruptcy of the other party, (b) if a material force majeure event remains uncured for a period of more than 90 days and (c) the granting of a permanent injunction to a third party claiming intellectual property infringement of ZILRETTA in the United States or UK. Upon termination of this agreement, we are obligated to pay for the costs associated with the removal of our manufacturing equipment and for Patheon's termination costs up to a specified maximum amount.

Commercial Strategy

We have established a commercial infrastructure designed to drive the adoption and sales of ZILRETTA with the approximately 10,500 prescribers who treat approximately 70% of patients diagnosed with OA pain of the knee who receive an IA treatment. Of these prescribers, approximately 80% are orthopedists and rheumatologists. We hired our full complement of MBMs immediately following ZILRETTA's approval on October 6, 2017. The MBMs were trained and deployed in the field as of November 20, 2017, when they began the process of promoting ZILRETTA to prescribing physicians. We distribute ZILRETTA solely through a limited network of contracted party specialty distributors and one specialty pharmacy. While we believe that the United States represents the most attractive market for ZILRETTA, we continue to evaluate opportunities and potential partnerships to develop and commercialize ZILRETTA in territories outside the United States where we believe there is the potential for value-based pricing and reimbursement.

Of patients who are treated for OA pain of the knee with an IA injection, we estimate that approximately 70% receive IA injections from orthopedic surgeons or their attendant physician extenders (i.e. physician assistants and nurse practitioners). Approximately 8% of patients receive IA injections from physical medicine and rehabilitation specialists and rheumatologists, and approximately 7% of patients are treated by sports medicine specialists. Approximately 11% are treated by primary care physicians. The remaining IA injections are administered by a wider array of health care providers, including physician assistants and nurse practitioners.

Competition

Our industry is highly competitive and subject to rapid and significant technological change. The large size and expanding scope of the pain market makes it an attractive therapeutic area for biopharmaceutical businesses. Our potential competitors include pharmaceutical, biotechnology, medical device and specialty pharmaceutical companies. Several of these companies have robust drug pipelines, readily available capital and established research and development organizations. We believe our success will be driven by our ability to develop and commercialize treatment options that make a meaningful difference for patients with musculoskeletal conditions, beginning with OA.

The key competitive factors that could affect the success of ZILRETTA's commercialization are likely to be efficacy, safety, price and the availability of reimbursement from government and other third-party payers. Immediate-release steroids and HAs are currently the two marketed classes of IA products that compete directly with ZILRETTA.

Also available are stem cell and platelet rich plasma, or PRP, injections, but these require on site preparation from tissue or blood taken from the patient, have generated questionable efficacy in controlled clinical trials, and we believe they are unlikely to be a broadly embraced therapeutic option for OA patients. Because these are minimally manipulated autologous therapies, they do not require and have not received FDA review or approval. For that reason, they are generally not reimbursed by payers and patients must pay out of pocket to receive these therapies. Furthermore, the American Association of Hip & Knee Surgeons recently issued a position statement indicating that

it cannot recommend biologic therapies, including stem cell and PRP injections, for the treatment of advanced hip or knee arthritis.

In addition to marketed IA medications for OA, other companies have OA product candidates in advanced stages of clinical development. These product candidates include:

- Anika Therapeutics, Inc.'s Cingal®, which is a mixture of Anika's Monovisc combined with a low dose of a commonly used immediate-release steroid. Anika filed a Pre-Market Application with the FDA for Cingal based on a single pivotal clinical trial. In December 2015, Anika announced that due to the steroid component of the product, it needed to file this product candidate under an NDA. In June 2018, Anika announced Cingal did not achieve statistical significance at the primary endpoint of 26 weeks in an active comparator study. Subsequently, Anika completed an extension study to 39 weeks and announced an intention to include the data in a package for a meeting with the FDA planned for the first quarter of 2019. In February 2019, Anika announced that, based on their discussions with the FDA, they will need to conduct another Phase III clinical trial before they can potentially obtain approval for Cingal in the U.S.
- Kolon TissueGene, Inc.'s Invossa™, which is a combination of human allogeneic chondrocytes and TGF- 1 transfected allogeneic chondrocytes. In November 2018, Kolon TissueGene announced they enrolled the first patient in a pivotal US Phase 3 trial. According to clinicaltrials.gov, the estimated primary completion date for the trial is April 2021.
- Ampio Pharmaceuticals, Inc.'s Ampion™, which is a derivative of human serum albumin, is described as having anti-inflammatory properties, and is formulated for immediate-release. Ampio stated that Ampion is in Phase 3 development but has not announced a timeline for potentially submitting a Biologics License Application, or BLA.
- Centrexion Therapeutics Corporation's CNTX-4975, which is a synthetic, ultra-pure injection of trans-capsaicin. In December 2018, Centrexion announced completion of patient enrollment in its Phase 3 VICTORY-1 trial. Topline results are expected to be reported in the first quarter of 2020.
- A number of investigational nerve growth factor antibodies are in development. Regeneron's fasinumab and Pfizer and Eli Lilly's tanezumab are both in Phase 3 development. Initial results from Phase 3 clinical trials for each were announced in 2018. In January 2019, Pfizer and Lilly announced results from a second Phase 3 study showing that the tanezumab 5 mg treatment arm met all three co-primary endpoints at 24 weeks, however in the 2.5 mg treatment arm, patients' overall assessment of their OA was not statistically different than placebo. Rapidly progressive OA was seen in 2.1% of tanezumab-treated patients and was not observed in the placebo arm.
- Servier and Galapagos NV's S201086/GLPG1972, an ADAMTS-5 inhibitor, is currently in Phase 2 clinical development.
- Taiwan Liposome Company's TLC599, which is a liposomal formulation of dexamethasone sodium phosphate. TLC599 is currently in Phase 2 clinical development.

Intellectual Property/Patents and Proprietary Rights

Intellectual Property and Exclusivity

We seek to protect ZILRETTA and our product candidates and technology through a combination of patents, trade secrets, proprietary know-how, FDA exclusivity and contractual restrictions on disclosure.

Patents and Patent Applications

Our policy is to seek to protect the proprietary position of ZILRETTA and our product candidates by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development of our business. U.S. patents generally have a term of 20 years

from the earliest effective date of the application.

As of January 31, 2019, we owned three U.S. issued patents, one pending U.S. application, and counterpart foreign patents and patent applications, all directed to ZILRETTA. One issued U.S. patent directed to ZILRETTA relates to its composition of matter and has an expiration date in 2031. A second issued U.S. patent directed to ZILRETTA relates to methods of manufacturing ZILRETTA and has an expiration date in 2031. A third issued U.S. patent directed to ZILRETTA relates to methods of using ZILRETTA and has an expiration date in 2031. The ZILRETTA composition of matter patent is the result of several unique discoveries relating to a narrow drug load specification, a certain release profile of polymers, specific polymer weights and ratios and clinical efficacy observed within a dose-range. The patents directed to ZILRETTA's composition of matter and methods of using ZILRETTA are listed in the FDA Orange Book. The pending U.S. application directed at compositions of matter similar to ZILRETTA, as well as methods of making and using the same, if resulting in an issued patent, could provide additional claims expiring in 2031.

During 2018, we expanded our patent portfolio with additional granted patents related to ZILRETTA outside the United States. In 2018, we had patents granted in Mexico, the Russian Federation and the Republic of China (Taiwan), further expanding to the scope of the previously granted patents in Australia, Canada, China, Indonesia, Japan, New Zealand, Saudi Arabia, Singapore, South Africa, Taiwan and Ukraine. Generally, these foreign patents are directed to compositions of matter for ZILRETTA, methods of manufacturing ZILRETTA and/or methods of using ZILRETTA and are similar in scope to the protection in the United States described above. In addition, we have applications pending in Europe and additional countries throughout the world directed to ZILRETTA and related inventions.

We have also exclusively licensed issued patents, owned by SwRI, directed to our proprietary microsphere manufacturing technology used in the production of ZILRETTA. These patents are scheduled to expire in 2025.

We have exclusively licensed patents and patent applications owned by Baylor College of Medicine for human applications directed to our FX201 product candidate. The Baylor patents are issued in Europe, with an expiry date in 2032, and in Australia, Japan and China with expiry dates in 2033, and pending in Canada, Eurasia, India, and the U.S. We received a notice of allowance for the U.S. patent application covering FX201 on February 11, 2019. Finally, we have other patent applications directed to formulations and/or uses of compounds that are not directly relevant to ZILRETTA or our current programs in development.

Trade Secrets and Proprietary Information

The ZILRETTA microsphere PLGA formulation has been refined and optimized to deliver the drug substance released over an extended period of time. In developing this unique combination of manufacturing process and formulation, we have established numerous trade secrets, including those that relate to a precise pharmaceutical release profile. In addition, due to the complexity of the extended-release technology and the time, costs and technical risks involved in demonstrating bioequivalence through clinical trials, we believe that the ability of manufacturers to gain market approval for generic alternatives to ZILRETTA upon expiration of our patents and FDA exclusivity will be challenging.

We seek to protect our proprietary information, including our trade secrets and proprietary know-how, by requiring our employees to execute a Proprietary Information, Inventions, Non-Solicitation, and Non-Competition Agreement upon the commencement of their employment. Consultants and other advisors are required to sign consulting agreements. These agreements generally provide that all confidential information developed or made known during the course of the relationship with us be kept confidential and not be disclosed to third parties except in specific circumstances. In the case of our employees, the agreements also typically provide that all inventions resulting from work performed for us, utilizing our property or relating to our business and conceived or completed during employment shall be our exclusive property to the extent permitted by law. Further, we require confidentiality

agreements from entities that receive our confidential data or materials.

Intellectual Property Agreements

Southwest Research Institute Manufacturing® (SwRI) License

In July 2014, we executed an exclusive worldwide licensing agreement with SwRI to utilize proprietary microsphere manufacturing technologies for production of our extended-release drug candidates, including ZILRETTA. The SwRI technologies employ a uniquely controlled and continuous atomizing technology that facilitated scale-up of commercial supply. This exclusive agreement provides for an expanded field of use in a variety of musculoskeletal disorders, as well as broader polymer and steroid ranges, which offers the flexibility to potentially explore different doses, disease indications, and drug-PLGA combinations. We have no further payment obligations following the amendment executed by the parties in February 2017 and the license remains in effect through patent term expiry.

FX201 Related Agreements

In December 2017, we entered into a definitive agreement with GeneQuine to acquire the global rights to FX201. As part of the asset purchase transaction with GeneQuine, we made an upfront payment of $2.0 million. In 2018, we paid GeneQuine a $750,000 milestone payment for initiating a GLP toxicology study of FX201. We may also be required to make additional milestone payments during the development of FX201, including up to $7.75 million through the Phase 2 proof of concept, or PoC, clinical trial and, following successful PoC, up to an additional $54 million in development and global regulatory approval milestone payments. As part of the transaction with GeneQuine, we became the direct licensee of certain underlying Baylor College of Medicine, or Baylor, patents and other proprietary rights related to FX201 for human applications. The Baylor license agreement grants us an exclusive, royalty-bearing, world-wide right and license (with a right to sublicense) for human applications under its patent and other proprietary rights directly related to FX201, with a similar non-exclusive license to certain Baylor intellectual property rights that are not specific to FX201. The license agreement with Baylor includes a low single-digit royalty on net sales of FX201 and requires us to use reasonable efforts to develop FX201 according to timelines set out in the license agreement. In December 2017, we also entered into a Master Production Services Agreement with SAFC Carlsbad, Inc., a part of MilliporeSigma, for the manufacturing of preclinical and initial clinical supplies of FX201.

Government Regulation and Product Approval

Government authorities in the United States at the federal, state and local level, and in other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of products such as those we are developing and commercializing.

U.S. Biopharmaceutical Product Development Process

In the United States, the FDA regulates biopharmaceutical products under the Federal Food, Drug, and Cosmetic Act, or FDCA, the Public Health Service Act, or PHSA, and implementing regulations. Biopharmaceutical products are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA’s refusal to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters, product recalls, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement

of profits or civil or criminal penalties. The process required by the FDA before a biopharmaceutical product may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests, animal studies and formulation studies according to Good Laboratory Practices, or GLP, or other applicable regulations;
- submission to the FDA of an investigational new drug, or IND, application, which must become effective before human clinical trials may begin;

- approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials according to the FDA's laws and regulations pertaining to the conduct of human clinical studies, collectively referred to as Good Clinical Practices, or GCP, and according to the International Council for Harmonization, or ICH, GCP guidelines, to establish the safety and efficacy of the proposed biopharmaceutical product for its intended use;
- submission to the FDA of an NDA for a proposed new drug product or a Biologics License Application, or BLA, for a biological product;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biopharmaceutical product is produced and tested to assess compliance with the FDA's cGMP requirements, to assure that the facilities, methods and controls are adequate to preserve the biopharmaceutical product's identity, strength, quality and purity;
- potential FDA audit of the non-clinical and clinical trial sites that generated the data in support of the NDA or BLA; and
- FDA review and approval or licensure of the NDA or BLA.

The lengthy process of seeking required approvals and the continuing need for compliance with applicable statutes and regulations require the expenditure of substantial resources and approvals are inherently uncertain.

Before testing any compounds with potential therapeutic value in humans, the biopharmaceutical product candidate enters the nonclinical testing stage, also referred to as preclinical testing. Preclinical tests include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the biopharmaceutical product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLP. The sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, among other documentation, to the FDA as part of the IND application. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a biopharmaceutical product candidate at any time before or during clinical trials due to safety concerns or non-compliance with applicable laws or regulations.

Clinical trials involve the administration of the biopharmaceutical product candidate to healthy subjects or patients with the target disease under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety. Each protocol must be submitted to the FDA as part of the IND. Clinical trials must be conducted in accordance with the FDA's regulations which reflect the ICH GCP requirements. Further, each clinical trial must be reviewed and approved by an IRB at, or servicing, each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until it is completed.

