NEKTAR THERAPEUTICS
Form 10-K
March 01, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-K

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 REPORTS PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934.
For the transition period from to

Commission File Number: 0-24006

NEKTAR THERAPEUTICS

(Exact name of registrant as specified in its charter)

Delaware	94-3134940
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)

455 Mission Bay Boulevard South

San Francisco, California 94158

(Address of principal executive offices and zip code)

415-482-5300

(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, $0.0001 par value	NASDAQ Global Select Market

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) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

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

Large accelerated filer	Accelerated filer
Non-accelerated filer	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 in Exchange Act Rule 12b-2). Yes No

The approximate aggregate market value of voting stock held by non-affiliates of the registrant, based upon the last sale price of the registrant's common stock on the last business day of the registrant's most recently completed second fiscal quarter, June 29, 2018, as reported on The NASDAQ Global Select Market, was approximately $8,366,439,130. This calculation excludes approximately 1,076,518 shares held by directors and executive officers of the registrant. Exclusion of these shares does not constitute a determination that each such person is an affiliate of the registrant.

As of February 22, 2019, the number of outstanding shares of the registrant's common stock was 174,104,459.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of registrant's definitive Proxy Statement to be filed for its 2019 Annual Meeting of Stockholders are incorporated by reference into Part III hereof. Such Proxy Statement will be filed with the Securities and Exchange Commission within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

NEKTAR THERAPEUTICS

2018 ANNUAL REPORT ON FORM 10-K

TABLE OF CONTENTS

		Page
	PART I	
Item 1.	Business	4
Item 1A.	Risk Factors	30
Item 1B.	Unresolved Staff Comments	45
Item 2.	Properties	45
Item 3.	Legal Proceedings	46
Item 4.	Mine Safety Disclosures	46
	PART II	
Item 5.	Market for Registrant’s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	47
Item 6.	Selected Financial Data	49
Item 7.	Management’s Discussion and Analysis of Financial Condition and Results of Operations	51
Item 7A.	Quantitative and Qualitative Disclosures About Market Risk	64
Item 8.	Financial Statements and Supplementary Data	65
Item 9.	Changes in and Disagreements With Accountants on Accounting and Financial Disclosure	98
Item 9A.	Controls and Procedures	98
Item 9B.	Other Information	99
	PART III	
Item 10.	Directors, Executive Officers and Corporate Governance	100
Item 11.	Executive Compensation	100
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	100
Item 13.	Certain Relationships and Related Transactions and Director Independence	100
Item 14.	Principal Accountant Fees and Services	100
	PART IV	
Item 15.	Exhibits and Financial Statement Schedules	101
Signatures		105

Forward-Looking Statements

This report includes “forward-looking statements” within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. All statements other than statements of historical fact are “forward-looking statements” for purposes of this annual report on Form 10-K, including any projections of market size, earnings, revenue, milestone payments, royalties, sales or other financial items, any statements of the plans and objectives of management for future operations (including, but not limited to, preclinical development, clinical trials and manufacturing), any statements related to our financial condition and future working capital needs, any statements regarding potential future financing alternatives, any statements concerning proposed drug candidates, any statements regarding the timing for the start or end of clinical trials or submission of regulatory approval filings, any statements regarding future economic conditions or performance, any statements regarding the initiation, formation or success of our collaboration arrangements, timing of commercial launches and product sales levels by our collaboration partners and future payments that may come due to us under these arrangements, any statements regarding our plans and objectives to initiate or continue clinical trials, any statements related to potential, anticipated, or ongoing litigation and any statements of assumptions underlying any of the foregoing. In some cases, forward-looking statements can be identified by the use of terminology such as “may,” “will,” “expects,” “plans,” “anticipates,” “estimates,” “potential” or “continue,” or the negative thereof or other comparable terminology. Although we believe that the expectations reflected in the forward-looking statements contained herein are reasonable, such expectations or any of the forward-looking statements may prove to be incorrect and actual results could differ materially from those projected or assumed in the forward-looking statements. Our future financial condition and results of operations, as well as any forward-looking statements, are subject to inherent risks and uncertainties, including, but not limited to, the risk factors set forth in Part I, Item 1A “Risk Factors” below and for the reasons described elsewhere in this annual report on Form 10-K. All forward-looking statements and reasons why results may differ included in this report are made as of the date hereof and we do not intend to update any forward-looking statements except as required by law or applicable regulations. Except where the context otherwise requires, in this annual report on Form 10-K, the “Company,” “Nektar,” “we,” “us,” and “our” refer to Nektar Therapeutics, a Delaware corporation, and, where appropriate, its subsidiaries.

Trademarks

The Nektar brand and product names, including but not limited to Nektar®, contained in this document are trademarks and registered trademarks of Nektar Therapeutics in the United States (U.S.) and certain other countries. This document also contains references to trademarks and service marks of other companies that are the property of their respective owners.

PART I

Item 1. Business

Nektar Therapeutics is a research-based biopharmaceutical company focused on discovering and developing innovative medicines in areas of high unmet medical need. Our research and development pipeline of new investigational drugs includes potential therapies for cancer, autoimmune disease and chronic pain. We leverage our proprietary and proven chemistry platform to discover and design new drug candidates. These drug candidates utilize our advanced polymer conjugate technology platforms, which are designed to enable the development of new molecular entities that target known mechanisms of action. We continue to make significant investments in building and advancing our pipeline of proprietary drug candidates as we believe that this is the best strategy to build long-term stockholder value. We refer to our drug candidates where we retain at least U.S. commercial rights as "proprietary programs" and our other drug candidate programs that we have licensed U.S. and potentially other commercial rights to collaboration partners as "collaboration partner programs."

Our Proprietary Programs

Immuno-oncology (I-O)

In the area of I-O, we are developing medicines that target biological pathways, which stimulate and sustain the body's immune response in order to fight cancer. We are developing medicines designed to directly or indirectly modulate the activity of key immune cells, such as cytotoxic T cells and natural killer (NK) cells, to increase their numbers and improve their function to recognize and attack cancer cells.

NKTR-214 (also known as bempegaldesleukin), our lead I-O candidate, is a biologic with biased signaling through one of the Interleukin-2 (IL-2) receptor subunits (CD 122) that can stimulate proliferation and growth of tumor-killing immune cells in the tumor micro-environment and increase expression of PD-1 on these immune cells. We are executing a comprehensive clinical development program for NKTR-214, including through a broad clinical collaboration with the Bristol-Myers Squibb Company (BMS), clinical collaborations with other third parties with pharmacological agents that have potential complementary mechanisms to NKTR-214, as well as pursuing our own independent clinical studies.

On February 13, 2018, we entered into a Strategic Collaboration Agreement (BMS Collaboration Agreement) with BMS, pursuant to which we and BMS are jointly developing NKTR-214, including combinations with BMS's Opdivo® (nivolumab), Opdivo® plus Yervoy® (ipilimumab), and certain other agents. The key economic components of the collaboration transaction included BMS making a non-refundable up-front payment of $1 billion to Nektar and an $850 million equity investment in our common stock at a premium over the 20-day VWAP for each share of common stock, BMS being responsible for a majority of the costs of the collaboration development plan, our annual funding obligation for collaboration development being limited to $125 million, Nektar retaining a 65% profit interest in NKTR-214, and recording global revenue for NKTR-214 commercial sales. We and BMS are jointly developing NKTR-214 under an expansive joint development plan (the Collaboration Development Plan) that encompasses more than 20 indications across nine tumor types. Together, we have started registrational studies in first-line melanoma, first-line renal cell carcinoma, cisplatin ineligible, locally advanced or metastatic urothelial cancer, second-line metastatic non-small cell lung cancer (post- checkpoint inhibitor and chemotherapy). Many other registrational studies in additional tumor types and indications are planned to begin in 2019.

We are also conducting a broad array of development activities evaluating NKTR-214 in combination with other agents that have potential complementary mechanisms of action. Our strategic objective is to establish NKTR-214 as a key component of many I-O combination regimens with the potential to improve the standard of care in multiple oncology settings. On November 6, 2018, we entered into a clinical trial collaboration with Pfizer, Inc. (Pfizer) to evaluate several combination regimens in multiple cancer settings, including metastatic castration-resistant prostate cancer and squamous cell carcinoma of the head and neck. The combination regimens in this collaboration will

evaluate NKTR-214 with avelumab, a human anti-PD-L1 antibody in development by Merck KGaA, and Pfizer; talazoparib, a poly (ADP-ribose) polymerase (PARP) inhibitor developed by Pfizer; or enzalutamide, an androgen receptor inhibitor in development by Pfizer and Astellas Pharma Inc. In February 2019, we started a Phase 1 dose-escalation study with Takeda Pharmaceutical Company Ltd. (Takeda) to evaluate NKTR-214 with Takeda's investigational medicine, TAK-659, a dual inhibitor of both spleen tyrosine kinase (SYK) and FLT-3, in up to 40 patients with advanced non-hodgkin lymphoma. We are also planning a Phase 1 study this year in pancreatic cancer patients in collaboration with BioXcel Therapeutics to evaluate a triplet combination of NKTR-214, BXCL-701 (a small molecule immune-modulator, DPP 8/9), and avelumab being supplied to BioXcel by Pfizer and Merck KGaA. We are also working in collaboration with Vaccibody AS to evaluate NKTR-214 in combination with Vaccibody's personalized cancer neoantigen vaccine in a Phase 1 proof-of-concept study.

Another key program in I-O, NKTR-262 is a small molecule agonist that targets toll-like receptors (TLRs) found on innate immune cells in the body. NKTR-262 is designed to stimulate the innate immune system and promote maturation and activation of antigen-presenting cells (APC), such as dendritic cells, which are critical to induce the body's adaptive immunity and create antigen-

specific cytotoxic T cells. NKTR-262 is being developed as an intra-tumoral injection in combination with systemic NKTR-214 in order to induce an abscopal response and achieve the goal of complete tumor regression in cancer patients treated with both therapies. The Phase 1 dose-escalation trial is currently ongoing.

NKTR-255 is a biologic that targets the interleukin-15 pathway in order to activate the body's innate and adaptive immunity. Signaling of the IL-15 pathway enhances the survival and activity of natural killer (NK) cells and enhances survival of both effector and CD8 memory T cells. Preclinical findings suggest NKTR-255 has the potential to synergistically combine with antibody-dependent cellular toxicity molecules as well as enhance CAR-T therapies. NKTR-255 is currently advancing through preclinical development and we plan to file an investigational new drug (IND) application for NKTR-255 this year and begin the first Phase 1 dose-escalation trial in multiple myeloma.

Immunology

We are currently developing NKTR-358, which is an investigational drug designed to correct the underlying immune system imbalance in the body that occurs in patients with autoimmune disease. The breakdown of mechanisms assuring recognition of self and non-self is what underlies all autoimmune diseases. A failure of the body's self-tolerance mechanisms is known to result from pathogenic auto reactive T lymphocytes. By increasing the number of regulatory T cells (which are specific immune cells in the body that modulate the immune system and prevent autoimmune disease by maintaining self-tolerance), these pathogenic auto reactive T cells can be reduced and the proper balance of effector and regulatory T cells can be achieved to restore the body's self-tolerance mechanisms. There is consistent evidence that suboptimal regulatory T cell numbers and their lack of activity play a significant role in a myriad of autoimmune diseases. NKTR-358 is designed to optimally target the IL-2 receptor complex in order to stimulate proliferation and growth of regulatory T cells. NKTR-358 is being developed as a once or twice monthly self-administered injection for a number of autoimmune diseases.

On July 23, 2017, we entered into a worldwide license agreement with Eli Lilly and Company (Lilly) to co-develop NKTR-358. We received an initial payment of $150.0 million in September 2017 and are eligible for up to an additional $250.0 million for development and regulatory milestones. We are responsible for completing Phase 1 clinical development and certain drug product development and supply activities. We also share Phase 2 development costs with Lilly, with 75% of those costs borne by Lilly and 25% of the costs borne by us. We will have the option to contribute funding to Phase 3 development on an indication-by-indication basis, ranging from zero to 25% of the global Phase 3 development costs. We are eligible for tiered royalties on global sales up to the low twenties that escalate based upon our level of contribution to Phase 3 development costs and the level of global product annual sales. Lilly will be responsible for all costs of global commercialization and we will have an option to co-promote in the U.S. under certain conditions. In February 2017, we filed an IND for NKTR-358. We have completed a Phase 1 dose-finding trial to evaluate single-ascending doses of NKTR-358 in approximately 100 healthy patients. Results from this study demonstrated a multiple-fold increase in regulatory T cells with no change in CD8 positive or natural killer (NK) cell levels and no dose-limiting toxicities observed. Data from this study are currently planned for presentation at the 2019 European Congress of Rheumatology Conference. The Phase 1 multiple-ascending dose trial to evaluate NKTR-358 in patients with systemic lupus erythematosus (SLE) was initiated in May 2018 and is currently enrolling patients.

Pain - NKTR-181

NKTR-181 (also known as oxycodegol) is a novel mu-opioid analgesic drug candidate that we are developing for chronic pain conditions. We have filed the new drug application (NDA) for NKTR-181 for the treatment of chronic low back pain in opioid-naïve adult patients and the current Prescription Drug User Fee Act (PDUFA) target action date is August 29, 2019. If approved, we plan to commercialize NKTR-181 through a separate subsidiary company, optionally with one or more partners with commercialization infrastructure and expertise and one or more strategic capital partners.

NKTR-181 met its primary and key secondary endpoints in the SUMMIT-07 Phase 3 efficacy study that compared twice-daily dosing of NKTR-181 tablets to placebo in the treatment of over 600 patients with moderate to severe chronic low back pain who were opioid-naïve. SUMMIT-07 evaluated four analgesic doses of NKTR-181 (100 mg, 200 mg, 300 mg and 400 mg). Patients in the trial achieved an average pain score reduction of over 65% (from 6.73 at screening to 2.32 at randomization) during the dose titration period. The primary efficacy endpoint of the study demonstrated significantly improved chronic back pain relief with NKTR-181 compared to placebo (p=0.0019). Key secondary endpoints of the study also achieved high statistical significance. The study demonstrated that NKTR-181 had a favorable safety profile and was well tolerated. The 52-week long-term safety study, which we call SUMMIT-LTS, was completed in December 2017, and evaluated the long-term safety and tolerability of NKTR-181 in 638 patients (opioid-naïve and opioid-experienced) with moderate to severe chronic low pain or chronic non-cancer pain. The study showed that NKTR-181 had a favorable safety profile with analgesic effect maintained over 52-weeks.

Additionally, on July 18, 2017, we announced positive top-line data for our pivotal human abuse potential study (HAP) for NKTR-181. The HAP study was designed to confirm and assess the relative oral abuse potential of NKTR-181, at its maximum analgesic therapeutic, dose (400 mg) studied in the SUMMIT-07 trial and at a supratherapeutic dose (3 times to 12 times greater than the

analgesic dose range of 100 mg to 400 mg used in the SUMMIT-07 trial), compared to common therapeutic doses of oxycodone (40 mg and 60 mg) in 54 healthy non-dependent recreational drug users. For the primary endpoint of Drug Liking, NKTR-181 (400 mg and 600 mg) rated less likable compared to oxycodone 40 mg and 60 mg ($p<0.0001$), and a supratherapeutic dose of NKTR-181 (1200 mg) rated less likable than oxycodone 60 mg ($p=0.0071$). Key secondary endpoints of Area Under Effect for Drug Liking (0-1 hours, 0-2 hours, 0-3 hours), Drug High and Take Drug Again scores also met statistical significance for all doses of NKTR-181 (1200 mg, 600 mg, 400 mg) compared to oxycodone (60 mg).

Oncology - ONZEALD™

ONZEALD™ (also known as NKTR-102, etirinotecan pegol) is our next-generation topoisomerase I inhibitor proprietary drug candidate. In March 2015, we announced top-line data from a Phase 3 clinical study for ONZEALD™, which we called the BEACON study, evaluating ONZEALD™ as a single-agent therapy for women with advanced metastatic breast cancer. The BEACON study compared ONZEALD™ to an active control arm comprised of a single chemotherapy agent of physician's choice (TPC) in patients who were heavily pre-treated with a median of three prior therapies for metastatic disease. In a top-line analysis of 852 patients from the trial, ONZEALD™ provided a 2.1 month improvement in median overall survival over TPC (12.4 months for patients receiving ONZEALD™ compared to 10.3 months for patients receiving TPC). Based on a stratified log-rank analysis, the primary endpoint measuring the Hazard Ratio (HR) for survival in the ONZEALD™ group compared to the active control arm was 0.87 with a p-value of 0.08, which did not achieve statistical significance. Secondary endpoints in the BEACON study included objective response rate and progression-free survival, which did not achieve statistical significance in the study. We also announced that we observed a significant overall survival benefit in two pre-specified subgroup populations—patients with a history of brain metastases and patients with baseline liver metastases at study entry.

Based on meetings with the European Union (EU) health authorities, in June 2016, we filed a Marketing Authorization Application (MAA) with the European Medicines Agency (EMA) for conditional approval of ONZEALD™ for adult patients with advanced breast cancer who have brain metastases and began enrolling in the ATTAIN study, which compared the overall survival in patients with breast cancer and brain metastases treated with ONZEALD™ versus physicians treatment of choice. On July 21, 2017, we were informed by the EMA's Committee for Medicinal Products for Human Use (CHMP) that it had adopted a negative opinion for the conditional marketing authorization application for ONZEALD™ in the European Union. The Phase 3 study (ATTAIN) in breast cancer patients having brain metastases is ongoing.

Collaboration Partner Programs

In 2014, we achieved the first approval of one of our proprietary drug candidates, MOVANTIK® (naloxegol), under a global license agreement with AstraZeneca AB (AstraZeneca). MOVANTIK® is an oral peripherally-acting opioid antagonist, for the treatment of opioid-induced constipation, a side effect caused by chronic administration of prescription opioid pain medicines. AstraZeneca markets and sells MOVANTIK® in the United States in collaboration with Daiichi Sankyo, Inc. (Daiichi Inc.). Kyowa Hakko Kirin Co. Ltd. (Kirin) has exclusive marketing rights to MOVENTIG® (the naloxegol brand name in the EU) in the EU, Iceland, Liechtenstein, Norway and Switzerland.

We have a collaboration with Baxalta Incorporated (a wholly-owned subsidiary of Takeda) to develop and commercialize PEGylated drug candidates with the objective of providing new long-acting therapies for hemophilia patients. Under this collaboration, we worked with Baxalta to develop ADYNOVATE®, an extended half-life recombinant factor VIII (rFVIII) treatment for Hemophilia A based on ADVATE® [Antihemophilic Factor (Recombinant)]. ADYNOVATE®, was first approved by the United States Food and Drug Administration (FDA) in late 2015 for Hemophilia A. ADYNOVATE® has also been approved in the European Union, Japan, Korea, Canada, and certain other countries.

We also have a number of license, manufacturing and supply agreements with other leading biotechnology and pharmaceutical companies, including Amgen, Inc., Pfizer and UCB Pharma (UCB). More than 10 products using our PEGylation technology have received regulatory approval in the U.S. or the EU. There are also a number of other products in clinical development that incorporate our advanced polymer conjugate technologies.

Corporate Information

We were incorporated in California in 1990 and reincorporated in Delaware in 1998. We maintain our executive offices at 455 Mission Bay Boulevard South, San Francisco, California 94158, and our main telephone number is (415) 482-5300. Our website is located at www.nektar.com. The information contained in, or that can be accessed through, our website is not part of, and is not incorporated in, this Annual Report on Form 10-K.

Our Technology Platform

As a leader in the polymer conjugation field, we have advanced our technology platform to include new advanced polymer technologies that can be tailored in specific and customized ways with the objective of optimizing and significantly improving the profile of a wide range of molecules, including many classes of drugs targeting numerous disease areas. Polymer conjugation or PEGylation has been a highly effective technology platform for the development of therapeutics with significant commercial success, such as Amgen's Neulasta® (pegfilgrastim) and UCB's CIMZIA (certolizumab pegol). Nearly all of the PEGylated drugs approved over the last fifteen years were enabled with our PEGylation technology through our collaborations and licensing partnerships with a number of well-known biotechnology and pharmaceutical companies. PEGylation is a versatile technology as a result of polyethylene glycol (PEG) being a water soluble, amphiphilic, non-toxic, non-immunogenic compound that has been shown to safely clear from the body. Its primary use to date has been in currently approved biologic drugs to favorably alter their pharmacokinetic or pharmacodynamic properties. However, in spite of its widespread success in commercial drugs, there are some limitations with the first-generation PEGylation approaches that have been used with biologics. For example, these techniques cannot be used successfully to create small molecule drugs which could potentially benefit from the application of the technology. Other limitations of the early applications of PEGylation technology include sub-optimal bioavailability and bioactivity, and its limited ability to be used to fine-tune properties of the drug, as well as its inability to be used to create oral drugs.

With our expertise and proprietary technology in polymer conjugation, we have created the next generation of PEGylation technology. Our advanced polymer conjugation technology platform is designed to overcome the limitations of the first generation of the technology platform and to allow the platform to be utilized with a broader range of molecules across many therapeutic areas. We have also developed robust manufacturing processes for generating second generation PEGylation reagents that allow us to utilize the full potential of these newer approaches.

Our advanced polymer conjugate technology platforms have the potential to offer one or more of the following benefits:

- improve efficacy or safety of a drug as a result of better pharmacokinetics, pharmacodynamics, longer half-life and sustained exposure of the drug;
- improve targeting or binding affinity of a drug to its target receptors with the potential to improve efficacy and reduce toxicity or drug resistance;
- improve solubility of a drug;
- enable oral administration of parenterally-administered drugs, or drugs that must be administered intravenously or subcutaneously, and increase oral bioavailability of small molecules;
- prevent drugs from crossing the blood-brain barrier, or reduce their rate of passage into the brain, thereby limiting undesirable central nervous system effects;
- reduce first-pass metabolism effects of certain drug classes with the potential to improve efficacy, which could reduce the need for other medicines and reduce toxicity;
- reduce the rates of drug absorption and of elimination or metabolism by improving stability of the drug in the body and providing it with more time to act on its target;
- differentially alter binding affinity of a drug for multiple receptors, improving its selectivity for one receptor over another; and
- reduce immune response to certain macromolecules with the potential to prolong their effectiveness with repeated doses.

We have a broad range of approaches that we may use when designing our own drug candidates, some of which are further described below.

Large Molecule Pro-Drug Releasable Polymer Conjugates (Cytokines)

Our customized approaches with large molecule polymer conjugates have expanded to include a new approach with biologics, in particular cytokines, which utilizes the polymer as a means to bias action to a certain receptor or receptor sub-type. In addition, a cytokine's pharmacokinetics and pharmacodynamics can be substantially improved and its half-life can be significantly extended. An example of this is NKTR-214, which is a CD122-preferential IL-2 pathway agonist designed to provide rapid activation and proliferation of cancer-killing CD8+ effector T cells and natural killer (NK) cells, without over-activating the immune system, with an every two or every three-week dosing schedule.

Large Molecule Polymer Conjugates (Proteins and Peptides)

Our customized approaches with large molecule polymer conjugates have enabled numerous successful PEGylated biologics on the market today. Based on our knowledge of the technology and biologics, our scientists have designed novel hydrolyzable linkers that in many cases can be used to optimize bioactivity. Through rational drug design, a protein or peptide's pharmacokinetics and pharmacodynamics can be substantially improved and its half-life can be significantly extended. An example of this is Baxalta's ADYNOVATE®, a longer-acting (PEGylated) form of a full-length recombinant factor VIII (rFVIII) protein, which was approved by the FDA in November 2015 for use in adults and adolescents, aged 12 years and older, who have Hemophilia A. In December 2016, the FDA expanded the approval of ADYNOVATE® for use in surgical settings for both adults and pediatric patients, and also for the treatment of Hemophilia A in pediatric patients under 12 years of age.

More recently, our scientists have shown that we can also optimize relative receptor binding characteristics of large molecule conjugates. For instance, the cytokine IL-2 has two different receptor complexes in the body that cause opposing effects on the immune system. We have engineered different novel conjugates of IL-2 with optimized differential receptor binding to the IL-2 receptor categories in the immune system. By biasing the receptor binding of these molecules in complementary ways, we have made two different drug candidates: NKTR-214, which selectively activates effector T cells, which kill tumors; and NKTR-358, which selectively activates regulatory T cells, which can reduce the pathological immune activation that underlies many autoimmune diseases.

Small Molecule Stable Polymer Conjugates

Our customized approach for small molecule polymer conjugates allows for the fine-tuning of the physicochemical and pharmacological properties of small molecule oral drugs to potentially increase their therapeutic benefit. In addition, this approach can enable oral administration of subcutaneously or intravenously delivered small molecule drugs that have low bioavailability when delivered orally. The benefits of this approach can also include: improved potency, modified biodistribution with enhanced pharmacodynamics, and reduced transport across specific membrane barriers in the body, such as the blood-brain barrier. An example of reducing transport across the blood-brain barrier is MOVANTIK®, an orally-available peripherally-acting opioid antagonist that is approved in the United States and the EU. An additional example of the application of membrane transport, specifically slowing transport across the blood-brain barrier is NKTR-181, an orally-available mu-opioid analgesic molecule for which an NDA for the treatment of chronic low back pain in opioid-naïve adult patients was accepted by the FDA for review.

