

MEDICINOVA INC
Form 10-K
February 13, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

Form 10-K

(Mark One)

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

or

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

For the transition period from. to

Commission file number: 001-33185

MEDICINOVA, INC.

(Exact Name of Registrant as Specified in its Charter)

Delaware
(State or Other Jurisdiction of

33-0927979
(I.R.S. Employer

Incorporation or Organization)

Identification No.)

4275 Executive Square, Suite 300, La Jolla, CA
(Address of Principal Executive Offices)

92037
(Zip Code)

(858) 373-1500

(Registrant's Telephone Number, Including Area Code)

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

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, par value \$0.001 per share	The NASDAQ Stock Market LLC

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

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

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 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 is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

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

<input type="checkbox"/> Large accelerated filer	<input type="checkbox"/> Accelerated filer
<input type="checkbox"/> Non-accelerated filer	<input type="checkbox"/> Smaller reporting company
<input type="checkbox"/> Emerging growth company	

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Securities Exchange Act of 1934). Yes No

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant was approximately \$314,684,033 based on the closing price of the registrant's common stock on the NASDAQ Global Market of \$7.96 per share on June 30, 2018. Shares of common stock held by each executive officer and director and each affiliated entity has been excluded from this calculation. This determination of affiliate status may not be conclusive for other purposes.

The number of outstanding shares of the registrant's common stock, par value \$0.001 per share, as of February 12, 2019 was 42,171,810.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Proxy Statement to be filed with the Securities and Exchange Commission pursuant to Regulation 14A in connection with the registrant's 2019 Annual Meeting of Stockholders, which will be filed subsequent to the date hereof, are incorporated by reference into Part III of this Form 10-K.

MEDICINOVA, INC.

FORM 10-K—ANNUAL REPORT

For the Fiscal Year Ended December 31, 2018

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PART I

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K includes forward-looking statements that involve a number of risks and uncertainties, many of which are beyond our control. The forward-looking statements are contained principally in the sections titled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations," but are also contained elsewhere in this report. Forward-looking statements include all statements that are not historical facts and, in some cases, can be identified by terms such as "believe," "may," "will," "estimate," "continue," "anticipate," "design," "intend," "expect," "could," "plan," "potential," "predict," "seek," "should," "would" or the negative version of these words and similar expressions.

Forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including those described in "Risk Factors" and elsewhere in this report. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Also, forward-looking statements represent our beliefs and assumptions only as of the date of this report. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. You should read this report completely and with the understanding that our actual future results may be materially different from what we expect.

The following factors are among those that may cause actual results to differ materially from our forward-looking statements:

- Inability to raise additional capital if needed;
- Inability to generate revenues from product sales to continue business operations;
- Inability to develop and commercialize our product candidates;
- Failure or delay in completing clinical trials or obtaining FDA or foreign regulatory approval for our product candidates in a timely manner;
- Unsuccessful clinical trials stemming from clinical trial designs, failure to enroll a sufficient number of patients, undesirable side effects and other safety concerns;
- Inability to demonstrate sufficient efficacy of product candidates;
- Reliance on the success of our MN-166 (ibudilast) and MN-001 (tipelukast) product candidates;
- Delays in commencement or completion of clinical trials or suspension or termination of clinical trials;
- Loss of our licensed rights to develop and commercialize a product candidate as a result of the termination of the underlying licensing agreement;
- Competitors may develop products rendering our product candidates obsolete and noncompetitive;
- Inability to successfully attract partners and enter into collaborations on acceptable terms;
- Dependence on third parties to conduct clinical trials and to manufacture product candidates;
- Dependence on third parties to market and distribute products;
- Our product candidates, if approved, may not gain market acceptance or obtain adequate coverage for third party reimbursement;
- Disputes or other developments concerning our intellectual property rights;
- Actual and anticipated fluctuations in our quarterly or annual operating results;
- Price and volume fluctuations in the overall stock markets;
- Litigation or public concern about the safety of our potential products;

International trade or foreign exchange restrictions, increased tariffs, foreign currency exchange;
High quality material for our products may become difficult to obtain or expensive;
Strict government regulations on our business;
Regulations governing the production or marketing of our product candidates;
Loss of, or inability to attract, key personnel; and
Economic, political, foreign exchange and other risks associated with international operations.

Item 1. Business

Overview

We are a biopharmaceutical company focused on developing novel, small molecule therapeutics for the treatment of serious diseases with unmet medical needs and a commercial focus on the United States market. Our current strategy is to focus our development activities on MN-166 (ibudilast) for neurological disorders such as progressive multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), chemotherapy-induced peripheral neuropathy, degenerative cervical myelopathy, glioblastoma, and substance dependence and addiction (e.g., methamphetamine dependence, opioid dependence, and alcohol dependence), and MN-001 (tipelukast) for fibrotic diseases such as nonalcoholic steatohepatitis (NASH) and idiopathic pulmonary fibrosis (IPF). Our pipeline also includes MN-221 (bedoradrine) for the treatment of acute exacerbation of asthma and MN-029 (denibulin) for solid tumor cancers.

MN-166 (ibudilast) is currently in development for several different neurological diseases as described below.

Progressive Multiple Sclerosis: We completed a Phase 2b clinical trial of MN-166 (ibudilast) for the treatment of relapsing multiple sclerosis (MS), in which positive safety and neuroprotective efficacy indicators were observed. The data from this trial indicated that MN-166 (ibudilast) may have potential in the treatment of progressive MS.