Clinical trials for biopharmaceutical product candidates are typically conducted in humans in three sequential phases that may overlap. In Phase 1 clinical trials, the biopharmaceutical product is initially introduced into healthy human subjects and tested for safety or adverse effects, dosage, tolerance, metabolism, distribution, excretion and clinical pharmacology. In Phase 2 clinical trials, the biopharmaceutical product is evaluated in a limited patient population to identify possible adverse side effects and safety risks, evaluate preliminarily the efficacy of the biopharmaceutical product for specific targeted indications and determine dosage tolerance, optimal dosage and dosing schedule for patients having the specific disease. Once a biopharmaceutical product shows evidence of effectiveness and is found to have an acceptable safety profile in Phase 2 evaluations, Phase 3 clinical trials are undertaken to more fully evaluate

clinical outcomes. In Phase 3 clinical trials, the biopharmaceutical product is

administered to an expanded patient population in adequate and well-controlled trials to generate sufficient data to statistically confirm the efficacy and safety of the biopharmaceutical product for approval, to establish the overall risk-benefit profile of the biopharmaceutical product and to provide adequate information for its labeling.

Post-approval studies, also referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication and may be required by the FDA as part of the approval process.

Progress reports detailing the status of biopharmaceutical product development and results of the clinical trials must be submitted at least annually to the FDA and written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse events or any finding from tests in laboratory animals that suggests a significant risk for human subjects or patients. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor or its data safety monitoring board (if applicable) may suspend a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the biopharmaceutical product has been associated with unexpected serious harm to study subjects.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the biopharmaceutical product as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the biopharmaceutical product candidate and, among other things, the manufacturer must develop methods for testing the safety, identity, strength, quality and purity of the final biopharmaceutical product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biopharmaceutical product candidate does not undergo unacceptable deterioration over its shelf life.

FDA Review and Approval Processes

The results of product development, preclinical studies and clinical studies for claimed indications as well as descriptions of the manufacturing process and controls, analytical tests conducted on the biopharmaceutical product, proposed labeling and other relevant information are submitted to the FDA as part of an NDA or BLA requesting approval to market the product. A supplement to an approved NDA or BLA is also required to be submitted for review when seeking major changes to manufacturing or labeling, including additional indications for use. Additionally, the results of product development, preclinical studies and clinical trials for the claimed indications in all relevant pediatric subpopulations and the support for dosing and administration for each pediatric subpopulation for which the product is safe and effective, are contained in an NDA or BLA. The FDA may grant deferrals for submission of pediatric data or full or partial waivers after the initial submission of a pediatric study plan following an end of Phase 2 meeting unless otherwise agreed upon by the FDA and the sponsor. The submission of an NDA or BLA is subject to the payment of substantial user fees; a waiver of such fees may be obtained under certain limited circumstances.

The FDA reviews all NDAs and BLAs submitted before it accepts them for filing and may request additional information rather than accepting the application for filing. Once the application is accepted for filing, the FDA begins an in-depth review. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or PDUFA, the FDA has 12 months after submission for a new molecular entity in which to complete its initial review and respond to the applicant, and eight months for a priority review application. In addition, the FDA has 10 months after submission of an NDA for a non-new molecular entity in which to complete its initial review of a standard NDA and respond to the applicant, and six months for a priority review NDA. The FDA does not always meet its PDUFA goal dates for review of standard and priority review applications. The review process and the PDUFA goal date may

be extended by additional three-month review periods whenever the FDA requests or the sponsor otherwise provides additional information or clarification regarding information already provided in the submission at any time during the review cycle.

The FDA reviews the NDA or BLA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. The FDA may refer applications for novel biopharmaceutical products which present difficult questions of safety or efficacy to an advisory committee,

typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the approval process, the FDA also will determine whether a risk evaluation and mitigation strategy, or REMS, is necessary to assure the safe use of the biopharmaceutical product. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS; the FDA will not approve the application without a REMS, if required.

Before approving an NDA or BLA, the FDA will typically inspect the facilities at which the product is to be manufactured. When an inspection is undertaken, the FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an application, the FDA will typically inspect one or more clinical sites to assure compliance with FDA regulations regarding conduct of clinical trials for the product's trials. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in a complete response letter to the applicant and often will request additional testing or information.

If a complete response letter is issued, the applicant may either resubmit the application, addressing all of the deficiencies identified in the letter, or withdraw the application.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling or REMS to assure safe use of the product through distribution or other controls. In addition, the FDA may require post approval studies, referred to as Phase 4 testing, which involves clinical trials designed to further assess a product's safety and effectiveness and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized.

Post-Approval Requirements

Any products for which we receive FDA approval are subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse experiences with the product, providing the FDA with updated safety and efficacy information, product sampling and distribution requirements, complying with certain electronic records and signature requirements and complying with FDA promotion and advertising requirements. These promotion and advertising requirements include, among other things, standards for direct-to-consumer advertising, prohibitions against promoting drugs for uses or in patient populations that are not described in the drug's approved labeling (known as "off-label use"), rules for conducting industry-sponsored scientific and educational activities, and promotional activities involving the internet. Failure to comply with FDA requirements can have negative consequences, including adverse publicity, enforcement letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses.

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products. Manufacturers of our products are required to comply with applicable FDA manufacturing requirements contained in the FDA's cGMP regulations. cGMP regulations require, among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are also required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved NDA. These restrictions may include suspension of a product until the FDA is assured that quality standards can be met, continuing oversight of manufacturing by the FDA under a consent decree of permanent injunction, which frequently includes the imposition of costs and continuing inspections over a period of many years, as well as possible withdrawal of the product from the market. In addition, changes to the manufacturing process generally require prior FDA approval before being implemented.

The FDA and other federal and state agencies closely regulate the promotion of drugs. Moreover, the FDA strictly regulates the promotional claims that may be made about drug and biologic products. In particular, a product may not be promoted for off label uses that are not approved by the FDA as reflected in the product's approved packaging label or are otherwise truthful and not misleading statements. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses.

Other types of changes to the approved product, such as adding new indications and additional labeling changes, are also subject to further FDA review and approval.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any biopharmaceutical product for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of coverage and adequate reimbursement from third-party payers.

In the United States, third-party payers include federal and state government payer programs, including Medicare and Medicaid, managed care organizations, private health insurers and other organizations. The process for determining whether a third-party payer will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the third-party payer will pay for the drug product. Third-party payers may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drug products for a particular indication. Third-party payers are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain FDA approvals. In addition, our biopharmaceutical products may not be considered medically necessary or cost-effective.

A third-party payer's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payer's determination to provide coverage for a drug product does not ensure that other payers also will provide coverage or an adequate reimbursement rate for the drug product. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

The cost of pharmaceuticals continues to generate substantial governmental and third-party payer scrutiny. We expect that the pharmaceutical industry will continue experiencing pricing pressures due to the trend toward managed healthcare, the increasing influence of managed care organizations and additional legislative proposals. Third-party payers are increasingly challenging the prices charged for medical products and services and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. If these third-party payers do not consider our products to be cost-effective compared to other available therapies, they may not cover our products after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products at a profit. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. Adoption of such controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals such as the drug candidates that we are developing and could adversely affect our net revenue and results.

Different pricing and reimbursement schemes exist in other countries. In the European Community, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national

healthcare systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular drug candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines but monitor and control company profits. The downward pressure on healthcare costs in general, and on prescription

drugs in particular, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country. There can be no assurance that any country that has price controls or reimbursement limitations for drug products will allow favorable reimbursement and pricing arrangements for any company.

Additionally, in order to be eligible for certain federal agencies and grantees to purchase ZILRETTA, or to have it paid for with federal funds under the Medicaid and Medicare Part B programs, we participate in the Department of Veterans Affairs, or VA, Federal Supply Schedule, or FSS, pricing program. We are obligated through the FSS program to sell ZILRETTA through a FSS contract and charge a price that is no higher than the statutory Federal Ceiling Price, or FCP, to four federal agencies (VA, U.S. Department of Defense, Public Health Service, and Coast Guard). The FCP is based on the non-federal Average Manufacturer Price, which we will need to calculate and report to the VA on a quarterly and annual basis. These obligations contain extensive disclosure and certification requirements.

Healthcare Reform

In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes to the healthcare system that could affect our future results of operations. In particular, there have been and continue to be a number of initiatives at the United States federal and state levels that seek to reduce healthcare costs, improve healthcare quality or expand access to healthcare.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The MMA expanded Medicare coverage to include outpatient prescription drug purchases made by the elderly by establishing Medicare Part D and introduced a new reimbursement methodology based on average sales prices for physician administered drugs under Medicare Part B. In addition, the MMA provided authority for limiting the number of drugs that would be covered in any therapeutic class under the Medicare Part D program. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and reimbursement rate that we receive for ZILRETTA and any of our other approved products. While the MMA applies only to drug benefits for Medicare beneficiaries, private payers often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payers.

In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively PPACA, was enacted as a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. Among the provisions of PPACA of importance to our potential drug candidates are the following:

- an annual, non-deductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- a new Medicare Part D coverage gap discount program, in which manufacturers must now agree to offer 70% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage

gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;

- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements under the federal Open Payments program, created under Section 6002 of PPACA, and its implementing regulations, that manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) report annually to Centers for Medicare and Medicaid Services, or CMS, information related to "payments or other transfers of value" made or distributed to physicians and teaching hospitals, and that applicable manufacturers and applicable group purchasing organizations report annually to CMS ownership and investment interests held by physicians (as defined above) and their immediate family members;
- a requirement to annually report drug samples that manufacturers and distributors provide to physicians;
- expansion of healthcare fraud and abuse laws, including the federal False Claims Act and the federal Anti-Kickback Statute, new government investigative powers, and enhanced penalties for non-compliance;
- an FDA-approval framework for follow-on biologic products;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and
- establishment of a Center for Medicare & Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Since its enactment, there have been judicial and Congressional challenges to numerous provisions of PPACA. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of PPACA or otherwise circumvent some of the requirements for health insurance mandated by PPACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of PPACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under PPACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or Tax Act, signed into law on December 22, 2017, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by PPACA on certain individuals that fail to maintain qualifying health coverage for all of part of a year commonly referred to as the "individual mandate." On January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain PPACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended PPACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." In July 2018, the Centers for Medicare and Medicaid Services, or CMS, published a final rule permitting further collections and payments to and from certain PPACA qualified health plans and health insurance issuers under PPACA risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On December 14, 2018, a Texas U.S. District Court Judge ruled that PPACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Act. While the Texas U.S. District Court Judge, as well as the Trump administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace PPACA will impact PPACA.

In addition, since the PPACA was enacted, other legislative changes have been proposed and adopted that may impact the extent to which we are able to successfully commercialize any of our product candidates that receive regulatory approval. For example, in August 2011, then-President Obama signed into law the Budget Control Act of

2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee on Deficit Reduction did not achieve a targeted deficit reduction, which triggered the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of, on average, two percent per fiscal year through 2027 unless Congress takes additional action. The American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices, including at the federal level several recent U.S. Congressional inquiries and legislation designed to, among other things, increase drug pricing transparency, reduce the cost of drugs under Medicare, review relationships between pricing and manufacturer patient assistance programs, and reform government program drug reimbursement methodologies. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Further, the Trump administration released a "Blueprint", or plan, to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. HHS has already started the process of soliciting feedback on some of these measures and, at the same time, is immediately implementing others under its existing authority. For example, in September 2018, CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019, and in October 2018, CMS proposed a new rule that would require direct-to-consumer television advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product. On January 31, 2019, the HHS Office of Inspector General proposed modifications to federal Anti-Kickback Statute safe harbors which, among other things, may affect rebates paid by manufacturers to Medicare Part D plans, the purpose of which is to further reduce the cost of drug products to consumers. Although a number of these, and other proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. Any reduction in reimbursement from Medicare or other government-funded programs may result in a similar reduction in payments from private payers. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, to encourage importation from other countries and bulk purchasing. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize ZILRETTA and any future products for which we receive regulatory approval.

We expect that PPACA reform, as well as other healthcare reform measures that have been and may be adopted in the future, may result in more rigorous coverage criteria and lower reimbursement, as well as additional downward pressure on the price that we receive for any approved product, including ZILRETTA.

Additionally, on May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded

access program. There is no obligation for a pharmaceutical manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

Accelerated Approval for Regenerative Advanced Therapies

As part of the 21st Century Cures Act, Congress recently amended the FDCA to create an accelerated approval program for regenerative advanced therapies, which include cell therapies, gene therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. Regenerative advanced therapies do not include those gene therapies, human cells, tissues, and cellular and tissue-based products regulated solely under section 361 of the Public Health Service Act and 21 CFR Part 1271. The new program is intended to facilitate efficient development and expedite review of regenerative advanced therapies, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition. A drug sponsor may request that the FDA designate a drug as a regenerative advanced therapy concurrently with or at any time after submission of an IND. The FDA has 60 calendar days to determine whether the drug meets the criteria, including whether there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs for a serious or life-threatening disease or condition. A NDA or BLA for a regenerative advanced therapy may be eligible for priority review or accelerated approval through surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of clinical trial sites. Benefits of such designation also include early interactions with the FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative advanced therapy that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence, clinical studies, patient registries, or other sources of real-world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval.