Small Molecule Pro-Drug Releasable Polymer Conjugates

The pro-drug polymer conjugation approach can be used to optimize the pharmacokinetics and pharmacodynamics of a small molecule drug to substantially increase its efficacy and improve its side effect profile. We are currently using this platform with oncolytics, which typically have sub-optimal half-lives that can limit their therapeutic efficacy. With our releasable polymer conjugate technology platform, we believe that these drugs can be modulated for programmed release within the body, optimized bioactivity and increased sustained exposure of active drug to tumor cells in the body.

Antibody Fragment Polymer Conjugates

This approach uses a large molecular weight PEG conjugated to antibody fragments in order to potentially improve their toxicity profile, extend their half-life and allow for ease of synthesis with the antibody. The specially designed PEG replaces the function of the fragment crystallizable (Fc) domain of full length antibodies with a branched architecture PEG with either stable or degradable linkage. This approach can be used to reduce antigenicity, reduce glomerular filtration rate, enhance uptake by inflamed tissues, and retain antigen-binding affinity and recognition. There is currently one approved product on the market that utilizes our technology with an antibody fragment, CIMZIA® (certoluzimab pegol), which was developed by our partner UCB and is approved for the treatment of

Crohn’s Disease and ankylosing spondylitis in the U.S., axial spondyloarthritis in the EU and psoriatic arthritis and rheumatoid arthritis in the U.S. and EU.

Our Strategy

The key elements of our business strategy are described below:

Advance Our Proprietary Clinical Pipeline of Drug Candidates that Leverage Our Advanced Polymer Conjugate Platform

Our objective is to create value by advancing our lead drug candidates through various stages of clinical development. To support this strategy, we have significantly expanded and added expertise to our internal research, preclinical, clinical development and regulatory departments. A key component of our development strategy is to potentially reduce the risks and time associated with drug development by capitalizing on the known safety and efficacy of existing drugs and drug candidates as well as established pharmacologic targets and drugs directed to those targets. For many of our novel drug candidates, we may seek to study the drug candidates in indications for which the parent drugs have not been studied or approved. We believe that the improved characteristics

of our drug candidates will provide meaningful benefit to patients compared to the existing therapies. In addition, in certain instances we have the opportunity to develop new treatments for patients for which the parent drugs are not currently approved.

Ensure Future Growth of our Proprietary Pipeline through Internal Research Efforts and Advancement of our Preclinical Drug Candidates into Clinical Trials

We believe it is important to maintain a diverse pipeline of new drug candidates to continue to build on the value of our business. Our discovery research organization is continuing to identify new drug candidates by applying our technology platform to a wide range of molecule classes, including small molecules and proteins, peptides and antibodies, across multiple therapeutic areas. We continue to advance our most promising research drug candidates into preclinical development with the objective of advancing these early-stage research programs to human clinical studies over the next several years.

Selectively Enter into Strategic Collaboration Agreements

We decide on a drug candidate-by-drug candidate basis, how far to advance clinical development (e.g. Phase 1, 2 or 3) and whether to commercialize products on our own, or seek a partner, or pursue a combination of these approaches. When we determine to seek a partner, our strategy is to evaluate the potential combination of that partner's drug with our own and to selectively access a partner's development, regulatory, or commercial capabilities with the structure of the collaboration depending on factors such as economic risk sharing, the cost and complexity of development, marketing and commercialization needs, therapeutic areas, potential for combination of drug programs, and geographic capabilities.

Transition to a Fully-Integrated Specialty Biotechnology Company with a Commercial Capability in the I-O Therapeutic Area

If we are successful with the development of NKTR-214 or one of our I-O drug candidates and one or more of them is approved, we plan to establish a commercial capability in the U.S. and other select major markets to market, sell and distribute these proprietary I-O therapies. Under our BMS Collaboration Agreement, we retained significant global commercial rights to NKTR-214 including global co-promotion rights for all combinations of NKTR-214 with any BMS proprietary therapy and we lead global commercialization for all other NKTR-214 combination regimens. We will also record all worldwide sales and revenue for NKTR-214 and we have final decision-making authority regarding the pricing of NKTR-214.

Continue to Build a Leading Intellectual Property Estate in the Field of Polymer Conjugate Chemistry across Therapeutic Modalities

We are committed to continuing to build on our intellectual property position in the field of polymer conjugate chemistry. To that end, we have a comprehensive patent strategy with the objective of developing a patent estate covering a wide range of novel inventions, including among others, polymer materials, conjugates, formulations, synthesis, therapeutic areas, methods of treatment and methods of manufacture.

Nektar Proprietary Programs

The following table summarizes our proprietary drugs and drug candidates that have either received regulatory approval or are being developed by us or in collaboration with other pharmaceutical companies or independent investigators. The table includes the type of molecule or drug, the target indications for the drug candidate, and the status of the clinical development program.

Drug Candidate	Target Indication	Status[(1)]
NKTR-181 (orally-available mu-opioid analgesic molecule)	Moderate to severe chronic pain	Phase 3/NDA Filed
ONZEALD™ (next-generation topoisomerase I inhibitor)	Advanced metastatic breast cancer in patients with brain metastases	Phase 3
NKTR-214 (CD122-preferential IL-2 pathway agonist)	Immuno-oncology	Phase 1, Phase 2, and Phase 3 studies ongoing in multiple indications
NKTR-358 (cytokine Treg stimulant)	Autoimmune Disease	Phase 1
NKTR-262 (toll-like receptor agonist)	Solid Tumors	Phase 1
NKTR-255 (IL-15 receptor agonist)	Immuno-oncology	Preclinical

(1) Status definitions are:
Phase 3 or Pivotal — drug candidate in large-scale clinical trials conducted to obtain regulatory approval to market and sell the drug (these trials are typically initiated following encouraging Phase 2 trial results).

Phase 2 — a drug candidate in clinical trials to establish dosing and efficacy in patients.

Phase 1 — a drug candidate in clinical trials, typically in healthy subjects, to test safety.

Research/Preclinical — a drug candidate is being studied in research by way of in vitro studies and/or animal studies

Overview of Nektar Proprietary Programs

Immuno-oncology (I-O)

NKTR-214 (bempegaldesleukin, cytokine immunostimulatory therapy)

NKTR-214 (also known as bempegaldesleukin) is a CD122-preferential IL-2 pathway agonist designed to provide rapid activation and proliferation of cancer-killing CD8+ effector T cells and natural killer (NK) cells, without over-activating the immune system. NKTR-214 stimulates these cancer-killing immune cells in the body by targeting CD122-specific receptors found on the surface of these immune cells. CD122, which is also known as the Interleukin-2 receptor beta subunit, is a key signaling receptor that is known to increase proliferation of these CD8+ effector T cells. This receptor selectivity is intended to increase efficacy and improve safety over existing immunostimulatory cytokine drugs.

Under a research collaboration with The University of Texas MD Anderson Cancer Center, in December 2015 we commenced a Phase 1 study to evaluate NKTR-214 as a monotherapy in a variety of tumor types to evaluate safety and efficacy, and define the recommended Phase 2 dose of NKTR-214 in patients with solid tumors. In addition, the study also assessed the safety profile of NKTR-214, the immunologic effect of NKTR-214 on tumor-infiltrating lymphocytes and other immune activation markers in both blood and tumor tissue, the pharmacokinetic and pharmacodynamic profile of NKTR-214.

The development program for NKTR-214 includes combinations with a number of therapeutic approaches where we believe there is a strong biologic rationale for complementary mechanisms of action. On September 21, 2016, we entered into a Clinical Trial Collaboration Agreement with BMS, pursuant to which we and BMS collaborated to conduct Phase 1/2 clinical trials evaluating NKTR-214 and BMS' human monoclonal antibody that binds PD-1, known as Opdivo® (nivolumab), as a potential combination treatment regimen in five tumor types and eight potential indications (each, a Combined Therapy Trial). In the first phase of the PIVOT-02 study, we evaluated the clinical benefit, safety, and tolerability of combining NKTR-214 with Opdivo® in thirty-eight patients. Interim data from the dose-escalation phase of the trial was presented at the 2017 SITC meeting in November 2017. We identified the recommended Phase 2 dose for NKTR-214 in combination with Opdivo®. The second phase of the expansion cohorts, which now falls under the BMS Collaboration Agreement entered into on February 13, 2018, and described below, is evaluating the safety and efficacy of combining NKTR-214 with Opdivo®. Under the initial Clinical Trial Collaboration Agreement, BMS was responsible for 50% of all out-of-pocket costs reasonably incurred in connection with third party contract research organization, laboratories, clinical sites and institutional review boards. Each party was otherwise be responsible for its own internal costs, including internal personnel costs, incurred in connection with each Combined Therapy Trial.

On February 13, 2018, we entered into the second agreement with BMS (the BMS Collaboration Agreement), pursuant to which we and BMS are jointly developing NKTR-214, including, without limitation, in combination with BMS's Opdivo® (nivolumab) and Opdivo® plus Yervoy® (ipilimumab), and other compounds of BMS, us or any third party. The parties have agreed to jointly commercialize NKTR-214 on a worldwide basis. On April 3, 2018, the closing date of the transaction, BMS paid us a non-refundable upfront cash payment of $1.0 billion and purchased $850.0 million of our common stock at a purchase price of $102.60 per share pursuant to a Share Purchase Agreement (Purchase Agreement). We are eligible to receive additional cash payments of a total of up to $1.43 billion upon achievement of certain development and regulatory milestones and a total of up to $350.0 million upon achievement of certain sales milestones. We will record all worldwide sales and revenue for NKTR-214. We will share global commercialization profits and losses with BMS for NKTR-214, with Nektar sharing 65% and BMS sharing 35% of the net profits and losses. BMS will lead commercialization for combinations of NKTR-214 with BMS proprietary medicines, and we will lead all other commercialization efforts for NKTR-214. We will have the final decision-making authority regarding the pricing for NKTR-214. NKTR-214 will be sold on a stand-alone basis and there will be no fixed-dose combinations or co-packaging without the consent of both parties.

Under the BMS Collaboration Agreement, we and BMS will collaborate to develop and conduct clinical studies of NKTR-214 pursuant to a joint development plan, which includes a series of registration-enabling trials in more than 20 indications in nine tumor types and may be revised only upon mutual agreement of the parties. The parties share the development costs for NKTR-214 in combination regimens, with BMS generally responsible of 67.5% and Nektar generally responsible for 32.5% of the development costs, based on each party's relative ownership interest in the compounds included in the regimens. For costs of producing NKTR-214, however, BMS is responsible for 35% and Nektar is responsible for 65% of costs. Our share of such development costs are limited to an annual cap of $125.0 million. Neither party will develop a therapy using an IL-2 agonist in combination with a small or large molecule that binds to the PD(L)-1 target (and in certain indications the anti-CTLA4 target), in indications included in the joint development plan (each, a Competing Combination), whether alone or in collaboration with any third party, during a limited exclusivity period from the closing date under the BMS Collaboration Agreement until the later of (i) the first commercial sale of NKTR-214 or (ii) the third anniversary of the closing date, but each party may develop a Competing Combination on its own (but not in collaboration with any third party) during the three years after the end of the foregoing limited exclusivity period. If a registration-enabling study included in the joint development plan does not have the first patient enrolled prior to the date which is 14 months from the closing date, subject to allowable delays, the indication covered by that study is no longer subject to the above exclusivity. Other

than as described above, Nektar may independently develop and commercialize NKTR-214 either alone or in combination with other Nektar proprietary compounds or third party compounds.

Outside of the Collaboration Development Plan with BMS, we are also conducting a broad array of development activities evaluating NKTR-214 in combination with other agents that have potential complementary mechanisms of action. Our strategic objective is to establish NKTR-214 as a key component with many immuno-oncology combination regimens with the potential to raise the standard of care in multiple oncology settings:

- On November 6, 2018, we entered into a clinical collaboration with Pfizer, Inc. to evaluate several combination regimens in multiple cancer settings, including metastatic castration-resistant prostate cancer and squamous cell carcinoma of the head and neck. The combination regimens in this collaboration will evaluate NKTR-214 with avelumab, a human anti-PD-L1 antibody in development by Merck KGaA and Pfizer; talazoparib, a poly (ADP-ribose) polymerase (PARP) inhibitor developed by Pfizer; or enzalutamide, an androgen receptor inhibitor in development by Pfizer and Astellas Pharma Inc.
- In February 2019, we started a Phase 1 dose-escalation study with Takeda to evaluate NKTR-214 with Takeda's investigational medicine, TAK-659, a dual inhibitor of both spleen tyrosine kinase (SYK) and FLT-3, in up to 40 patients with advanced non-hodgkin lymphoma.
- We are planning a Phase 1 study this year in pancreatic cancer patients in collaboration with BioXcel to evaluate a triplet combination of NKTR-214, BXCL-701 (a small molecule immune-modulator, DPP 8/9), and avelumab (being supplied to BioXcel by Pfizer and Merck KGaA).
- We are also working in collaboration with Vaccibody AS to evaluate NKTR-214 with Vaccibody's personalized cancer neoantigen vaccine in a Phase 1 proof-of-concept study.

With our non-BMS clinical collaborations for NKTR-214, we generally share clinical development costs on a substantially pro-rata basis. We expect to continue to make significant and increasing investments exploring the potential of NKTR-214 with mechanisms of action that we believe are synergistic with NKTR-214 based on emerging scientific findings in cancer biology and preclinical development work

In addition to these non-BMS clinical collaborations for NKTR-214, we intend to initiate further clinical development programs, on our own or in collaboration with other potential partners, to explore the potential of combining NKTR-214 with other therapies such as cancer vaccines (other than Vaccibody's personalized cancer neoantigen vaccine), adoptive cell therapy, and other small molecules and biological agents in order to generate novel immuno-oncology approaches.

NKTR-262

NKTR-262 is a small molecule agonist that targets toll-like receptors (TLRs) found on innate immune cells in the body. NKTR-262 is designed to overcome the body's dysfunction of antigen-presenting cells (APC), such as dendritic cells, which are critical to induce the body's adaptive immunity and create antigen-specific cytotoxic T cells. NKTR-262 is being developed as a single intra-tumoral injection to be administered at the start of therapy with NKTR-214 in order to induce an abscopal response and achieve the goal of complete tumor regression in cancer patients treated with both therapies. We initiated enrollment of patients in the initial Phase 1/2 clinical study in April 2018, which we call the REVEAL study, and the dose-escalation portion of this clinical study is ongoing.

NKTR-255

NKTR-255 is a biologic that targets the interleukin-15 pathway in order to activate the body's innate and adaptive immunity. Signaling of the IL-15 pathway enhances the survival and function of natural killer (NK) cells and induces survival of both effector and CD8 memory T cells. Native rhIL-15 is rapidly cleared from the body and must be administered frequently and in high doses limiting its utility due to toxicity. NKTR-255 is designed with IL-15 receptor alpha specificity to optimize biological activity and is uniquely engineered to provide optimal exposure and an improved safety profile. Preclinical findings suggest NKTR-255 has the potential to synergistically combine with

antibody dependent cellular toxicity molecules as well as enhance CAR-T therapies. NKTR-255 is currently advancing through preclinical development and we plan to file an IND for NKTR-255 this year and begin the first Phase 1 dose-escalation study in multiple myeloma.

Immunology

NKTR-358 is designed to correct the underlying immune system imbalance in the body which occurs in patients with autoimmune disease. Current systemic treatments for autoimmune disease, including corticosteroids and anti-TNF agents, suppress the immune system broadly and come with severe side effects. NKTR-358 targets the CD25 sub-receptor in the interleukin-2 pathway in order to stimulate proliferation and growth of regulatory T cells, which are specific immune cells in the body that modulate the immune system and prevent autoimmune disease by maintaining self-tolerance.

On July 23, 2017, we entered into the Lilly Agreement, pursuant to which we and Lilly will co develop NKTR-358. Under the terms of the Lilly Agreement, we received an initial payment of $150.0 million in September 2017 and are eligible for up to $250.0 million in additional development and regulatory milestones. We are responsible for completing Phase 1 clinical development and certain drug product development and supply activities. We will also share Phase 2 development costs with Lilly, with 75% of those costs borne by Lilly and 25% of the costs borne by us. We will have the option to contribute funding to Phase 3 development on an indication-by-indication basis, ranging from zero to 25% of the global Phase 3 development costs. We are eligible to receive up to double-digit sales royalty rates that escalate based upon our contribution to Phase 3 development cost and the level of global product annual sales. Lilly will be responsible for all costs of global commercialization and we will have an option to co-promote in the U.S. under certain conditions.

In February 2017, we filed an IND for NKTR-358. We have completed a Phase 1 dose-finding trial of NKTR-358 to evaluate single-ascending doses of NKTR-358 in approximately 100 healthy patients. Results from this study demonstrated a multiple-fold increase in regulatory T cells with no change in CD8 positive or natural killer cell levels and no dose-limiting toxicities were observed. Data from this study is currently planned for presentation at the 2019 European Congress of Rheumatology Conference. The Phase 1 multiple-ascending dose trial to evaluate NKTR-358 in patients with systemic lupus erythematosus (SLE) was initiated in May 2018 and is currently enrolling patients.

Pain - NKTR-181 (mu-opioid analgesic molecule for chronic pain)

NKTR-181 (also known as oxycodegol) is an orally-available novel mu-opioid analgesic molecule in development as a long-acting analgesic to treat chronic pain. NKTR-181 is designed with the objective to address the abuse liability and serious central nervous system (CNS) side effects associated with current opioid therapies. NKTR-181 was created using Nektar’s proprietary polymer conjugate technology, which provides it with a long-acting profile and slows its entry into the CNS. The abuse deterrent properties of NKTR-181 are inherent to its novel molecular structure and do not rely on a formulation approach to prevent its conversion into a more abusable form of an opioid. In May 2012, the FDA granted Fast Track designation for the NKTR-181 development program.

In June 2012, we initiated a Phase 2 clinical study to evaluate the efficacy, safety and tolerability of NKTR-181 in patients with moderate to severe chronic pain from osteoarthritis of the knee. The Phase 2 clinical study utilized a double-blind, placebo-controlled, randomized withdrawal, enriched enrollment study design. The study enrolled 295 opioid-naïve patients with osteoarthritis of the knee who were not getting adequate pain relief from their current non-opioid pain medication. Patients who qualified during the baseline period entered a titration phase, during which they were titrated on NKTR-181 tablets administered orally twice-daily until a dose was reached that provided a reduction of at least 20% in the patient’s pain score as compared to the patient’s own baseline. Patients that achieved this level of analgesia were then randomized on a 1:1 basis to either continue to receive their analgesic dose of NKTR-181 or to receive placebo for up to 25 days. The primary endpoint of the study was the average change in a patient’s pain score from baseline to the end of the double-blind, randomized treatment period.

In the first half of 2013, we conducted a human abuse liability study, or HAL study, for NKTR-181. In this study, NKTR-181 had highly statistically significant lower “drug liking” scores and reduced “feeling high” scores as compared to oxycodone at all doses tested ($p < 0.0001$). On June 19, 2013, we presented data from the HAL study at the 2013 Annual Meeting of The College on Problems of Drug Dependence in San Diego, California.

On September 26, 2013, we announced results from this Phase 2 efficacy study. Of the 295 patients that entered the study, only nine patients (representing 3% of the patient population) were unable to achieve meaningful pain relief with NKTR-181. A total of 213 patients achieved an average 40% reduction in pain and entered the randomized phase of the study. NKTR-181 performed as expected as an opioid analgesic throughout the study with patients continuing to show a reduction in pain scores throughout the randomized phase of the study. However, patients who were randomized to placebo did not show the expected increase in pain scores observed in similar enriched enrollment, randomized withdrawal studies. This unusual lack of a placebo rebound caused the Phase 2 study to miss the primary

endpoint in the study.

In October 2014, we engaged in an end-of-Phase 2 meeting for NKTR-181 with the FDA, which included discussions of the design of the Phase 3 clinical study program. We enrolled the first patient in the first Phase 3 efficacy study, which we call SUMMIT-07 in February 2015 and we completed enrollment in the study in the fourth quarter of 2016. In this study, we randomized patients with chronic low back pain in an enriched enrollment randomized withdrawal design which included a qualifying screening period, an open-label titration period where NKTR-181 was given to all patients, followed by a 12-week double-blind randomized period where subjects were randomized on a 1:1 basis to receive either NKTR-181 or placebo. In January 2017, we started enrollment in a second human abuse liability study where we are assessing abuse liability of supra-therapeutic doses of NKTR-181 in order to further evaluate NKTR-181 for labeling and scheduling purposes. On March 20, 2017, we announced that NKTR-181 met its primary and key secondary endpoints in the SUMMIT-07 Phase 3 efficacy study that compared twice-daily dosing of NKTR-181 tablets to placebo in the treatment of over 600 patients with moderate to severe chronic low back pain who were new to opioid therapy (opioid-naïve).

SUMMIT-07 evaluated four analgesic doses of NKTR-181 (100 mg, 200 mg, 300 mg and 400 mg). Patients in the trial achieved an average pain score reduction of over 65% (from 6.73 at screening to 2.32 at randomization) during the dose titration period. The primary efficacy endpoint of the study demonstrated significantly improved chronic back pain relief with NKTR-181 compared to placebo (p=0.0019). Key secondary endpoints of the study also achieved high statistical significance. The study demonstrated that NKTR-181 had a favorable safety profile and was well tolerated.

Additionally, on July 18, 2017, we announced positive top-line data for our pivotal human abuse potential study (HAP) for NKTR-181. The HAP study was designed to confirm and assess the relative oral abuse potential of NKTR-181, at its maximum analgesic therapeutic, dose (400 mg) studied in the SUMMIT-07 trial and at a supratherapeutic dose (3 times to 12 times greater than the analgesic dose range of 100 mg to 400 mg used in the SUMMIT-07 trial), compared to common therapeutic doses of oxycodone (40 mg and 60 mg) in 54 healthy non-dependent recreational drug users. For the primary endpoint of Drug Liking, NKTR-181 (400 mg and 600 mg) rated less likable compared to oxycodone 40 mg and 60 mg (p<0.0001), and a supratherapeutic dose of NKTR-181 (1200 mg) rated less likable than oxycodone 60 mg (p=0.0071). Key secondary endpoints of Area Under Effect for Drug Liking (0-1 hours, 0-2 hours, 0-3 hours), Drug High and Take Drug Again scores met statistical significance for all doses of NKTR-181 (1200 mg, 600 mg, 400 mg) compared to oxycodone (60 mg).

The SUMMIT Phase 3 program also included a 52-week long-term safety study, which we call SUMMIT-LTS. This study evaluated the long-term safety and tolerability of NKTR-181 in 638 patients (opioid-naïve and opioid-experienced) with moderate to severe chronic low pain or chronic non-cancer pain. The study showed that NKTR-181 had a favorable safety profile and analgesic effect maintained over 52-weeks. On July 30, 2018, we announced that the NDA for NKTR-181 for the treatment of chronic low back pain in adult patients new to opioid therapy was accepted by the FDA for review. In February 2019, the FDA informed us it had adjusted the Prescription Drug User Fee Act (PDUFA) target action date from May 29, 2019 to August 29, 2019. If approved, we are evaluating several strategic alternatives to commercialize NKTR-181 including, without limitation, establishing a separate subsidiary company or joint venture with one or more partners with commercial capabilities and/or strategic capital partners. Since we have not yet established a commercial launch capability for NTKR-181, if approved, there remains substantial risk and uncertainties related to successful and timely completion of this process.

According to a 2013 report from the World Health Organization, approximately 149 million work days are lost every year because of low back pain, with total costs estimated to be $100 to $200 billion a year (of which two-thirds is due to lost wages and lower productivity). Opioids are considered to be the most effective therapeutic option for pain. However, opioids cause significant problems for physicians and patients because of their serious side effects such as respiratory depression and sedation, as well as the risks they pose for addiction, abuse, misuse, and diversion. The FDA has cited prescription opioid analgesics as being at the center of a major public health crisis of addiction, misuse, abuse, overdose and death. According to the American Society of Addiction Medicine 2016 report, there are 1.9 million Americans which have a substance use disorder involving prescription pain relievers. This same report attributes 18,893 overdose deaths in 2015 were related to prescription pain relievers.