We partnered with investigators on a Phase 2b clinical trial of MN-166 (ibudilast) in primary progressive and secondary progressive MS which was conducted by NeuroNEXT and funded by the National Institute of Health's (NIH) National Institute of Neurological Diseases and Stroke (NINDS). This progressive MS trial, known as SPRINT-MS, completed randomization of 255 subjects in 2015, which exceeded the goal of 250 subjects that were planned for participation. In October 2017, we announced the presentation of positive top-line results from the SPRINT-MS Phase 2b clinical trial of MN-166 (ibudilast) in progressive MS. The trial achieved both primary endpoints of whole brain atrophy and safety and tolerability. MN-166 (ibudilast) demonstrated a statistically significant 48% reduction in the rate of progression of whole brain atrophy compared to placebo ($p=0.04$) as measured by MRI analysis using brain parenchymal fraction (BPF) and there was not an increased rate of serious adverse events in the MN-166 (ibudilast) group compared to the placebo group. In February 2018, we announced the presentation of positive clinical efficacy trends from this trial regarding the important secondary endpoint of confirmed disability progression. MN-166 (ibudilast) demonstrated a 26% reduction in the risk of confirmed disability progression compared to placebo (hazard ratio = 0.74), as measured by EDSS (Expanded Disability Status Scale). Results of the SPRINT-MS Phase 2b clinical trial of MN-166 (ibudilast) in progressive MS were published in the New England Journal of Medicine in August 2018.

The United States Food and Drug Administration (FDA) has granted Fast Track designation for the development of MN-166 (ibudilast) for the treatment of patients with progressive MS.

•**Amyotrophic Lateral Sclerosis (ALS):** We initiated a clinical trial of MN-166 (ibudilast) in amyotrophic lateral sclerosis (ALS) in the second half of 2014, and this trial was completed during the second half of 2017. In December 2017, we announced positive top-line results from this trial. The trial achieved the primary endpoint of safety and tolerability. In addition, there was a higher rate of responders on the ALSFRS-R total score in the MN-166 (ibudilast) group compared to the placebo group. The Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) total score measures the functional activity of an ALS subject. In July 2018, we announced data from ad-hoc subgroup analyses in ALS subjects who had either bulbar onset or upper limb onset. In September 2018, we received feedback from the FDA regarding our Phase 3 clinical development plan for MN-166 (ibudilast) in ALS. In January 2019, we received a Notice of Allowance from the U.S. Patent and Trademark Office for a pending patent application which covers the combination of MN-166 (ibudilast) and riluzole for the treatment of ALS and other neurodegenerative diseases.

We have collaborated with Massachusetts General Hospital (MGH) to conduct a clinical trial to study the effects of MN-166 (ibudilast) on reducing brain microglial activation in ALS subjects which can be monitored by a biomarker. This ongoing clinical trial, which we refer to as the ALS / Biomarker study, will

also evaluate several clinical outcomes. In July 2018, we announced that the ALS / Biomarker study was fully enrolled.

The FDA has granted Fast Track designation to MN-166 (ibudilast) for the treatment of ALS as well as Orphan-Drug designation for the treatment of ALS, which will provide seven years of marketing exclusivity if it is approved for ALS. The European Commission also granted Orphan Medicinal Product Designation for MN-166 (ibudilast) for the treatment of ALS.

•**Substance Dependence and Addiction:** In the area of addiction, the National Institute on Drug Abuse (NIDA) funded a Phase 2 clinical trial studying the use of MN-166 (ibudilast) for the treatment of methamphetamine addiction. In collaboration with the University of California, Los Angeles (UCLA), this clinical trial commenced in 2013 and enrollment was completed in September 2017. In March 2018, we announced that this trial did not meet the primary endpoint of methamphetamine abstinence confirmed via urine drug screens during the final two weeks of treatment. In November 2017, we announced a collaboration with Oregon Health & Science University to initiate a biomarker study for evaluating MN-166 (ibudilast) in methamphetamine use disorder and this trial is ongoing.

Investigators at Columbia University and the New York State Psychiatric Institute (NYSPI) previously completed a Phase 1b/2a clinical trial of MN-166 (ibudilast) in opioid withdrawal that was funded by NIDA. Investigators at Columbia University and the NYSPI also conducted a NIDA-funded, Phase 2a clinical trial to evaluate the efficacy of MN-166 (ibudilast) in the treatment of patients addicted to prescription opioids or heroin. In March 2016, we announced that positive findings from the results of this completed study in opioid dependence were presented at the Behavior, Biology and Chemistry: Translational Research in Addiction Meeting.

Researchers at UCLA were granted approval and funding by the National Institute on Alcoholism and Alcohol Abuse (NIAAA) for a clinical trial to evaluate MN-166 (ibudilast) for the treatment of alcohol dependence. This clinical trial has been completed and results were presented at the American College of Neuropsychopharmacology (ACNP)'s 54th Annual Meeting in December 2015. In May 2018, we announced a new NIDA-funded clinical trial of MN-166 (ibudilast) in alcohol dependence and withdrawal in collaboration with researchers at UCLA and this trial is ongoing. In August 2018, we announced a new NIAAA-funded Phase 2b clinical trial of MN-166 (ibudilast) which will evaluate heavy drinking days in subjects with alcohol dependence in collaboration with researchers at UCLA and this trial is ongoing.

•**Chemotherapy-Induced Peripheral Neuropathy:** In March 2018, we announced plans to initiate a clinical trial to evaluate MN-166 (ibudilast) in chemotherapy-induced peripheral neuropathy, which is funded by the University of Sydney Concord Cancer Centre in Australia, and this trial is ongoing.

•**Degenerative Cervical Myelopathy:** In August 2018, we announced plans to initiate a clinical trial of MN-166 (ibudilast) in degenerative cervical myelopathy (DCM) in collaboration with the University of Cambridge. The trial is funded by a grant from the National Institute for Health Research (NIHR) in the United Kingdom (UK) and enrollment is expected to begin in mid-2019.