Other U.S. Healthcare Laws and Compliance Requirements

In the United States, our activities are subject to regulation by various federal, state and local authorities in addition to the FDA, including CMS, other divisions of HHS (e.g., the Office of Inspector General), the United States Department of Justice and individual United States Attorney offices within the Department of Justice, and state and local governments. For example, various activities, including but not limited to sales, marketing and scientific/educational grant programs, must comply with the anti-fraud and abuse provisions of the Social Security Act, the federal Anti-Kickback Statute, the federal False Claims Act and similar state laws, each as amended. Failure to comply with such requirements could potentially result in substantial penalties to us. Even if we structure our programs with the intent of compliance with such laws, there can be no certainty that we would not need to defend against enforcement or litigation, in light of the fact that there is significant enforcement interest in pharmaceutical companies in the United States, and some of the applicable laws are quite broad in scope.

The federal Anti-Kickback Statute prohibits any person or entity, including a prescription drug manufacturer (or a party acting on its behalf), from knowingly and willfully soliciting, receiving, offering or providing remuneration, directly or indirectly, to induce or reward either the referral of business, or the furnishing, recommending, or arranging for the purchase, lease or order of a good, facility, item or service, for which payment may be made under a federal healthcare program, such as the Medicare or Medicaid program. This statute has been interpreted broadly to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers, among others, on the other. The term “remuneration” has been broadly interpreted to include anything of value, including for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payments, ownership interests and providing anything at less than its fair market value.

Federal false claims and false statements laws, including the federal False Claims Act, prohibit, among other things, any person or entity from knowingly presenting, or causing to be presented, a false or fraudulent claim for items or services, including drugs, for payment to, or approval by, a federal healthcare program, including Medicare or Medicaid. The qui tam provisions of the federal False Claims Act allow a private individual to bring a civil action on

behalf of the federal government alleging that the defendant has submitted a false claim to the federal government, and to share in any monetary recovery. In recent years, the number of suits brought by private individuals has increased dramatically.

The Health Insurance Portability and Accountability Act of 1996, or HIPAA, created several new federal crimes, including healthcare fraud and false statements relating to healthcare matters. The healthcare fraud statute

prohibits knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including third-party payers. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.

The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to CMS information related to payments or other transfers of value made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members.

Also, many states have similar laws and regulations, such as anti-kickback and false claims laws that may be broader in scope and may apply regardless of payer, in addition to items and services reimbursed under Medicaid and other state programs. Additionally, we may be subject to state laws that require pharmaceutical companies to comply with the federal government's and/or pharmaceutical industry's voluntary compliance guidelines, state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, as well as state and foreign laws governing the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA.

HIPAA, as amended by the Health Information Technology and Clinical Health Act of 2009, and their respective implementing regulations, impose requirements on certain healthcare providers, health plans, and healthcare clearinghouses, known as covered entities, as well as their business associates that perform services involving the use or disclosure of individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information.

Where our activities involve foreign government officials, they may also potentially be subject to the Foreign Corrupt Practices Act, which prohibits companies and individuals from engaging in specified activities to obtain or retain business or to influence a person working in an official capacity. Under the FCPA, it is illegal to pay, offer to pay, or authorize the payment of anything of value to any foreign government official, governmental staff members, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the corporation and to devise and maintain an adequate system of internal accounting controls.

If we seek to have a product covered in the United States by the Medicaid programs, various obligations, including government price reporting, are required under the Medicaid rebate requirements of the Omnibus Budget Reconciliation Act of 1990 and the Veterans Health Care Act of 1992, each as amended, which generally require products to be offered at substantial rebates/discounts to such programs and certain purchasers. In order to distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of pharmaceutical products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain. Many of our current as well as possible future activities are potentially subject to federal and state consumer protection and unfair competition laws. We must also comply with laws that require clinical trial registration and reporting of clinical trial results on the publicly available clinical trial databank maintained by the National Institutes of Health at www.ClinicalTrials.gov. We are subject to various environmental, health and safety regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous substances. From time to time, and in the future, our operations may

involve the use of hazardous materials.

To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

U.S. Marketing Exclusivity

Hatch-Waxman Exclusivity. Market exclusivity provisions under the FDCA can delay the submission or approval of certain applications of other companies seeking to reference another company's NDA. If the new drug is a new chemical entity subject to an NDA, the FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a Section 505(b)(2) NDA submitted by another company for another version of such drug where the applicant does not own or have a legal right of reference to all the data required for approval. However, such an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. The FDCA also provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the original active agent. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Rest of World Government Regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our future products.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Employees

As of December 31, 2018, we had 272 full-time employees. None of our employees is represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Research and Development

We invested $53.1 million, $51.2 million, and $41.3 million in research and development in the years ended December 31, 2018, 2017 and 2016, respectively.

Corporate and Other Information

We were incorporated in Delaware in November 2007. Our principal executive offices are located at 10 Mall Road, Suite 301, Burlington, Massachusetts 01803, and our telephone number is (781) 305-7777. Our corporate website

address is www.flexiontherapeutics.com. Information contained on or accessible through our website is not a part of this Annual Report, and the inclusion of our website address in this Annual Report is an inactive textual reference only. Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to reports filed pursuant to Sections 13(a) and 15(d) of the Exchange Act are available free of

charge on our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. We also regularly post copies of our press releases as well as copies of presentations and other updates about our business on our website at www.flexiontherapeutics.com. Information contained in our website does not constitute a part of this Annual Report or our other filings with the SEC. The SEC maintains an internet site that contains our public filings with the SEC and other information regarding our company, at www.sec.gov. These reports and other information concerning our company may also be accessed at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330.

This Annual Report contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this Form 10-K, including logos, artwork and other visual displays, may appear without the ® or TM symbols, but such references are not intended to indicate, in any way, that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. We do not intend our use or display of other companies' trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

## ITEM 1A. RISK FACTORS

You should consider carefully the risks described below, together with the other information contained in this Annual Report on Form 10-K and other documents we file with the Securities and Exchange Commission. The risks and uncertainties below are those identified by us as material, but there are also additional risks and uncertainties that we are unaware of that may become important factors that affect us. If any of the following risks actually occurs, our business, financial condition, results of operations and future growth prospects would likely be materially and adversely affected, and the market price of our common stock would likely decline.

### Risks Related to Our Financial Condition and Need for Additional Capital

We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses over the next few years.

We have a limited operating history. To date, we have focused primarily on developing our commercialized product, ZILRETTA. Any additional product candidates we develop will require substantial development time and resources before we would be able to apply for or receive regulatory approvals and begin generating revenue from product sales. We have incurred significant net losses in each year since our inception, including net losses of $169.7 million, $137.5 million, and $71.9 million for fiscal years 2018, 2017, and 2016, respectively. As of December 31, 2018, we had an accumulated deficit of $518.8 million. We expect to incur net losses over the next few years as we continue to invest in the commercialization of ZILRETTA and advance our development programs.

We have devoted most of our financial resources to product development, including our nonclinical development activities and clinical trials, and more recently to commercial efforts. To date, we have financed our operations exclusively through the sale of equity securities and debt. The size of our future net losses will depend, in part, on the rate of future expenditures and our ability to generate revenue. The U.S. Food and Drug Administration, or FDA, granted marketing approval and we launched commercial sales of ZILRETTA in the fourth quarter of 2017. We have not generated significant revenues from sales of ZILRETTA and cannot guarantee that our commercialization efforts will result in substantial product revenues.

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We also expect to continue to incur substantial and increased expenses as we invest in the commercialization of ZILRETTA, scale up commercial manufacturing of ZILRETTA, conduct additional clinical trials for this product and continue our development activities with respect to ZILRETTA, FX201 and other future product candidates. As a result of the foregoing, we expect to continue to incur significant losses and negative cash flows over the next few years.

We have not generated significant revenue and may never be profitable.

Our ability to generate significant revenue and achieve profitability depends primarily on our ability to successfully commercialize ZILRETTA, as well as our ability to obtain regulatory approval for and then successfully commercialize other product candidates. We may never succeed in these activities and may never generate revenues that are significant enough to achieve profitability.

Because of the numerous risks and uncertainties associated with new pharmaceutical products and development efforts, we are unable to predict the timing or amount of increased expenses, when, or if, we will begin to generate meaningful revenue from product sales, or when, or if, we will be able to achieve or maintain profitability. In addition, our expenses could increase beyond expectations if we determine that additional sales and marketing personnel or other resources are necessary to successfully commercialize ZILRETTA or if we face any product liability claims related to the commercialization of ZILRETTA.

If we are unable to generate significant revenues from product sales, particularly from sales of ZILRETTA, or to maintain an acceptable cost structure related to our operations, we may not become profitable and may need to obtain additional funding to continue operations.

If we fail to obtain additional financing, we may be forced to delay, reduce or eliminate our product development programs and/or commercialization activities.

Developing and commercializing pharmaceutical products, including conducting preclinical studies and clinical trials, and building and maintaining sales and marketing capabilities, is expensive. We expect our expenses to increase in connection with our ongoing activities, particularly as we expand our sales and marketing activities, continue to commercialize ZILRETTA and advance our clinical programs.

As of December 31, 2018, we had cash, cash equivalents and marketable securities of approximately $258.8 million and working capital of $248.4 million. Based upon our current operating plan, we believe that our existing cash, cash equivalents, and marketable securities will enable us to fund our operating expenses and capital requirements for at least the next 12 months from the issuance date of the financial statements included in this report. Regardless of our expectations as to how long our cash, cash equivalents, and marketable securities will fund our operations, changing circumstances beyond our control may cause us to consume capital more rapidly than we currently anticipate.

Attempting to secure additional financing may divert our management from our day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. If we are unable to raise additional capital when required or on acceptable terms, we may be required to:

- significantly scale back or discontinue commercialization of ZILRETTA or the further development of ZILRETTA or our product candidates;
- seek corporate partners for our product candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available;
-

seek corporate partners to assist in the commercialization of ZILRETTA on terms that are less favorable than might otherwise be available;

- relinquish or license on unfavorable terms, our rights to technologies or product candidates that we otherwise would seek to develop or commercialize ourselves; or
- significantly curtail, or cease, operations.

We may sell additional equity or debt securities to fund our operations, which may result in dilution to our stockholders and impose restrictions on our business.

In order to raise additional funds to support our operations, we may sell additional equity or debt securities, which could adversely impact our existing stockholders as well as our business. The sale of additional equity or convertible debt securities would result in the issuance of additional shares of our capital stock and dilution to all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and could also result in certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business.

Our existing indebtedness contains restrictions that limit our flexibility in operating our business. In addition, we may be required to make a prepayment or repay our outstanding indebtedness earlier than we expect, which could have a materially adverse effect on our business, or may otherwise be unable to repay our indebtedness as it becomes due.

On August 4, 2015, we entered into a credit and security agreement with MidCap Financial SBIC, LP, or MidCap, as administrative agent, and MidCap Funding XIII Trust and Silicon Valley Bank, as agent lenders, to borrow up to $30.0 million and contemporaneously drew down $15.0 million under the credit facility. The credit agreement contains various covenants that limit our ability to engage in specified types of transactions. These covenants limit our ability to, among other things:

- incur or assume certain debt;
- merge or consolidate or acquire all or substantially all of the capital stock or property of another entity;
    - enter into any transaction or series of related transactions that would be deemed to result in a change in control of us under the terms of the agreement;
- change the nature of our business;
- change our organizational structure or type;
- amend, modify or waive any of our organizational documents;
- license, transfer or dispose of certain assets;
- grant certain types of liens on our assets;
- make certain investments;
- pay cash dividends;
- enter into material transactions with affiliates; and
- amend or waive provisions of material agreements in certain manners.

The restrictive covenants in the credit agreement could prevent us from pursuing business opportunities that we or our stockholders may consider beneficial.

A breach of any of these covenants could result in an event of default under the credit agreement. An event of default will also occur if, among other things, a material adverse change in our business, operations or condition occurs, which could potentially include a material impairment of the prospect of our repayment of any portion of the amounts we owe under the credit agreement occurs. In the case of a continuing event of default under the credit agreement, the lenders could elect to declare all amounts outstanding to be immediately due and payable, proceed against the collateral in which we granted the lenders a security interest under the credit agreement, or otherwise exercise the rights of a secured creditor. Amounts outstanding under the credit agreement are secured by all of our existing and future assets, excluding intellectual property, which is subject to a negative pledge arrangement.

In April 2017, we also issued $201.3 million principal amount of our 3.375% Convertible Senior Notes due 2024, or the 2024 Convertible Notes. The 2024 Convertible Notes will mature on May 1, 2024, unless earlier redeemed, repurchased or converted in accordance with the terms of the indenture governing the notes. If specified bankruptcy,

insolvency or reorganization-related events of default occur, or if certain other events of default occur and the trustee or certain holders of the 2024 Convertible Notes elect, the principal of, and accrued and unpaid

interest on, all of the then-outstanding 2024 Convertible Notes will automatically become due and payable. In addition, if we undergo certain fundamental change transactions specified in the indenture governing the 2024 Convertible Notes, the holders of the notes may require us to repurchase their notes at a price equal to 100% of the principal amount of the notes, plus any accrued and unpaid interest.

We may not have enough available cash or be able to raise additional funds on satisfactory terms, if at all, through equity or debt financings to repay or refinance our indebtedness at the time any such repayment or repurchase is required. In such an event, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts or grant to others rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. Our business, financial condition and results of operations could be materially adversely affected as a result.

Risks Related to Commercialization Activities

Our prospects are highly dependent on the successful commercialization of ZILRETTA. To the extent ZILRETTA is not commercially successful, our business, financial condition and results of operations may be materially adversely affected.

ZILRETTA is our only drug that has been approved for sale and it has only been approved for the management of osteoarthritis, or OA, pain of the knee for patients in the United States. We are focusing a significant portion of our activities and resources on ZILRETTA, and we believe our prospects are highly dependent on, and a significant portion of the value of our company relates to, our ability to successfully commercialize ZILRETTA in the United States.