Oncology - ONZEALD™ (next generation, long-acting topoisomerase I inhibitor)

ONZEALD™ (previously known as NKTR-102 or etirinotecan pegol) is our next-generation topoisomerase I inhibitor proprietary drug candidate. In 2015, we announced top-line data from a Phase 3 clinical study for ONZEALD™, which we call the BEACON study (BrEAst Cancer Outcomes with ONZEALD™), as a single-agent therapy for women with advanced metastatic breast cancer. The BEACON study compared ONZEALD™ to an active control arm comprised of a single chemotherapy agent of physician's choice (TPC) in patients who were heavily pre-treated with a median of three prior therapies for metastatic disease. In a top-line analysis of 852 patients from the trial, ONZEALD™ provided a 2.1 month improvement in median overall survival over TPC (12.4 months for patients receiving ONZEALD™ compared to 10.3 months for patients receiving TPC). Based on a stratified log-rank analysis, the primary endpoint measuring the hazard ratio for survival in the ONZEALD™ group compared to the active

control arm was 0.87 with a p-value of 0.08, which did not achieve statistical significance. Secondary endpoints in the BEACON study included objective response rate and progression-free survival, which did not achieve statistical significance in the study. We also announced that we observed a significant overall survival benefit in two pre-specified subgroups—patients with a history of brain metastases and patients with baseline liver metastases at study entry.

Based on meetings with European Union (EU) health authorities, in June 2016, we filed a Marketing Authorization Application (MAA) with the European Medicines Agency (EMA) for conditional approval of ONZEALD™ for adult patients with advanced breast cancer who have brain metastases and began enrolling patients in the ATTAIN study, which is comparing the overall survival in patients with breast cancer and brain metastases treated with ONZEALD™ versus physicians treatment of choice. On July 21, 2017, we were informed by the EMA's Committee for Medicinal Products for Human Use (CHMP) that it had adopted a negative opinion for the conditional marketing authorization application for ONZEALD™ in the EU. The Phase 3 study (ATTAIN) in breast cancer patients having brain metastases is ongoing.

According to the American Cancer Society and World Health Organization, more than 1.4 million women worldwide are diagnosed with breast cancer globally every year. The chance of developing invasive breast cancer at some time in a woman's life is a little less than one in eight (approximately 12%). In 2017, the American Cancer Society estimated there will be 252,710 new cases of invasive breast cancer diagnosed in the U.S. and about 40,610 women will die from breast cancer. Anthracyclines and taxanes are the among the most active and widely used chemotherapeutic agents for breast cancer, but the increased use of these agents at an early stage of disease often renders tumors resistant to these drugs by the time the disease recurs, thereby reducing the number of treatment options for metastatic disease. There are currently no FDA-approved topoisomerase I inhibitors indicated to treat breast cancer.

Collaboration Partner Programs

The following table outlines our collaborations with a number of pharmaceutical companies that currently license our intellectual property and, in some cases, purchase our proprietary PEGylation materials for their drug products. More than ten products using our PEGylation technology have received regulatory approval in the U.S. or Europe. There are also a number of other candidates that have been filed for approval or are in various stages of clinical development. These collaborations generally contain one or more elements including a license to our intellectual property rights and manufacturing and supply agreements under which we may receive manufacturing revenue, milestone payments, and/or royalties on commercial sales of drug products.

	Primary or Target	Drug	
Drug	Indications	Marketer/Partner	Status(1)
ADYNOVATE® (previously referred to as BAX 855, PEGylated rFVIII) and ADYNOVI® (brand name for ADYNOVATE® in Europe)	Hemophilia A	Takeda	Approved 2015
MOVANTIK® (naloxegol tablets) and MOVENTIG® (brand name for MOVANTIK® in Europe)	Opioid-induced constipation in adult patients with chronic non-cancer pain (US); Opiod-induced constipation in adult patients who have and inadequate response to laxatives (EU).	AstraZeneca AB	Approved 2014
CIMZIA® (certolizumab pegol)	Crohn's disease, Rheumatoid arthritis, and Psoriasis/ Ankylosing Spondylitis	UCB Pharma	Approved 2008*
MIRCERA® (C.E.R.A.) (Continuous Erythropoietin Receptor Activator)	Anemia associated with chronic kidney disease in patients on dialysis and patients not on dialysis	F. Hoffmann-La Roche Ltd	Approved 2007*
Macugen® (pegaptanib sodium injection)	Age-related macular degeneration	Bausch Health Companies Inc. (formerly, Valeant Pharmaceuticals	Approved 2004

		International, Inc.)	
Somavert® (pegvisomant)	Acromegaly	Pfizer Inc.	Approved 2003
Neulasta® (pegfilgrastim)	Neutropenia	Amgen Inc.	Approved 2002
Dapirolizumab Pegol	Systemic Lupus Erythematosus	UCB Pharma (Biogen)	Phase 2
PEGPH20	Pancreatic, Non-Small Cell Lung Cancer, and other multiple tumor types	Halozyme Therapeutics, Inc.	Phase 1, 2, and 3
Longer-acting blood clotting proteins	Hemophilia	Takeda	Research/Preclinical

(1) Status definitions are:
Approved — regulatory approval to market and sell product obtained in one or more of the U.S., EU or other countries. Year indicates first regulatory approval.

Filed — an application for approval and marketing has been filed with the applicable government health authority.

Phase 3 or Pivotal — drug candidate in large-scale clinical trials conducted to obtain regulatory approval to market and sell the drug

(these trials are typically initiated following encouraging Phase 2 trial results).

Phase 2 — a drug candidate in clinical trials to establish dosing and efficacy in patients.

Phase 1 — a drug candidate in clinical trials, typically in healthy subjects, to test safety.

Research/Preclinical — a drug candidate is being studied in research by way of in vitro studies and/or animal studies

* In February 2012, we sold our rights to receive royalties on future worldwide net sales of CIMZIA® and MIRCERA® effective as of January 1, 2012.

With respect to all of our collaboration and license agreements with third parties, please refer to Item 1A, Risk Factors, including without limitation, "We are a party to numerous collaboration agreements and other significant agreements which contain complex commercial terms that could result in disputes, litigation or indemnification liability that could adversely affect our business, results of operations and financial condition."

Overview of Collaboration Partner Programs

We have a number of product candidates in clinical development and approved products in collaboration with our partners where we invented the drug candidate or where our collaboration partners have licensed our proprietary intellectual property to enable one of their drug candidates. Our agreements with collaboration partners may involve several elements including a technology license as well as the development, commercialization, and manufacturing and supply obligations. We typically receive consideration from our collaboration partners in the form of upfront payments, or milestone payments and royalties on sales. In certain cases, we also manufacture and supply our proprietary polymer materials to our partners.

ADYNOVATE® (previously referred to as BAX 855), ADYNOVI® (brand name for ADYNOVATE® in Europe) and Longer-Acting Blood Clotting Proteins for Hemophilia A, Agreement with Subsidiaries of Baxalta Incorporated

In September 2005, we entered into an exclusive research, development, license, manufacturing and supply agreement (Baxalta License Agreement) with certain subsidiaries of Baxalta (which has been acquired by Takeda), formerly Baxter before the separation of Baxalta from Baxter in July 2015, to develop products with an extended half-life for the treatment and prophylaxis of Hemophilia A patients using our proprietary PEGylation technology. The first product in this collaboration, ADYNOVATE® (previously referred to as BAX 855), is a longer-acting (PEGylated) form of a full-length recombinant factor VIII (rFVIII) protein. ADYNOVATE® is a full-length PEGylated longer-acting recombinant factor VIII (rFVIII) that was developed to increase the half-life of ADVATE® (Antihemophilic Factor (Recombinant) Plasma/Albumin-Free Method). ADYNOVATE® was first approved by the FDA on November 30, 2015. Since then it has been approved in one or more indications for Hemophilia A in the EU, Japan, and other countries around the world.

We are entitled to $35.0 million of sales milestone payments, as well as royalties on net sales varying by product and country of sale. The royalties start in the mid-single digits for net sales of ADYNOVATE® up to $1.2 billion and then in the low teens for net sales exceeding $1.2 billion. Our right to receive these royalties in any particular country will

expire upon the later of ten years after the first commercial sale of the product in that country or the expiration of patent rights in certain designated countries or in that particular country.

In October 2017, we entered into a right to sublicense agreement with Baxalta, under which we granted to Baxalta the right to grant a nonexclusive sublicense to certain patents to a third party that were previously exclusively licensed to Baxalta under the Baxalta License Agreement. Under the right to sublicense agreement, Baxalta paid us $12.0 million in November 2017 and agreed to pay us single digit royalty payments based upon net sales of the third party products covered under the sublicense throughout the term of the right to sublicense agreement.

Hemophilia A, also called factor VIII (FVIII) deficiency or classic hemophilia, is a genetic disorder caused by missing or defective factor VIII, a clotting protein. According to the US Centers for Disease Control and Prevention, hemophilia occurs in approximately one in 5,000 live births and there are about 20,000 people with hemophilia in the US. All races and ethnic groups are affected. Hemophilia A is four times as common as Hemophilia B while more than half of patients with Hemophilia A have the severe form of hemophilia. In 2014, according to the Evaluate Group, sales of FVIII replacement products exceeded $6.0 billion globally.

MOVANTIK® and MOVENTIG® (brand name for MOVANTIK® in Europe), License Agreement with AstraZeneca AB

In September 2009, we entered into a global license agreement with AstraZeneca AB (AstraZeneca) pursuant to which we granted AstraZeneca a worldwide, exclusive, perpetual, royalty-bearing license under our patents and other intellectual property to develop, market and sell MOVANTIK®. MOVANTIK® was developed using our oral small molecule polymer conjugate technology and we advanced this drug through the completion of Phase 2 clinical studies prior to licensing it to AstraZeneca. MOVANTIK® is an orally-available peripherally-acting mu-opioid antagonist which is a medication for the treatment of opioid-induced constipation (OIC), which is a common side effect of prescription opioid medications. Opioids attach to specific proteins called opioid receptors. When the opioids attach to certain opioid receptors in the gastrointestinal tract, constipation may occur. OIC is a result of decreased fluid absorption and lower gastrointestinal motility due to opioid receptor binding in the gastrointestinal tract.

On September 16, 2014, the FDA approved MOVANTIK® as the first once-daily oral peripherally-acting mu-opioid receptor antagonist (PAMORA) medication for the treatment of OIC in adult patients with chronic, non-cancer pain. On December 9, 2014, the European Commission, or EC, granted Marketing Authorisation to MOVENTIG® (the naloxegol brand name in the EU) as the first once-daily oral PAMORA to be approved in the EU for the treatment of OIC in adult patients who have had an inadequate response to laxative(s). The EC's approval applies to all 28 EU member countries plus Iceland and Norway. AstraZeneca launched the commercial sales of MOVANTIK® in the U.S. in March 2015 and MOVENTIG® in Germany, the first EU member country, in August 2015. Under the terms of our license agreement with AstraZeneca, AstraZeneca made an initial license payment of $125.0 million to us and has responsibility for all activities and bears all costs associated with research, development and commercialization for MOVANTIK®. We received milestone payments of $70.0 million and $25.0 million upon the acceptance of regulatory approval applications of MOVANTIK® by the FDA and the EMA, respectively, in 2013. We received an additional developmental milestone payment of $35.0 million upon the FDA's approval of MOVANTIK® in 2014 and a total of $140.0 million upon commercial launches in 2015, including $100.0 million for MOVANTIK® in the U.S. and $40.0 million for MOVENTIG® in Germany. We are also entitled to up to $375.0 million in sales milestones for MOVANTIK® if the program achieves certain annual commercial sales levels and significant double-digit royalty payments starting at 20% of net sales in the U.S. and 18% of net sales in the EU and rest of world, varying by country of sale and level of annual net sales. On March 1, 2016, AstraZeneca announced that it had entered into an agreement with Kyowa Hakko Kirin Co. Ltd. (Kirin), granting Kirin exclusive marketing rights to MOVENTIG® in the EU, Iceland, Liechtenstein, Norway and Switzerland. Nektar's receipt of a 40% share of royalty payments made by Kirin to AstraZeneca will be financially equivalent to Nektar receiving high single-digit to low double-digit royalties depending on Kirin's annual net sales levels. Our right to receive royalties (subject to certain adjustments) in any particular country will expire upon the later of (a) a specified period of time after the first commercial sale of the product in that country or (b) the expiration of patent rights in that particular country. AstraZeneca has agreed to use commercially reasonable efforts to develop one MOVANTIK® fixed-dose combination product and has the right to develop multiple products which combine MOVANTIK® with opioids.

There are a number of patents relevant to MOVANTIK®, some of which are listed in the FDA's "Orange Book." The "Orange Book" currently lists six patents for MOVANTIK®. Four patents (i.e., U.S. Patent Nos. 7,056,500, 7,662,365, 7,786,133 and 9,012,469) are "composition of matter patents" - one of which has a patent expiry extending into 2032. In addition, two patents (i.e., U.S. Patent Nos. 8,067,431 and 8,617,530) are directed to methods of treatment.

CIMZIA®, Agreement with UCB

In December 2000, we entered into a license, manufacturing and supply agreement covering our proprietary PEGylation materials for use in CIMZIA® (certolizumab pegol) with Celltech Chiroscience Ltd., which was acquired by UCB in 2004. Under the terms of the agreement, UCB is responsible for all clinical development, regulatory, and commercialization expenses. We also manufacture and supply UCB with our proprietary PEGylation reagent used in the manufacture of CIMZIA® on a fixed price per gram. We were also entitled to receive royalties on net sales of the

CIMZIA® product for the longer of ten years from the first commercial sale of the product anywhere in the world or the expiration of patent rights in a particular country. In February 2012, we sold our rights to receive royalties on future worldwide net sales of CIMZIA® effective as of January 1, 2012 until the agreement with UCB is terminated or expires. This sale is further discussed in Note 7 of our Consolidated Financial Statements. Our agreement with UCB Pharma expires upon the expiration of all of UCB's royalty obligations, provided that the agreement can be extended for successive two year renewal periods upon mutual agreement of the parties. In addition, UCB may terminate the agreement should it cease the development and marketing of CIMZIA® and either party may terminate for cause under certain conditions.

MIRCERA® (C.E.R.A.) (Continuous Erythropoietin Receptor Activator), Agreement with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc.

In December 2000, we entered into a license, manufacturing and supply agreement with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. (Roche), which was amended and restated in its entirety in December 2005. Pursuant to the agreement, we license our intellectual property related to our proprietary PEGylation materials for the manufacture and commercialization of Roche's MIRCERA® product. MIRCERA® is a novel continuous erythropoietin receptor activator indicated for the treatment of anemia associated with chronic kidney disease in patients on dialysis and patients not on dialysis. As of the end of 2006, we were no longer required to manufacture and supply our proprietary PEGylation materials for MIRCERA® under our original agreement. In February 2012, we entered into a toll-manufacturing agreement with Roche under which we manufactured our proprietary PEGylation material for MIRCERA®. Roche entered into the toll-manufacturing agreement with the objective of establishing us as a secondary back-up source on a non-exclusive basis through December 31, 2016. Under the terms of this agreement, Roche paid us an up-front payment of $5.0 million plus a total of $22.0 million in performance-based milestone payments upon our achievement of certain manufacturing readiness, validation and production milestones, including the delivery of specified quantities of PEGylation materials, all of which were successfully completed by the end of January 2013. In 2013, we delivered additional quantities of PEGylation materials used by Roche to produce PEGASYS® and MIRCERA® for total consideration of approximately $18.6 million. We were also entitled to receive royalties on net sales of the MIRCERA® product. In February 2012, we sold all of our future rights to receive royalties on future worldwide net sales of MIRCERA® effective as of January 1, 2012. This sale is further discussed in Note 7 of our Consolidated Financial Statements. As of December 31, 2016, we no longer had any continuing manufacturing or supply obligations under this MIRCERA® agreement.

Macugen®, Agreement with Bausch Health Companies Inc., formerly Valeant Pharmaceuticals International, Inc.

In 2002, we entered into a license, manufacturing and supply agreement with Eyetech, Inc. (subsequently acquired by Valeant Pharmaceuticals International, Inc. or Valeant), pursuant to which we license certain intellectual property related to our proprietary PEGylation technology for the development and commercialization of Macugen®, a PEGylated anti-vascular endothelial growth factor aptamer currently approved in the U.S. and EU for age-related macular degeneration. Under the terms of the agreement, we will receive royalties on net product sales in any particular country for the longer of ten years from the date of the first commercial sale of the product in that country or the duration of patent coverage. Our agreement with Valeant expires upon the expiration of our last relevant patent containing a valid claim. In addition, Valeant may terminate the agreement if marketing authorization is withdrawn or marketing is no longer feasible due to certain circumstances, and either party may terminate for cause if certain conditions are met.

Somavert®, Agreement with Pfizer, Inc.

In January 2000, we entered into a license, manufacturing and supply agreement with Sensus Drug Development Corporation (subsequently acquired by Pharmacia Corp. in 2001 and then acquired by Pfizer, Inc. in 2003), for the PEGylation of Somavert® (pegvisomant), a human growth hormone receptor antagonist for the treatment of acromegaly. We currently manufacture our proprietary PEGylation reagent for Pfizer, Inc. on a price per gram basis.

Neulasta®, Agreement with Amgen, Inc.

In July 1995, we entered into a non-exclusive supply and license agreement (the 1995 Agreement) with Amgen, Inc., pursuant to which we licensed our proprietary PEGylation technology to be used in the development and manufacture of Neulasta®. Neulasta® selectively stimulates the production of neutrophils that are depleted by cytotoxic chemotherapy, a condition called neutropenia that makes it more difficult for the body to fight infections. On October 29, 2010, we amended and restated the 1995 Agreement by entering into a supply, dedicated suite and manufacturing guarantee agreement (the 2010 Agreement) and an amended and restated license agreement with

Amgen Inc. and Amgen Manufacturing, Limited (together referred to as Amgen). Under the terms of the 2010 Agreement, we guarantee the manufacture and supply of our proprietary PEGylation materials (Polymer Materials) to Amgen in an existing manufacturing suite to be used exclusively for the manufacture of Polymer Materials for Amgen in our manufacturing facility in Huntsville, Alabama. This supply arrangement is on a non-exclusive basis (other than the use of the manufacturing suite and certain equipment) whereby we are free to manufacture and supply the Polymer Materials to any other third party and Amgen is free to procure the Polymer Materials from any other third party. Under the terms of the 2010 Agreement, we received a $50.0 million upfront payment in return for guaranteeing supply of certain quantities of Polymer Materials to Amgen and the Additional Rights described below, and Amgen will pay manufacturing fees calculated based on fixed and variable components applicable to the Polymer Materials ordered by Amgen and delivered by us. Amgen has no minimum purchase commitments. If quantities of the Polymer Materials ordered by Amgen exceed specified quantities (with each specified quantity representing a small portion of the quantity that we historically supplied to Amgen), significant additional payments become payable to us in return for guaranteeing supply of additional quantities of the Polymer Materials.

The term of the 2010 Agreement runs through October 29, 2020. In the event we become subject to a bankruptcy or insolvency proceeding, we cease to own or control the manufacturing facility in Huntsville, Alabama, we fail to manufacture and supply the

Polymer Materials or certain other events occur, Amgen or its designated third party will have the right to elect, among certain other options, to take title to the dedicated equipment and access the manufacturing facility to operate the manufacturing suite solely for the purpose of manufacturing the Polymer Materials (Additional Rights). Amgen may terminate the 2010 Agreement for convenience or due to an uncured material default by us. Either party may terminate the 2010 Agreement in the event of insolvency or bankruptcy of the other party.

Dapirolizumab Pegol

In 2010, we entered into a license, manufacturing and supply agreement with UCB Pharma S.A., (UCB) under which we granted UCB a worldwide, exclusive license to certain of our proprietary PEGylation technology to develop, manufacture and commercialize an anti-CD40L PEGylated Fab being developed by UCB and their partner Biogen Idec, for the treatment of autoimmune disorders, including systemic lupus erythemastosus (SLE). In 2014, UCB and Biogen completed a Phase 1b randomized, double-blind, placebo-controlled clinical study in approximately 24 patients with SLE. Data from the study was published in September 2015 at the Annual American College of Rheumatology Meeting and showed that multiple administrations of dapirolizumab pegol given over 12 weeks were well-tolerated and the safety profile supported further development of the compound. Exploratory analyses from the same study showed greater improvement in clinical measures of disease activity in the dapriolizumab pegol group versus placebo. In 2016, UCB initiated a multi-center, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging Phase 2 clinical study followed by an observational period to evaluate the efficacy and safety of patients with moderately to severely active SLE receiving stable standard of care medications. In October 2018, UCB announced that the primary endpoint of the study to demonstrate a dose response at 24 weeks on the British Isles Lupus Assessment Group (BILAG) based Composite Lupus Assessment (BICLA) was not met and stated that it and Biogen will continue to further evaluate these data while assessing potential next steps.

PEGPH20, Agreement with Halozyme Therapeutics, Inc.

In December 2006, we entered into a license agreement with Halozyme pursuant to which we granted Halozyme a worldwide, limited exclusive license to certain of our proprietary PEGylation technology to develop, manufacture and commercialize particular products that use our proprietary PEGylation materials linked only with certain qualifying hyaluronidase protein molecules including PEGPH20. According to Halozyme, certain cancers, including pancreatic, breast, colon and prostate, have been shown to accumulate high levels of hyaluronan (HA). Halozyme's FDA-approved, HYLENEX® recombinant human hyaluronidase, rHuPH20, is administered subcutaneously and temporarily and reversibly degrades HA to facilitate the absorption and dispersion of other injected drugs or fluids and for subcutaneous fluid administration. However, rHuPH20 acts only locally at the injection site, is rapidly inactivated in the body, and does not survive in the blood. PEGPH20 is an investigational PEGylated form of rHuPH20, under development by Halozyme to increase the half-life of the compound in the blood and allow for intravenous administration. Halozyme is currently evaluating PEGPH20 in a Phase 3 clinical study combining PEGPH20 with ABRAXANE® (nab-paclitaxel) and gemcitabine in stage IV pancreatic ductal adenocarcinoma (PDA) (HALO 301), in Phase 1b clinical testing for PEGPH20 with KEYTRUDA® (pembrolizumab) in non-small cell lung cancer and gastric cancer (HALO 101), in Phase 1b/2 clinical testing for PEGPH20 with HALAVEN® (eribulin) in patients treated with up to two lines of prior therapy for HER2-negative metastatic breast cancer, in Phase 1b/2 clinical testing for PEGPH20 with Tecentriq® (atezolizumab) in patients with previously treated metastatic PDA, in Phase 1b/2 clinical testing for PEGPH20 with Tecentriq in patients with gastric cancer and in Phase 1b/2 clinical testing for PEGPH20 with Tecentriq in patients with cholangiocarcinoma and gall bladder cancer (HALO 110-101/MATRIX). We are entitled to future development milestones and royalties on net sales subject to reduction in the absence of patent coverage. Our right to receive royalties in any particular country will expire upon the later of twelve years after first commercial sale of the product or expiration of patent rights in the particular country. We also manufacture and supply Halozyme with clinical and future commercial supply of our proprietary PEGylation materials used in the manufacture of PEGPH20.

Government Regulation

Product Development and Approval Process

The research and development, clinical testing, manufacture and marketing of products using our technologies are subject to regulation by the FDA and by comparable regulatory agencies in other countries. These national agencies and other federal, state and local entities regulate, among other things, research and development activities and the testing (in vitro, in animals, and in human clinical trials), manufacture, labeling, storage, recordkeeping, approval, marketing, advertising and promotion of our products.

The approval process required by the FDA before a product using any of our technologies may be marketed in the U.S. depends on whether the chemical composition of the product has previously been approved for use in other dosage forms. If the product is a new chemical entity that has not been previously approved, the process includes the following:

- extensive preclinical laboratory and animal testing;
- submission of an IND prior to commencing clinical trials;

- adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug for the intended indication;
- extensive pharmaceutical development for the characterization of the chemistry, manufacturing process and controls for the active ingredient and drug product; and
- submission to the FDA of an NDA for approval of a drug, a Biological License Application (BLA) for approval of a biological product or a Premarket Approval Application (PMA) or Premarket Notification 510(k) for a medical device product (a 510(k)).

If the active chemical ingredient has been previously approved by the FDA, the approval process is similar, except that certain preclinical tests, including those relating to systemic toxicity normally required for the IND and NDA or BLA, and clinical trials, may not be necessary if the company has a right of reference to existing preclinical or clinical data under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) or is eligible for approval under Section 505(b)(2) of the FDCA or the biosimilars provisions of the Public Health Services Act.