•**Glioblastoma:** We have initiated clinical development to evaluate MN-166 (ibudilast) for the treatment of glioblastoma. In June 2017, we announced positive results from an animal model study that examined the potential clinical efficacy of MN-166 (ibudilast) for the treatment of glioblastoma. These results were presented at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting. In May 2018, we announced that the Investigational New Drug Application (IND) for MN-166 (ibudilast) for treatment of glioblastoma was accepted and opened with the FDA. In October 2018, we announced that the FDA granted orphan-drug designation to MN-166 (ibudilast) as adjunctive therapy to temozolomide for the treatment of glioblastoma. In January 2019, we announced the initiation of enrollment in a clinical trial of MN-166 (ibudilast) in combination with temozolomide (TMZ, Temodar ®) for the treatment of recurrent glioblastoma at the Dana-Farber Cancer Institute in Boston.

MN-001 (tipelukast) is currently in development for fibrotic diseases including nonalcoholic steatohepatitis (NASH) and idiopathic pulmonary fibrosis (IPF), which are described below.

•Nonalcoholic Steatohepatitis (NASH) and Nonalcoholic Fatty Liver Disease (NAFLD): We announced positive results of MN-001 (tipelukast) in two different NASH mouse models in 2014 and we opened the IND (Investigational New Drug) application for MN-001 (tipelukast) for the treatment of NASH with the FDA in 2015. The FDA subsequently granted Fast Track designation to MN-001 (tipelukast) for the treatment of patients with NASH with fibrosis. We then initiated a clinical trial to investigate MN-001 (tipelukast) for the treatment of hypertriglyceridemia in NASH and NAFLD patients. In April 2018, we announced that we would terminate this trial early after positive results from an interim analysis in which MN-001 (tipelukast) significantly reduced mean serum triglycerides, a primary endpoint. This data was presented at the International Liver Congress 2018, the 53rd annual meeting of the European Association for the Study of the Liver (EASL) in Paris, France in April 2018.

•Idiopathic Pulmonary Fibrosis (IPF): In 2014, we announced positive results of MN-001 (tipelukast) in a mouse model of pulmonary fibrosis. The FDA subsequently granted Orphan-Drug designation to MN-001 (tipelukast) for treatment of IPF which will provide seven years of marketing exclusivity if MN-001 (tipelukast) is approved for IPF. The FDA granted Fast Track designation to MN-001 (tipelukast) for the treatment of patients with IPF in September 2015. We then initiated a Phase 2 clinical trial of MN-001 (tipelukast) to treat IPF and this trial is currently enrolling patients.

We completed a Phase 2 clinical trial of MN-221 (bedoradrine) for the treatment of acute exacerbations of asthma treated in the emergency room and conducted an End-of-Phase 2 meeting with the United States Food and Drug Administration (FDA) in October 2012. In that meeting, the FDA identified the risk/benefit profile of MN-221 (bedoradrine) as a focal point for further development and advised that a clinical outcome, such as a reduction in hospitalizations, would need to be a pivotal trial primary endpoint. We believe the appropriate clinical development for MN-221 (bedoradrine) would involve conducting dose regimen and acute exacerbations of asthma trial design optimization studies prior to commencing pivotal trials. We are working to identify a partner for financial support before further clinical development is commenced.

We have acquired licenses to MN-166 (ibudilast), MN-001 (tipelukast), MN-221 (bedoradrine), and MN-029 (denibulin) for the development of these product candidates. We have pursued development of these product candidates in various indications including progressive MS, ALS, chemotherapy-induced peripheral neuropathy, degenerative cervical myelopathy, glioblastoma, various addictions, NASH and NAFLD, IPF, acute exacerbations of asthma, and solid tumor cancers.

Our Strategy

Our goal is to build a sustainable biopharmaceutical business through the successful development of differentiated products for the treatment of serious diseases with unmet medical needs in high-value therapeutic areas. Key elements of our strategy are as follows:

-

Pursue the development of MN-166 (ibudilast) for multiple potential indications with the support of non-dilutive financings.

We intend to advance our diverse MN-166 (ibudilast) program through a combination of investigator-sponsored clinical trials, trials funded through government grants or other grants, and trials funded by us. In addition to providing drug supply and regulatory support, we have funded portions of some of the consortium-sponsored trials. For example, we contributed financially to the Secondary and Primary Progressive Ibudilast NeuroNEXT Trial in Multiple Sclerosis (SPRINT-MS) Phase 2b clinical trial of MN-166 (ibudilast) for the treatment of progressive MS, which was primarily funded by the NIH. In addition, we contributed financially to the clinical trial of MN-166 (ibudilast) for the treatment of ALS as well as the ongoing ALS / Biomarker study. We intend to pursue additional strategic alliances to help support further clinical development of MN-166 (ibudilast).

Pursue the development of MN-001 (tipelukast) for fibrotic and other diseases.

We intend to advance development of MN-001 (tipelukast) through a variety of means, which may include investigator-sponsored trials with or without grant funding as well as trials funded by us.

◆ Consider strategic partnerships with one or more leading pharmaceutical companies to complete late-stage product development and successfully commercialize our products.

We develop and maintain relationships with pharmaceutical companies that are therapeutic category leaders. Upon completion of proof-of-concept Phase 2 clinical trials, we intend to discuss strategic alliances with leading pharmaceutical companies who seek late-stage product candidates, such as MN-166 (ibudilast), MN-001 (tipelukast), MN-221 (bedoradrine) and MN-029, which could support further clinical development and product commercialization.

Our Product Candidates and Programs

Our product development programs address diseases that we believe are not well served by currently available therapies and represent significant commercial opportunities. We believe that we have product candidates that offer innovative therapeutic approaches that may provide significant advantages relative to current therapies.

Our product acquisitions have focused primarily on product candidates with significant preclinical and early clinical testing data that have been developed by the licensors outside of the United States. We utilize the existing data in preparing Investigational New Drug (INDs) Applications or their foreign equivalents, and in designing and implementing additional preclinical or clinical trials to advance the development programs in the United States or abroad.