Successful commercialization of ZILRETTA is subject to many risks. We have never, as an organization, commercialized a product prior to ZILRETTA, and there is no guarantee that we will be able to do so successfully with ZILRETTA for its approved indication. There are numerous examples of failures to meet high expectations of market potential, including by pharmaceutical companies with more experience and resources than us.

Market acceptance of ZILRETTA and any other product for which we receive approval, will depend on a number of factors, including:

- the efficacy and safety as demonstrated in clinical trials;
- the timing of market introduction of the product as well as competitive products;
- the clinical indications for which the product is approved;
- acceptance by physicians, the medical community and patients of the product as a safe and effective treatment;
- the ability to distinguish safety and efficacy from existing, less expensive generic alternative therapies;
- the convenience of prescribing, administrating and initiating patients on the product;
- the potential and perceived advantages of the product over alternative treatments;
- the potential and perceived value of the product over alternative treatments;
- the cost of treatment in relation to alternative treatments, including any similar generic treatments;
- the availability of coverage and adequate reimbursement by third-party payers and government authorities to support ZILRETTA’s pricing;
- the prevalence and severity of adverse side effects; and
- the effectiveness of sales and marketing efforts.

With respect to ZILRETTA, while we have established our commercial team and sales force, there are many factors that could cause the commercialization of ZILRETTA to be unsuccessful, including a number of factors that are outside our control. The commercial success of ZILRETTA depends on the extent to which patients and physicians accept and adopt ZILRETTA as a treatment for OA pain of the knee, and we do not know whether our or

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others' revenue estimates in this regard will be accurate. For example, if the patient population suffering from OA pain of the knee is smaller than we estimate or if physicians are unwilling to prescribe or patients are unwilling to use ZILRETTA, the commercial potential of ZILRETTA will be limited. In addition, if ZILRETTA is not convenient for physicians to use, then it may not achieve widespread adoption, regardless of its efficacy and safety. For example, ZILRETTA must be administered only by a health care professional in an office, clinic or hospital setting. In addition, ZILRETTA requires a multi-step preparation process, which may discourage some physicians from using ZILRETTA. Moreover, ZILRETTA's product label indicates that it is not intended for repeat administration, and we believe this has negatively impacted our commercialization efforts. While we successfully completed a Phase 3b repeat dose study of ZILRETTA and have submitted an sNDA to the FDA, we cannot predict whether or when the FDA may agree to modify the ZILRETTA product label with respect to repeat administration. We also do not know how physicians, patients and payers will respond to the pricing of ZILRETTA in the long-term. In particular, as part of our initial launch strategy we have provided product samples during a trial period, and do not know whether physicians that initially use ZILRETTA will continue to do so after using the product samples. If we experience any disruption in the commercial supply of ZILRETTA due to manufacturing or distribution issues, the disruption would impact ZILRETTA sales and may adversely affect physicians', patients' and payers' assessment of ZILRETTA, negatively impacting uptake and long-term commercialization efforts.

Physicians may not prescribe ZILRETTA and patients may be unwilling to use ZILRETTA if coverage is not provided or reimbursement is inadequate to cover a significant portion of the cost. Additionally, any negative development for ZILRETTA in clinical development in additional indications, may adversely impact the commercial results and potential of ZILRETTA. Thus, significant uncertainty remains regarding the commercial potential of ZILRETTA.

If the commercialization of ZILRETTA is unsuccessful or perceived as disappointing, our stock price could decline significantly, and the long-term success of the product and our company could be harmed.

If we are unable to differentiate ZILRETTA from existing generic therapies for the treatment of OA, or if the FDA or other applicable regulatory authorities approve generic products that compete with ZILRETTA, our ability to successfully commercialize ZILRETTA would be adversely affected.

Immediate-release TA and other injectable immediate-release steroids, which are the current intra-articular, or IA, standard of care for OA pain, are available in generic form and are therefore relatively inexpensive compared to the pricing for ZILRETTA. These generic steroids also have well-established market positions and familiarity with physicians, healthcare payers and patients. Although we believe the proven and extended pain relief evidenced in our clinical trials demonstrate that ZILRETTA represents a clinically meaningful and highly efficacious option for patients and physicians, it is possible that we will receive data from additional clinical trials or in a post-marketing setting from physician and patient experiences with the commercial product that does not continue to support such interpretations. It is also possible that the FDA, physicians and healthcare payers will not agree with our interpretation of our existing and future clinical trial data. If we are unable to demonstrate the value of ZILRETTA based on our data, our opportunity for ZILRETTA to maintain premium pricing and be commercialized successfully would be adversely affected. For example, although ZILRETTA showed numeric improvements through week 12 in validated, OA specific pain, stiffness, function and quality of life exploratory measures and showed numeric improvements in average daily pain, it did not achieve statistical significance at the week 12 ADP timepoint compared to immediate-release TA. As a result, it is possible that healthcare payers will not agree with our assessment that ZILRETTA's proven pain relief supports premium pricing.

In addition to existing generic steroids, such as immediate-release TA, the FDA or other applicable regulatory authorities may approve other generic products that could compete with ZILRETTA, if we cannot adequately protect it with our patent portfolio. Once an NDA, including a Section 505(b)(2) application, is approved, the product covered

thereby becomes a “listed drug” which can, in turn, be cited by potential competitors in support of approval of an abbreviated new drug application, or ANDA. The FDCA, FDA regulations and other applicable regulations and policies provide incentives to manufacturers to create modified, non-infringing versions of a drug to facilitate the approval of an ANDA or other application for generic substitutes. These manufacturers might only be required to conduct a relatively inexpensive study to show that their product has the same active ingredient(s), dosage form, strength, route of administration, conditions of use, or labeling as our product candidate and that the generic product is bioequivalent to ours, meaning it is absorbed in the body at the same rate and to the same extent

as ZILRETTA. These generic equivalents, which must meet the same quality standards as branded pharmaceuticals, would be significantly less costly than ours to bring to market and companies that produce generic equivalents are generally able to offer their products at lower prices. Thus, after the introduction of a generic competitor, a significant percentage of the sales of any branded product is typically lost to the generic product. Accordingly, competition from generic equivalents to our products would materially adversely impact our ability to successfully commercialize ZILRETTA.

We face significant competition from other biopharmaceutical companies, and our operating results will suffer if we fail to compete effectively.

The biopharmaceutical industries are intensely competitive and subject to rapid and significant technological change. In addition, the competition in the pain and OA market is intense. We have competitors both in the United States and internationally, including major multinational pharmaceutical and biotechnology companies. For example, the injectable OA treatment market today includes many injectable immediate-release steroids, including TA, the active ingredient in ZILRETTA, as well as hyaluronic acid, or HA, injections. In addition, we expect that injectable therapies, such as ZILRETTA, will continue to be used primarily after oral medications no longer provide adequate pain relief. To the extent that new or improved oral or other systemically administered pain medications are introduced that demonstrate better long-term efficacy and safety, patients and physicians may further delay the introduction of injectable therapies, such as ZILRETTA in the OA treatment continuum. ZILRETTA could also face competition from other formulations or devices that deliver pain medication on an extended basis, such as transdermal delivery systems or implantable devices.

Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staffs and experienced commercial and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. As a result, these companies may obtain regulatory approval more rapidly than we are able and may be more effective in selling and marketing their products as well. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis drug products or drug delivery technologies that are more effective or less costly than ZILRETTA or any other product candidate that we are currently developing or that we may develop.

We believe that our ability to successfully compete will depend on, among other things:

- the efficacy and safety of ZILRETTA and our other product candidates, including as relative to marketed products and product candidates in development by third parties;
- the ability to distinguish safety and efficacy from existing, less expensive generic alternative therapies;
- the time it takes for our product candidates to complete clinical development and receive marketing approval;
    - the ability to maintain a good relationship with regulatory authorities;
- the ability to commercialize and market ZILRETTA and any of our other product candidates that receive regulatory approval;
- the price of ZILRETTA and any of our future products, including in comparison to branded or generic competitors;
- whether coverage and adequate levels of reimbursement are available under private and governmental health insurance plans, including Medicare;
- the ability to protect our intellectual property rights;
- the ability to manufacture on a cost-effective basis and sell commercial quantities of ZILRETTA and any of our other product candidates that receive regulatory approval; and

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- acceptance of ZILRETTA and any of our other product candidates that receive regulatory approval by patients, physicians and other healthcare providers.

If our competitors market products that are more effective, safer or less expensive than ZILRETTA, we may not achieve commercial success. In addition, the biopharmaceutical industry is characterized by rapid technological change. Because we have limited research and development capabilities, it may be difficult for us to stay abreast of the rapid changes in each technology. If we fail to stay at the forefront of technological change, we may be unable to compete effectively. Technological advances or products developed by our competitors may render our technologies, products or product candidates obsolete, less competitive or not economical.

If we are unable to maintain sales and marketing capabilities or enter into agreements with third parties to market, distribute and sell our product candidates, we may be unable to generate adequate revenue.

Our strategy is to commercialize ZILRETTA in the United States with a targeted sales and marketing organization. While we have established our commercial team and our sales force, we do not have prior experience commercializing pharmaceutical products as an organization. In order to successfully market ZILRETTA, we must continue to build and maintain our sales, marketing, managerial, compliance and related capabilities or make arrangements with third parties to perform these services. These efforts will continue to be expensive and time-consuming, and we will be competing with other pharmaceutical and biotechnology companies to recruit, hire, train and retain marketing and sales personnel. If we are unable to maintain adequate sales, marketing and distribution capabilities, whether independently or with third parties, we may not generate significant revenue from ZILRETTA.

Additionally, our strategy in the United States includes distributing ZILRETTA solely through a limited network of third-party specialty distributors and one specialty pharmacy. While we have entered into agreements with a specialty pharmacy and specialty distributors to distribute ZILRETTA in the United States, they may not perform as agreed or they may terminate their agreements with us. For example, ZILRETTA sales are concentrated with two specialty distributors, which together represented approximately 81% and 94% of our sales for the years ended December 31, 2018 and 2017, respectively. Loss of either specialty distributor through contract termination or its failure to distribute effectively would adversely affect ZILRETTA’s distribution. Also, we may need to enter into agreements with additional specialty distributors or specialty pharmacies, and there is no guarantee that we will be able to do so on commercially reasonable terms or at all. In the event that our specialty distributors or specialty pharmacy do not fulfill their contractual obligations to us, the agreements are terminated without adequate notice, or we are unable to expand our network, shipments of ZILRETTA through, and associated revenues from, these sales channels would be adversely affected. In addition, we expect that it would take a significant amount of time to negotiate new contracts if we were required to change our specialty distributors or specialty pharmacy.

To date, we have not entered into any strategic collaborations for ZILRETTA or any of our other product candidates. We face significant competition in seeking appropriate strategic partners, and these strategic collaborations can be intricate and time consuming to negotiate and finalize. We may not be able to negotiate strategic collaborations for territories outside of the United States on acceptable terms, or at all. We are unable to predict when, if ever, we will enter into any strategic collaboration outside of the United States because of the numerous risks and uncertainties associated with establishing strategic collaborations. To the extent that we enter into strategic collaborations, our future collaborators may not dedicate sufficient resources to the commercialization of our product candidates or may otherwise fail in their commercialization due to factors beyond our control. If we are unable to establish effective collaborations to enable the sale of ZILRETTA or our other product candidates in territories outside of the United States, or if our potential future collaborators do not successfully commercialize our product candidates in these territories, our ability to generate revenue from product sales will be adversely affected.

We and any future collaborators that we may engage will be competing with many companies that currently have extensive and well-funded marketing and sales operations. If we, alone or with commercialization partners, are unable

to compete successfully against these established companies, the commercial success of ZILRETTA or any other approved products will be limited. In addition, if we are unable to effectively develop and maintain our commercial team, including our U.S. sales force, or maintain and, if needed, expand, our network of specialty distributors and specialty pharmacies, our ability to effectively commercialize ZILRETTA and generate product revenues would be limited.

If we are unable to effectively train and equip our sales force, our ability to successfully commercialize ZILRETTA will be harmed.

ZILRETTA is a newly-marketed drug and, therefore, the members of our sales force do not have significant experience promoting ZILRETTA. As a result, we are required to expend significant time and resources to train our sales force to be credible, persuasive and compliant with applicable laws in marketing ZILRETTA for the treatment of patients with OA of the knee. In addition, we must train our sales force to ensure that an appropriate and compliant message about ZILRETTA is being delivered. If we are unable to maintain an effectively trained sales force and equip them with compliant and effective materials, including medical and sales literature to help them appropriately inform and educate regarding the potential benefits and safety of ZILRETTA and its proper administration, our efforts to successfully commercialize ZILRETTA could be put in jeopardy, which would negatively impact our ability to generate product revenues.

If we are unable to achieve and maintain adequate levels of third-party payer coverage and reimbursement for ZILRETTA, or, if approved, any other product candidates, on reasonable pricing terms, their commercial success may be severely hindered.

Successful sales of ZILRETTA and any other approved product candidates depend on the availability of coverage and adequate reimbursement from third-party payers, including governmental healthcare programs, such as Medicare and Medicaid, managed care organizations and commercial payers, among others. Patients who are prescribed medicine for the treatment of their conditions generally rely on third-party payers to reimburse all or part of the costs associated with their prescription drugs. Coverage and adequate reimbursement from third-party payers are critical to new product acceptance. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. The resulting reimbursement payment rates for ZILRETTA and, if approved, our other product candidates, might not be adequate or may require co-payments that patients find unacceptably high.