Preclinical tests include laboratory evaluation of product chemistry and animal studies to assess the safety and efficacy of the product and its chosen formulation. Preclinical safety tests must be conducted by laboratories that comply with FDA good laboratory practices (GLP) regulations. The results of the preclinical tests for drugs, biological products and combination products subject to the primary jurisdiction of the FDA's Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) are submitted to the FDA as part of the IND and are reviewed by the FDA before clinical trials can begin. Clinical trials may begin 30 days after receipt of the IND by the FDA, unless the FDA raises objections or requires clarification within that period. Clinical trials involve the administration of the drug to healthy volunteers or patients under the supervision of a qualified, identified medical investigator according to a protocol submitted in the IND for FDA review. Drug products to be used in clinical trials must be manufactured according to current good manufacturing practices (cGMP). Clinical trials are conducted in accordance with protocols that detail the objectives of the study and the parameters to be used to monitor participant safety and product efficacy as well as other criteria to be evaluated in the study. Each protocol is submitted to the FDA in the IND.

Apart from the IND process described above, each clinical study must be reviewed by an independent Institutional Review Board (IRB) and the IRB must be kept current with respect to the status of the clinical study. The IRB considers, among other things, ethical factors, the potential risks to subjects participating in the trial and the possible liability to the institution where the trial is conducted. The IRB also reviews and approves the informed consent form to be signed by the trial participants and any significant changes in the clinical study.

Clinical trials are typically conducted in three sequential phases. Phase 1 involves the initial introduction of the drug into healthy human subjects (in most cases) and the product generally is tested for tolerability, pharmacokinetics, absorption, metabolism and excretion. Phase 2 involves studies in a limited patient population to:

- determine the preliminary efficacy of the product for specific targeted indications;
- determine dosage and regimen of administration; and
- identify possible adverse effects and safety risks.

If Phase 2 trials demonstrate that a product appears to be effective and to have an acceptable safety profile, Phase 3 trials are undertaken to evaluate the further clinical efficacy and safety of the drug and formulation within an expanded patient population at geographically dispersed clinical study sites and in large enough trials to provide statistical proof of efficacy and tolerability. The FDA, the clinical trial sponsor, the investigators or the IRB may suspend clinical trials at any time if any one of them believes that study participants are being subjected to an unacceptable health risk. In some cases, the FDA and the drug sponsor may determine that Phase 2 trials are not needed prior to entering Phase 3 trials.

Following a series of formal meetings and communications between the drug sponsor and the regulatory agencies, the results of product development, preclinical studies and clinical studies are submitted to the FDA as an NDA or BLA for approval of the marketing and commercial shipment of the drug product. The FDA may deny approval if

applicable regulatory criteria are not satisfied or may require additional clinical or pharmaceutical testing or requirements. Even if such data are submitted, the FDA may ultimately decide that the NDA or BLA does not satisfy all of the criteria for approval. Additionally, the approved labeling may narrowly limit the conditions of use of the product, including the intended uses, or impose warnings, precautions or contraindications which could significantly limit the potential market for the product. Further, as a condition of approval, the FDA may impose post-market surveillance, or Phase 4, studies or risk evaluation and mitigation strategies. Product approvals, once obtained, may be withdrawn if compliance with regulatory standards is not maintained or if safety concerns arise after the product reaches the market. The FDA may require additional post-marketing clinical testing and pharmacovigilance programs to monitor the effect of drug products that have been commercialized and has the power to prevent or limit future marketing of the product based on the results of

such programs. After approval, there are ongoing reporting obligations concerning adverse reactions associated with the product, including expedited reports for serious and unexpected adverse events.

Each manufacturing establishment producing the active pharmaceutical ingredient and finished drug product for the U.S. market must be registered with the FDA and typically is inspected by the FDA prior to NDA or BLA approval of a drug product manufactured by such establishment. Such inspections are also held periodically after the commercialization. Establishments handling controlled substances must also be licensed by the U.S. Drug Enforcement Administration. Manufacturing establishments of U.S. marketed products are subject to inspections by the FDA for compliance with cGMP and other U.S. regulatory requirements. They are also subject to U.S. federal, state, and local regulations regarding workplace safety, environmental protection and hazardous and controlled substance controls, among others.

In situations where our partners are responsible for clinical and regulatory approval procedures, we may still participate in this process by submitting to the FDA a drug master file developed and maintained by us which contains data concerning the manufacturing processes for polymer conjugation materials or drug. For our proprietary products, we prepare and submit an IND and are responsible for additional clinical and regulatory procedures for product candidates being developed under an IND. The clinical and manufacturing, development and regulatory review and approval process generally takes a number of years and requires the expenditure of substantial resources. Our ability to manufacture and market products, whether developed by us or under collaboration agreements, ultimately depends upon the completion of satisfactory clinical trials and success in obtaining marketing approvals from the FDA and equivalent foreign health authorities.

Sales of our products outside the U.S. are subject to local regulatory requirements governing clinical trials and marketing approval for drugs. Such requirements vary widely from country to country.

In the U.S., under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the U.S. The company that obtains the first FDA approval for a designated orphan drug for a rare disease receives marketing exclusivity for use of that drug for the designated condition for a period of seven years. In addition, the Orphan Drug Act provides for protocol assistance, tax credits, research grants, and exclusions from user fees for sponsors of orphan products. Once a product receives orphan drug exclusivity, a second product that is considered to be the same drug for the same indication generally may be approved during the exclusivity period only if the second product is shown to be “clinically superior” to the original orphan drug in that it is more effective, safer or otherwise makes a “major contribution to patient care” or the holder of exclusive approval cannot assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. Similar incentives also are available for orphan drugs in the EU.

In the U.S., the FDA may grant Fast Track or Breakthrough Therapy designation to a product candidate, which allows the FDA to expedite the review of new drugs that are intended for serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. Important features of Fast Track or Breakthrough Therapy designation include a potentially reduced clinical program and close, early communication between the FDA and the sponsor company to improve the efficiency of product development.

Coverage, Reimbursement, and Pricing

Sales of any products for which we may obtain regulatory approval depend, in part, on the coverage and reimbursement status of those products. In the U.S., sales of any products for which we may receive regulatory approval for commercial sale will depend in part on the availability of coverage and reimbursement from third-party payors. Third-party payors include government programs such as Medicare, Medicaid, TRICARE and the Veterans Administration, as well as managed care providers, private health insurers and other organizations.

The process for determining whether a payor will provide coverage for a product is typically separate from the process for setting the reimbursement rate that the payor will pay for the product. Third-party payors may limit coverage to specific products on an approved list or formulary which might not include all of the FDA-approved products for a particular indication. Third-party payors may also refuse to include a particular branded drug on their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or other alternative is available. Further, private payors often follow the coverage and payment policies established by certain government programs, such as Medicare and Medicaid, which require manufacturers to comply with certain rebate, price reporting, and other obligations. For example, the Medicaid Drug Rebate Program, which is part of the Medicaid program (a program for financially needy patients, among others), requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services under which the manufacturer agrees to report certain prices to the government and pay rebates to state Medicaid programs on outpatient drugs furnished to Medicaid patients, as a condition for receiving federal reimbursement for the manufacturer's outpatient drugs furnished to Medicaid patients. Further, in order for a pharmaceutical product to receive federal reimbursement under Medicare Part B and Medicaid programs or to

be sold directly to U.S. government agencies, the manufacturer must extend discounts to entities eligible to participate in the Public Health Service's 340B drug pricing program.

Third-party payors 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. Additionally, the containment of healthcare costs has become a priority of federal and state governments, and the price of therapeutics have been a focus in this effort. The U.S. government and state legislatures have shown significant interest in implementing cost-containment programs, including price controls and restrictions on reimbursement, among other controls. Adoption of price controls or other cost-containment measures could limit coverage for or the amounts that federal and state governments or private payors will pay for health care products and services, which could also result in reduced demand for our drug candidates or additional pricing pressures and affect our ultimate profitability. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover an approved product or, if they do, the level of payment may not be sufficient to allow us to sell our products at a profit.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Other Healthcare Laws and Regulations

If we obtain regulatory approval of our products, we may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our proposed sales and marketing programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering, or paying remuneration (a term interpreted broadly to include anything of value, including, for example, gifts, discounts, and credits), directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order, or recommendation of, an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment to Medicare, Medicaid, or other third-party payors that are false or fraudulent, or making a false statement or record material to payment of a false claim or avoiding, decreasing, or concealing an obligation to pay money owed to the federal government;
- provisions of the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes, referred to as the "HIPAA All-Payor Fraud Prohibition," that prohibit knowingly and willfully executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- federal transparency laws, including the federal Physician Payment Sunshine Act, which require manufacturers of certain drugs and biologics to track and disclose payments and other transfers of value they make to U.S. physicians and teaching hospitals as well as physician ownership and investment interests in the manufacturer, and that such information is subsequently made publicly available in a searchable format on a CMS website;
- provisions of HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers, state transparency reporting

and compliance laws; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and which may not have the same effect, thus complicating compliance efforts.

The Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act (collectively, the "Affordable Care Act"), enacted in 2010, expanded the reach of the fraud and abuse laws by, among other things, amending the intent

requirement of the federal Anti-Kickback Statute and the applicable criminal fraud statutes contained within 42 U.S.C. § 1320a-7b. Pursuant to the Affordable Care Act, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act or the civil monetary penalties statute. Many states have adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs.

The federal False Claims Act prohibits anyone from, among other things, knowingly presenting, or causing to be presented, for payment to federal programs (including Medicare and Medicaid) claims for items or services that are false or fraudulent. Although we would not submit claims directly to payors, manufacturers can be held liable under these laws if they are deemed to "cause" the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. In addition, our future activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state, and third-party reimbursement for our products, and the sale and marketing of our products, are subject to scrutiny under this law. For example, pharmaceutical companies have been prosecuted under the federal False Claims Act in connection with their alleged off-label promotion of drugs, purportedly concealing price concessions in the pricing information submitted to the government for government price reporting purposes, and allegedly providing free product to customers with the expectation that the customers would bill federal health care programs for the product. Penalties for a False Claims Act violation include three times the actual damages sustained by the government, plus mandatory civil penalties of between $10,781 and $21,916 for each separate false claim, the potential for exclusion from participation in federal healthcare programs, and, although the federal False Claims Act is a civil statute, conduct that results in a False Claims Act violation may also implicate various federal criminal statutes. In addition, private individuals have the ability to bring actions under the federal False Claims Act and certain states have enacted laws modeled after the federal False Claims Act.

Legislative and Regulatory Landscape

From time to time, legislation is drafted, introduced and passed in Congress that could significantly change the statutory provisions governing the testing, approval, manufacturing, marketing, coverage and reimbursement of products regulated by the FDA or other government agencies. In addition to new legislation, FDA and healthcare fraud and abuse and coverage and reimbursement regulations and policies are often revised or interpreted by the agency in ways that may significantly affect our business and our products. Further, the 2016 Presidential and Congressional elections and subsequent developments have caused the future state of many core aspects of the current health care marketplace to be uncertain, as the new Presidential Administration and Congress have repeatedly expressed a desire to repeal all or portions of the Affordable Care Act. While specific changes and their timing are not yet apparent, there may be significant changes to the healthcare environment in the future that could have an adverse effect on anticipated revenues from therapeutic candidates that we may successfully develop and for which we may obtain regulatory approval. Furthermore, federal agencies, Congress, state legislatures, and the privacy sector have shown significant interest in implementing cost containment programs to limit the growth of health care costs, including price controls, restrictions on reimbursement and other fundamental changes to the healthcare delivery system. Any proposed or actual changes could limit coverage for or the amounts that federal and state governments will pay for health care products and services, which could also result in reduced demand for our products or additional pricing pressures and affect our ultimate profitability.

Patents and Proprietary Rights

We own more than 275 U.S. and 850 foreign patents and a number of pending patent applications that cover various aspects of our technologies. We have filed patent applications, and plan to file additional patent applications, covering

various aspects of our advanced polymer conjugate technologies and our proprietary product candidates. More specifically, our patents and patent applications cover polymer architecture, drug conjugates, formulations, methods of making polymers and polymer conjugates, methods of administering polymer conjugates, and methods of manufacturing polymers and polymer conjugates. Our patent portfolio contains patents and patent applications that encompass our advanced polymer conjugate technology platforms. Our patent strategy is to file patent applications on innovations and improvements to cover a significant majority of the major pharmaceutical markets in the world. Generally, patents have a term of twenty years from the earliest priority date (assuming all maintenance fees are paid). In some instances, patent terms can be increased or decreased, depending on the laws and regulations of the country or jurisdiction that issued the patent.

We also rely on trade secret protection for our confidential and proprietary information. No assurance can be given that we can meaningfully protect our trade secrets. Others may independently develop substantially equivalent confidential and proprietary information or otherwise gain access to, or disclose, our trade secrets. Please refer to Item 1A, Risk Factors, including but not limited to “We rely on trade secret protection and other unpatented proprietary rights for important proprietary technologies, and any loss of such rights could harm our business, results of operations and financial condition.” In certain situations in which we work with drugs

covered by one or more patents, our ability to develop and commercialize our technologies may be affected by limitations in our access to these proprietary drugs. Even if we believe we are free to work with a proprietary drug, we cannot guarantee that we will not be accused of, or determined to be, infringing a third party's rights and be prohibited from working with the drug or found liable for damages. Any such restriction on access or liability for damages would have a material adverse effect on our business, results of operations and financial condition.

The patent positions of pharmaceutical and biotechnology companies, such as ours, are uncertain and involve complex legal and factual issues. There can be no assurance that patents that have issued will be held valid and enforceable in a court of law. Even for patents that are held valid and enforceable, the legal process associated with obtaining such a judgment is time consuming and costly. Additionally, issued patents can be subject to opposition or other proceedings that can result in the revocation of the patent or maintenance of the patent in amended form (and potentially in a form that renders the patent without commercially relevant or broad coverage). Further, our competitors may be able to circumvent and otherwise design around our patents. Even if a patent is issued and enforceable, because development and commercialization of pharmaceutical products can be subject to substantial delays, patents may expire early and provide only a short period of protection, if any, following the commercialization of products encompassed by our patent. We may have to participate in interference proceedings declared by the U.S. Patent and Trademark Office, which could result in a loss of the patent and/or substantial cost to us. Please refer to Item 1A, Risk Factors, including without limitation, "If any of our pending patent applications do not issue, or are deemed invalid following issuance, we may lose valuable intellectual property protection."

U.S. and foreign patent rights and other proprietary rights exist that are owned by third parties and relate to pharmaceutical compositions and reagents, and equipment and methods for preparation, packaging and delivery of pharmaceutical compositions. We cannot predict with any certainty which, if any, of these rights will be considered relevant to our technology by authorities in the various jurisdictions where such rights exist, nor can we predict with certainty which, if any, of these rights will or may be asserted against us by third parties. We could incur substantial costs in defending ourselves and our partners against any such claims. Furthermore, parties making such claims may be able to obtain injunctive or other equitable relief, which could effectively block our ability to develop or commercialize some or all of our products in the U.S. and abroad and could result in the award of substantial damages. In the event of a claim of infringement, we or our partners may be required to obtain one or more licenses from third parties. There can be no assurance that we can obtain a license to any technology that we determine we need on reasonable terms, if at all, or that we could develop or otherwise obtain alternative technology. The failure to obtain licenses if needed may have a material adverse effect on our business, results of operations and financial condition. Please refer to Item 1A, Risk Factors, including without limitation, "We may not be able to obtain intellectual property licenses related to the development of our drug candidates on a commercially reasonable basis, if at all."

It is our policy to require our employees and consultants, outside scientific collaborators, sponsored researchers and other advisors who receive confidential information from us to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. The agreements provide that all inventions conceived by an employee shall be our property. There can be no assurance, however, that these agreements will provide meaningful protection or adequate remedies for our trade secrets in the event of unauthorized use or disclosure of such information.

Customer Concentrations

Our revenue is derived from our collaboration agreements with partners, under which we may receive a combination of revenue elements including up-front payments for licensing agreements, milestone payments based on clinical progress, regulatory progress or net sales achievements, royalties or product sales revenue. Our revenues are concentrated among a limited number of collaboration partners under long-term arrangements. In particular, our

collaboration arrangements with BMS and Lilly represent 89% of our revenues for the year ended December 31, 2018 and 42% of our revenues for the year ended December 31, 2017, respectively, and these arrangements provide for the most significant portion of our potential future development and regulatory milestones. The relative portion of such revenues in any particular year, however, is dependent upon the mix of any milestone or other license revenues recognized and volume of recurring royalty revenues and product sales. Additionally, we derive substantially all of our cash royalty revenue from our collaboration arrangements with Takeda for ADYNOVATE®/ADYNOVI™ and AstraZeneca for MOVANTIK®/MOVENTIG® and we derive the significant majority of our product sales from two other partners.

Backlog

Pursuant to our collaboration agreements, we manufacture and supply our proprietary polymer conjugation materials. Inventory is produced and sales are made pursuant to customer purchase orders for delivery generally based on rolling four to eight quarter forecasts, of which at least two quarters are generally binding. Our backlog is not significant. In light of industry practice and our own experience, we do not believe that backlog as of any particular date is indicative of future results.

Competition

Competition in the pharmaceutical and biotechnology industry is intense and characterized by aggressive research and development and rapidly-evolving science, technology, and standards of medical care throughout the world. We frequently compete with pharmaceutical companies and other institutions with greater financial, research and development, marketing and sales, manufacturing and managerial capabilities. We face competition from these companies not just in product development but also in areas such as recruiting employees, acquiring technologies that might enhance our ability to commercialize products, establishing relationships with certain research and academic institutions, enrolling patients in clinical trials and seeking program partnerships and collaborations with larger pharmaceutical companies.

Science and Technology Competition

We believe that our proprietary and partnered products will compete with others in the market on the basis of one or more of the following parameters: efficacy, safety, ease of use and cost. We face intense science and technology competition from a multitude of technologies seeking to enhance the efficacy, safety and ease of use of approved drugs and new drug molecule candidates. A number of the drug candidates in our pipeline have direct and indirect competition from large pharmaceutical companies and biopharmaceutical companies. With our advanced polymer conjugate technologies, we believe we have competitive advantages relating to factors such as efficacy, safety, ease of use and cost for certain applications and molecules. We constantly monitor scientific and medical developments in order to improve our current technologies, seek licensing opportunities where appropriate, and determine the best applications for our technology platforms.

In the fields of advanced polymer conjugate technologies, our competitors include Biogen Idec Inc., Crealta Pharma, Dr. Reddy’s Laboratories, Ltd., Mountain View Pharmaceuticals, Inc., SunBio Corporation, NOF Corporation, and Novo Nordisk A/S (assets formerly held by Neose Technologies, Inc.). Several other chemical, biotechnology and pharmaceutical companies may also be developing advanced polymer conjugate technology or technologies intended to deliver similar scientific and medical benefits. Some of these companies license intellectual property or PEGylation materials to other companies, while others apply the technology to create their own drug candidates.

Product and Program Specific Competition

NKTR-181 (mu-opioid analgesic molecule for chronic pain)

There are numerous companies developing pain therapies designed to have less abuse potential primarily through formulation technologies and techniques applied to existing pain therapies. Potential competitors include Acura Pharmaceuticals, Inc., Cara Therapeutics, Inc., Collegium Pharmaceutical, Inc., Egalet Ltd, Elite Pharmaceuticals, Inc., Endo Health Solutions Inc., KemPharm, Inc., Eli Lilly & Co., Pfizer, Purdue Pharma L.P., and Teva Pharmaceutical Industries Ltd.

NKTR-214 (bempegaldesleukin)(CD122-preferential IL-2 pathway agonist)

There are numerous companies engaged in developing immunotherapies to be used alone, or in combination, to treat a wide range of oncology indications targeting both solid and liquid tumors. In particular, we expect to compete with therapies with tumor infiltrating lymphocytes, or TILS, chimeric antigen receptor-expressing T cells, or CAR-T, cytokine-based therapies, and checkpoint inhibitors. Potential competitors in the TIL and CAR-T space include Gilead Sciences, Inc. (through its acquisition of Kite Pharma)/NCI, Apeiron Biologics, Philogen S.p.A., IRX Therapeutics, Anaveon AG, and Adaptimmune LLC. In the cytokine-based therapies space, potential competitors include Novartis, Alkermes, Altor Bioscience, Eli Lilly & Co. (through its acquisition of Armo Biosciences), Roche, and Synthorx, Inc., and in the checkpoint inhibitor space potential competitors include Tesaro, Inc., Macrogenics, Inc., Merck, Bristol-Myers Squibb, and Roche.

NKTR-358 (IL-2 conjugate regulator T Cell stimulator)

There are a number of competitors in various stages of clinical development that are working on programs which are designed to correct the underlying immune system imbalance in the body due to autoimmune disease. In particular, we expect to compete with therapies that could be cytokine-based therapies (Symbiotix, LLC and Tizona Therapeutics), regulatory T cell therapies (Targazyme, Inc., Caladrius BioSciences, Inc., and Tract Therapeutics, Inc.), or IL-2 based therapies (Amgen, Inc.).

ONZEALD™ (next-generation, long acting topoisomerase I inhibitor)

There are a number of chemotherapies and cancer therapies approved today and in various stages of clinical development for advanced breast cancer. These therapies are only partially effective in treating advanced or metastatic breast cancer and none of them have a specific indication in either the U.S. or Europe for treatment of patients with advanced breast cancer and co-existing brain metastases. These therapies include but are not limited to: Abraxane® (paclitaxel protein-bound particles for injectable suspension (albumin bound)), Afinitor® (everolimus), Ellence® (epirubicin), Gemzar® (gemcitabine), Halaven® (eribulin), Herceptin®

(trastuzumab), Ixempra® (ixabepilone), Navelbine® (vinolrebine), Xeloda® (capecitabine) and Taxotere® (docetaxel). Major pharmaceutical or biotechnology companies with approved drugs or drugs in development for these cancers include Bristol-Myers Squibb Company, Eisai, Inc., Roche Holding Group (including its Genentech subsidiary), GlaxoSmithKline plc, Pfizer, Inc., Eli Lilly & Co., Sanofi Aventis S.A., and others.

MOVANTIK® (previously referred to as naloxegol and NKTR-118) (orally-available peripheral opioid antagonist)

There are no other once-daily oral drugs that act specifically to block or reverse the action of opioids on receptors in the gastrointestinal tract which are approved specifically for the treatment of opioid-induced constipation (OIC) or opioid bowel dysfunction (OBD) in patients with chronic, non-cancer pain. The only approved oral treatment for opioid-induced constipation in adults with chronic, non-cancer pain is a twice daily oral therapy called AMITIZA® (lubiprostone), which acts by specifically activating CIC-2 chloride channels in the gastrointestinal tract to increase secretions. AMITIZA® is marketed by Sucampo Pharmaceuticals and Takeda. There is also a subcutaneous treatment and an oral treatment known as RELISTOR® which is marketed by Bausch Health Companies Inc. (formerly, Valeant Pharmaceuticals International, Inc., which previously acquired Salix) under a license from Progenics Pharmaceuticals, Inc. In 2014, RELISTOR® Subjectaneous Injection was approved by the FDA for adult patients with chronic non-cancer pain. On July 22, 2016, Relistor (methylnaltrexone bromide) oral tablets for the treatment of OCI in adult patients with chronic non-cancer pain was approved by FDA. Other therapies used to treat OIC and OBD include over-the-counter laxatives and stool softeners, such as docusate sodium, senna, and milk of magnesia. These therapies do not address the underlying cause of constipation as a result of opioid use and are generally viewed as ineffective or only partially effective to treat the symptoms of OIC and OBD.

There are a number of companies developing potential products which are in various stages of clinical development and are being evaluated for the treatment of OIC and OBD in different patient populations. Potential competitors include Merck, GlaxoSmithKline plc, Ironwood Pharmaceuticals, Inc. in collaboration with Actavis plc, Purdue Pharma L.P. in collaboration with Shionogi & Co., Ltd., Mundipharma Int. Limited, Theravance, Inc., Develco Pharma, Sucampo Pharmaceuticals, Inc., and Takeda Pharmaceutical Company Limited.

ADYNOVATE® (previously referred to as BAX 855, PEGylated rFVIII)

On June 6, 2014, the FDA approved Biogen Idec's ELOCTATE™ [antihemophilic factor (recombinant), Fc fusion protein] for the control and prevention of bleeding episodes, perioperative (surgical) management and routine prophylaxis in adults and children with Hemophilia A. ELOCTATE™ is intended to be an extended half-life Factor VIII therapy with prolonged circulation in the body with the potential to extend the interval between prophylactic infusions. Prior to its 2014 approval, the fusion protein in ELOCTATE™ was not used outside of the clinical trial setting for Hemophilia A patients. On August 31, 2018, Bayer Healthcare received FDA approval for JIVI® (antihemophilic factor (recombinant) PEGylated-aucl), an extended half-life Factor VIII for Hemophilia A treatment in patients 12 and older which became commercially available in the third quarter of 2018. In addition, on February 19, 2019, Novo Nordisk received FDA approval for ESPEROCT® [antihemophilic factor (recombinant), glycoPEGylated-exei] a glycoPEGylated Factor VIII product with an extended half-life for use in adults and children with Hemophilia A, and is expected to be commercially available in 2020. The Bayer product and the Novo Nordisk product (upon launch) are competitors in the extended half-life Factor VIII market.