Following are the details of our product development programs:

MN-166 (ibudilast)

MN-166 (ibudilast) is a novel, first-in-class, oral, anti-inflammatory and neuroprotective agent. MN-166 (ibudilast) inhibits macrophage migration inhibitory factor (MIF) and certain phosphodiesterases (PDEs). MN-166 (ibudilast) also attenuates activated glia cells, which play a major role in certain neurological conditions. While it has been in use for more than 20 years in Japan and Korea for the treatment of asthma and post-stroke dizziness, we are developing MN-166 (ibudilast) for the treatment of primary progressive and secondary progressive MS, ALS, chemotherapy-induced peripheral neuropathy, degenerative cervical myelopathy, glioblastoma, and substance dependence. We licensed MN-166 (ibudilast) from Kyorin Pharmaceuticals (Kyorin) in 2004.

The FDA has granted Fast Track designations to MN-166 (ibudilast) for three separate indications: the treatment of progressive MS, the treatment of ALS, and the treatment of methamphetamine dependence. Fast track designation is a process designed to facilitate the development and expedite the review of drugs that are intended to treat serious diseases and have the potential to fill an unmet medical need. An important feature of the FDA's Fast Track program is that it emphasizes early and frequent communication between the FDA and the sponsor throughout the entire drug development and review process to improve the efficiency of product development. Accordingly, Fast Track status can potentially lead to a shortened timeline to ultimate drug approval.

The FDA has granted Orphan-Drug designation to MN-166 (ibudilast) for the treatment of ALS, which will provide seven years of marketing exclusivity if it is approved for ALS in the U.S. The European Commission also granted Orphan Medicinal Product Designation for MN-166 (ibudilast) for the treatment of ALS which offers potential benefits including 10 years of marketing exclusivity if it is approved for ALS in Europe. The FDA has also granted Orphan-Drug designation to MN-166 (ibudilast) as adjunctive therapy to temozolomide for the treatment of glioblastoma.

We have filed patent applications for multiple uses of MN-166 (ibudilast) for the treatment of neurological conditions. Some of the patent estate has received allowance in the United States and foreign countries. For example, we have been granted separate U.S. patents that cover the use of MN-166 (ibudilast) for the treatment of progressive MS, for the treatment of ALS, for the treatment of drug addiction or dependence, and for the treatment of neuropathic pain.

Primary and Secondary Progressive Multiple Sclerosis: MS is a complex disease with predominantly unknown etiology and affects approximately 2.3 million people worldwide, according to the National Multiple Sclerosis Society, or NMSS. Also, according to NMSS, approximately 85 percent of people with MS are initially diagnosed with relapsing-remitting MS, or RRMS, and most people who are initially diagnosed with RRMS will eventually transition to secondary progressive MS, or SPMS. About 15 percent of people with MS are diagnosed with primary progressive MS, or PPMS. There is only one approved drug for PPMS and it is administered by intravenous infusion. There are no approved drugs generally considered safe and efficacious for SPMS in the absence of relapses. There is a significant medical need for a safe, effective, and conveniently administered therapy for patients with PPMS and SPMS. MN-166 (ibudilast) may meet these needs.

Based on promising results from a Phase 2 trial in relapsing MS completed in 2008, investigators from NeuroNEXT, a NIH-funded Phase 2 clinical trial network, evaluated MN-166 (ibudilast) in PPMS and SPMS patients in the United States. SPRINT-MS is the name of the Phase 2b, randomized, double-blind, placebo-controlled trial that evaluated the safety and tolerability of MN-166 (ibudilast) (up to 100 mg/day) in PPMS and SPMS patients. Recruitment and enrollment at 28 medical centers in the United States commenced in late 2013 and randomization of 255 subjects was completed in June 2015. In October 2017, we announced the presentation of positive top-line results from the SPRINT-MS Phase 2b clinical trial of MN-166 (ibudilast) in progressive MS. The trial achieved both primary endpoints of whole brain atrophy and safety and tolerability. MN-166 (ibudilast) demonstrated a statistically significant 48% reduction in the rate of progression of whole brain atrophy compared to placebo ($p=0.04$) as measured by MRI analysis using brain parenchymal fraction (BPF) and there was not an increased rate of serious adverse events in the MN-166 (ibudilast) group compared to the placebo group. In February 2018, we announced the presentation of positive clinical efficacy trends from this trial regarding the important secondary endpoint of confirmed disability progression. MN-166 (ibudilast) demonstrated a 26% reduction in the risk of confirmed disability progression compared to placebo (hazard ratio = 0.74), as measured by EDSS (Expanded Disability Status Scale). Results of the SPRINT-MS Phase 2b clinical trial of MN-166 (ibudilast) in progressive MS were published in the *New England Journal of Medicine* in August 2018. We were granted Fast Track designation from the FDA for MN-166 (ibudilast) for the treatment of progressive MS in 2016.

Amyotrophic Lateral Sclerosis (ALS): ALS, also known as Lou Gehrig's disease, is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. The nerves lose the ability to trigger specific muscles, which causes the muscles to become weak. As a result, ALS affects voluntary movement and patients in the later stages of the disease may become totally paralyzed. Average life expectancy of an ALS patient is three years from diagnosis. According to the ALS Association, there are approximately 20,000 ALS patients in the United States and approximately 5,000 people in the United States are diagnosed with ALS each year.

We have worked with Carolinas Neuromuscular/ALS-MDA Center at Carolinas HealthCare System Neurosciences Institute, which has conducted a clinical trial of MN-166 (ibudilast) in ALS. The trial was a randomized, double-blind, placebo-controlled study which included a six-month treatment period followed by a six-month open-label extension. The study evaluated the safety and tolerability of MN-166 (ibudilast) 60 mg/day versus placebo when administered in combination with riluzole in subjects with ALS, as well as several efficacy endpoints. Subject enrollment began in October 2014. In April 2016, we announced that interim efficacy data from a mid-study analysis of the clinical trial of MN-166 (ibudilast) in ALS was presented at the American Academy of Neurology (AAN) 68th Annual Meeting.