As of January 1, 2019, we received a product-specific J-Code for ZILRETTA (J-3304), which may reduce reluctance by physicians to prescribe ZILRETTA based on reimbursement concerns. However, third-party payers nevertheless may require documented proof that patients meet certain eligibility criteria in order to be reimbursed for ZILRETTA, for example requiring that a patient first try and fail treatment with an injection of generic corticosteroid. Also, third-party payers may require that pre-approval, or prior-authorization, be obtained from the payer for reimbursement of ZILRETTA, or limit coverage to one injection or a limited number of injections over a set time period. Patients are unlikely to use ZILRETTA and, if approved, any other products, unless coverage is provided, and reimbursement is adequate to cover a significant portion of the cost of our products. For example, ZILRETTA is sold to physicians on a “buy and bill” basis. Buy and bill products must be purchased by healthcare providers before they can be administered to patients. Healthcare providers subsequently must seek reimbursement for the product from the applicable third-party payer, such as Medicare or a health insurance company. Healthcare providers may be reluctant to administer ZILRETTA because they would have to fund the purchase of the product and then seek reimbursement, which may be different from their purchase price, or because they do not want the additional administrative burden required to obtain reimbursement for the product.

In addition, the market for ZILRETTA and any of our other product candidates may depend significantly on access to third-party payers’ medical policies, drug formularies, or lists of medications for which third-party payers provide coverage and reimbursement, as well as inclusion of ZILRETTA on the reimbursement policies and formularies used by large physician practices and hospitals. The industry competition to be included in such policies or formularies often leads to downward pricing pressures on pharmaceutical companies, and we may be required to offer discounted rates to certain government and other payers to ensure coverage of our drugs. Also, third-party payers, physician practices and hospitals may refuse to include a particular branded drug in their policies or formularies or otherwise

restrict patient access to a branded drug when a less costly generic equivalent or other alternative is available, or when the reimbursement landscape is unclear.

Third-party payers, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. In addition, in the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payers.

Therefore, coverage and reimbursement for drug products can differ significantly from payer to payer and one payer's determination to provide coverage for ZILRETTA does not ensure that other payers also will provide coverage. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payer separately, with no assurance that coverage and adequate reimbursement will be obtained.

Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the United States and in international markets. Third party coverage and reimbursement for ZILRETTA or, if approved, any of our other product candidates, may not be available or adequate in either the United States or international markets, or may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sales and distribution costs. If coverage and reimbursement are not available or only available at limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval, including ZILRETTA, which could have a material adverse effect on our business, results of operations, financial condition and prospects.

Guidelines and recommendations published by various organizations can reduce the use of ZILRETTA and any other products we may commercialize.

Government agencies promulgate regulations and guidelines directly applicable to us and to our products and product candidates. In addition, professional societies, such as the American Academy of Orthopedic Surgeons, practice management groups, private health and science foundations and organizations involved in various diseases from time to time may also publish guidelines or recommendations to the healthcare and patient communities with respect to specific products. Recommendations of government agencies or these other groups or organizations may relate to such matters as usage, dosage, route of administration and use of concomitant therapies. Recommendations or guidelines that do not recognize ZILRETTA or our other product candidates, suggest limitations or inadequacies of ZILRETTA or our other product candidates, or suggest the use of competitive or alternative products as the standard of care to be followed by patients and healthcare providers, could result in decreased use or adoption of ZILRETTA or any future products.

ZILRETTA is available to a much larger number of patients and in broader populations through our commercialization efforts as compared to the patients in the clinical studies. We do not know whether the results of ZILRETTA's use in such larger number of patients and broader populations will be consistent with the results from our clinical studies.

While the FDA granted approval of ZILRETTA based on the data included in the NDA, including data from our completed pivotal Phase 3 clinical trial, we do not know whether the results that served as the basis for the FDA's approval of ZILRETTA will be consistent with commercial results as a large number of patients and broader populations are exposed to ZILRETTA and are exposed over longer periods of time, including results related to safety and efficacy. New data relating to ZILRETTA, including from adverse event reports or our on-going studies of ZILRETTA related to hip OA or synovitis in knee OA, may result in changes to the product label and may adversely affect sales, or result in withdrawal of ZILRETTA from the market. The FDA and regulatory authorities in other jurisdictions may also consider any new data in connection with further marketing approval applications. If ZILRETTA or any additional approved products cause serious or unexpected side effects after receiving market approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw their approval of the product or impose restrictions on its distribution in the form of a modified Risk Evaluation and Mitigation Strategy;

- regulatory authorities may require the addition of labeling statements, such as warnings or contraindications;
- we may be required to change the way the product is promoted or administered or conduct additional clinical studies;
- we could be sued and held liable for harm caused to patients; or

- our reputation may suffer.

Any of these events could prevent us from maintaining market acceptance of the affected product and could substantially increase the costs of commercializing ZILRETTA or any additional products.

Recently enacted and future legislation, including health care reform measures, may increase the difficulty and cost for us to commercialize ZILRETTA and any future products and may affect the prices we may obtain.

The United States and some foreign jurisdictions are considering, or have enacted, a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell ZILRETTA, and if approved for sale, our other potential products, profitably. Among policy makers and third-party payers in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been, and may continue to be, significantly affected by major legislative, congressional and enforcement initiatives. Moreover, in some foreign jurisdictions, pricing of prescription pharmaceuticals is already subject to government control.

In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or PPACA, was enacted, which was intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add transparency requirements for the healthcare and health insurance industries, impose taxes and fees on the health industry and impose additional health policy reforms. Among the PPACA provisions of importance to the pharmaceutical industry are the following:

- an annual, non-deductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- a new Medicare Part D coverage gap discount program, in which manufacturers must now agree to offer 70% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements under the federal Open Payments program, created under Section 6002 of PPACA, and its implementing regulations that require manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to "payments or other transfers of value" made or distributed to physicians and teaching hospitals, and that applicable manufacturers and applicable group purchasing organizations report annually to CMS ownership and investment interests held by physicians and their immediate family members;

- a requirement to annually report drug samples that manufacturers and distributors provide to physicians;
- expansion of healthcare fraud and abuse laws, including the federal False Claims Act and the federal Anti-Kickback Statute, new government investigative powers, and enhanced penalties for non-compliance;
- an FDA-approval framework for follow-on biologic products;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and
- establishment of a Center for Medicare & Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Some of the provisions of PPACA have yet to be implemented, and there have been legal and political challenges to certain aspects of PPACA. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay, circumvent, or loosen certain requirements mandated by PPACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of PPACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under PPACA have been signed into law. The Tax Cuts and Jobs Act of 2017, signed into law on December 22, 2017, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by PPACA on certain individuals that fail to maintain qualifying health coverage for all of part of a year commonly referred to as the "individual mandate." On January 22, 2018, President Trump signed a continuing resolution on appropriation for fiscal year 2018 that delayed the implementation of certain PPACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans and the annual fee imposed on certain health insurance providers based on market share. The Bipartisan Budget Act of 2018, among other things, amended PPACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." In July 2018, CMS announced published a final rule permitting further collections and payments to and from certain PPACA qualified health plans and health insurance issuers under PPACA risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On December 14, 2018, a Texas U.S. District Court Judge ruled that PPACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Act. While the Texas U.S. District Court Judge, as well as the Trump administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace PPACA will impact PPACA and our business.

In addition, since the PPACA was enacted, other legislative changes have been proposed and adopted that may impact the extent to which we are able to successfully commercialize any of our product candidates that receive regulatory approval. For example, in August 2011, then-President Obama signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee on Deficit Reduction did not achieve a targeted deficit reduction, which triggered the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of, on average, two percent per fiscal year through 2027 unless Congress takes additional action. The American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices, including at the federal level several recent U.S. Congressional inquiries and legislation designed to, among other things, increase drug pricing transparency, reduce the cost of drugs under Medicare, review relationships between pricing and manufacturer patient assistance programs, and reform government program drug reimbursement methodologies. Any reduction in reimbursement from Medicare, Medicaid or other government-funded programs may result in a similar reduction in payments from private payers. The Trump administration's budget proposal for fiscal

year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to

negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Further, the Trump administration released a "Blueprint", or plan, to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. The Department of Health and Human Services, or HHS, has already started the process of soliciting feedback on some of these measures and, at the same time, is immediately implementing others under its existing authority. For example, in September 2018, CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019, and in October 2018, CMS proposed a new rule that would require direct-to-consumer television advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product. On January 31, 2019, the HHS Office of Inspector General proposed modifications to federal Anti-Kickback Statute safe harbors which, among other things, may affect rebates paid by manufacturers to Medicare Part D plans, the purpose of which is to further reduce the cost of drug products to consumers. Although a number of these, and other proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, to encourage importation from other countries and bulk purchasing. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize ZILRETTA and any future products for which we receive regulatory approval.

We expect that PPACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and lower reimbursement, as well as additional downward pressure on the price that we receive for any approved product, including ZILRETTA.

Risks Related to Product Development and Regulatory Compliance

We may never obtain regulatory approval of ZILRETTA for repeat administration or additional indications, approval of our other product candidates in the United States, or we may never obtain approval for or commercialize ZILRETTA or our other product candidates outside of the United States, which would limit our ability to realize their full market potential.

While ZILRETTA has been approved for the management of OA pain of the knee, the approved product label contains a limitation of use, or LOU, stating that ZILRETTA is not intended for repeat administration. On December 17, 2018, we submitted a supplemental new drug application, or sNDA, to the FDA to revise the product label for ZILRETTA. The sNDA is based on data from an open-label Phase 3b clinical trial, which indicated that repeat administration of ZILRETTA for treatment of OA knee pain was safe and well tolerated with no deleterious impact on cartilage or joint structure observed through X-ray analysis. We may not be successful in our efforts to modify or remove the LOU. It is possible that the FDA will disagree with our analysis or will find the data submitted in the sNDA insufficient to approve a label revision. If we are unable to revise or expand the label for ZILRETTA to allow for repeat dosing, our ability to fully market ZILRETTA may be limited.

While ZILRETTA has been approved by the FDA for the treatment of patients with OA of the knee in the United States, it has not been approved in any other jurisdiction for this indication or for any other indication. In order to market ZILRETTA for other indications or in other jurisdictions, or in order to market any of our other product candidates, we must obtain regulatory approval for each indication and in each applicable jurisdiction, and we may never be able to get such approval for ZILRETTA or our other product candidates. In particular, FX201 is at an early

stage of development and may never reach IND submission or human clinical trials, in which case we may never recover our investment.

Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approval could result in difficulties and costs for us and

require additional non-clinical studies or clinical trials, which could be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our potential future products in those countries. Other than ZILRETTA in the United States, we do not have any products approved for sale in any jurisdiction, and we do not have experience in obtaining regulatory approval in international markets. If we do not receive marketing approval for ZILRETTA for any other indication or from any regulatory agency other than the FDA, we will never be able to commercialize ZILRETTA for any other indication in the United States or for any indication in any other jurisdiction. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals for our other product candidates, or if regulatory approval in international markets is delayed, our potential market will be reduced and our ability to realize the full market potential of ZILRETTA or our other product candidates will be harmed. Even if we do receive additional regulatory approvals, we may not be successful in commercializing those opportunities.

Clinical development is a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results. Clinical failure can occur at any stage of clinical development.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of subsequent clinical trials. In particular, the results generated in our completed ZILRETTA pivotal Phase 3 clinical trial do not ensure that any ongoing or future ZILRETTA clinical trial, including our ongoing and planned clinical trials of ZILRETTA in hip OA and synovitis in knee OA, will be successful or consistent with the results generated in the Phase 3 trial.

Product candidates may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. In addition to the safety and efficacy trials of any product candidate, clinical trial failures may result from a multitude of factors including flaws in trial design, dose selection, placebo effect and patient enrollment criteria. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. In addition, data obtained from trials and studies are susceptible to varying interpretations, and regulators may not interpret our data as favorably as we do, which may delay, limit or prevent regulatory approval. In any event, our future clinical trials may not be successful.

If ZILRETTA or any other product candidate is found to be unsafe or lack efficacy in particular indications, we will not be able to obtain regulatory approval for the indication and our business could be materially harmed.

Delays in clinical trials are common and have many causes, and any delay could result in increased costs to us and jeopardize or delay our ability to obtain regulatory approval for our product candidates.

We may experience delays in clinical trials of our products and product candidates. Our clinical trials may not begin on time, have an effective design, enroll a sufficient number of patients, or be completed on schedule, if at all. Our clinical trials can be delayed for a variety of reasons, including:

- inability to raise funding necessary to initiate or continue a trial;
- delays in obtaining regulatory approval to commence a trial;
- delays in reaching agreement with the FDA on final trial design;
- imposition of a clinical hold for safety reasons or following an inspection of our clinical trial operations or trial sites by the FDA or other regulatory authorities;
- delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;
- delays in obtaining required institutional review board approval at each site;

- delays in recruiting suitable patients to participate in a trial;
- delays in having patients complete participation in a trial or return for post-treatment follow-up;

- clinical sites dropping out of a trial to the detriment of enrollment;
- time required to add new clinical sites; or
- delays by our contract manufacturers to produce and deliver sufficient supply of clinical trial materials.

For example, our ZILRETTA IND was placed on clinical hold at two points during product development, which delayed completion of our trials and resulted in additional expense. We cannot guarantee that any existing or future IND we submit will not be subject to similar holds.

If initiation or completion of our clinical trials are delayed for any of the above reasons or other reasons, our development costs may increase, our approval process could be delayed and our ability to commercialize our product candidates could be materially harmed, which could have a material adverse effect on our business.

The regulatory approval process of the FDA is lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for our product candidates or for ZILRETTA in additional indications, our business will be harmed.

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. Although we received regulatory approval of ZILRETTA for the treatment of OA knee pain, it is possible that none of our other product candidates will ever obtain regulatory approval or that we will not be able to obtain regulatory approval for ZILRETTA in additional indications.

Our product candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design, scope or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a product candidate is safe and effective for its proposed indication;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of an NDA or other submission or to obtain regulatory approval in the United States or elsewhere;
- the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may change significantly in a manner rendering our clinical data insufficient for approval.