Research and Development

Our total research and development expenditures can be disaggregated into the following significant types of expenses (in millions):

	Year Ended December 31,		
	2018	2017	2016
Third party and direct materials costs	$206.9	$125.4	$98.2
Personnel, overhead and other costs	130.8	113.5	84.6
Stock-based compensation and depreciation	61.8	29.6	21.0
Research and development expense	$399.5	$268.5	$203.8

Manufacturing and Supply

We have a manufacturing facility located in Huntsville, Alabama that is capable of manufacturing our proprietary PEGylation materials for active pharmaceutical ingredients (APIs). The facility is also used to produce APIs to support the early phases of clinical development of our proprietary drug candidates. The facility and associated equipment are designed and operated to be consistent with all applicable laws and regulations. As we do not maintain the capability to manufacture biologics nor finished drug products for our development programs, we primarily utilize contract manufacturers to manufacture biologics and finished drug product for us. We

also utilize the services of contract manufacturers to manufacture APIs and finished drug products required for later phases of clinical development and eventual commercialization under all applicable laws and regulations.

We source drug starting materials for our manufacturing activities from one or more suppliers. For the drug starting materials necessary for our proprietary drug candidate development, we have agreements for the supply of such drug components with drug manufacturers or suppliers that we believe have sufficient capacity to meet our demands. However, from time to time, we source critical raw materials and services from one or a limited number of suppliers and there is a risk that if such supply or services were interrupted, it would materially harm our business. In addition, we typically order raw materials and services on a purchase order basis for early phase clinical development products and enter into long-term supply arrangements only for late stage products nearing regulatory approval for marketing authorization.

Environment

As a manufacturer of PEG reagents for the U.S. market, we are subject to inspections by the FDA and EPA for compliance with cGMP and other U.S. regulatory requirements, including U.S. federal, state and local regulations regarding environmental protection and hazardous and controlled substance controls, among others. Environmental laws and regulations are complex, change frequently and have tended to become more stringent over time. We have incurred, and may continue to incur, significant expenditures to ensure we are in compliance with these laws and regulations. We would be subject to significant penalties for failure to comply with these laws and regulations.

Employees and Consultants

As of December 31, 2018, we had 618 employees, of which 493 employees were engaged in research and development, manufacturing, commercial operations and quality activities and 125 employees in general administration and business development. Of the 618 employees, 547 were located in the U.S. and 71 were located in India. We have a number of employees who hold advanced degrees, such as Ph.D. None of our employees are covered by a collective bargaining agreement, and we have experienced no work stoppages. We believe that we maintain good relations with our employees.

To complement our own expert professional staff, we utilize specialists in regulatory affairs, pharmacovigilance, process engineering, manufacturing, quality assurance and clinical development. These individuals include scientific advisors as well as independent consultants.

Available Information

Our website address is http://www.nektar.com. The information in, or that can be accessed through, our website is not part of this annual report on Form 10-K. Our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K and amendments to those reports are available, free of charge, on or through our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities Exchange Commission (SEC). The public may read and copy any materials we file with the SEC at the SEC’s Public Reference Room at 100 F Street, NE, Washington, D.C. 20549. Information on the operation of the Public Reference Room can be obtained by calling 1-800-SEC-0330. The SEC maintains an Internet site that contains reports, proxy and information statements and other information regarding our filings at www.sec.gov.

EXECUTIVE OFFICERS OF THE REGISTRANT

The following table sets forth the names, ages and positions of our executive officers as of February 22, 2019:

Name	Age	Position
Howard W. Robin	66	Director, President and Chief Executive Officer

Stephen K. Doberstein, Ph.D.	60	Senior Vice President, Research & Development and Chief Research & Development Officer
Maninder Hora, Ph.D	65	Senior Vice President, Pharmaceutical Development and Chief Technical Operations Officer
Gil M. Labrucherie, J.D.	47	Senior Vice President and Chief Financial Officer
John Nicholson	67	Senior Vice President and Chief Operating Officer
Jillian B. Thomsen	53	Senior Vice President, Finance and Chief Accounting Officer

Howard W. Robin has served as our President and Chief Executive Officer since January 2007 and has served as a member of our board of directors since February 2007. Mr. Robin served as Chief Executive Officer, President and a director of Sirna Therapeutics, Inc., a biotechnology company, from July 2001 to November 2006 and from January 2001 to June 2001, served as their

Chief Operating Officer, President and as a director. From 1991 to 2001, Mr. Robin was Corporate Vice President and General Manager at Berlex Laboratories, Inc. (Berlex), a pharmaceutical products company that is a subsidiary of Schering, AG, and from 1987 to 1991 he served as Vice President of Finance and Business Development and Chief Financial Officer of Berlex. From 1984 to 1987, Mr. Robin was Director of Business Planning and Development at Berlex. He was a Senior Associate with Arthur Andersen & Co. prior to joining Berlex. Mr. Robin serves as a director of the Biotechnology Industry Organization, the world's largest biotechnology industry trade organization, and also serves as a director of BayBio, a non-profit trade association serving the Northern California life sciences community. He received his B.S. in Accounting and Finance from Fairleigh Dickinson University in 1974.

Stephen K. Doberstein, Ph.D. has served as our Senior Vice President, Research & Development and Chief Research & Development Officer since November 2017. Dr. Doberstein served as Senior Vice President and Chief Scientific Officer from January 2010 to November 2017 when he was promoted to Senior Vice President, Research & Development and Chief Research & Development Officer. From October 2008 through December 2009, Dr. Doberstein served as Vice President, Research at Xoma (US) LLC, a publicly traded clinical stage biotechnology company. From July 2004 until August 2008, he served as Vice President, Research at privately held Five Prime Therapeutics, Inc., a clinical stage biotechnology company. From September 2001 until July 2004, Dr. Doberstein was Vice President, Research at privately held Xencor, Inc., a clinical stage biotechnology company. From 1997 to 2000, he held various pharmaceutical research positions at Exelixis, Inc. (Exelixis), a publicly traded clinical stage biotechnology company. Prior to working at Exelixis, Dr. Doberstein was a Howard Hughes Postdoctoral Fellow and a Muscular Dystrophy Association Senior Postdoctoral Fellow at the University of California, Berkeley. Dr. Doberstein received his Ph.D. in Biochemistry, Cell and Molecular Biology from the Johns Hopkins University School of Medicine and received a B.S. in Chemical Engineering from the University of Delaware.

Maninder Hora, Ph.D. has served as our Senior Vice President, Pharmaceutical Development and Chief Technical Operations Officer since November 2017 and served as Senior Vice President, Pharmaceutical Development and Manufacturing from August 2010 to November 2017. From July 2006 to July 2010, he held various executive positions most recently as Vice President, Product and Quality Operations at Facet Biotech Corporation (now Abbvie Biotherapeutics), a clinical stage biotechnology company, which was acquired in 2010 by Abbvie Biotherapeutics (formerly Abbot). From 1986 to 2006, Dr. Hora held positions of increasing responsibility with Chiron Corporation (acquired in 2005 by Novartis), a pharmaceutical company, serving most recently at Chiron as Vice President of Process and Product Development. Dr. Hora has also held positions at Wyeth Pharmaceuticals and GlaxoSmithKline plc prior to joining Chiron. Dr. Hora served as a key member of various teams that successfully registered ten drugs or vaccines in the U.S. and Europe during his professional career. Dr. Hora completed his Ph.D. in Bioengineering from the Indian Institute of Technology, Delhi, India, and was a Fulbright Scholar at the University of Washington, and received his B.S. in chemistry from the University of Jabalpur.

Gil M. Labrucherie has served as our Senior Vice President and Chief Financial Officer since June 2016. Mr. Labrucherie served as our Vice President, Corporate Legal from October 2005 through April 2007 and served as our Senior Vice President, General Counsel and Secretary from April 2007 through June 2016 when he was promoted to Senior Vice President and Chief Financial Officer. From October 2000 to September 2005, Mr. Labrucherie was Vice President of Corporate Development at E2open. While at E2open, Mr. Labrucherie was responsible for global corporate alliances and merger and acquisitions. Prior to E2open, he was the Senior Director of Corporate Development at AltaVista Company, an Internet search company, where he was responsible for strategic partnerships and mergers and acquisitions. Mr. Labrucherie began his career as an associate in the corporate practice of the law firm of Wilson Sonsini Goodrich & Rosati, P.C. Mr. Labrucherie received his J.D. from the Berkeley Law School and a B.A. from the University of California Davis.

John Nicholson has served as our Senior Vice President and Chief Operating Officer since June 2016. Mr. Nicholson joined the Company as Senior Vice President of Corporate Development and Business Operations in October 2007 and was appointed Senior Vice President and Chief Financial Officer in December 2007 and served as our Chief Financial Officer until June 2016 when he was promoted to Senior Vice President and Chief Operating Officer.

Before joining Nektar, Mr. Nicholson spent 18 years in various executive roles at Schering Berlin, Inc., the U.S. management holding company of Bayer Schering Pharma AG, a pharmaceutical company. From 1997 to September 2007, Mr. Nicholson served as Schering Berlin Inc.'s Vice President of Corporate Development and Treasurer. From 2001 to September 2007, he concurrently served as President of Schering Berlin Insurance Co., and from February 2007 through September 2007, he also concurrently served as President of Bayer Pharma Chemicals and Schering Berlin Capital Corp. Mr. Nicholson holds a B.B.A. from the University of Toledo.

Jillian B. Thomsen has served as our Senior Vice President, Finance and Chief Accounting Officer since February 2010. From March 2006 through March 2008, Ms. Thomsen served as our Vice President Finance and Corporate Controller and from April 2008 through January 2010 she served as our Vice President Finance and Chief Accounting Officer. Before joining Nektar, Ms. Thomsen was Vice President Finance and Deputy Corporate Controller of Calpine Corporation from September 2002 to February 2006. Ms. Thomsen began her career as a certified public accountant at Arthur Andersen LLP, where she worked from 1990 to 2002, and specialized in audits of multinational consumer products, life sciences, manufacturing and energy companies. Ms. Thomsen holds a Masters of Accountancy from the University of Denver and a B.A. in Business Economics from Colorado College.

29

Item 1A. Risk Factors

We are providing the following cautionary discussion of risk factors, uncertainties and assumptions that we believe are relevant to our business. These are factors that, individually or in the aggregate, we think could cause our actual results to differ materially from expected and historical results and our forward-looking statements. We note these factors for investors as permitted by Section 21E of the Exchange Act and Section 27A of the Securities Act. You should understand that it is not possible to predict or identify all such factors. Consequently, you should not consider this section to be a complete discussion of all potential risks or uncertainties that may substantially impact our business. Moreover, we operate in a competitive and rapidly changing environment. New factors emerge from time to time and it is not possible to predict the impact of all of these factors on our business, financial condition or results of operations.

Risks Related to Our Business

We are highly dependent on the success of NKTR-214, our lead I-O candidate. We are executing a broad development program for NKTR-214 and clinical and regulatory outcomes for NKTR-214, if not successful, will significantly harm our business.

Our future success is highly dependent on our ability to successfully develop, obtain regulatory approval for, and commercialize NKTR-214. In general, most early stage investigatory drugs, including oncology drug candidates such as NKTR-214, do not become approved drugs. Accordingly, there is a very meaningful risk that NKTR-214 will not succeed in one or more clinical trials sufficient to support one or more regulatory approvals. To date, reported clinical outcomes from NKTR-214 have had a significant impact on our market valuation, financial position, and business prospects and we expect this to continue in future periods. If one or more clinical studies of NKTR-214 are delayed or not successful, it would materially harm our market valuation, prospects, financial condition and results of operations. For example, under the BMS Collaboration Agreement, we are entitled to up to $1.43 billion in development milestones that are based upon clinical and regulatory successes from the NKTR-214 development program. One or more failures in NKTR-214 studies could jeopardize such milestone payments, and any product sales or royalty revenue or commercial milestones that we would otherwise be entitled to receive could be reduced, delayed or eliminated.

Delays in clinical studies are common and have many causes, and any significant delay in clinical studies being conducted by us or our partners could result in delay in regulatory approvals and jeopardize the ability to proceed to commercialization.

We or our partners may experience delays in clinical trials of drug candidates. We have ongoing trials evaluating NKTR-214 including a trial evaluating NKTR-214 as a potential combination treatment with BMS's Opdivo® (nivolumab) as well as other ongoing and planned combination trials. We also have an ongoing Phase 1 multiple-ascending dose trial to evaluate NKTR-358 in patients with systemic lupus erythematosus. We also continue to enroll patients in a Phase 1/2 study evaluating NKTR-214 in combination with NKTR-262. These and other clinical studies may not begin on time, enroll a sufficient number of patients or be completed on schedule, if at all. Clinical trials for any of our product candidates could be delayed for a variety of reasons, including:

- delays in obtaining regulatory authorization to commence a clinical study;
- delays in reaching agreement with applicable regulatory authorities on a clinical study design;
- imposition of a clinical hold by the FDA or other health authorities, which may occur at any time including after any inspection of clinical trial operations or trial sites;
- suspension or termination of a clinical study by us, our partners, the FDA or foreign regulatory authorities due to adverse side effects of a drug on subjects in the trial;
- 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 rates;

- delays in manufacturing and delivery of sufficient supply of clinical trial materials; and
- changes in regulatory authorities policies or guidance applicable to our drug candidates.

If the initiation or completion of any of the planned clinical studies for our drug candidates is delayed for any of the above or other reasons, the regulatory approval process would be delayed and the ability to commercialize and commence sales of these drug candidates could be materially harmed, which could have a material adverse effect on our business, financial condition and results of operations. Clinical study delays could also shorten any commercial periods during which our products have patent protection and may allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

The outcomes from competitive I-O and combination therapy clinical trials, and the discovery and development of new potential oncology therapies, could have a material and adverse impact on the value of our I-O research and development pipeline.

The research and development of I-O therapies is a very competitive global segment in the biopharmaceutical industry attracting billions of dollars of investment each year. Our clinical trial plans for NKTR-214, NKTR-262, and NKTR-255 face substantial competition from other I-O combination regimens already approved, and many more combination therapies that are either ahead of or in parallel development in patient populations where we are studying our drug candidates. I-O drug development entails substantial risks and uncertainties that include rapidly changing standards of care, patient enrollment competition, evolving regulatory frameworks to evaluate combination regimens, and varying risk-benefit profiles of competing therapies, any or all of which could have a material and adverse impact on the probability of success of I-O drug candidates.

Drug development is a long and inherently uncertain process with a high risk of failure at every stage of development.

We have a number of proprietary drug candidates and partnered drug candidates in research and development ranging from the early discovery research phase through preclinical testing and clinical trials. Preclinical testing and clinical studies are long, expensive, difficult to design and implement and highly uncertain as to outcome. It will take us or our collaborative partners many years to conduct extensive preclinical tests and clinical trials to demonstrate the safety and efficacy in humans of our product candidates. The start or end of a clinical study is often delayed or halted due to changing regulatory requirements, manufacturing challenges, required clinical trial administrative actions, slower than anticipated patient enrollment, changing standards of care, availability or prevalence of use of a comparator drug or required prior therapy, clinical outcomes, or our and our partners' financial constraints.

Drug development is a highly uncertain scientific and medical endeavor, and failure can unexpectedly occur at any stage of preclinical and clinical development. Typically, there is a high rate of attrition for drug candidates in preclinical and clinical trials due to scientific feasibility, safety, efficacy, changing standards of medical care (including commercialization of a competing therapy in the same or similar indication for which our drug candidate is being studied) and other variables (such as commercial supply challenges). The risk of failure increases for our drug candidates that are based on new technologies, such as the application of our advanced polymer conjugate technology to NKTR-214, NKTR-358, NKTR-262, NKTR-255, NKTR-181, ONZEALD®, and other drug candidates currently in discovery research or preclinical development. The failure of one or more of our drug candidates could have a material adverse effect on our business, financial condition and results of operations.

The risk of clinical failure for any drug candidate remains high prior to regulatory approval.

A number of companies have suffered significant unforeseen failures in clinical studies due to factors such as inconclusive efficacy or safety, even after achieving preclinical proof-of-concept or positive results from earlier clinical studies that were satisfactory both to them and to reviewing regulatory authorities. Clinical study outcomes remain very unpredictable and it is possible that one or more of our clinical studies could fail at any time due to efficacy, safety or other important clinical findings or regulatory requirements. The results from preclinical testing or early clinical trials of a product candidate may not predict the results that will be obtained in later phase clinical trials of the product candidate. We, the FDA, an independent Institutional Review Board (IRB), an independent ethics committee, or other applicable regulatory authorities may suspend clinical trials of a product candidate at any time for various reasons, including a belief that patients participating in such trials are being exposed to unacceptable health risks or adverse side effects. Similarly, an IRB or ethics committee may suspend a clinical trial at a particular trial site. If one or more of our drug candidates fail in clinical studies, it could have a material adverse effect on our business, financial condition and results of operations.

If we or our contract manufacturers are not able to manufacture drugs or drug substances in sufficient quantities that meet applicable quality standards, it could delay clinical studies, result in reduced sales or constitute a breach of our contractual obligations, any of which could significantly harm our business, financial condition and results of operations.

If we or our contract manufacturers are not able to manufacture and supply sufficient drug quantities meeting applicable quality standards required to support large clinical studies or commercial manufacturing in a timely manner, it could delay our or our collaboration partners' clinical studies or result in a breach of our contractual obligations, which could in turn reduce the potential commercial sales of our or our collaboration partners' products. As a result, we could incur substantial costs and damages and any product sales or royalty revenue that we would otherwise be entitled to receive could be reduced, delayed or eliminated. In most cases, we rely on contract manufacturing organizations to manufacture and supply drug product for our clinical studies and those of our collaboration partners. The manufacturing of drugs involves significant risks and uncertainties related to the demonstration of adequate stability, sufficient purification of the drug substance and drug product, the identification and elimination of impurities, optimal formulations, process and analytical methods validations, and challenges in controlling for all of these variables. We have faced and may in the future face significant difficulties, delays and unexpected expenses as we validate third party contract

manufacturers required for API and drug product supply to support our clinical studies and the clinical studies and products of our collaboration partners. Failure by us or our contract manufacturers to supply API or drug products in sufficient quantities that meet all applicable quality requirements could result in supply shortages for our clinical studies or the clinical studies and commercial activities of our collaboration partners. Such failures could significantly and materially delay clinical trials and regulatory submissions or result in reduced sales, any of which could significantly harm our business prospects, results of operations and financial condition.

Building and validating large-scale clinical or commercial-scale manufacturing facilities and processes, recruiting and training qualified personnel and obtaining necessary regulatory approvals is complex, expensive and time-consuming. In the past, we have encountered challenges in scaling up manufacturing to meet the requirements of large scale clinical trials without making modifications to the drug formulation, which may cause significant delays in clinical development. There continues to be substantial and unpredictable risk and uncertainty related to manufacturing and supply until such time as the commercial supply chain is validated and proven.

We purchase some of the starting material for drugs and drug candidates from a single source or a limited number of suppliers, and the partial or complete loss of one of these suppliers could cause production delays, clinical trial delays, substantial loss of revenue and contract liability to third parties.

We often face very limited supply of a critical raw material that can only be obtained from a single, or a limited number of, suppliers, which could cause production delays, clinical trial delays, substantial lost revenue opportunities or contract liabilities to third parties. For example, there are only a limited number of qualified suppliers, and in some cases single source suppliers, for the raw materials included in our PEGylation and advanced polymer conjugate drug formulations. Any interruption in supply or failure to procure such raw materials on commercially feasible terms could harm our business by delaying our clinical trials, impeding commercialization of approved drugs or increasing our costs.

Our manufacturing operations and those of our contract manufacturers are subject to laws and other governmental regulatory requirements, which, if not met, would have a material adverse effect on our business, results of operations and financial condition.

We and our contract manufacturers are required in certain cases to maintain compliance with current good manufacturing practices (cGMP), including cGMP guidelines applicable to active pharmaceutical ingredients and drug products, and with laws and regulations governing manufacture and distribution of controlled substances, and are subject to inspections by the FDA, the Drug Enforcement Administration or comparable agencies in other jurisdictions administering such requirements. We anticipate periodic regulatory inspections of our drug manufacturing facilities and the manufacturing facilities of our contract manufacturers for compliance with applicable regulatory requirements. Any failure to follow and document our or our contract manufacturers' adherence to such cGMP and other laws and governmental regulations or satisfy other manufacturing and product release regulatory requirements may disrupt our ability to meet our manufacturing obligations to our customers, lead to significant delays in the availability of products for commercial use or clinical study, result in the termination or hold on a clinical study or delay or prevent filing or approval of marketing applications for our products. Failure to comply with applicable laws and regulations may also result in sanctions being imposed on us, including fines, injunctions, civil penalties, failure of regulatory authorities to grant marketing approval of our products, delays, suspension or withdrawal of approvals, license revocation, seizures, administrative detention, or recalls of products, operating restrictions and criminal prosecutions, any of which could harm our business. Regulatory inspections could result in costly manufacturing changes or facility or capital equipment upgrades to satisfy the FDA that our manufacturing and quality control procedures are in substantial compliance with cGMP. Manufacturing delays, for us or our contract manufacturers, pending resolution of regulatory deficiencies or suspensions could have a material adverse effect on our business, results of operations and financial condition.

If we or our partners do not obtain regulatory approval for our drug candidates on a timely basis, or at all, or if the terms of any approval impose significant restrictions or limitations on use, our business, results of operations and financial condition will be negatively affected.

We or our partners may not obtain regulatory approval for drug candidates on a timely basis, or at all, or the terms of any approval (which in some countries includes pricing approval) may impose significant restrictions or limitations on use. Drug candidates must undergo rigorous animal and human testing and an extensive review process for safety and efficacy by the FDA and equivalent foreign regulatory authorities. The time required for obtaining regulatory decisions is uncertain and difficult to predict. The FDA and other U.S. and foreign regulatory authorities have substantial discretion, at any phase of development, to terminate clinical studies, require additional clinical development or other testing, delay or withhold registration and marketing approval and mandate product withdrawals, including recalls. For example, while data from certain pre-specified subgroups in our BEACON study for ONZEALD® in 2015 was positive, the study did not achieve statistical significance for its primary endpoint and the FDA and European Medicines Agency rarely approve drugs on the basis of studies that do not achieve statistical significance on the primary endpoint. Further, regulatory authorities have the discretion to analyze data using their own methodologies that may differ from those

used by us or our partners, which could lead such authorities to arrive at different conclusions regarding the safety or efficacy of a drug candidate. In addition, undesirable side effects caused by our drug candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restricted label or the delay or denial of regulatory approval by regulatory authorities. For example, AstraZeneca is conducting a post-marketing, observational epidemiological study comparing MOVANTIK® to other treatments of opioid-induced constipation (OIC) in patients with chronic, non-cancer pain and the results of this study could at some point in the future negatively impact the labeling, regulatory status, and commercial potential of MOVANTIK®.

Even if we or our partners receive regulatory approval of a product, the approval may limit the indicated uses for which the drug may be marketed. Our and our partnered drugs that have obtained regulatory approval, and the manufacturing processes for these products, are subject to continued review and periodic inspections by the FDA and other regulatory authorities. Discovery from such review and inspection of previously unknown problems may result in restrictions on marketed products or on us, including withdrawal or recall of such products from the market, suspension of related manufacturing operations or a more restricted label. The failure to obtain timely regulatory approval of product candidates, any product marketing limitations or a product withdrawal would negatively impact our business, results of operations and financial condition.

The NKTR-181 program is subject to important risks and uncertainties related to likelihood of FDA approval, commercial potential, and nonconvertibility of NKTR-181, any of which could significantly and negatively impact the economic value of NKTR-181.

On May 31, 2018, we announced that we submitted an NDA for NKTR-181 and on July 30, 2018, we announced that the NDA for NKTR-181 for the treatment of chronic low back pain in opioid-naïve adult patients was accepted by the FDA for review. The FDA has assigned a PDUFA target action date of August 29, 2019. While the results from the Phase 3 study of NKTR-181 were positive, and NKTR-181 has Fast Track designation, the regulatory pathway for NKTR-181 remains subject to substantial uncertainty including the amount of data required to support an approval of NKTR-181. In addition, regulations concerning and controlling the access to opioid-based pharmaceuticals are strict and there is no guarantee which scheduling category will apply to NKTR-181 if regulatory approval is achieved. The commercial potential of NKTR-181 remains difficult to predict due to factors that include, for example, the safety and efficacy compared to other available treatments, changing standards of care, third party payer reimbursement standards, scope and contents of the NKTR-181 label, constraints on marketing, patient and physician preferences, drug scheduling status, current and future litigation involving analgesic pharmaceuticals, perceived or actual resistance to the introduction of new controlled substances to the market, the availability of competitive alternatives that may emerge either during or after approval, the availability of generic versions of our NKTR-181, and the countries in which we receive regulatory approvals. If the market potential for NKTR-181 is lower than we anticipated, it could significantly and negatively impact the commercial potential and value of NKTR-181. In the event that we commercialize and market NKTR-181 products, we would be required to build, either internally or through third-party contracts, a sales and marketing organization and infrastructure, which would require a significant investment, and we may not be successful in building this organization and infrastructure in a timely or efficient manner. An important objective of our NKTR-181 drug development program is to create a unique opioid molecule that does not rapidly enter a patient's central nervous system, thereby having the potential to be less susceptible to abuse than alternative opioid therapies. To date, we have conducted numerous experiments using laboratory and home-based chemistry techniques that have been unable to convert NKTR-181 into a rapidly-acting, more abusable form of opioid. In the future, an alternative chemistry technique, process or method of administration, or combination thereof, may be discovered to enable the conversion of NKTR-181 into a more abusable opioid.