In December 2017, we announced positive top-line results from the ALS trial at Carolinas Neuromuscular/ALS-MDA Center. The trial achieved the primary endpoint of safety and tolerability. In addition, there was a higher rate of responders on the ALSFRS-R total score in the MN-166 (ibudilast) group compared to the placebo group. The Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) total score measures the functional activity of an ALS subject. There was also a higher rate of responders on the ALSAQ-5 score in the MN-166 (ibudilast) group compared to the placebo group. The Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-5) score measures the physical mobility, activities of daily living and independence, eating and drinking, communication, and emotional functioning of an ALS subject. In July 2018, we announced data from ad-hoc subgroup analyses in subjects who had either bulbar onset or upper limb onset in the ALS trial at Carolinas Neuromuscular/ALS-MDA Center. In September 2018, we received feedback from the FDA regarding our Phase 3 clinical development plan for MN-166 (ibudilast) in ALS.

In December 2015, we announced that the FDA granted Fast Track designation to MN-166 (ibudilast) for the treatment of patients with ALS. In March 2016, we announced that we received a Notice of Allowance from the United States Patent and Trademark Office (PTO) for a new patent which covers MN-166 (ibudilast) for the treatment of ALS. In October 2016, we announced that the FDA granted Orphan-Drug designation to MN-166 (ibudilast) for the treatment of ALS, which will provide seven years of marketing exclusivity if it is approved for ALS. In December 2016, we announced that the European Commission granted Orphan Medicinal Product Designation for MN-166 (ibudilast) for the treatment of ALS. In January 2019, we received a Notice of Allowance from the U.S. PTO for a pending patent application which covers the combination of MN-166 (ibudilast) and riluzole for the treatment of ALS and other neurodegenerative diseases.

In February 2016, we entered into an agreement to collaborate with Massachusetts General Hospital (MGH) to study the effects of MN-166 (ibudilast) on reducing brain microglial activation in ALS subjects measured by a positron emission tomography (PET) biomarker. This ongoing clinical trial, which we refer to as the ALS / Biomarker study, will also evaluate safety and tolerability as well as several clinical outcomes including ALS functional rating scale (ALSFRS-R), slow vital capacity (SVC), and muscle strength measured by hand-held dynamometry (HHD). In July 2018, we announced that the ALS / Biomarker study was fully enrolled.

Methamphetamine Addiction: Methamphetamine is a central nervous system stimulant drug that is similar in structure to amphetamine. It is a Schedule II drug, meaning that it has high abuse potential and low therapeutic potential. According to the Substance Abuse and Mental Health Services Administration's (SAMHSA) 2017 National Survey on Drug Use and Health, there are approximately 964,000 people aged 12 or older with methamphetamine use disorder (includes those with dependence or abuse) in the United States. According to the Rand Corporation, the estimate of the economic burden in the United States of methamphetamine use, based on the most recent year for which data are available, is approximately \$23.4 billion. Currently, there is no pharmaceutical treatment approved for methamphetamine dependence. Based on non-clinical results of the effects of MN-166 (ibudilast) in an animal model of methamphetamine relapse, investigators at UCLA conducted a Phase 1b clinical trial funded by NIDA to examine the safety and preliminary efficacy of MN-166 (ibudilast) in non-treatment-seeking, methamphetamine-dependent users in an inpatient trial that was completed in 2012. Subsequently, UCLA investigators received NIDA grant funding for a Phase 2 clinical trial to evaluate MN-166 (ibudilast) in methamphetamine-dependent users in an outpatient trial setting that commenced in 2013. In March 2018, we announced that this trial did not meet the primary endpoint of methamphetamine abstinence confirmed via urine drug screens during the final two weeks of treatment. In November 2017, we announced a collaboration with Oregon Health & Science University to initiate a biomarker study to evaluate MN-166 (ibudilast) in methamphetamine use disorder and this study is ongoing. We were granted Fast Track designation from the FDA for MN-166 (ibudilast) for the treatment of methamphetamine dependence in 2013.

Opioid Withdrawal and Dependency: According to the SAMHSA's 2017 National Survey on Drug Use and Health, there are approximately 1.7 million people aged 12 or older with pain reliever use disorder (includes those with dependence or abuse) and approximately 652,000 people aged 12 or older with heroin use disorder (includes those with dependence or abuse) in the United States. Access to prescription opioids has recently become more difficult due to more stringent policies on prescribing opioids. An unintended consequence of this policy is increased use of heroin. Heroin is attractive to prescription opioid addicts because it is less expensive and more accessible than prescription opioids. Heroin poses serious health issues, such as risk of HIV and Hepatitis C infection, overdose and death (Knopf, 2012). There is an urgent, significant unmet medical need for a safe, effective non-addictive, non-opioid therapy for the treatment of prescription opioid and heroin addiction. Investigators at Columbia University and NYSPI previously completed a NIDA-funded, randomized, double-blind, placebo-controlled in-unit Phase 1b/2a clinical trial to evaluate

the ability of MN-166 (ibudilast) to reduce opioid withdrawal symptoms in humans. Subsequently, investigators at Columbia University and NYSPI conducted a NIDA-funded Phase 2a clinical trial of MN-166 (ibudilast) for the treatment of prescription opioid or heroin dependence. In March 2016, we announced that positive findings from the results of this completed study in opioid dependence were presented at the Behavior, Biology and Chemistry: Translational Research in Addiction Meeting.