The lengthy approval process, as well as the unpredictability of future clinical trial results, may result in our failing to obtain regulatory approval to market ZILRETTA in additional indications or to market our other product candidates at all, which would harm our business, results of operations and prospects.

In addition, even if we were to obtain approval for other product candidates or for ZILRETTA in other indications, regulatory authorities may approve such product candidates or indications for fewer or more limited indications than we request, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or

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desirable for the successful commercialization of that product candidate. Any of the foregoing scenarios could harm the commercial prospects for our product candidates.

Our product candidates may not receive regulatory approval despite success in clinical trials. Even if we successfully obtain regulatory approval to market one or more of our product candidates, our revenue will be dependent, to a significant extent, upon the size of the markets in the territories for which we gain regulatory approval. If the markets for patients or indications that we are targeting are not as significant as we estimate, we may not generate significant revenue from sales of such products, if approved.

Changes in funding for the FDA and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies on which our operations may rely, including those that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies or for labeling supplements and other regulatory requests to be acted upon, which would adversely affect our business. For example, over the last several years, including beginning on December 22, 2018 and ending on January 25, 2019, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical government employees and stop critical activities. If repeated or prolonged government shutdowns occur, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, and negatively impact other government operations on which we rely, which could have a material adverse effect on our business.

The FDA granted marketing approval of ZILRETTA for the treatment of patients with OA pain of the knee, and we could face liability if a regulatory authority determines that we are promoting ZILRETTA for any off-label uses.

A company may not promote “off-label” uses for its drug products. An off-label use is the use of a product for an indication that is not described in the product’s FDA-approved label in the United States or for uses in other jurisdictions that differ from those approved by the applicable regulatory agencies. Physicians, on the other hand, may prescribe products for off-label uses. Although the FDA and other regulatory agencies do not regulate a physician’s choice of drug treatment made in the physician’s independent medical judgment, they do restrict promotional communications from pharmaceutical companies or their employees, including sales representatives, with respect to off-label uses of products for which marketing clearance has not been issued. A company that is found to have promoted off-label use of its product may be subject to significant liability, including civil and criminal sanctions. We intend to comply with the requirements and restrictions of the FDA and other regulatory agencies with respect to our promotion of ZILRETTA and any future products, but we cannot be sure that the FDA or other regulatory agencies will agree that we have not violated their restrictions. For example, as part of our promotion strategy for ZILRETTA we communicate certain results from our Phase 3 clinical trial and other clinical data that are consistent with, but not directly included in, the product label. While we believe our communication of this data is in accordance with FDA guidance and applicable laws, we cannot be certain that the FDA or other regulatory agencies will agree with our use of this data or our sales force may use such data in a way that is inconsistent with our policies. As a result, we may be subject to criminal and civil liability. In addition, our management’s attention could be diverted to handle any such

alleged violations. A significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of products for unapproved uses and other sales practices, including the Department of Justice and various U.S. Attorneys' Offices, the Office of Inspector General of HHS, the FDA, the Federal Trade Commission and various state Attorneys

General offices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the Federal Food, Drug, and Cosmetic Act, or the FDCA, the federal False Claims Act, the Prescription Drug Marketing Act, anti-kickback laws, and other alleged violations in connection with the promotion of products for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. If the FDA or any other governmental agency initiates an enforcement action against us or if we are the subject of a qui tam suit and it is determined that we violated prohibitions relating to the promotion of products for unapproved uses, we could be subject to substantial civil or criminal fines or damage awards and other sanctions such as consent decrees and corporate integrity agreements pursuant to which our activities would be subject to ongoing scrutiny and monitoring to ensure compliance with applicable laws and regulations. Any such fines, awards or other sanctions would have an adverse effect on our revenue, business, financial prospects and reputation.

Any relationships with healthcare professionals, principal investigators, consultants, actual and potential customers, and third-party payers in connection with our current and future business activities are and will continue to be subject, directly or indirectly, to federal and state healthcare laws. If we are unable to comply, or have not fully complied, with such laws, we could face criminal sanctions, civil penalties, administrative penalties, imprisonment, exclusion, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and/or oversight, and curtailment or restructuring of our operations.

Our operations are directly or indirectly subject to various federal and state healthcare laws, including without limitation, fraud and abuse laws, false claims laws, marketing expenditure tracking and disclosure (or “sunshine”) laws, government price reporting, and health information privacy and security laws. Our potential exposure under such laws increased significantly with the commercialization of ZILRETTA in the United States through our dedicated sales force. Our costs associated with compliance are also likely to increase. These laws may impact, among other things, our current activities with investigators and research subjects, as well as sales, marketing, promotion, manufacturing, distribution, pricing, discounting, customer incentive programs, physician speaker programs, and other business arrangements and activities. In addition, we may be subject to patient privacy regulation by the federal government and by the U.S. states and foreign jurisdictions in which we conduct our business. The laws that may affect our ability to operate include, but are not limited to:

- the federal Anti-Kickback Statute, which prohibits, among other things, individuals and entities from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual, or the purchase, lease, order or arranging for the purchase, lease, or order of any good, item or service for which payment may be made under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalties laws, including the federal False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, to the federal government claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for, among other things, executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, which impose requirements on certain healthcare providers, health plans, and healthcare clearinghouses, known as covered entities, as well as their business associates that perform services involving the use or disclosure of individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information;
- the federal Open Payments program, created under Section 6002 of the PPACA, and its implementing regulations, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children’s Health Insurance Program (with certain exceptions) to report annually to CMS

information related to “payments or other transfers of value” made to physicians (defined to include doctors, dentists, optometrists, podiatrists and

chiropractors) and teaching hospitals, and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by physicians (as defined above) and their immediate family members;

- state, local, and foreign law equivalents of each of the above federal laws and regulations, such as anti-kickback and false claims laws which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by any third-party payer, including commercial insurers; state and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to healthcare providers and entities, or marketing expenditures; state and local laws requiring the registration of pharmaceutical sales and medical representatives; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, and often are not preempted by HIPAA, thus complicating compliance efforts;
- the Foreign Corrupt Practices Act, or FCPA, a U.S. law which regulates certain financial relationships with foreign government officials (which could include, for example, certain medical professionals);
- federal and state consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;
- state and federal government price reporting laws that require us to calculate and report complex pricing metrics to government programs, where such reported prices may be used in the calculation of reimbursement, rebates and/or discounts on our marketed drugs (participation in these programs and compliance with the applicable requirements may subject us to potentially significant discounts on our products, increased infrastructure costs, and potentially limit our ability to offer certain marketplace discounts); and
- the European Union's General Data Protection Regulation ((EU) 2016/679), or GDPR, which went into effect in May 2018, and which introduces strict requirements for processing personal data of individuals within the EU.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations may involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices, including activities undertaken by third parties on our behalf, may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, civil, criminal, and administrative penalties, damages, fines, disgorgement, imprisonment, possible exclusion from participation in Medicare, Medicaid and other government healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and curtailment or restructuring of our operations. Moreover, while we do not bill third-party payers directly and our customers make the ultimate decision on how to submit claims, from time-to-time we may provide reimbursement guidance to patients and healthcare providers. If a government authority were to conclude that we provided improper advice and/or encouraged the submission of a false claim for reimbursement, we could face action against us by government authorities. If any of the physicians or other providers or entities with whom we do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs and imprisonment. If any of the above occurs, it could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our product candidates outside of the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

ZILRETTA is still subject to substantial, ongoing regulatory requirements, and our other product candidates may face future development and regulatory difficulties.

The FDA approved ZILRETTA only for the treatment of OA knee pain. If any other ongoing clinical studies of ZILRETTA are negative, the FDA could decide to withdraw approval, add warnings or narrow the approved indication in the product label.

ZILRETTA is, and, if approved, our other product candidates, will also be, subject to ongoing FDA requirements governing the labeling, packaging, storage, distribution, safety surveillance, advertising, promotion, record-keeping and reporting of safety and other post-market information. The holder of an approved NDA is obligated to monitor and report adverse events, or AEs, and any failure of a product to meet the specifications in the NDA. The holder of an approved NDA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, manufacturers of drug products and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with current good manufacturing practices, or cGMP, and adherence to commitments made in the NDA. If we or a regulatory agency discover previously unknown problems with a product, such as AEs of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facility, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

We rely on third party collaborators to assist us in meeting our reporting and related obligations. While we work closely with these third parties, we do not control all of their activities. If our third-party collaborators do not meet the relevant commitments, we may fail to meet our applicable regulatory requirements.

If we fail to comply with applicable regulatory requirements for ZILRETTA or for any other approved product candidate, a regulatory agency may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending NDA or supplements to an NDA submitted by us;
- seize product; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our products and generate revenue.

If we fail to develop, acquire or in-license other potential future product candidates or products, our business and prospects will be limited.

Our long-term growth strategy is to develop, acquire or in-license and commercialize a portfolio of potential future product candidates in addition to ZILRETTA. Our primary means of expanding our pipeline of product candidates is to select and acquire or in-license product candidates for the treatment of therapeutic indications that complement or augment our current pipeline, or that otherwise fit into our development or strategic plans on terms that are acceptable to us, and/or develop improved formulations and delivery methods for existing FDA-approved products. Developing

new formulations or delivery methods of existing or potential future product candidates or identifying, selecting and acquiring or in-licensing promising product candidates requires substantial technical,

financial and human resources expertise. Efforts to do so may not result in the actual development, acquisition or in-license of a particular product candidate, potentially resulting in a diversion of our management's time and the expenditure of our resources with no resulting benefit. If we are unable to add additional product candidates to our pipeline, our long-term business and prospects will be limited.

Risks Related to Our Reliance on Third Parties

We rely completely on third parties to manufacture our commercial supplies of ZILRETTA and our preclinical and clinical drug supplies for our other product candidates.

If we were to experience an unexpected loss of supply of ZILRETTA or our other product candidates for any reason, whether as a result of manufacturing, supply or storage issues or otherwise, we could experience disruptions in commercial supply of ZILRETTA or delays, suspensions or terminations of clinical trials or regulatory submissions. We do not currently have nor do we plan to acquire the infrastructure or capability internally to manufacture our preclinical and clinical drug supplies and we lack the resources and the capability to manufacture any of our product candidates on a clinical or commercial scale. The facilities used by our contract manufacturers or other third-party manufacturers to manufacture our products and product candidates, including Patheon with respect to finished drug supplies of ZILRETTA, must obtain and maintain approval by the FDA. While we work closely with our third-party manufacturers on the manufacturing process for our products and product candidates, including quality audits, we generally do not control the implementation of the manufacturing process of, and are completely dependent on, our contract manufacturers or other third-party manufacturers for compliance with cGMP regulatory requirements and for manufacture of both active drug substances and finished drug products. If our contract manufacturers or other third-party manufacturers cannot successfully manufacture material that conforms to applicable specifications and the strict regulatory requirements of the FDA or others, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities.

In addition, we have no control over the ability of our contract manufacturers or other third-party manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve, or withdraws approval for, these facilities for the manufacture of our products and product candidates, we may need to find alternative manufacturing facilities, which would significantly impact our ability to commercialize, develop, or obtain or maintain regulatory approval for our products and product candidates.

We are particularly reliant on Patheon with respect to maintaining ZILRETTA manufacturing suites. These Patheon facilities required approval from the FDA as a condition of regulatory approval for ZILRETTA, as we rely exclusively on Patheon for commercial supplies of ZILRETTA. In addition, because Patheon manufactures ZILRETTA in the United Kingdom, or U.K., it needs to maintain and update its facility license with the applicable U.K. regulatory agencies and any delay or inability to do so would delay or prevent Patheon from being able to produce commercial supplies of ZILRETTA. Furthermore, the manufacturing process for ZILRETTA is unique and involves specialized equipment and proprietary processes, which subjects us to heightened risks that Patheon will experience delays in the manufacturing process.

We also rely on our manufacturers to purchase from third-party suppliers the materials necessary to produce ZILRETTA and our other product candidates for our clinical trials and commercial sales. There are a limited number of suppliers for raw materials that we use to manufacture our products and product candidates and we may need to assess alternate suppliers to prevent a possible disruption of the manufacture of the materials necessary to produce our product candidates for our clinical trials and ZILRETTA for commercial sale. We do not have any control over the process or timing of the acquisition of these raw materials by our manufacturers. Moreover, we currently do not have any agreements for the commercial production of these raw materials. Although we generally do not begin a clinical

trial unless we believe we have a sufficient supply of a product candidate to complete the clinical trial, any significant delay in the supply of a product candidate, or the raw material components thereof, for an ongoing clinical trial due to the need to replace a contract manufacturer or other third-party manufacturer could considerably delay completion of our clinical trials, product testing and potential regulatory approval of our product candidates. If our manufacturers or we are unable to purchase these raw materials for ZILRETTA or for any other approved products, there would be a shortage in supply, which would impair our ability to generate revenue from the sale of our products, including ZILRETTA.

We expect to continue to depend on contract manufacturers or other third-party manufacturers for the foreseeable future. We have entered into long-term commercial supply agreements with our current contract manufacturers in order to maintain adequate supplies to manufacture finished ZILRETTA drug product. We may, however, be unable to enter into such agreements or do so on commercially reasonable terms for potential future product candidates, which could have a material adverse impact upon our business.

We rely on certain sole sources of supply for our products and product candidates and any disruption in the chain of supply may disrupt commercialization of ZILRETTA or cause delay in developing, obtaining approval for, and commercializing our products and product candidates.