If NKTR-181 is approved by FDA, the ability to market and promote NKTR-181 will depend on the scope and content of the final FDA-approved labeling, which could have a material and adverse impact on the market potential of NKTR-181.

If NKTR-181 is approved by the FDA, the commercial success of NKTR-181 will be materially impacted by the FDA-approved label which will set forth the patient population covered by the approved indication in the label, the required warnings, a description of efficacy outcomes, and the human abuse potential profile of NKTR-181, among other matters, for healthcare providers and patients. FDA approval is required to make safety and efficacy claims regarding a product. As a result, there is substantial risk and uncertainty regarding the content of the final label and package insert for NKTR-181, if approved by FDA, which could materially and adversely impact the commercial potential of NKTR-181.

Our results of operations and financial condition depend significantly on the ability of our collaboration partners to successfully develop and market drugs and they may fail to do so.

Under our collaboration agreements with various pharmaceutical or biotechnology companies (other than the BMS Collaboration Agreement), our collaboration partner is generally solely responsible for:

- designing and conducting large scale clinical studies;
- preparing and filing documents necessary to obtain government approvals to sell a given drug candidate; and/or

- marketing and selling the drugs when and if they are approved.

Our reliance on collaboration partners poses a number of significant risks to our business, including risks that:

- we have very little control over the timing and level of resources that our collaboration partners dedicate to commercial marketing efforts such as the amount of investment in sales and marketing personnel, general marketing campaigns, direct-to-consumer advertising, product sampling, pricing agreements and rebate strategies with government and private payers, manufacturing and supply of drug product, and other marketing and selling activities that need to be undertaken and well executed for a drug to have the potential to achieve commercial success;
- collaboration partners with commercial rights may choose to devote fewer resources to the marketing of our partnered drugs than they devote to their own drugs or other drugs that they have in-licensed;
- we have very little control over the timing and amount of resources our partners devote to development programs in one or more major markets;
- disagreements with partners could lead to delays in, or termination of, the research, development or commercialization of product candidates or to litigation or arbitration proceedings;
- disputes may arise or escalate in the future with respect to the ownership of rights to technology or intellectual property developed with partners;
- we do not have the ability to unilaterally terminate agreements (or partners may have extension or renewal rights) that we believe are not on commercially reasonable terms or consistent with our current business strategy;
- partners may be unable to pay us as expected; and
- partners may terminate their agreements with us unilaterally for any or no reason, in some cases with the payment of a termination fee penalty and in other cases with no termination fee penalty.

Given these risks, the success of our current and future collaboration partnerships is highly unpredictable and can have a substantial negative impact on our business. If the approved drugs fail to achieve commercial success or the drugs in development fail to have positive late stage clinical outcomes sufficient to support regulatory approval in major markets, it could significantly impair our access to capital necessary to fund our research and development efforts for our proprietary drug candidates. If we are unable to obtain sufficient capital resources to advance our drug candidate pipeline, it would negatively impact the value of our business, results of operations and financial condition.

We have substantial future capital requirements and there is a risk we may not have access to sufficient capital to meet our current business plan. If we do not receive substantial milestone or royalty payments from our existing collaboration agreements, execute new high value collaborations or other arrangements, or are unable to raise additional capital in one or more financing transactions, we would be unable to continue our current level of investment in research and development.

As of December 31, 2018, we had cash and investments in marketable securities valued at approximately $1.9 billion and had debt of $250.0 million in principal of senior secured notes. Our cash and investments balance at December 31, 2018 reflects $1.85 billion received from BMS. As described above and in Note 10 to our Consolidated Financial Statements, in February 2018, we entered into the BMS Collaboration Agreement under which BMS paid us a non-refundable upfront cash payment of $1.0 billion on April 3, 2018. We also entered into the Share Purchase Agreement under which BMS purchased $850.0 million of shares of our common stock on April 3, 2018. While we believe that our cash position will be sufficient to meet our liquidity requirements through at least the next 12 months, our future capital requirements will depend upon numerous unpredictable factors, including:

- the cost, timing and outcomes of clinical studies and regulatory reviews of our proprietary drug candidates that we have licensed to our collaboration partners — important examples include NKTR-214 in collaboration with BMS and NKTR-358 licensed to Lilly;
- the commercial launch and sales levels of products marketed by our collaboration partners for which we are entitled to royalties and sales milestones — importantly, the level of success in marketing and selling MOVANTIK® by AstraZeneca in the U.S. and ADYNOVATE® by Baxalta (a wholly-owned subsidiary of Takeda) globally, as well as MOVENTIG® (the naloxegol brand name in the EU) by Kirin in the EU;
-

if and when we receive potential milestone payments and royalties from our existing collaborations if the drug candidates subject to those collaborations achieve clinical, regulatory or commercial success;

- the progress, timing, cost and results of our clinical development programs;

- the success, progress, timing and costs of our efforts to implement new collaborations, licenses and other transactions that increase our current net cash, such as the sale of additional royalty interests held by us, term loan or other debt arrangements, and the issuance of securities;
- the number of patients, enrollment criteria, primary and secondary endpoints, and the number of clinical studies required by the regulatory authorities in order to consider for approval our drug candidates and those of our collaboration partners;
- our general and administrative expenses, capital expenditures and other uses of cash; and
- disputes concerning patents, proprietary rights, or license and collaboration agreements that negatively impact our receipt of milestone payments or royalties or require us to make significant payments arising from licenses, settlements, adverse judgments or ongoing royalties.

A significant multi-year capital commitment is required to advance our drug candidates through the various stages of research and development in order to generate sufficient data to enable high value collaboration partnerships with significant upfront payments or to successfully achieve regulatory approval. In the event we do not enter into any new collaboration partnerships with significant upfront payments and we choose to continue our later stage research and development programs, we may need to pursue financing alternatives, including dilutive equity-based financings, such as an offering of convertible debt or common stock, which would dilute the percentage ownership of our current common stockholders and could significantly lower the market value of our common stock. If sufficient capital is not available to us or is not available on commercially reasonable terms, it could require us to delay or reduce one or more of our research and development programs. If we are unable to sufficiently advance our research and development programs, it could substantially impair the value of such programs and result in a material adverse effect on our business, financial condition and results of operations.

The commercial potential of a drug candidate in development is difficult to predict. If the market size for a new drug is significantly smaller than we anticipate, it could significantly and negatively impact our revenue, results of operations and financial condition.

It is very difficult to estimate the commercial potential of product candidates due to important factors such as safety and efficacy compared to other available treatments, including potential generic drug alternatives with similar efficacy profiles, changing standards of care, third party payer reimbursement standards, patient and physician preferences, drug scheduling status, the availability of competitive alternatives that may emerge either during the long drug development process or after commercial introduction, and the availability of generic versions of our product candidates following approval by regulatory authorities based on the expiration of regulatory exclusivity or our inability to prevent generic versions from coming to market by asserting our patents. If due to one or more of these risks the market potential for a drug candidate is lower than we anticipated, it could significantly and negatively impact the commercial potential of the drug candidate, the commercial terms of any collaboration partnership potential for such drug candidate, or if we have already entered into a collaboration for such drug candidate, the revenue potential from royalty and milestone payments could be significantly diminished and this would negatively impact our business, financial condition and results of operations. We also depend on our relationships with other companies for sales and marketing performance and the commercialization of product candidates. Poor performance by these companies, or disputes with these companies, could negatively impact our revenue and financial condition.

If government and private insurance programs do not provide payment or reimbursement for our partnered products or proprietary products, those products will not be widely accepted, which would have a negative impact on our business, results of operations and financial condition.

In both domestic and foreign markets, sales of our partnered and proprietary products that have received regulatory approval will depend in part on market acceptance among physicians and patients, pricing approvals by government authorities and the availability of coverage and payment or reimbursement from third-party payers, such as government programs, including Medicare and Medicaid, managed care providers, private health insurers and other organizations. However, eligibility for coverage does not necessarily signify that a drug candidate will be adequately

reimbursed in all cases or at a rate that covers costs related to research, development, manufacture, sale, and distribution. Third-party payers are increasingly challenging the price and cost effectiveness of medical products and services. Therefore, significant uncertainty exists as to the coverage and pricing approvals for, and the payment or reimbursement status of, newly approved healthcare products.

Moreover, legislation and regulations affecting the pricing of pharmaceuticals may change before regulatory agencies approve our proposed products for marketing and could further limit coverage or pricing approvals for, and reimbursement of, our products from government authorities and third-party payers. For example, Congress passed the Affordable Care Act in 2010 which enacted a number of reforms to expand access to health insurance while also reducing or constraining the growth of healthcare spending, enhancing remedies against fraud and abuse, adding new transparency requirements for healthcare industries, and imposing new taxes

on fees on healthcare industry participants, among other policy reforms. Federal agencies, Congress and state legislatures have continued to show interest in implementing cost containment programs to limit the growth of health care costs, including price controls, restrictions on reimbursement and other fundamental changes to the healthcare delivery system. In addition, in recent years, Congress has enacted various laws seeking to reduce the federal debt level and contain healthcare expenditures, and the Medicare and other healthcare programs are frequently identified as potential targets for spending cuts. New government legislation or regulations related to pricing or other fundamental changes to the healthcare delivery system as well as a government or third-party payer decision not to approve pricing for, or provide adequate coverage or reimbursement of, our products hold the potential to severely limit market opportunities of such products.

If we are unable to establish and maintain collaboration partnerships on attractive commercial terms, our business, results of operations and financial condition could suffer.

We intend to continue to seek partnerships with pharmaceutical and biotechnology partners to fund a portion of our research and development capital requirements. The timing of new collaboration partnerships is difficult to predict due to availability of clinical data, the outcomes from our clinical studies, the number of potential partners that need to complete due diligence and approval processes, the definitive agreement negotiation process and numerous other unpredictable factors that can delay, impede or prevent significant transactions. If we are unable to find suitable partners or negotiate collaboration arrangements with favorable commercial terms with respect to our existing and future drug candidates or the licensing of our intellectual property, or if any arrangements we negotiate, or have negotiated, are terminated, it could have a material adverse effect on our business, financial condition and results of operations.

Our revenue is exclusively derived from our collaboration agreements, which can result in significant fluctuation in our revenue from period to period, and our past revenue is therefore not necessarily indicative of our future revenue.

Our revenue is exclusively derived from our collaboration agreements, from which we receive upfront fees, contract research payments, milestone and other contingent payments based on clinical progress, regulatory progress or net sales achievements, royalties and product sales. Significant variations in the timing of receipt of cash payments and our recognition of revenue can result from payments based on the execution of new collaboration agreements, the timing of clinical outcomes, regulatory approval, commercial launch or the achievement of certain annual sales thresholds. The amount of our revenue derived from collaboration agreements in any given period will depend on a number of unpredictable factors, including our ability to find and maintain suitable collaboration partners, the timing of the negotiation and conclusion of collaboration agreements with such partners, whether and when we or our collaboration partners achieve clinical, regulatory and sales milestones, the timing of regulatory approvals in one or more major markets, reimbursement levels by private and government payers, and the market introduction of new drugs or generic versions of the approved drug, as well as other factors. Our past revenue generated from collaboration agreements is not necessarily indicative of our future revenue. If any of our existing or future collaboration partners fails to develop, obtain regulatory approval for, manufacture or ultimately commercialize any product candidate under our collaboration agreement, our business, financial condition, and results of operations could be materially and adversely affected.

We are a party to numerous collaboration agreements and other significant agreements which contain complex commercial terms that could result in disputes, litigation or indemnification liability that could adversely affect our business, results of operations and financial condition.

We currently derive, and expect to derive in the foreseeable future, substantially all of our revenue from collaboration agreements with biotechnology and pharmaceutical companies. These collaboration agreements contain complex commercial terms, including:

•

clinical development and commercialization obligations that are based on certain commercial reasonableness performance standards that can often be difficult to enforce if disputes arise as to adequacy of our partner's performance;

- research and development performance and reimbursement obligations for our personnel and other resources allocated to partnered drug candidate development programs;
- clinical and commercial manufacturing agreements, some of which are priced on an actual cost basis for products supplied by us to our partners with complicated cost allocation formulas and methodologies;
- intellectual property ownership allocation between us and our partners for improvements and new inventions developed during the course of the collaboration;
- royalties on drug sales based on a number of complex variables, including net sales calculations, geography, scope of patent claim coverage, patent life, generic competitors, bundled pricing and other factors; and
- indemnity obligations for intellectual property infringement, product liability and certain other claims.

We are a party to numerous significant collaboration agreements and other strategic transaction agreements (e.g., financings and asset divestitures) that contain complex representations and warranties, covenants and indemnification obligations. If we are found to have materially breached such agreements, it could subject us to substantial liabilities and harm our financial condition.

From time to time, we are involved in litigation matters involving the interpretation and application of complex terms and conditions of our agreements. One or more disputes may arise or escalate in the future regarding our collaboration agreements, transaction documents, or third-party license agreements that may ultimately result in costly litigation and unfavorable interpretation of contract terms, which would have a material adverse effect on our business, financial condition and results of operations.

If we, or our partners through our collaborations, are not successful in recruiting sales and marketing personnel or in building a sales and marketing infrastructure, we will have difficulty commercializing our products, which would adversely affect our business, results of operations and financial condition.

To the extent we rely on other pharmaceutical or biotechnology companies with established sales, marketing and distribution systems to market our products, we will need to establish and maintain partnership arrangements, and we may not be able to enter into these arrangements on acceptable terms or at all. To the extent that we enter into co-promotion or other arrangements, any revenue we receive will depend upon the efforts of third parties, which may not be successful and over which we have little or no control —important examples of this risk include MOVANTIK® partnered with AstraZeneca and ADYNOVATE® (previously referred to as BAX 855) partnered with Baxalta (a wholly-owned subsidiary of Takeda). In the event that we market our products without a partner, we would be required to build, either internally or through third-party contracts, a sales and marketing organization and infrastructure, which would require a significant investment, and we may not be successful in building this organization and infrastructure in a timely or efficient manner.

If we are unable to create robust sales, marketing and distribution capabilities or to enter into agreements with third parties to perform these functions, we will be unable to commercialize our product candidates successfully.

We currently have no sales or distribution capabilities. To commercialize any of our drugs that receive regulatory approval for commercialization, we must develop robust internal sales, marketing and distribution capabilities, and manage inventory, supply, labeling, storage, record keeping, and advertising and promotion capabilities, which would be expensive and time consuming, or enter into collaboration arrangements with third parties to perform these services. If we decide to market our products directly, we must commit significant financial and managerial resources to develop a marketing and sales force with technical expertise and with supporting distribution, administration and compliance capabilities. Factors that may inhibit our efforts to commercialize our products directly or through partnerships include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to or successfully educate adequate numbers of physicians about the potential benefits associated with the use of, and to subsequently prescribe, our products;
- the lack of complementary products or multiple product pricing arrangements may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating and sustaining an independent sales and marketing organization.

We depend on third parties to conduct the clinical trials for our proprietary product candidates and any failure of those parties to fulfill their obligations could harm our development and commercialization plans.

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct clinical trials for our proprietary product candidates. We rely heavily on these parties for the successful execution of our clinical trials. Though we are ultimately responsible for the results of their activities, many aspects of their activities are beyond our control. For example, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trials, but the independent clinical investigators may prioritize other projects over ours or communicate issues regarding our products to us in an untimely manner. Third parties may not complete activities on schedule or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The early termination of any of our clinical trial arrangements, the failure of third parties to comply with the regulations and requirements governing clinical trials or the failure of third parties to properly conduct our clinical trials could hinder or delay the development, approval and commercialization of our product candidates and would adversely affect our business, results of operations and financial condition.

We expect to continue to incur substantial losses and negative cash flow from operations and may not achieve or sustain profitability in the future.

Due to the recognition of $1,059.8 million of revenue from the upfront payment of our BMS Collaboration Agreement as described in Note 10 to our Consolidated Financial Statements, for the year ended December 31, 2018, we reported net income of $681.3 million. Excluding this revenue item, if and when we achieve profitability depends upon a number of factors, including the timing and recognition of milestone and other contingent payments and royalties received, the timing of revenue under our collaboration agreements, the amount of investments we make in our proprietary product candidates and the regulatory approval and market success of our product candidates. We may not be able to achieve and sustain profitability.

Other factors that will affect whether we achieve and sustain profitability include our ability, alone or together with our partners, to:

- develop drugs utilizing our technologies, either independently or in collaboration with other pharmaceutical or biotechnology companies;
- effectively estimate and manage clinical development costs, particularly the cost of the clinical studies for NKTR-214, NKTR-358, NKTR-262, NKTR-255, and ONZEALD®;
- receive necessary regulatory and marketing approvals;
- maintain or expand manufacturing at necessary levels;
- achieve market acceptance of our partnered products;
- receive royalties on products that have been approved, marketed or submitted for marketing approval with regulatory authorities; and
- maintain sufficient funds to finance our activities.

Significant competition for our polymer conjugate chemistry technology platforms and our partnered and proprietary products and product candidates could make our technologies, products or product candidates obsolete or uncompetitive, which would negatively impact our business, results of operations and financial condition.

Our advanced polymer conjugate chemistry platforms and our partnered and proprietary products and product candidates compete with various pharmaceutical and biotechnology companies. Competitors of our polymer conjugate chemistry technologies include Biogen Inc., Savient Pharmaceuticals, Inc., Dr. Reddy's Laboratories Ltd., SunBio Corporation, Mountain View Pharmaceuticals, Inc., Novo Nordisk A/S (formerly assets held by Neose Technologies, Inc.), and NOF Corporation. Several other chemical, biotechnology and pharmaceutical companies may also be developing polymer conjugation technologies or technologies that have similar impact on target drug molecules. Some of these companies license or provide the technology to other companies, while others are developing the technology for internal use.

There are many competitors for our proprietary product candidates currently in development. For NKTR-214, there are numerous companies engaged in developing immunotherapies to be used alone, or in combination, to treat a wide range of oncology indications targeting both solid and liquid tumors. In particular, we expect to compete with therapies with tumor infiltrating lymphocytes, or TILS, chimeric antigen receptor-expressing T cells, or CAR-T, cytokine-based therapies, and checkpoint inhibitors. Potential competitors in the TIL and CAR-T space include Gilead Sciences, Inc. (through its acquisition of Kite Pharma, Inc.)/NCI, Apeiron Biologics, Philogen S.p.A., IRX Therapeutics, Anaveon AG, Adaptimmune LLC, and Novartis AG, Alkermes plc, Altor Bioscience, Roche, Synthorx, Inc., and Eli Lilly & Co. (through its acquisition of Armo BioSciences) in the cytokine-based therapies space, and Tesaro, Inc., Macrogenics, Inc., Merck, Bristol-Myers Squibb Company, and Roche in the checkpoint inhibitor space. For NKTR 358, there are a number of competitors in various stages of clinical development that are working on programs which are designed to correct the underlying immune system imbalance in the body due to autoimmune disease. In particular, we expect to compete with therapies that could be cytokine-based therapies (Symbiotix, LLC and Tizona Therapeutics), regulatory T cell therapies (Targazyme, Inc., Caladrius BioSciences, Inc., and Tract Therapeutics, Inc.), or IL-2-based-therapies (Amgen Inc.). For MOVANTIK®, there are currently several alternative

therapies used to address opioid-induced constipation (OIC) and opioid-induced bowel dysfunction (OBD), including RELISTOR® Subcutaneous Injection (methylnaltrexone bromide), oral therapy AMITIZA® (lubiprostone), and oral and rectal over-the-counter laxatives and stool softeners such as docusate sodium, senna and milk of magnesia. For ADYNOVATE®, there is substantial competition from Sanofi's Fc fusion protein ELOCTATE™ for Hemophilia A treatment, JIVI® (antihemophilic factor (recombinant) PEGylated-aucl, an extended half-life Factor VIII for Hemophilia A treatment, approved in the U.S. in August 2018, and marketed by Bayer Healthcare, and Novo Nordisk which is expected to launch an extended half-life product in 2020. In addition, technologies other than those based on Fc fusion and polymer conjugation approaches (such as gene therapy approaches being developed by BioMarin Pharmaceutical Inc. and others) are being pursued to treat patients with Hemophilia A. For NKTR-181, there are numerous companies developing pain therapies designed to have less abuse potential primarily through formulation technologies and techniques applied to existing pain therapies. Potential competitors include Acura

Pharmaceuticals, Inc., Cara Therapeutics, Inc., Collegium Pharmaceutical, Inc., Egalet Ltd, Elite Pharmaceuticals, Inc., Endo Health Solutions Inc., KemPharm, Inc., Pfizer/Eli Lilly & Co., Purdue Pharma L.P., and Regeneron Pharmaceuticals, Inc./Teva Pharmaceutical Industries Ltd. For ONZEALD® there are a number of chemotherapies and cancer therapies approved today and in various stages of clinical development for breast cancer, including, but not limited to: Abraxane® (paclitaxel protein-bound particles for injectable suspension (albumin bound)), Xeloda® (capecitabine), Afinitor® (everolimus), Ellence® (epirubicin), Gemzar® (gemcitabine), Halaven® (eribulin), Herceptin® (trastuzumab), Ixempra® (ixabepilone), Navelbine® (vinolrebine), and Taxotere® (docetaxel). Major pharmaceutical or biotechnology companies with approved drugs or drugs in development for breast cancers include, but are not limited to, Bristol-Myers Squibb Company, Eli Lilly & Co., Roche, GlaxoSmithKline plc, Pfizer Inc., Eisai Inc., and Sanofi Aventis S.A. There can be no assurance that we or our partners will successfully develop, obtain regulatory approvals for and commercialize next-generation or new products that will successfully compete with those of our competitors. Many of our competitors have greater financial, research and development, marketing and sales, manufacturing and managerial capabilities. We face competition from these companies not just in product development but also in areas such as recruiting employees, acquiring technologies that might enhance our ability to commercialize products, establishing relationships with certain research and academic institutions, enrolling patients in clinical trials and seeking program partnerships and collaborations with larger pharmaceutical companies. As a result, our competitors may succeed in developing competing technologies, obtaining regulatory approval or gaining market acceptance for products before we do. These developments could make our products or technologies uncompetitive or obsolete.

We may not be able to manage our growth effectively, which could adversely affect our operations and financial performance.

The ability to manage and operate our business as we execute our development and growth strategy will require effective planning. Significant rapid growth could strain our management and internal resources, and other problems may arise that could adversely affect our financial performance. We expect that our efforts to grow will place a significant strain on personnel, management systems, infrastructure and other resources. Our ability to effectively manage future growth will also require us to successfully attract, train, motivate, retain and manage new employees and continue to update and improve our operational, financial and management controls and procedures. If we do not manage our growth effectively, our operations and financial performance could be adversely affected.

Our future depends on the proper management of our current and future business operations and their associated expenses.

Our business strategy requires us to manage our business to provide for the continued development and potential commercialization of our proprietary and partnered drug candidates. Our strategy also calls for us to undertake increased research and development activities and to manage an increasing number of relationships with partners and other third parties, while simultaneously managing the capital necessary to support this strategy. If we are unable to manage effectively our current operations and any growth we may experience, our business, financial condition and results of operations may be adversely affected. If we are unable to effectively manage our expenses, we may find it necessary to reduce our personnel-related costs through reductions in our workforce, which could harm our operations, employee morale and impair our ability to retain and recruit talent. Furthermore, if adequate funds are not available, we may be required to obtain funds through arrangements with partners or other sources that may require us to relinquish rights to certain of our technologies, products or future economic rights that we would not otherwise relinquish or require us to enter into other financing arrangements on unfavorable terms.

Because competition for highly qualified technical personnel is intense, we may not be able to attract and retain the personnel we need to support our operations and growth.