Alcohol Addiction: According to SAMHSA's 2017 National Survey on Drug Use and Health, there are approximately 14.5 million people aged 12 or older with alcohol use disorder (includes those with dependence or abuse) in the United States. The Centers for Disease Control and Prevention (CDC) reports that excessive alcohol use cost the United States \$249 billion in 2010, the latest year for which complete data are available. Medicines that

have been approved by the FDA to treat alcohol dependence include Antabuse[®], Vivitrol[®], Campral[®] and Revia[®]. However, the search for a safe and effective drug remains elusive due to limited success of these FDA-approved compounds (Witkiewitz et al., 2012). In a non-clinical trial (Bell et al., 2013), MN-166 (ibudilast) was examined in rats and mice and was found to reduce alcohol drinking in alcohol-preferring P rats and high-alcohol drinking (HAD1) rats by 50%, and in mice made dependent on alcohol at doses which had no effect on non-dependent mice. Investigators at UCLA received funding from the NIAAA to conduct a study to evaluate MN-166 (ibudilast) in a randomized, double-blind, placebo-controlled within-subject crossover design to determine the safety, tolerability and initial human laboratory efficacy of MN-166 (ibudilast) in a sample of 24 non-treatment seeking individuals with either alcohol abuse or dependence. The study was initiated in early 2014 and completed enrollment of 24 subjects in June 2015. Results of the alcohol dependence study were presented at the American College of Neuropsychopharmacology (ACNP)'s 54th Annual Meeting in December 2015. MN-166 (ibudilast), but not placebo, significantly decreased basal, daily alcohol craving over the course of the study ($p < 0.05$). MN-166 (ibudilast) did not affect cue- and stress-induced alcohol craving. However, MN-166 (ibudilast) increased positive mood during both the cue reactivity and stress procedures. MN-166 (ibudilast) was safe and well-tolerated during the study. In May 2018, we announced plans to initiate an NIH-funded clinical trial of MN-166 (ibudilast) in alcohol dependence and withdrawal in collaboration with researchers at UCLA. This clinical trial, which is currently ongoing, is evaluating whether MN-166 (ibudilast) reduces basal level negative affect during abstinence, and in doing so, will interfere with alcohol-induced blunting of negative affectivity. In August 2018, we announced a new NIAAA-funded Phase 2b clinical trial of MN-166 (ibudilast) in alcohol dependence in collaboration with researchers at UCLA. This clinical trial, which is currently ongoing, is evaluating whether MN-166 (ibudilast) will decrease the percentage of heavy drinking days (defined as ≥ 5 drinks for men and ≥ 4 drinks for women), as compared to placebo, over the course of the 12-week trial.

Chemotherapy-Induced Peripheral Neuropathy: Peripheral neuropathy is a set of symptoms caused by damage to peripheral nerves, the nerves that are away from the brain and spinal cord. Some of the chemotherapy and other drugs used to treat cancer can damage peripheral nerves which carry sensations to the brain and control the movement of the arms and legs. This damage results in chemotherapy-induced peripheral neuropathy (CIPN) which can be a disabling side effect of cancer treatment. Common symptoms of CIPN include pain, burning, tingling, loss of feeling, coordination and balance problems, muscle weakness, trouble swallowing and passing urine, constipation, and blood pressure changes. Severe CIPN may require chemotherapy dose reduction or cessation. According to a meta-analysis which included more than 4,000 patients, CIPN prevalence was 68% when measured in the first month after chemotherapy, 60% at 3 months, and 30% at 6 months or more ("Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis," Seretny M et al 2014). In March 2018, we announced plans to initiate a clinical trial to evaluate MN-166 (ibudilast) in chemotherapy-induced peripheral neuropathy which is funded by the University of Sydney Concord Cancer Centre in Australia. This is an ongoing, open-label, sequential cross-over pilot study assessing acute neurotoxicity, chemotherapy-induced peripheral neuropathy, and drug interactions of MN-166 (ibudilast) in patients with metastatic gastrointestinal cancer (colorectal cancer and upper gastrointestinal cancers) who are receiving oxaliplatin.

Degenerative Cervical Myelopathy: Degenerative cervical myelopathy (DCM), also known as cervical spondylotic myelopathy, involves spinal cord dysfunction from compression in the neck. Degenerative cervical myelopathy is the most common form of spinal cord impairment in adults and results in disability and reduced quality of life. Patients report neurological symptoms such as pain and numbness in limbs, poor coordination, imbalance, and bladder problems. According to the American Association of Neurological Surgeons, more than 200,000 cervical procedures are performed each year to relieve compression on the spinal cord or nerve roots. There are no pharmaceuticals approved for the treatment of DCM. In August 2018, we announced plans to initiate a clinical trial of MN-166 (ibudilast) in DCM in collaboration with the University of Cambridge. The trial, which is funded by a grant from the

National Institute for Health Research (NIHR) in the United Kingdom (UK), will evaluate MN-166 (ibudilast) as an adjuvant treatment for DCM following spinal surgery to determine whether MN-166 (ibudilast) is more effective than placebo in improving outcomes after spinal surgery. The primary endpoint is the modified Japanese Orthopaedic Association (mJOA) Score, which evaluates motor dysfunction in upper and lower extremities, loss of sensation, and bladder sphincter dysfunction, at 6 months after surgery.

Glioblastoma: According to the American Association of Neurological Surgeons, glioblastoma is an aggressive brain tumor that develops from glial cells (astrocytes and oligodendrocytes), grows rapidly, and commonly spreads

into nearby brain tissue. The American Brain Tumor Association reports that glioblastomas represent about 15% of all primary brain tumors and 56% of all gliomas. Glioblastoma has the highest number of cases of all malignant tumors, with an estimated 12,760 new cases predicted for 2018. Median survival is about 14.6 months for adults with more aggressive glioblastoma treated with temozolomide and radiation therapy. In June 2017, we announced positive results from an animal model study that examined the potential clinical efficacy of MN-166 (ibudilast) for the treatment of glioblastoma which were presented at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting. Results of the glioblastoma mouse model study showed that median survival was higher in the group that received combination treatment with MN-166 (ibudilast) plus temozolomide compared to the group that received temozolomide alone. In May 2018, we announced that the Investigational New Drug Application (IND) for MN-166 (ibudilast) for treatment of glioblastoma was accepted and opened with the FDA. We were also informed by the FDA that the proposed clinical investigation of MN-166 (ibudilast) in combination with temozolomide for treatment of glioblastoma may proceed. In October 2018, we announced that the FDA granted orphan-drug designation to MN-166 (ibudilast) as adjunctive therapy to temozolomide for the treatment of glioblastoma. In January 2019, we announced the initiation of enrollment in a clinical trial of MN-166 (ibudilast) in combination with temozolomide (TMZ, Temodar ®) for the treatment of recurrent glioblastoma at the Dana-Farber Cancer Institute in Boston.