Currently, we use the following sole sources of supply for manufacturing ZILRETTA: Farmabios SpA for TA, Evonik Corporation for PLGA, and Patheon for finished microspheres drug product. Because of the unique equipment and process for loading TA onto PLGA microspheres, transferring finished drug product manufacturing activities for ZILRETTA to an alternate supplier would be a time-consuming and costly endeavor, and there are only a limited number of manufacturers that we believe are capable of performing this function for us. Switching ZILRETTA finished drug suppliers may involve substantial cost and could result in a failure to maintain adequate supplies of ZILRETTA. We expect that for the foreseeable future Patheon will be the only manufacturer qualified as a commercial supplier of ZILRETTA with the FDA. From time to time, commercial batches of ZILRETTA may fail to meet required specifications and be unavailable for commercial sale. If we experience multiple successive batch failures, or if supply from Patheon is otherwise interrupted, there could be a significant disruption in commercial supply. Any alternative vendor would need to be qualified through an NDA supplement, which could result in further delay. The FDA or other regulatory agencies outside of the United States may also require additional studies if a new ZILRETTA supplier is relied upon for commercial production.

Our other product candidates, including FX201, also rely on sole sources of supply for the preclinical and clinical supply of materials. The manufacturing processes for FX201 and our other product candidates are complex, and it may difficult or impossible to finalize appropriate processes for the scaled manufacture of the product candidates.

These factors could cause the disruption of the commercialization of ZILRETTA; delay clinical trials, regulatory submissions, required approvals or commercialization of any of our other product or product candidates; cause us to incur higher costs; or prevent us from commercializing them successfully. Furthermore, if our suppliers fail to deliver the required clinical or commercial quantities of active pharmaceutical ingredient on a timely basis and at commercially reasonable prices and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical trials may be delayed or we could lose potential revenue in the event of a product stockout for ZILRETTA or any of our other product candidates that is approved and launched.

Manufacturing issues may arise that could increase product and regulatory approval costs or disrupt or delay commercialization.

As we scale up manufacturing of ZILRETTA and other product candidates, we may encounter product, packaging, equipment and process-related issues that may require refinement or resolution in order to proceed with our planned clinical trials or maintain regulatory approval for commercial marketing. In the future, we may identify impurities or other product related issues, which could result in increased scrutiny by regulatory authorities, suspensions of commercial activities or product recalls, delays in our clinical program and regulatory approval, increases in our operating expenses, or failure to obtain or maintain approval for our products or product candidates.

We rely on third parties to conduct our preclinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates and our business could be substantially harmed.

We rely upon and plan to continue to rely upon third-party CROs to monitor and manage data for our preclinical and clinical programs. We rely on these parties for execution of our preclinical studies and clinical trials, and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our

reliance on the CROs does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with FDA laws and regulations regarding current good clinical practice, or GCP, which are also required by the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities in the form of International Council for Harmonization guidelines for all of our products in clinical development. Regulatory authorities enforce GCP through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs fail to comply with applicable GCP, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot be certain that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations. In addition, our clinical trials must be conducted with product produced under cGMP regulations. While we have agreements governing activities of our CROs, we have limited influence over their actual performance. In addition, portions of the clinical trials for our product candidates may be conducted outside of the United States, which will make it more difficult for us to monitor CROs and perform visits of our clinical trial sites and will force us to rely heavily on CROs to ensure the proper and timely conduct of our clinical trials and compliance with applicable regulations, including GCP. Failure to comply with applicable regulations in the conduct of the clinical trials for our product candidates may require us to repeat clinical trials, which would delay the regulatory approval process.

Some of our CROs have an ability to terminate their respective agreements with us if, among other reasons, it can be reasonably demonstrated that the safety of the subjects participating in our clinical trials warrants such termination, if we make a general assignment for the benefit of our creditors or if we are liquidated. If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our preclinical and clinical programs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. Consequently, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase substantially and our ability to generate revenue could be delayed significantly.

Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

We may not be successful in establishing development and commercialization collaborations, which could adversely affect, and potentially prohibit, our ability to fully commercialize ZILRETTA or to develop our product candidates.

Because developing pharmaceutical products, conducting clinical trials, obtaining regulatory approval, establishing manufacturing capabilities and marketing approved products are expensive, we are exploring collaborations with third parties outside of the United States that have more resources and experience. For example, we are exploring selective partnerships with third parties for ZILRETTA’s development and commercialization outside of the United States. If we are unable to obtain a partner for ZILRETTA, we may be unable to advance the development of ZILRETTA in territories outside of the United States, which may limit its market potential. In situations where we enter into a development and commercial collaboration arrangement for a product candidate, we may also seek to establish additional collaborations for development and commercialization in territories outside of those addressed by the first

collaboration arrangement for such product candidate. If any of our product candidates, in addition to ZILRETTA, receives marketing approval, we may enter into sales and marketing arrangements with third parties with respect to otherwise unlicensed or unaddressed territories outside of the United States. There are a limited number of potential partners, and we expect to face competition in seeking appropriate partners. If we are unable to enter into any development and commercial collaborations and/or sales and marketing arrangements on

acceptable terms, or at all, we may be unable to successfully develop and seek regulatory approval for our product candidates and/or effectively market and sell ZILRETTA and any other future approved products, if any, in all of the territories outside of the United States where it may otherwise be valuable to do so.

We may not be successful in maintaining development and commercialization collaborations, and our partners may not devote sufficient resources to the development or commercialization of our products or product candidates or may otherwise fail in development or commercialization efforts, which could adversely affect our ability to develop or commercialize certain of our products or product candidates and our financial condition and operating results.

Even if we are able to establish collaboration arrangements, any such collaboration may not ultimately be successful, which could have a negative impact on our business, results of operations, financial condition and growth prospects. If we partner with a third party for development and commercialization of a product candidate, we can expect to relinquish some or all of the control over the future success of that product candidate to the third party. It is possible that a partner may not devote sufficient resources to the development or commercialization of our product candidate or may otherwise fail in development or commercialization efforts, in which event the development and commercialization of such product candidate could be delayed or terminated, and our business could be substantially harmed. In addition, the terms of any collaboration or other arrangement that we establish may not prove to be favorable to us or may not be perceived as favorable, which may negatively impact the trading price of our common stock. In some cases, we may be responsible for continuing development of a product or product candidate or research program under collaboration and the payment we receive from our partner may be insufficient to cover the cost of this development. Moreover, collaborations and sales and marketing arrangements are complex and time consuming to negotiate, document and implement and they may require substantial resources to maintain.

We may become subject to a number of additional risks associated with our dependence on collaborations with third parties, the occurrence of which could cause our collaboration arrangements to fail. Conflicts may arise between us and partners, such as conflicts concerning the interpretation of clinical data, the achievement of milestones, the division of development or commercialization responsibilities or expenses, the interpretation of financial provisions or the ownership of intellectual property developed during the collaboration. If any such conflicts arise, a partner could act in its own self-interest, which may be adverse to our best interests. Any such disagreement between us and a partner could result in one or more of the following, each of which could delay or prevent the development or commercialization of our products or product candidates, and in turn prevent us from generating sufficient revenue to achieve or maintain profitability:

- reductions in the payment of royalties or other payments we believe are due pursuant to the applicable collaboration arrangement;
- actions taken by a partner inside or outside our collaboration which could negatively impact our rights or benefits under our collaboration; or
- unwillingness on the part of a partner to keep us informed regarding the progress of its development and commercialization activities or to permit public disclosure of the results of those activities.

Risks Related to Our Business Operations and Industry

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on the principal members of our executive team, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements or offer letters with each of our executive officers, any of them could leave our employment at any time, as all of our employees are “at will” employees. Recruiting and retaining other qualified employees for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives and other technically

qualified personnel in our industry, particularly in the greater Boston, Massachusetts area where our headquarters is located, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous biotechnology and pharmaceutical companies for

individuals with similar skill sets. In addition, failure to succeed in the commercialization of ZILRETTA or clinical studies of our product candidates may make it more challenging to recruit and retain qualified personnel. The inability to recruit or the loss of the services of any executive or key employee might impede the progress of our development and commercialization objectives.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability.

The use of our product candidates in clinical trials and the sale of ZILRETTA and any other products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products or product candidates. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation and perception of our products in the market;
- withdrawal or suspension of marketing approvals;
- withdrawal of clinical trial participants;
- costs due to related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- the inability to commercialize our product candidates;
- decreased demand for our products approved for commercial sale; and
- reputational harm.

Our current product liability insurance coverage may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive and in the future we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. On occasion, large judgments have been awarded in class action or mass tort lawsuits based on drugs that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

If we collaborate with third parties to develop and commercialize products outside of the United States, a variety of risks associated with international operations could materially and adversely affect our business.

If we enter into agreements with third parties to market ZILRETTA, and if approved, our other product candidates, outside of the United States, we expect to be subject to additional risks related to entering into international business relationships, including:

- different regulatory requirements for drug approvals in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incidental to doing business in another country;

- workforce uncertainty in countries where labor unrest is more common than in the United States;
- different government payer systems, multiple payer-reimbursement regimes or patient self-pay systems, and price controls;
- potential noncompliance with the FCPA, the U.K. Bribery Act 2010, or similar antibribery and anticorruption laws in other jurisdictions as well as various regulations pertaining to data privacy, such as the GDPR;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters, including earthquakes, typhoons, floods and fires.

We rely significantly on information technology and any failure, inadequacy, interruption or security lapse of that technology, including any cybersecurity incidents, could harm our ability to operate our business effectively.

Despite the implementation of security measures, our internal computer systems and those of third parties with which we contract are vulnerable to damage from cyber-attacks, computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. System failures, accidents or security breaches could cause interruptions in our operations, and could result in a material disruption of our commercial and clinical activities and business operations, in addition to possibly requiring substantial expenditures of resources to remedy. The loss of clinical trial data could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and our development programs, and the development of our product candidates could be delayed.

If we fail to comply with applicable U.S. and foreign privacy and data protection laws and regulation, we may be subject to liabilities that adversely affect our business, operations and financial performance.

We are subject to laws and regulations requiring that we take measures to protect the privacy and security of certain information we gather and use in our business. For example, HIPAA, and its implementing regulations impose, among other requirements, certain regulatory and contractual requirements regarding the privacy and security of personal health information on covered entities, such as health plans, healthcare clearinghouses and certain healthcare providers, as well as their business associates that perform certain services involving the use or disclosure of personal health information. In addition to HIPAA, numerous other federal and state laws, including, without limitation, state security breach notification laws, state health information privacy laws and federal and state consumer protection laws, govern the collection, use, and storage of personal information.

We may also be subject to or affected by foreign laws and regulation, including regulatory guidance, governing the collection, use, disclosure, security, transfer and storage of personal data, such as information that we collect about patients and healthcare providers in connection with clinical trials and our other operations in the U.S. and abroad. The global legislative and regulatory landscape for privacy and data protection continues to evolve, and implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future. This evolution may create uncertainty in our business, result in liability or impose additional costs on us. The cost of compliance with these laws, regulations and standards is high and is likely to increase in the future. For example, the EU has adopted the GDPR, which introduces strict requirements for processing personal data. The GDPR is likely to increase compliance burdens on us, including by mandating potentially burdensome documentation requirements and granting certain rights to individuals to control how we collect, use, disclose, retain and leverage information about them. In addition, the GDPR provides for breach reporting requirements, more robust regulatory enforcement and fines of up to 20 million euros or up to 4% of the annual global revenue. While companies are afforded some flexibility in determining how to comply with the GDPR's various requirements, it has and will continue to require significant effort and expense to ensure continuing compliance with the GDPR. Moreover, the requirements under

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the GDPR may change periodically or may be modified by European Union, or EU, national law, and could have an effect on our business operations if compliance becomes substantially costlier than under current requirements. It is possible that each of these privacy laws may be interpreted and applied in a manner that is inconsistent with our practices. Any failure or perceived failure by us to comply with federal, state or foreign laws or self-regulatory standards could result in negative publicity, diversion of management time and effort and proceedings against us by governmental entities or others. In many jurisdictions, enforcement actions and consequences for noncompliance are rising. As we continue to expand into other foreign countries and jurisdictions, we may be subject to additional laws and regulations that may affect how we conduct business.

Business interruptions could delay us in the process of developing or commercializing our products and product candidates.

Our headquarters are located in Burlington, Massachusetts. We are vulnerable to natural disasters such as hurricanes, tornadoes and severe storms, as well as other events that could disrupt our operations. We do not carry insurance for natural disasters and we may not carry sufficient business interruption insurance to compensate us for losses that may occur. Any losses or damages we incur could have a material adverse effect on our business operations.

Exposure to U.K. political developments, including the outcome of the referendum on membership in the European Union, could impact our suppliers and harm our business.

The U.K.'s referendum to leave the EU, or "Brexit," has caused and may continue to cause disruptions to capital and currency markets worldwide. The full impact of the Brexit decision, however, remains uncertain. A process of negotiation will determine the future terms of the U.K.'s relationship with the EU. During this period of negotiation, our results of operations and access to capital may be negatively affected by interest rate, exchange rate and other market and economic volatility, as well as regulatory and political uncertainty. The tax consequences of the U.K.'s withdrawal from the EU are uncertain as well. Brexit may also have a detrimental effect on our suppliers, which could, in turn, adversely affect our revenues and financial condition.

Risks Related to Our Intellectual Property

If we are unable to obtain or protect intellectual property rights, we may not be able to compete effectively in our market.

We rely upon a combination of patents, trade secret protection, confidentiality agreements and proprietary know how, and intend to seek marketing exclusivity for any approved product, including ZILRETTA, in order to protect the intellectual property related to our products and product candidates, and to date we have three issued patents covering ZILRETTA in the United States.

The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights and our current or future licensors' or collaborators' patent rights are highly uncertain. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our products or product candidates in the United States, including through the inter-partes review process, or in other foreign countries. Even for our issued patents and if other patents do successfully issue, third parties may challenge their inventorship, ownership, validity, enforceability or scope in the courts or patent offices in the United States and abroad. This may result in such patents being narrowed or invalidated, which could limit our ability to stop others from using or commercializing similar or identical technologies or products, or limit the duration of the patent protection for our technologies and products. If this were to occur, early generic competition could be expected against ZILRETTA and potentially reduce the value of our product candidates in development. Also, a third party may challenge our rights to patents and patent

applications that we license from third parties. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims.