We must attract and retain experts in the areas of clinical testing, manufacturing, research, regulatory and finance, and may need to attract and retain commercial, marketing and distribution experts and develop additional expertise in our

existing personnel. We face intense competition from other biopharmaceutical companies, research and academic institutions and other organizations for qualified personnel. Many of the organizations with which we compete for qualified personnel have greater resources than we have. Because competition for skilled personnel in our industry is intense, companies such as ours sometimes experience high attrition rates with regard to their skilled employees. Further, in making employment decisions, job candidates often consider the value of the stock options they are to receive in connection with their employment. Our equity incentive plan and employee benefit plans may not be effective in motivating or retaining our employees or attracting new employees, and significant volatility in the price of our stock may adversely affect our ability to attract or retain qualified personnel. If we fail to attract new personnel or to retain and motivate our current personnel, our business and future growth prospects could be severely harmed.

We are dependent on our management team and key technical personnel, and the loss of any key manager or employee may impair our ability to develop our products effectively and may harm our business, operating results and financial condition.

Our success largely depends on the continued services of our executive officers and other key personnel. The loss of one or more members of our management team or other key employees could seriously harm our business, operating results and financial

condition. The relationships that our key managers have cultivated within our industry make us particularly dependent upon their continued employment with us. We are also dependent on the continued services of our technical personnel because of the highly technical nature of our products and the regulatory approval process. Because our executive officers and key employees are not obligated to provide us with continued services, they could terminate their employment with us at any time without penalty. We do not have any post-employment noncompetition agreements with any of our employees and do not maintain key person life insurance policies on any of our executive officers or key employees.

The price of our common stock has, and may continue to fluctuate significantly, which could result in substantial losses for investors and securities class action litigation.

Our stock price is volatile. During the year ended December 31, 2018, based on closing prices on The NASDAQ Global Select Market, the closing price of our common stock ranged from $30.43 to $108.44 per share. Plaintiffs' securities litigation firms have recently publicly announced that they are investigating a potential breach of fiduciary duty claim involving our board of directors. Additionally, on October 30, 2018, the Company and its CEO and CFO were named in a putative securities class action entitled, Mulquin v. Nektar Therapeutics et. al., N.D. Cal. Also, on February 13, 2019, and February 18, 2019, shareholder derivative complaints were filed in the U.S. District Court for the District of Delaware naming the CEO, CFO and certain members of Nektar's board. Both the class action and shareholder derivative actions assert, among other things, that for a period beginning at least from November 11, 2017 through October 2, 2018, the Company's stock was inflated due to alleged misrepresentations about the efficacy and safety of NKTR-214. We expect our stock price to remain volatile. A variety of factors may have a significant effect on the market price of our common stock, including the risks described in this section titled "Risk Factors" and the following:

- announcements of data from, or material developments in, our clinical studies and those of our collaboration partners, including data regarding efficacy and safety, delays in clinical development, regulatory approval or commercial launch – in particular, data from clinical studies of NKTR-214 has had a significant impact on our stock price;
- announcements by collaboration partners as to their plans or expectations related to drug candidates and approved drugs in which we have a substantial economic interest;
- announcements regarding terminations or disputes under our collaboration agreements;
- fluctuations in our results of operations;
- developments in patent or other proprietary rights, including intellectual property litigation or entering into intellectual property license agreements and the costs associated with those arrangements;
- announcements of technological innovations or new therapeutic products that may compete with our approved products or products under development;
- announcements of changes in governmental regulation affecting us or our competitors;
- litigation brought against us or third parties to whom we have indemnification obligations;
- public concern as to the safety of drug formulations developed by us or others;
- our financing needs and activities; and
- general market conditions.

At times, our stock price has been volatile even in the absence of significant news or developments. The stock prices of biotechnology companies and securities markets generally have been subject to dramatic price swings in recent years.

We have implemented certain anti-takeover measures, which make it more difficult to acquire us, even though such acquisitions may be beneficial to our stockholders.

Provisions of our certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us, even though such acquisitions may be beneficial to our stockholders. These anti-takeover provisions include:

- establishment of a classified board of directors such that not all members of the board may be elected at one time;
- lack of a provision for cumulative voting in the election of directors, which would otherwise allow less than a majority of stockholders to elect director candidates;
- the ability of our board to authorize the issuance of "blank check" preferred stock to increase the number of outstanding shares and thwart a takeover attempt;

- prohibition on stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of stockholders;
- establishment of advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon by stockholders at stockholder meetings; and
- limitations on who may call a special meeting of stockholders.

Further, provisions of Delaware law relating to business combinations with interested stockholders may discourage, delay or prevent a third party from acquiring us. These provisions may also discourage, delay or prevent a third party from acquiring a large portion of our securities or initiating a tender offer or proxy contest, even if our stockholders might receive a premium for their shares in the acquisition over the then-current market prices. We also have a change of control severance benefit plan, which provides for certain cash severance, stock award acceleration and other benefits in the event our employees are terminated (or, in some cases, resign for specified reasons) following an acquisition. This severance plan could discourage a third party from acquiring us.

The indenture governing our 7.75% senior secured notes imposes significant operating and financial restrictions on us and our subsidiaries that may prevent us from pursuing certain business opportunities and restrict our ability to operate our business.

On October 5, 2015, we issued $250.0 million in aggregate principal amount of 7.75% senior secured notes due October 2020. The indenture governing the senior secured notes contains covenants that restrict our and our subsidiaries' ability to take various actions, including, among other things:

- incur or guarantee additional indebtedness or issue disqualified capital stock or cause certain of our subsidiaries to issue preferred stock;
- pay dividends or distributions, redeem equity interests or subordinated indebtedness or make certain types of investments;
- create or incur liens;
- transfer, sell, lease or otherwise dispose of assets and issue or sell equity interests in certain of our subsidiaries;
- incur restrictions on certain of our subsidiaries' ability to pay dividends or other distributions to the Company or to make intercompany loans, advances or asset transfers;
- enter into transactions with affiliates;
- engage in any business other than businesses which are the same, similar, ancillary or reasonably related to our business as of the date of the indenture; and
- consummate a merger, consolidation, reorganization or business combination, sell, lease, convey or otherwise dispose of all or substantially all of our assets or other change of control transaction.

This indenture also requires us to maintain a minimum cash and investments in marketable securities balance of $60.0 million. We have certain reporting obligations under the indenture regarding cash position and royalty revenue. The indenture specifies a number of events of default, some of which are subject to applicable grace or cure periods, including, among other things, non-payment defaults, covenant defaults, cross-defaults to other material indebtedness, bankruptcy and insolvency defaults, non-payment of material judgments, loss of any material business license, criminal indictment of the Company, and certain civil forfeiture proceedings involving material assets of the Company. Our ability to comply with these covenants will likely be affected by many factors, including events beyond our control, and we may not satisfy those requirements. Our failure to comply with our obligations could result in an event of default under our other indebtedness and the acceleration of our other indebtedness, in whole or in part, could result in an event of default under the indenture governing the senior secured notes.

The restrictions contained in the indenture governing the senior secured notes could also limit our ability to plan for or react to market conditions, meet capital needs or otherwise restrict our activities or business plans and adversely affect our ability to finance our operations, enter into acquisitions or to engage in other business activities that would be in our interest.

Preliminary and interim data from our clinical studies that we announce or publish from time to time are subject to audit and verification procedures that could result in material changes in the final data and may change as more patient data become available.

From time to time, we publish preliminary or interim data from our clinical studies. Preliminary data remain subject to audit confirmation and verification procedures that may result in the final data being materially different from the preliminary data we previously published. Interim data are also subject to the risk that one or more of the clinical outcomes may materially change as

patient enrollment continues and more patient data become available. As a result, preliminary and interim data should be viewed with caution until the final data are available. Material adverse changes in the final data could significantly harm our business prospects.

We may not be able to obtain intellectual property licenses related to the development of our drug candidates on a commercially reasonable basis, if at all.

Numerous pending and issued U.S. and foreign patent rights and other proprietary rights owned by third parties relate to pharmaceutical compositions, methods of preparation and manufacturing, and methods of use and administration. We cannot predict with any certainty which, if any, patent references will be considered relevant to our or our collaboration partners' technology or drug candidates by authorities in the various jurisdictions where such rights exist, nor can we predict with certainty which, if any, of these rights will or may be asserted against us by third parties. In certain cases, we have existing licenses or cross-licenses with third parties; however, the scope and adequacy of these licenses is very uncertain and can change substantially during long development and commercialization cycles for biotechnology and pharmaceutical products. There can be no assurance that we can obtain a license to any technology that we determine we need on reasonable terms, if at all, or that we could develop or otherwise obtain alternate technology. If we are required to enter into a license with a third party, our potential economic benefit for the products subject to the license will be diminished. If a license is not available on commercially reasonable terms or at all, we may be prevented from developing and commercializing the drug, which could significantly harm our business, results of operations, and financial condition.

If any of our pending patent applications do not issue, or are deemed invalid following issuance, we may lose valuable intellectual property protection.

The patent positions of pharmaceutical and biotechnology companies, such as ours, are uncertain and involve complex legal and factual issues. We own more than 275 U.S. and 850 foreign patents and have a number of pending patent applications that cover various aspects of our technologies. There can be no assurance that patents that have issued will be held valid and enforceable in a court of law. Even for patents that are held valid and enforceable, the legal process associated with obtaining such a judgment is time consuming and costly. Additionally, issued patents can be subject to opposition, inter partes review or other proceedings that can result in the revocation of the patent or maintenance of the patent in amended form (and potentially in a form that renders the patent without commercially relevant and/or broad coverage). Further, our competitors may be able to circumvent and otherwise design around our patents. Even if a patent is issued and enforceable, because development and commercialization of pharmaceutical products can be subject to substantial delays, patents may expire early and provide only a short period of protection, if any, following the commercialization of products encompassed by our patents. We may have to participate in post grant or inter parties review before the U.S. Patent and Trademark Office, which could result in a loss of the patent and/or substantial cost to us.

We have filed patent applications, and plan to file additional patent applications, covering various aspects of our PEGylation and advanced polymer conjugate technologies and our proprietary product candidates. There can be no assurance that the patent applications for which we apply would actually issue as patents, or do so with commercially relevant and/or broad coverage. The coverage claimed in a patent application can be significantly reduced before the patent is issued. The scope of our claim coverage can be critical to our ability to enter into licensing transactions with third parties and our right to receive royalties from our collaboration partnerships. Since publication of discoveries in scientific or patent literature often lags behind the date of such discoveries, we cannot be certain that we were the first inventor of inventions covered by our patents or patent applications. In addition, there is no guarantee that we will be the first to file a patent application directed to an invention.

An adverse outcome in any judicial proceeding involving intellectual property, including patents, could subject us to significant liabilities to third parties, require disputed rights to be licensed from or to third parties or require us to cease using the technology in dispute. In those instances where we seek an intellectual property license from another,

we may not be able to obtain the license on a commercially reasonable basis, if at all, thereby raising concerns on our ability to freely commercialize our technologies or products.

We rely on trade secret protection and other unpatented proprietary rights for important proprietary technologies, and any loss of such rights could harm our business, results of operations and financial condition.

We rely on trade secret protection for our confidential and proprietary information. No assurance can be given that others will not independently develop substantially equivalent confidential and proprietary information or otherwise gain access to our trade secrets or disclose such technology, or that we can meaningfully protect our trade secrets. In addition, unpatented proprietary rights, including trade secrets and know-how, can be difficult to protect and may lose their value if they are independently developed by a third party or if their secrecy is lost. Any loss of trade secret protection or other unpatented proprietary rights could harm our business, results of operations and financial condition.

If product liability lawsuits are brought against us, we may incur substantial liabilities.

The manufacture, clinical testing, marketing and sale of medical products involve inherent product liability risks. If product liability costs exceed our product liability insurance coverage, we may incur substantial liabilities that could have a severe negative impact on our financial position. Whether or not we are ultimately successful in any product liability litigation, such litigation would consume substantial amounts of our financial and managerial resources and might result in adverse publicity, all of which would impair our business. Additionally, we may not be able to maintain our clinical trial insurance or product liability insurance at an acceptable cost, if at all, and this insurance may not provide adequate coverage against potential claims or losses.

If we or current or future collaborators or service providers fail to comply with healthcare laws and regulations, we or they could be subject to enforcement actions and civil or criminal penalties.

Although we do not currently have any products on the market, once we begin commercializing our drug candidates, we will be subject to additional healthcare statutory and regulatory requirements and enforcement by the federal and state governments of the jurisdictions in which we conduct our business. Healthcare providers, physicians and third-party payers play a primary role in the recommendation and prescription of any drug candidates for which we obtain marketing approval. Our future arrangements with third-party payers and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our therapeutic candidates for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering, or paying remuneration (a term interpreted broadly to include anything of value, including, for example, gifts, discounts, and credits), directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order, or recommendation of, an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment to Medicare, Medicaid, or other third-party payers that are false or fraudulent, or making a false statement or record material to payment of a false claim or avoiding, decreasing, or concealing an obligation to pay money owed to the federal government;
- provisions of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), which created new federal criminal statutes, referred to as the “HIPAA All-Payer Fraud Prohibition,” that prohibit knowingly and willfully executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- federal transparency laws, including the federal Physician Payment Sunshine Act, which require manufacturers of certain drugs and biologics to track and disclose payments and other transfers of value they make to U.S. physicians and teaching hospitals as well as physician ownership and investment interests in the manufacturer, and that such information is subsequently made publicly available in a searchable format on a CMS website;
- provisions of HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payer, including commercial insurers, state transparency reporting and compliance laws; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and which may not have the same effect, thus complicating compliance efforts.

Ensuring that our future business arrangements with third-parties comply with applicable healthcare laws and regulations could involve substantial costs. If our operations are found to be in violation of any such requirements, we may be subject to penalties, including civil or criminal penalties, monetary damages, the curtailment or restructuring of our operations, or exclusion from participation in government contracting, healthcare reimbursement or other

government programs, including Medicare and Medicaid, any of which could adversely affect financial results. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, these risks cannot be entirely eliminated. Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management's attention from the operation of our business, even if our defense is successful. In addition, achieving and sustaining compliance with applicable laws and regulations may be costly to us in terms of money, time and resources.

We are involved in legal proceedings and may incur substantial litigation costs and liabilities that will adversely affect our business, financial condition and results of operations.

From time to time, third parties have asserted, and may in the future assert, that we or our partners infringe their proprietary rights, such as patents and trade secrets, or have otherwise breached our obligations to them. A third party often bases its assertions on a claim that its patents cover our technology platform or drug candidates or that we have misappropriated its confidential or proprietary information. Similar assertions of infringement could be based on future patents that may issue to third parties. In certain of our agreements with our partners, we are obligated to indemnify and hold harmless our collaboration partners from intellectual property infringement, product liability and certain other claims, which could cause us to incur substantial costs and liability if we are called upon to defend ourselves and our partners against any claims. If a third party obtains injunctive or other equitable relief against us or our partners, they could effectively prevent us, or our partners, from developing or commercializing, or deriving revenue from, certain drugs or drug candidates in the U.S. and abroad. Costs associated with litigation, substantial damage claims, indemnification claims or royalties paid for licenses from third parties could have a material adverse effect on our business, financial condition and results of operations.

We are involved in legal proceedings where we or other third parties are enforcing or seeking intellectual property rights, invalidating or limiting patent rights that have already been allowed or issued, or otherwise asserting proprietary rights through one or more potential legal remedies. For example, we are currently involved in a German litigation proceedings whereby Bayer is seeking co-ownership rights in certain of our patent filings pending at the European Patent Office covering, among other things, PEGylated Factor VIII which we have exclusively licensed to Baxalta (a wholly-owned subsidiary of Takeda). The subject matter of our patent filings in this proceeding relates to Bayer's PEGylated recombinant Factor VIII compound, BAY 94-9027, now commercially marketed as JIVI®. We believe that Bayer's claim to an ownership interest in these patent filings is without merit and are vigorously defending sole and exclusive ownership rights to this intellectual property. In addition, Nektar has filed claims in Germany seeking ownership rights of certain Bayer patent applications. In the U.S., Bayer filed a complaint against Baxalta and Nektar alleging the ADYNOVATE® product infringes a Bayer patent. Although the U.S. court dismissed all of Bayer's claims against Nektar and Nektar was removed as a defendant, a jury found the Bayer patent was valid and infringed, and awarded Bayer damages, the responsibility of which are borne fully by Baxalta. This damages award does not impact our royalties from sales of ADYNOVATE® under our collaboration with Baxalta. In other U.S. proceedings, Nektar and Baxalta filed complaints against Bayer Healthcare alleging Bayer's JIVI® product infringes a total of twelve Nektar patents. In addition, in response to notices AstraZeneca and we received from the generic companies, Apotex (Apotex Inc. and Apotex Corp.) and MSN Laboratories Pvt. Ltd., alerting us that they had filed abbreviated new drug applications (ANDAs) with the FDA to market a generic version of MOVANTIK® ("Paragraph IV Certifications"), AstraZeneca and we together filed patent infringement suits against each of these generic companies in December 2018. In the Paragraph IV Certifications, both generic companies only alleged one patent, U.S. Patent No. 9,012,469, was either invalid, unenforceable and/or not infringed by the manufacture, use or sale of their respective genetic products. At this time, none of the other five Orange Book listed patents associated with MOVANTIK® are being challenged by these generics companies. We are also regularly involved in opposition proceedings at the European Patent Office where third parties seek to invalidate or limit the scope of our allowed European patent applications covering (among other things) our drugs and platform technologies. The cost to us in initiating or defending any litigation or other proceeding, even if resolved in our favor, could be substantial, and litigation would divert our management's attention. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could delay our research and development efforts or result in financial implications either in terms of seeking license arrangements or payment of damages or royalties.

Our internal computer systems, or those of our partners, vendors, CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs or the theft of our confidential information or patient confidential information.

Despite the implementation of security measures, our internal computer systems and those of our partners, vendors, contract research organizations (CROs) and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Such events could cause interruptions of our operations. For instance, the loss of preclinical data or data from any future

clinical trial involving our product candidates could result in delays in our development and regulatory filing efforts and significantly increase our costs. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data, or inappropriate disclosure of confidential or proprietary information of our company or clinical patients, we could suffer or be subject to reputational harm, monetary fines, civil suits, civil penalties or criminal sanctions and requirements to disclose the breach, and other forms of liability, and the development of our product candidates could be delayed.

Global economic conditions may negatively affect us and may magnify certain risks that affect our business.

Our operations and performance have been, and may continue to be, affected by global economic conditions. As a result of global economic conditions, some third-party payers may delay or be unable to satisfy their reimbursement obligations. Job losses or other economic hardships may also affect patients' ability to afford healthcare as a result of increased co-pay or deductible obligations, greater cost sensitivity to existing co-pay or deductible obligations, lost healthcare insurance coverage or for other reasons. We believe

such conditions have led and could continue to lead to reduced demand for our and our collaboration partners' drug products, which could have a material adverse effect on our product sales, business and results of operations.

Further, rising international trade tensions, new or increased tariffs and changes in the U.S. trade policy may increase the costs of materials and products imported into the U.S. and may adversely affect our business. Tariffs, trade restrictions or sanctions imposed by the U.S. or other countries could increase the prices of our and our collaboration partners' drug products, affect our and our collaboration partners' ability to commercialize such drug products, or create adverse tax consequences in the U.S. or other countries. As a result, changes in international trade policy, changes in trade agreements and the imposition of tariffs or sanctions by the U.S. or other countries could materially adversely affect our results of operations and financial condition.

If earthquakes or other catastrophic events strike, our business may be harmed.

Our corporate headquarters, including a substantial portion of our research and development operations, are located in the San Francisco Bay Area, a region known for seismic activity and a potential terrorist target. In addition, we own facilities for the manufacture of products using our advanced polymer conjugate technologies in Huntsville, Alabama and own and lease offices in Hyderabad, India. There are no backup facilities for our manufacturing operations located in Huntsville, Alabama. In the event of an earthquake or other natural disaster, political instability, or terrorist event in any of these locations, our ability to manufacture and supply materials for drug candidates in development and our ability to meet our manufacturing obligations to our customers would be significantly disrupted and our business, results of operations and financial condition would be harmed. Our collaborative partners may also be subject to catastrophic events, such as earthquakes, floods, hurricanes and tornadoes, any of which could harm our business, results of operations and financial condition. We have not undertaken a systematic analysis of the potential consequences to our business, results of operations and financial condition from a major earthquake or other catastrophic event, such as a fire, sustained loss of power, terrorist activity or other disaster, and do not have a recovery plan for such disasters. In addition, our insurance coverage may not be sufficient to compensate us for actual losses from any interruption of our business that may occur.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

California

We lease a 134,356 square foot facility in the Mission Bay Area of San Francisco, California (Mission Bay Facility), under an operating lease which expires in 2030. The Mission Bay Facility is our corporate headquarters and also includes our research and development operations.

In May 2018, we entered into a lease agreement for 135,936 square feet of office space in San Francisco (the Third Street Facility), under an operating lease which expires in 2030. A total of 68,831 square feet was delivered for our use as of the end of 2018, and the remaining space will be delivered in phases during 2019. The Third Street Facility will allow us to expand personnel to support our expanding research and development activities.

Alabama

We currently own facilities consisting of approximately 124,000 square feet in Huntsville, Alabama, which house laboratories as well as administrative, clinical and commercial manufacturing facilities for our PEGylation and advanced polymer conjugate technology operations as well as manufacturing of APIs for early clinical studies.

In June 2018, we completed the sale of one of our buildings located in Huntsville that we had ceased using for research activities.

India

We own a research and development facility consisting of approximately 88,000 square feet, near Hyderabad, India. In addition, we lease approximately 1,600 square feet of office space in Hyderabad, India, under a three-year operating lease that will expire in 2021.

Item 3. Legal Proceedings

From time to time, we are subject to legal proceedings. We are not currently a party to or aware of any proceedings that we believe will have, individually or in the aggregate, a material adverse effect on our business, financial condition or results of operations.

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

Our common stock trades on The NASDAQ Global Select Market under the symbol "NKTR." The table below sets forth the high and low closing sales prices for our common stock as reported on The NASDAQ Global Select Market during the periods indicated.

	High	Low
Year Ended December 31, 2017:		
1st Quarter	$24.20	$11.75
2nd Quarter	22.57	17.54
3rd Quarter	24.00	17.79
4th Quarter	60.50	23.02
Year Ended December 31, 2018:		
1st Quarter	$108.44	$57.40
2nd Quarter	104.45	46.25
3rd Quarter	68.49	46.46
4th Quarter	56.65	30.43

Holders of Record

As of February 22, 2019, there were approximately 164 holders of record of our common stock.

Dividend Policy

We have never declared or paid any cash dividends on our common stock. We currently expect to retain any future earnings for use in the operation and expansion of our business and do not anticipate paying any cash dividends on our common stock in the foreseeable future.

There were no sales of unregistered securities and there were no common stock repurchases made during the year ended December 31, 2018.

Securities Authorized for Issuance Under Equity Compensation Plans

Information regarding our equity compensation plans as of December 31, 2018 is disclosed in Item 12 "Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters" of this Annual Report on Form 10-K and is incorporated herein by reference from our proxy statement for our 2019 annual meeting of stockholders to be filed with the SEC pursuant to Regulation 14A not later than 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

Performance Measurement Comparison

The material in this section is being furnished and shall not be deemed “filed” with the SEC for purposes of Section 18 of the Exchange Act or otherwise subject to the liability of that section, nor shall the material in this section be deemed to be incorporated by reference in any registration statement or other document filed with the SEC under the Securities Act or the Exchange Act, except as otherwise expressly stated in such filing.

The following graph compares, for the five year period ended December 31, 2018, the cumulative total stockholder return (change in stock price plus reinvested dividends) of our common stock with (i) the NASDAQ Composite Index, (ii) the NASDAQ Pharmaceutical Index, (iii) the RDG SmallCap Pharmaceutical Index, (iv) the NASDAQ Biotechnology Index and (v) the RDG SmallCap Biotechnology Index. Measurement points are the last trading day of each of our fiscal years ended December 31, 2014, December 31, 2015, December 31, 2016, December 31, 2017 and December 31, 2018. The graph assumes that $100 was invested on December 31, 2013 in the common stock of the Company, the NASDAQ Composite Index, the Nasdaq Pharmaceutical Index, the RDG SmallCap Pharmaceutical Index, the NASDAQ Biotechnology Index and the RDG SmallCap Biotechnology Index and assumes reinvestment of any dividends. The stock price performance in the graph is not intended to forecast or indicate future stock price performance.

Item 6. Selected Financial Data

SELECTED CONSOLIDATED FINANCIAL INFORMATION

(In thousands, except per share information)

The selected consolidated financial data set forth below should be read together with the consolidated financial statements and related notes, “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” and the other information contained herein.