MN-221 (bedoradrine)

MN-221 (bedoradrine) is a novel, highly selective β_2 -adrenergic receptor agonist which has been developed for the treatment of acute exacerbations of asthma. We licensed MN-221 (bedoradrine) from Kissei Pharmaceutical Co., Ltd. (Kissei) in February 2004. Current inhaled beta-agonist treatments for asthma exacerbations are limited by bronchoconstriction or insufficient airflow due to inflammation and airway constriction, which reduces the amount of inhaled drug that can get into the lungs. In addition, the amount of inhaled treatments a patient can tolerate is limited due to the potential for cardiovascular side effects (e.g. increased heart rate).

MN-221 (bedoradrine) is designed to treat acute exacerbations of asthma via intravenous (i.v.) infusion, bypassing constricted airways to deliver the drug to the lungs. Preclinical studies showed MN-221 (bedoradrine) to have a high affinity for the β_2 -adrenergic receptor, found primarily in the lungs, and a much lower affinity for the β_1 -adrenergic receptor found primarily in cardiac tissue. MN-221 (bedoradrine)'s improved delivery to the lungs and its cardiac safety profile has potential to help fill an unmet need for patients with acute exacerbations of asthma, helping them to breathe easier and avoid a costly hospital stay.

Acute Exacerbation of Asthma: According to the most recent data available from the United States National Center for Health Statistics, there were 1.74 million emergency department visits due to asthma in 2015, 439,000 hospitalizations due to asthma in 2010 (the most recent year for which data is available), and 3,518 deaths due to asthma in 2016. According to the United States National Heart, Lung and Blood Institute, the direct costs associated with hospital care due to asthma were estimated at \$5.5 billion in the United States in 2010 (the most recent year for which data is available).

We completed a Phase 2b randomized, double-blind, placebo-controlled clinical trial (N=175) evaluating MN-221 (bedoradrine) in patients with acute exacerbations of asthma in the emergency department setting. MN-221 (bedoradrine) did not statistically meet the primary endpoint, improvement in FEV₁ (Forced Expiratory Volume in One Second) compared to placebo. However, MN-221 (bedoradrine) treatment demonstrated statistically significant improvements in endpoints associated with Dyspnea Index scores. MN-221 (bedoradrine) treatment significantly increased (improved) the change from baseline in Dyspnea Index scale score over Hours 0-3 compared to placebo (based on AUC [0-3 hr], p = 0.0405), significantly increased the change from baseline in Dyspnea Index scale scores at Hour 2 compared to placebo (based on mean score, p = 0.0042), and significantly increased the percentage of subjects who had improvement in the Dyspnea Index score ≥ 1 point at Hour 2 compared to placebo (p = 0.0323). A post-hoc analysis was performed to evaluate the Treatment Failure rate defined as the number of subjects who were either hospitalized or who returned to the emergency department during the course of the study. In subjects who received corticosteroids greater than 3 hours prior to study drug infusion, the number of treatment failures was significantly greater in the placebo group (74%) versus the MN-221 (bedoradrine) group (43%), p=0.0489. No safety/tolerability issues of clinical significance were observed.

In October 2012, we met with the FDA to review future development of this product candidate. The FDA identified the risk/benefit profile of MN-221 (bedoradrine) as a focal point for further development and advised that a clinical outcome, such as a reduction in hospitalizations, would need to be a pivotal trial primary endpoint. We have decided that any future MN-221 (bedoradrine) development will be designed based on the feedback received from the FDA and that any future MN-221 (bedoradrine) clinical trial development for asthma will be partner-dependent from a funding perspective.

MN-001 (tipelukast)

MN-001 (tipelukast) is a novel, orally bioavailable small molecule compound which exerts its effects through several mechanisms to produce its anti-fibrotic and anti-inflammatory activity in preclinical models, including leukotriene (LT) receptor antagonism, inhibition of PDEs (mainly 3 and 4), and inhibition of 5-lipoxygenase (5-LO). The 5-LO/LT pathway has been postulated as a pathogenic factor in fibrosis development and the inhibitory effect of MN-001 (tipelukast) on 5-LO and the 5-LO/LT pathway is considered to be a novel approach to treat fibrosis. MN-001 (tipelukast) has been shown to down-regulate expression of genes that promote fibrosis including LOXL2, Collagen Type 1 and TIMP-1. MN-001 (tipelukast) has also been shown to down-regulate expression of genes that promote inflammation including CCR2 and MCP-1. In addition, histopathological data shows that MN-001 (tipelukast) reduces fibrosis in multiple animal models. We licensed MN-001 (tipelukast) from Kyorin in 2002. In addition to granting MN-001 (tipelukast) Fast Track designation for the treatment of NASH with fibrosis, the FDA has also granted MN-001 (tipelukast) Orphan-Drug designation and Fast Track designation for treatment of idiopathic pulmonary fibrosis (IPF).

Previously, we evaluated MN-001 (tipelukast) for its potential clinical efficacy in asthma and completed a Phase 2 study in asthma with positive results. MN-001 (tipelukast) has been exposed to more than 600 subjects and is considered generally safe and well-tolerated.