If our patent applications with respect to ZILRETTA or our other product candidates fail to issue or if their breadth or strength of protection is threatened, it could dissuade companies from collaborating with us to develop

ZILRETTA or our other product candidates and threaten our ability to commercialize any resulting products. We cannot offer any assurances about which, if any, patents will issue or whether any issued patents will not be found invalid and unenforceable or will go unthreatened by third parties. Further, if we encounter delays in regulatory approvals for additional indications or in additional jurisdictions, the period of time during which we could market ZILRETTA or any product candidate under patent protection could be reduced. See “Business—Patents and Patent Applications” in this Annual Report on Form 10-K for additional information regarding our material patents and patent applications.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug development process that involve proprietary know-how, information or technology that is not covered by patents. For example, we maintain trade secrets with respect to certain of the formulation and manufacturing techniques related to the TA-formulated PLGA microspheres in ZILRETTA, including those that relate to precise pharmaceutical release. Although we generally require all of our employees to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

Third party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and inter party reexamination proceedings before the U.S. Patent and Trademark Office, or U.S. PTO. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we and our collaborators are commercializing or developing product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our products and product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of ZILRETTA and/or our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our products or product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our products or product candidates, any drug substance formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product or product candidate unless we obtain a license under the applicable patents, or until such patents expire. Similarly, if any third-party patent were held by a court of competent jurisdiction to cover aspects of our formulations or methods of use, the holders of any such patent may be

able to block our ability to develop and commercialize the applicable product or product candidate unless we obtain a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may request and/or obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our products or product

candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing products or manufacturing processes, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available at all or whether it would be available on commercially reasonable terms. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research, manufacture clinical trial supplies or allow commercialization of our product candidates. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to further develop and commercialize one or more of our products or product candidates, which could harm our business significantly. We cannot provide any assurances that third party patents do not exist which might be enforced against our products, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our issued patents, licensed patents or our other intellectual property. In some cases, it may be difficult or impossible to detect third-party infringement or misappropriation of our intellectual property rights, even in relation to issued patent claims, and proving any such infringement may be even more difficult. Accordingly, for such undetectable infringement or misappropriation our ability to recover damages will be negligible, and we could be at a market disadvantage because we may lack the resources of some of our competitors to monitor for and detect infringement. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in any patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology. An adverse result in litigation proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submissions, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the U.S. PTO and foreign patent agencies in several stages over the lifetime of the patent. The U.S. PTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering our product candidates, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on all of our product candidates throughout the world would be prohibitively expensive, and the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Consequently, we may not be able to prevent third parties from infringing on our intellectual property rights in all countries outside the United States, and competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products in jurisdictions where we do not have any issued

patents and our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

Our owned or licensed patents directed to our product candidates may expire or have limited commercial life before the product candidate is approved for marketing in a relevant jurisdiction.

Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting our product candidates might expire before or shortly after our product candidates obtain regulatory approval, which may subject us to increased competition and reduce or eliminate our ability to recover our development costs. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. Although we may be able to seek extensions of patent terms where available, including in the United States under the Drug Price Competition and Patent Term Restoration Act of 1984, which permits a patent term extension of up to five years beyond the expiration of the patent, we cannot be certain that an extension will be granted, or if granted, what the applicable time period or the scope of patent protection afforded during any extended period will be. The applicable authorities, including the EMA, FDA, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may take advantage of our investment in development and trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case.

We have in-licensed or acquired a portion of our intellectual property necessary to develop our product candidates, and if we fail to comply with our obligations under any of these arrangements, we could lose such intellectual property rights.

We are a party to and rely on several arrangements with third parties, which give us rights to intellectual property that is necessary for the manufacture of ZILRETTA and the development of FX201. In addition, we may enter into similar arrangements in the future. Our current arrangements impose various development, royalty and other obligations on us. If we materially breach these obligations or if our counterparts fail to adequately perform their respective obligations, these exclusive arrangements could be terminated, which would result in our inability to develop, manufacture and sell products that are covered by such intellectual property.

Risks Related to Ownership of Our Common Stock

The market price of our common stock may be highly volatile, you may not be able to resell your shares at a desired market price and you could lose all or part of your investment.

The trading price of our common stock is likely to be volatile. Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following:

- the success or perceived success of the commercialization of ZILRETTA;
    - failure to successfully develop and commercialize additional product candidates;
- changes in the structure of healthcare payment systems;
- adverse results or delays in clinical trials;
- inability to obtain additional funding;
- changes in laws or regulations applicable to our products or product candidates;
- inability to obtain adequate product supply for our products or product candidates, or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products or technologies by our competitors;
- failure to meet or exceed product development or financial projections we provide to the public;
- failure to meet or exceed the estimates and projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent, product liability or stockholder litigation;
- changes in the market valuations of similar companies;
- sales of our common stock by us or our stockholders in the future; and
- trading volume of our common stock.

The trading price of our common stock may also be dependent upon the valuations and recommendations of the analysts who cover our company. If our results do not meet these analysts' forecasts, the expectations of our investors or any financial guidance or expectations we provide to investors in any period, the market price of our common stock could decline. Our ability to meet analysts' forecasts (including revenue and profitability), investors' expectations and our own guidance or financial expectations is substantially dependent on our ability to increase sales of ZILRETTA and to successfully commercialize ZILRETTA in the United States. Because we are in the early stages of the ZILRETTA launch, we and the analysts who cover our company have limited ability to accurately predict future sales results, and actual results may differ materially from our expectations or those of such analysts.

In addition, the stock market in general, and the Nasdaq Global Market in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of companies like ours. Broad market and industry factors may continue to negatively affect the market price of our common stock, regardless of our actual operating performance.

Our principal stockholders and management own a significant percentage of our stock and are able to exert significant control over matters subject to stockholder approval.

As of December 31, 2018, our executive officers, directors and stockholders affiliated with our officers and directors beneficially owned approximately 15.4% of our voting stock. Therefore, these stockholders may have the ability to influence us through this ownership position. These stockholders may be able to determine or significantly influence all matters requiring stockholder approval. For example, these stockholders, acting together, may be able to control or significantly influence elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404 of the Sarbanes-Oxley Act, or the subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our consolidated financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our common stock.

We will continue to incur significant increased costs as a result of operating as a public company, and our management is required to devote substantial time to new compliance initiatives.

We completed our initial public offering on February 18, 2014. As a public company, we incur significant legal, accounting and other expenses that we did not incur as a private company. For example, we are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, which require, among other things, that we file with the SEC annually, quarterly and current reports with respect to our business and financial condition. We have incurred and will continue to incur costs associated with the preparation and filing of these reports. In addition, the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC, and the Nasdaq Global Market have imposed various other requirements on public companies. In July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas such as “say on pay” and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact (in ways we cannot currently anticipate) the manner in which we operate our business. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have and will continue to increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, these rules and regulations have made it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain our current levels of such coverage.

Sales of a substantial number of shares of our common stock in the public market by our existing stockholders could cause our stock price to fall.

Sales of a substantial number of shares of our common stock in the public market or the perception that these sales might occur, could depress the market price of our common stock and could impair our ability to raise capital through the sale of additional equity and/or convertible debt securities. We are unable to predict the effect that sales may have on the prevailing market price of our common stock.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We may need significant additional capital in the future to continue our planned operations. To the extent we raise additional capital by issuing equity securities; our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

Pursuant to our 2013 equity incentive plan, our management is authorized to grant stock options and other equity-based awards to our employees, directors and consultants. The number of shares available for future grant under the 2013 plan will automatically increase each year by 4% of all shares of our capital stock outstanding as of December 31 of the prior calendar year, subject to the ability of our board of directors to take action to reduce the size of the increase in any given year. Currently, we plan to register the increased number of shares available for issuance under the 2013 plan each year. If our board of directors elects to increase the number of shares available for future grant by the maximum amount each year, our stockholders may experience additional dilution, which could cause our stock price to fall.

We are at risk of securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management’s attention and resources, which could harm our business.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

Section 382 of the Internal Revenue Code of 1986, as amended, or Section 382, contains rules that limit the ability of a company that undergoes an ownership change to utilize its net operating losses, or NOLs, and tax credits existing as of the date of such ownership change. Under the rules, such an ownership change is generally any change in ownership of more than 50% of a company’s stock within a rolling three-year period. The rules generally operate by focusing on changes in ownership among stockholders considered by the rules as owning, directly or indirectly, 5% or more of the stock of a company and any change in ownership arising from new issuances of stock by the company. We have experienced multiple ownership changes since our inception, however, based on the annual limitations calculated at each ownership change date, we expect that substantially all net operating loss carryforwards will be available to offset future taxable income. Approximately $0.3 million of NOLs are expected to expire unused. Future ownership changes as defined by Section 382 may further limit the amount of NOL carryforwards that could be utilized annually to offset future taxable income.

Under the newly enacted federal income tax law, federal NOLs incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal NOLs is limited and could be subject to future limitations under Section 382.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividend on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or

paying any cash dividends for the foreseeable future. Additionally, our credit and security agreement with MidCap and Silicon Valley Bank contains covenants that restrict our ability to pay dividends. Any return to stockholders will therefore be limited to the appreciation of their stock.

Provisions in our amended and restated certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders, and may prevent or frustrate attempts by our stockholders to replace or remove our current management.

Some provisions of our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management. These provisions include:

- authorizing the issuance of "blank check" preferred stock, the terms of which may be established and shares of which may be issued without stockholder approval;
- limiting the removal of directors by the stockholders;
- creating a staggered board of directors;
- prohibiting stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders;
- eliminating the ability of stockholders to call a special meeting of stockholders; and
- establishing advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon at stockholder meetings.

These provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management. In addition, we are subject to Section 203 of the Delaware General Corporation Law, which generally prohibits a Delaware corporation from engaging in any of a broad range of business combinations with an interested stockholder of such corporation for a period of three years following the date on which the stockholder became an interested stockholder, unless such transactions are approved by our board of directors. This provision could have the effect of delaying or preventing a change of control, whether or not it is desired by or beneficial to our stockholders. Further, other provisions of Delaware law may also discourage, delay or prevent someone from acquiring us or merging with us.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

Our offices are located in Burlington, Massachusetts at a leased facility used primarily for corporate functions. Due to increased headcount and future growth plans, during 2018, we amended the lease to expand the facility to approximately 36,500 square feet. The lease for the office space expires in October 2023. In addition, we lease approximately 5,300 square feet of laboratory space in Woburn, Massachusetts under a lease that expires in 2022.

Item 3. Legal Proceedings

We are not currently a party to any material legal proceedings.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our common stock is listed on the Nasdaq Global Market and trades under the symbol "FLXN".

Comparative Stock Performance Graph

The following performance graph and related information shall not be deemed "soliciting material" or to be "filed" with the SEC, nor shall such information be incorporated by reference into any future filing under the Securities Act or Exchange Act, except to the extent that we specifically incorporate it by reference into such filing.

The following graph shows a comparison from February 12, 2014 (the date our common stock commenced trading on The NASDAQ Global Market) through December 31, 2018 of the cumulative total return for our common stock, the Russell 2000 Growth and Biotech index and the NASDAQ Composite Index. The graph assumes an initial investment of $100 on February 12, 2014. The comparisons in the graph are not intended to forecast or be indicative of possible future performance of our common stock.

Holders of Record

As of February 25, 2019, there were approximately 15 stockholders of record of our common stock. Certain shares are held in "street" name and accordingly, the number of beneficial owners of such shares is not known or included in the foregoing number.

Securities Authorized for Issuance under Equity Compensation Plans

Information about our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report.

Item 6. Selected Financial Data

The following selected financial data should be read together with "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations" and our consolidated financial statements and related notes included elsewhere in this Annual Report. The selected consolidated financial data in this section are not intended to replace our consolidated financial statements and the related notes. Our historical results are not necessarily indicative of the results that may be expected in the future.

We have derived the consolidated statements of operations data for the years ended December 31, 2018, 2017 and 2016 and the consolidated balance sheet data as of December 31, 2018 and December 31, 2017 from our audited consolidated financial statements appearing elsewhere in this Annual Report. The selected consolidated statement of operations data for the years ended December 31, 2015 and 2014 and the selected consolidated balance sheet data as of December 31, 2016, 2015 and 2014 are derived from our audited consolidated financial statements not included in this document. The selected consolidated financial data for all periods presented reflects the 1-for-8.13 reverse stock split we effected on January 27, 2014.

| | Year Ended December 31, | | | | |
|---|---|---|---|---|---|
| | 2018 | 2017 | 2016 | 2015 | 2014 |
| | (in thousands) | | | | |
| Consolidated Statement of Operations Data: | | | | | |
| Revenues: | | | | | |
| Product revenue, net | $22,524 | $355 | $— | $— | $— |
| Operating expenses: | | | | | |
| Cost of sales | 7,336 | 4 | — | — | — |
| Research and development | 53,079 | 51,231 | 41,314 | 32,691 | 17,923 |
| Selling, general and administrative | 121,311 | 78,801 | 28,466 | 13,372 | 9,064 |
| Total operating expenses | 181,726 | 130,036 | 69,780 | 46,063 | 26,987 |
| Loss from operations | (159,202) | (129,681) | (69,780) | (46,063) | (26,987) |
| Other (expense) income | | | | | |
| Interest income | 4,567 | 3,718 | 1,521 | 1,246 | 479 |
| Interest expense | (15,712) | (11,268) | (1,748) | (571) | (401) |
| Other income (expense) | 688 | (250) | (1,887) | (927) | |