	Year Ended December 31,				
	2018	2017	2016	2015	2014
Statements of Operations Data:					
Revenue:					
Product sales	$20,774	$32,688	$55,354	$40,155	$25,152
Royalty revenue	41,976	33,527	19,542	2,967	329
Non-cash royalty revenue related to sale of future royalties[1]	33,308	30,531	30,158	22,058	21,937
License, collaboration and other revenue	1,097,265	210,965	60,382	165,604	153,289
Total revenue	1,193,323	307,711	165,436	230,784	200,707
Operating costs and expenses:					
Research and development	399,536	268,461	203,801	182,787	147,734
Other operating expenses[2]	105,855	98,892	74,490	77,368	69,458
Total operating costs and expenses[2]	505,391	367,353	278,291	260,155	217,192
Income (loss) from operations	687,932	(59,642)	(112,855)	(29,371)	(16,485)
Non-cash interest expense on liability related to sale of future royalties[1]	(21,196)	(18,869)	(19,712)	(20,619)	(20,888)
Interest income (expense) and other income (expense), net	15,989	(17,565)	(20,081)	(16,602)	(17,055)
Loss on extinguishment of debt	—	—	—	(14,079)	—
Provision (benefit) for income taxes	1,412	616	876	506	(512)
Net income (loss)	$681,313	$(96,692)	$(153,524)	$(81,177)	$(53,916)
Net income (loss) per share[3]					
Basic	$4.02	$(0.62)	$(1.10)	$(0.61)	$(0.42)
Diluted	$3.78	$(0.62)	$(1.10)	$(0.61)	$(0.42)
Weighted average shares outstanding used in computing net income (loss) per share[3]					
Basic	169,600	155,953	139,596	132,458	126,783
Diluted	180,119	155,953	139,596	132,458	126,783

	As of December 31,				
	2018	2017	2016	2015	2014
Balance Sheet Data:					
Cash, cash equivalents and investments in marketable securities	$1,918,239	$353,220	$389,102	$308,944	$262,824

Working capital	$1,355,685	$270,657	$353,730	$288,805	$224,153
Total assets	$2,150,172	$508,866	$568,871	$498,642	$441,621
Deferred revenue	$24,636	$37,970	$66,239	$83,854	$101,384
Senior secured notes, net	$246,950	$245,207	$243,464	$241,699	$125,000
Liability related to the sale of future royalties[1]	$82,911	$94,655	$105,950	$116,029	$120,471
Other long-term liabilities	$9,990	$5,992	$7,223	$10,813	$18,204
Accumulated deficit	$(1,424,051)	$(2,117,941)	$(2,021,010)	$(1,867,486)	$(1,786,309)
Total stockholders' equity	$1,717,575	$87,828	$88,125	$6,429	$36,332

(1) In February 2012, we sold all of our rights to receive future royalty payments on net sales of UCB's CIMZIA® and Roche's MIRCERA®. As described in Note 7 to our Consolidated Financial Statements, this royalty sale transaction has been recorded as a liability that amortizes over the estimated royalty payment period. As a result of this liability accounting, even though the

royalties from UCB and Roche are remitted directly to the purchaser of these royalty interests starting in the second quarter of 2012, we will continue to record non-cash revenue for these royalties and related non-cash interest expense.

(2) Operating costs and expenses in 2017 includes $16.0 million for the impairment of equipment and related costs resulting from the termination of the Amikacin Inhale development program.

(3) Basic net income (loss) per share is based upon the weighted average number of common shares outstanding. Diluted net income (loss) per share is based on the weighted-average number of shares of common stock outstanding, including potentially dilutive securities.

The following discussion contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those discussed here. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this section as well as factors described in "Part I, Item 1A — Risk Factors."

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

Overview

Strategic Direction of Our Business

Nektar Therapeutics is a research-based biopharmaceutical company focused on discovering and developing innovative new medicines in areas of high unmet medical need. Our research and development pipeline of new investigational drugs includes treatments for cancer, autoimmune disease and chronic pain. We leverage our proprietary and proven chemistry platform to discover and design new drug candidates. These drug candidates utilize our advanced polymer conjugate technology platforms, which are designed to enable the development of new molecular entities that target known mechanisms of action. We continue to make significant investments in building and advancing our pipeline of proprietary drug candidates as we believe that this is the best strategy to build long-term stockholder value.

In immuno-oncology, we are executing a broad clinical development for NKTR-214 in collaboration with BMS as well as other independent development work evaluating NKTR-214 in combination with other agents with potential complementary mechanisms of action. We expect our research and development expense to continue to grow over the next few years as we expand and execute a very broad clinical development program for NKTR-214. For development work within our collaboration development plan, we share development costs based on each party's relative ownership interest in the compounds included in the regimen. For example, we share development costs for NKTR-214 in combination with Opdivo®, BMS 67.5% and Nektar 32.5%, and for NKTR-214 in a triplet combination with Opdivo® and Yervoy®, BMS 78% and Nektar 22%. For costs of producing NKTR-214, however, BMS is responsible for 35% and Nektar is responsible for 65% of costs. Under our collaboration development plan, we have started registration enabling studies in first line melanoma, first line renal cell carcinoma, cisplatin ineligible, locally advanced or metastatic urothelial cancer, second line metastatic non-small cell lung cancer (post-checkpoint inhibitor and chemotherapy), and several more registrational studies in additional tumor types and indications are planned to begin in 2019. Our share of such development costs under the collaboration development plan is limited to an annual cap of $125 million. To the extent this annual cap is exceeded, we will recognize our full share of the research and development expense and BMS will reimburse us for the amount over the annual cap and it will be recorded as a contingent liability. This contingent liability will be paid to BMS only if NKTR-214 is approved and solely by reducing our share of a portion of our net profits following the first commercial sale of NKTR-214. In addition, under the BMS collaboration agreement, we are entitled to $1.43 billion of regulatory and commercial launch milestones, $650 million of which are associated with approval and launch of NKTR-214 in its first indication in the U.S., EU and Japan. As a result, whether and when NKTR-214 is approved in any indication will have a significant impact on our future results of operations and financial condition.

Outside of the collaboration development plan with BMS, we are conducting a broad array of development activities evaluating NKTR-214 in combination with other agents that have potential complementary mechanisms of action. Our strategic objective is to establish NKTR-214 as a key component of many immuno-oncology combination regimens with the potential to enhance the standard of care in multiple oncology settings. On November 6, 2018, we entered into a clinical collaboration with Pfizer to evaluate several combination regimens in multiple cancer settings, including metastatic castration-resistant prostate cancer and squamous cell carcinoma of the head and neck. The combination regimens in this collaboration will evaluate NKTR-214 with avelumab, a human anti-PD-L1 antibody in

development by Merck KGaA, and Pfizer; talazoparib, a poly (ADP-ribose) polymerase (PARP) inhibitor developed by Pfizer; or enzalutamide, an androgen receptor inhibitor in development by Pfizer and Astellas Pharma Inc. In February 2019, we started a Phase 1 dose-escalation study with Takeda to evaluate NKTR-214 with Takeda's investigational medicine, TAK-659, a dual inhibitor of both spleen tyrosine kinase (SYK) and FLT-3, in up to 40 patients with advanced non-hodgkin lymphoma. We are planning a Phase 1 study this year in pancreatic cancer patients in collaboration with BioXcel to evaluate a triplet combination of NKTR-214, BXCL-701 (a small molecule immune-modulator, DPP 8/9), and avelumab being supplied to BioXcel by Pfizer and Merck KGaA. We are also working in collaboration with Vaccibody AS to evaluate in a Phase 1 proof-of-concept study combining NKTR-214 with Vaccibody's personalized cancer neoantigen vaccine. With our non-BMS clinical collaborations for NKTR-214, we generally equally share clinical development costs on a substantially pro-rata basis. We expect to continue to make significant and increasing investments exploring the potential of NKTR-214 with mechanisms of action that we believe are synergistic with NKTR-214 based on emerging scientific findings in cancer biology and preclinical development work.

We are also advancing other molecules in our immuno-oncology portfolio. NKTR-262 is a small molecule agonist that targets toll-like receptors found on innate immune cells in the body. NKTR-262 is designed to stimulate the innate immune system and promote maturation and activation of antigen-presenting cells (APC), such as dendritic cells, which are critical to induce the body's adaptive immunity and create antigen-specific cytotoxic T cells. NKTR-262 is being developed as an intra-tumoral injection in combination with systemic NKTR-214 in order to induce an abscopal response and achieve the goal of complete tumor regression in cancer patients treated with both therapies. The Phase 1 dose-escalation trial is currently ongoing. NKTR-255 is a biologic that targets

the interleukin-15 (IL-15) pathway in order to activate the body's innate and adaptive immunity. Signaling of the IL-15 pathway enhances the survival and function of natural killer (NK) cells and induces survival of both effector and CD8 memory T cells. Preclinical findings suggest NKTR-255 has potential to synergistically combine with antibody dependent cellular toxicity molecules as well as enhance CAR-T therapies. NKTR-255 is currently advancing through preclinical development and we plan to file an IND for NKTR-255 this year and begin a Phase 1 dose-escalation study in multiple myeloma. Over the next several years, we plan to continue to make significant investments to advance our early drug candidate pipeline.

In immunology, we are developing NKTR-358, which is designed to correct the underlying immune system imbalance in the body that occurs in patients with autoimmune disease. NKTR-358 is designed to optimally target the IL-2 receptor complex in order to stimulate proliferation and growth of regulatory T cells. NKTR-358 is being developed as a once or twice monthly self-administered injection for a number of autoimmune diseases. In 2017, we entered into a worldwide license agreement with Eli Lilly and Company (Lilly) to co-develop NKTR-358. We received an initial payment of $150.0 million in September 2017 and are eligible for up to an additional $250.0 million for development and regulatory milestones. We are responsible for completing Phase 1 clinical development and certain drug product development and supply activities. We also share Phase 2 development costs with Lilly, with 75% of those costs borne by Lilly and 25% of the costs borne by us. We will have the option to contribute funding to Phase 3 development on an indication-by-indication basis, ranging from zero to 25% of the Phase 3 development costs. Lilly will be responsible for all costs of global commercialization and we will have an option to co-promote in the U.S. under certain conditions. We have completed the first Phase 1 dose-finding trial of NKTR-358 to evaluate single-ascending doses of NKTR-358 in approximately 100 healthy patients. The study has completed enrollment. The Phase 1 multiple-ascending dose trial to evaluate NKTR-358 in patients with systemic lupus erythematosus (SLE) was initiated in May of 2018 and is currently enrolling patients. Over the next several years, we plan to continue to fund our share of the development costs under this collaboration.

In pain, we have filed the NDA for NKTR-181 for the treatment of chronic low back pain in adult opioid-naïve patients and the FDA's current Prescription Drug User Fee Act target action date is August 29, 2019. NKTR-181 met its primary and key secondary endpoints in the SUMMIT-07 Phase 3 efficacy study in opioid-naïve patients with chronic low back pain and also demonstrated positive results in a pivotal human abuse potential study, long-term safety study, and several other clinical and non-clinical studies included in the NDA data package. If approved, we plan to commercialize NKTR-181 through a separate subsidiary company with one or more partners with commercial infrastructure and expertise and one or more strategic capital partners. Since we have not yet completed our work to establish a commercial launch capability for NTKR-181, there remains substantial risk and uncertainties related to successful and timely completion of establishing this commercialization infrastructure for NKTR-181.

The level of our future research and development investment will depend on a number of trends and uncertainties including clinical outcomes, future studies required to advance programs to regulatory approval, and the economics related to potential future collaborations that may include up-front payments, development funding, milestones, and royalties.

We have historically derived all of our revenue and substantial amounts of operating capital from our collaboration agreements including the BMS collaboration for NKTR-214 that was completed on April 3, 2018, pursuant to which we recognized $1.06 billion in revenue and recorded $790.2 million in additional paid in capital for shares of our common stock issued in the transaction. While in the near-term we continue to expect to generate substantially all of our revenue from collaboration arrangements, including the potential $1.43 billion in development and regulatory milestones under the BMS collaboration, in the medium- to long-term our plan is to generate significant revenue from proprietary products including NKTR-181 and NKTR-214. Since we do not have experience commercializing products or an established commercialization organization, there will be substantial risks and uncertainties in future years as we build commercial, organizational, and operational capabilities.

We also receive royalties and milestone from two approved drugs. We have a collaboration with AstraZeneca for MOVANTIK®, an oral peripherally-acting mu-opioid antagonist for the treatment of opioid-induced constipation in adult patients with non-cancer pain which was approved and subsequently launched in March 2015 and MOVENTIG®, for the treatment of opioid-induced constipation in adult patients who have an inadequate response to laxatives, which was approved by health authorities in the European Union and many other countries beginning in 2014. We have a collaboration with Baxalta (a wholly-owned subsidiary of Takeda) for ADYNOVATE®, that was approved by the FDA in late 2015 for use in adults and adolescents, aged 12 years and older, who have Hemophilia A. ADYNOVI™ was approved by health authorities in Europe in January 2018, and has also been approved in many other countries.

Our business is subject to significant risks, including the risks inherent in our development efforts, the results of our clinical trials, our dependence on the marketing efforts by our collaboration partners, uncertainties associated with obtaining and enforcing patents, the lengthy and expensive regulatory approval process and competition from other products. For a discussion of these and some of the other key risks and uncertainties affecting our business, see Item 1A "Risk Factors" of this Annual Report on Form 10-K.

While the approved drugs and clinical development programs described above are key elements of our future success, we believe it is critically important that we continue to make substantial investments in our earlier-stage drug candidate pipeline. We have

several drug candidates in earlier stage clinical development or being explored in research that we are preparing to advance into the clinic in future years. We are also advancing several other drug candidates in preclinical development in the areas of cancer immunotherapy, immunology, and other therapeutic indications. We believe that our substantial investment in research and development has the potential to create significant value if one or more of our drug candidates demonstrates positive clinical results, receives regulatory approval in one or more major markets and achieves commercial success, drug research and development is an inherently uncertain process and there is a high risk of failure at every stage prior to approval and the timing and outcome of clinical trial results are extremely difficult to predict. Clinical development successes and failures can have a disproportionately positive or negative impact on our scientific and medical prospects, financial condition and prospects, results of operations and market value.

Key Developments and Trends in Liquidity and Capital Resources

We estimate that we have working capital to fund our current business plans through at least March 1, 2020. At December 31, 2018, we had approximately $1.9 billion in cash and investments in marketable securities and had debt of $250.0 million in principal of senior secured notes due in October 2020.

Results of Operations

Years Ended December 31, 2018, 2017, and 2016

Revenue (in thousands, except percentages)

	Year Ended December 31,			Increase/ (Decrease) 2018 vs. 2017	Increase/ (Decrease) 2017 vs. 2016	Percentage Increase/ (Decrease) 2018 vs. 2017	Percentage Increase/ (Decrease) 2017 vs. 2016
	2018	2017	2016				
Product sales	$20,774	$32,688	$55,354	$(11,914)	$(22,666)	(36)%	(41)%
Royalty revenue	41,976	33,527	19,542	8,449	13,985	25 %	72 %
Non cash royalty revenue related to sale of future royalties	33,308	30,531	30,158	2,777	373	9 %	1 %
License, collaboration and other revenue	1,097,265	210,965	60,382	886,300	150,583	> 100 %	> 100 %
Total revenue	$1,193,323	$307,711	$165,436	$885,612	$142,275	> 100 %	86 %

As described in Note 1 to our Consolidated Financial Statements, on January 1, 2018, we adopted Accounting Standards Codification (ASC) 606, Revenue Recognition - Revenue from Contracts with Customers. ASC 606 supersedes the guidance in ASC 605, Revenue Recognition. We adopted ASC 606 on a modified retrospective basis under which we recognized the $12.7 million cumulative effect of adoption as a reduction to opening accumulated deficit. Revenue for the year ended December 31, 2017 and 2016 was recorded under ASC 605, while revenue for the year ended December 31, 2018 was recorded under ASC 606. If we had continued to use ASC 605 during 2018,

revenue would have been $1.18 billion for the year ended December 31, 2018. The primary difference between revenue recognition under ASC 605 and ASC 606 during 2018 relates to the recognition of royalty revenue for certain of our royalty programs. Under ASC 605, we recognized certain of our royalty arrangements on a cash basis, generally one quarter in arrears. Under ASC 606, we recognize royalty revenue and related sales milestones when the underlying sales occur based on our best estimates of sales of the drugs.

Our revenue is derived from our collaboration agreements, under which we may receive product sales revenue, royalties, and license fees, as well as development and sales milestones and other contingent payments. Under ASC 606, revenue is recognized when we transfer promised goods or services to our collaboration partners. The amount of upfront fees received under our license and collaboration agreements allocated to continuing obligations, such as manufacturing and supply commitments, is generally recognized as we deliver products or provide development services. As a result, there may be significant variations in the timing of receipt of cash payments and our recognition of revenue. We make our best estimate of the timing and amount of products and services expected to be required to fulfill our performance obligations. Given the uncertainties in research and development collaborations, significant judgment is required to make these estimates.

Product sales

Product sales include predominantly fixed price manufacturing and supply agreements with our collaboration partners and are the result of firm purchase orders from those partners. The timing of shipments is based solely on the demand and requirements of our collaboration partners and is not ratable throughout the year.

Product sales decreased for the years ended December 31, 2018 and 2017 compared to the years ended December 31, 2017 and 2016, respectively, primarily due to decreased product demand from our collaboration partner Ophthotech related to its drug candidate Fovista®. In the year ended December 31, 2017, we recognized $10.4 million of product sales to Ophthotech based on prior binding purchase commitments. Our agreement with Ophthotech was terminated in October 2017 following Ophthotech's announcement that the third and final Fovista® Phase 3 trial also failed to meet its primary endpoint, following previous failures of the first two studies.

We expect product sales in 2019 to be consistent with 2018. However, if NKTR-181 receives regulatory approval and commercial sales begin in 2019, we expect an increase in product sales in 2019 compared to 2018.

Royalty revenue

We receive royalty revenue from certain of our collaboration partners based on their net sales of commercial products. Royalty revenue increased for the years ended December 31, 2018 and 2017 compared to the years ended December 31, 2017 and 2016, respectively, due primarily to the annual sales growth of ADYNOVATE® /ADYNOVI™ in 2018 and 2017 and MOVANTIK®/ MOVENTIG® in 2017. We expect royalty revenue in 2019 to increase marginally as compared to 2018.

As part of its approval of MOVANTIK®, the FDA required AstraZeneca to perform a post-marketing, observational epidemiological study comparing MOVANTIK® to other treatments of OIC in patients with chronic, non-cancer pain. As a result, the royalty rate payable to us from net sales of MOVANTIK® in the U.S. by AstraZeneca can be reduced by up to two percentage points to fund 33% of the external costs incurred by AstraZeneca to fund such post approval study, subject to a $35.0 million aggregate cap. As of December 31, 2018, our cumulative share of the post-approval study expenses since 2015 has been $1.3 million. Any costs incurred by AstraZeneca can only be recovered by the reduction of the royalty paid to us. In no case can amounts be recovered by the reduction of a contingent payment due from AstraZeneca to us or through a payment from us to AstraZeneca.

Non-cash royalty revenue related to sale of future royalties

In February 2012, we sold all of our rights to receive future royalty payments on CIMZIA® and MIRCERA®. As described in Note 7 to our Consolidated Financial Statements, this royalty sale transaction has been recorded as a liability that amortizes over the estimated royalty payment period. As a result of this liability accounting, even though the royalties from UCB and Roche are remitted directly to the purchaser of these royalty interests, we will continue to record revenue for these royalties. We expect non-cash royalties from net sales of CIMZIA® and MIRCERA® in 2019 to increase marginally compared to 2018.

License, collaboration and other revenue

License, collaboration and other revenue includes the recognition of upfront payments, milestone and other contingent payments received in connection with our license and collaboration agreements and certain research and development activities. The level of license, collaboration and other revenue depends in part upon the estimated recognition period of the upfront payments allocated to continuing performance obligations, the achievement of milestones and other contingent events, the continuation of existing collaborations, the amount of research and development work, and entering into new collaboration agreements, if any.

License, collaboration and other revenue increased for the year ended December 31, 2018 compared to the year ended December 31, 2017 primarily due to the recognition of $1,059.8 million from the BMS Collaboration Agreement as described in Note 10 to our Consolidated Financial Statements. In addition, we recognized a $10.0 million milestone payment received in March 2018 as a result of the marketing authorization of ADYNOVI™ in the EU in January 2018, and we recognized an additional $10.0 million milestone in the fourth quarter of 2018 for annual sales of ADYNOVATE® reaching a certain specified amount. For the years ended December 31, 2018 and 2017, we

recognized $11.6 million and $130.1 million, respectively, of the $150.0 million upfront payment we received in September 2017 from our collaboration agreement with Eli Lilly for NKTR-358 as described in Note 10 to our Consolidated Financial Statements.

License, collaboration and other revenue increased for the year ended December 31, 2017 compared to the year ended December 31, 2016 primarily due to the recognition of revenue from the Lilly collaboration described above. In addition, for the year ended December 31, 2017, we recognized $34.7 million related to the termination of our collaboration agreements with Bayer and Ophthotech as described in Note 10 to our Consolidated Financial Statements. These increases in 2017 were partially offset by the recognition of $28.0 million in March 2016 for our 40% share of the $70.0 million sublicense payment received by AstraZeneca from Kirin for sublicense rights to MOVENTIG® in Europe.

We expect that our license, collaboration and other revenue will decrease significantly in 2019 compared to 2018 as a result of the revenue recognized in 2018 for the BMS Collaboration Agreement.

The timing and future success of our drug development programs and those of our collaboration partners are subject to a number of risks and uncertainties. See “Part I, Item 1A — Risk Factors” for discussion of the risks associated with the complex nature of our collaboration agreements.

Revenue by geography (in thousands)

Revenue by geographic area is based on the headquarters or shipping locations of our partners. The following table sets forth revenue by geographic area:

	Year Ended December 31,		
	2018	2017	2016
United States	$1,090,794	$190,810	$39,147
Europe	102,529	116,901	126,289
Total revenue	$1,193,323	$307,711	$165,436

The increase in revenue attributable to the U.S. for the year ended December 31, 2018 compared to the year ended December 31, 2017 is primarily attributable to the recognition of $1,059.8 million from the BMS Collaboration Agreement as described above. The increase in revenue attributable to the U.S. for the year ended December 31, 2017 compared to the year ended December 31, 2016 is primarily attributable to the recognition of $130.1 million of the $150.0 million upfront payment we received from Lilly, as described above.

Cost of goods sold (in thousands, except percentages)

	Year Ended December 31,			Increase/ (Decrease) 2018 vs. 2017	Increase/ (Decrease) 2017 vs. 2016	Percentage Increase/ (Decrease) 2018 vs. 2017	Percentage Increase/ (Decrease) 2017 vs. 2016
	2018	2017	2016				
Cost of goods sold	$24,412	$30,547	$30,215	$ (6,135)	$ 332	(20)%	1 %
Product gross profit	(3,638)	2,141	25,139	(5,779)	(22,998)	(270)%	(91)%
Product gross margin	(18)%	7 %	45 %				

Our strategy is to manufacture and supply polymer reagents to support our proprietary drug candidates or our third-party collaborators where we have a strategic development and commercialization relationship or where we derive substantial economic benefit. We have elected to only enter into and maintain those manufacturing relationships associated with long-term collaboration agreements which include multiple sources of revenue, which we view holistically and in aggregate. We have a predominantly fixed cost base associated with our manufacturing activities. As a result, our product gross profit and margin are significantly impacted by the mix and volume of products sold in each period.

Cost of goods sold decreased for the year ended December 31, 2018 compared to the year ended December 31, 2017 primarily due to decreased product sales. Cost of goods sold during the year ended December 31, 2017 was consistent

with the year ended December 31, 2016. The decreases in product gross profit and product gross margin during the years ended December 31, 2018 and 2017 compared to the years ended December 31, 2017 and 2016, respectively, are primarily due to decreased product sales as well as a less favorable product mix in 2018 and 2017 compared to 2017 and 2016, respectively. In particular, we have a manufacturing arrangement with a partner that includes a fixed price which is less than the fully burdened manufacturing cost for the reagent, and we expect this situation to continue with this partner in future years. There were more shipments to this partner relative to shipments to other customers during 2018 and 2017 compared to 2017 and 2016, respectively. In addition to product sales from reagent materials supplied to the partner where our sales are less than our fully burdened manufacturing cost, we also receive royalty revenue from this collaboration. In the years ended December 31, 2018, 2017 and 2016, the royalty revenue from this collaboration exceeded the related negative gross profit.

We expect product gross margin to continue to fluctuate in future periods depending on the level and mix of manufacturing orders from our customers. We currently expect product gross margin to be negative in 2019 as a result of the anticipated unfavorable product mix described above. However, if NKTR-181 receives regulatory approval and commercial sales begin, we expect an increase in product sales, which would improve our margin.

Research and development expense (in thousands, except percentages)

	Year Ended December 31,			Increase/ (Decrease)	Increase/ (Decrease)	Percentage Increase/ (Decrease)	Percentage Increase/ (Decrease)
	2018	2017	2016	2018 vs. 2017	2017 vs. 2016	2018 vs. 2017	2017 vs. 2016
Research and development expense	$399,536	$268,461	$203,801	$ 131,075	$ 64,660	49	