Nonalcoholic Steatohepatitis (NASH) and Nonalcoholic Fatty Liver Disease (NAFLD): Nonalcoholic steatohepatitis (NASH) is a condition in which there is fat in the liver along with inflammation and damage to liver cells. NASH is a common liver disease that resembles alcoholic liver disease but occurs in people who drink little or no alcohol. According to the United States National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NASH prevalence in adults in the United States is 3-12%, and an additional 30-40% of adult Americans have nonalcoholic fatty liver disease (NAFLD). The underlying cause of NASH is unclear, but it most often occurs in persons who are middle-aged and overweight or obese. Many patients with NASH have elevated serum lipids, diabetes or pre-diabetes. Progression of NASH can lead to liver cirrhosis. Liver transplantation is the only treatment for advanced cirrhosis with liver failure. At this time, there is no pharmaceutical treatment approved for NASH.

We completed a pre-clinical study evaluating the potential clinical efficacy of MN-001 (tipelukast) for the treatment of NASH. MN-001 (tipelukast) administered orally once daily (10, 30, and 100 mg/kg for three weeks) was evaluated in the STAM™ (NASH-HCC) mouse model of NASH, as measured by liver biochemistry and histopathology, NAFLD activity score (NAS), and percent of fibrosis and gene expression. MN-001 (tipelukast), in a dose-dependent manner, significantly reduced fibrosis area compared with placebo ($p < 0.01$) as demonstrated by a reduction in liver

hydroxyproline content, supporting the anti-fibrotic properties of MN-001 (tipelukast). MN-001 (tipelukast) significantly improved NAS ($p < 0.01$). MN-001 (tipelukast), in this animal model, improved NASH pathology by inhibiting hepatocyte damage ($p < 0.01$) and ballooning ($p < 0.01$). At the same time, MN-001 (tipelukast) was also shown to reduce certain gene expression levels in the liver, thus implying that MN-001 (tipelukast) reduces the formation of fibrosis in the NASH model. We completed a second preclinical study that examined the potential clinical efficacy of MN-001 (tipelukast) for the treatment of advanced NASH. This study used mice in more advanced stages of NASH as compared to the first study of MN-001 (tipelukast) in a NASH mouse model. MN-001 (tipelukast) showed anti-NASH and anti-fibrotic effects in the advanced NASH mouse model. NAFLD activity score (NAS) was significantly reduced in the MN-001 (tipelukast)-treated group compared to the non-treated group ($p < 0.001$). The reduction was observed consistently in all NAS components including hepatocyte ballooning score ($p < 0.001$), lobular inflammation score ($p < 0.01$), and steatosis score ($p < 0.05$). Percent fibrosis area was also reduced in the MN-001 (tipelukast) treated group ($p < 0.01$). In addition, alpha-SMA-positive staining area was significantly reduced in the MN-001 (tipelukast)-treated group ($p < 0.001$). Collectively, these results provided compelling evidence that MN-001 (tipelukast) warrants further evaluation for the treatment of NASH in humans. We have an open IND and the FDA has approved two different Phase 2 clinical trial protocols for

MN-001 (tipelukast) for the treatment of NASH in the United States. In April 2018, we announced that we would terminate early the Phase 2 clinical trial of MN-001 (tipelukast) in NASH and NAFLD patients with hypertriglyceridemia based on the significant positive results from an interim analysis. This data was presented at the International Liver Congress 2018, the 53rd annual meeting of the European Association for the Study of the Liver (EASL) in Paris, France in April 2018. MN-001 (tipelukast) significantly reduced mean serum triglycerides by 135.7 mg/dL, resulting in a 41.3% reduction ($p=0.02$), which includes the data from the 15 subjects who completed 8 weeks of treatment. Excluding one outlier with an extremely high triglyceride level of 1288 mg/dL before treatment, MN-001 (tipelukast) significantly reduced mean serum triglycerides by 74.9 mg/dL, resulting in a 28.8% reduction ($p=0.00006$). The FDA has granted Fast Track designation to MN-001 (tipelukast) for the treatment of patients with NASH with fibrosis.

Idiopathic Pulmonary Fibrosis (IPF): Pulmonary fibrosis (PF) is a progressive disease characterized by scarring of the lungs that thickens the lining, causing an irreversible loss of the tissue's ability to transport oxygen. The causes of PF vary and can be due to anti-cancer drug therapy or exposure to chemicals. Idiopathic pulmonary fibrosis (IPF) is one type of PF without a clear cause. According to the Pulmonary Fibrosis Foundation, IPF affects between 132,000 – 200,000 people in the United States, and an estimated 50,000 new cases are diagnosed annually. The prognosis for IPF is poor with a median survival of only two to three years following diagnosis and more than two-thirds of IPF patients die within five years.

We completed a pre-clinical study evaluating the potential clinical efficacy of MN-001 (tipelukast) for the treatment of pulmonary fibrosis. MN-001 (tipelukast), which was administered orally once daily (30, 100 and 300 mg/kg) for two weeks, was evaluated in a mouse model of bleomycin-induced pulmonary fibrosis (PF) as measured by CT evaluation of lung density, degree of pulmonary fibrosis using the Ashcroft score based on histopathological staining, and hydroxyproline content, which is an indicator of fibrosis or storage of collagen in tissue. MN-001 (tipelukast) significantly decreased the Ashcroft score compared to Vehicle group ($p<0.05$) after two weeks of treatment and MN-001 (tipelukast) reduced lung density when compared to the Vehicle-treated group. Moreover, lung hydroxyproline content was significantly reduced compared to the Vehicle group ($p<0.01$). These results show that treatment with MN-001 (tipelukast) has significant anti-fibrogenic effects in bleomycin-induced pulmonary fibrosis in mice. We have an open IND and the FDA approved a Phase 2 clinical trial protocol for MN-001 (tipelukast) for the treatment of IPF in the United States. A Phase 2 clinical trial of MN-001 (tipelukast) in IPF is currently ongoing at Penn State. The FDA has granted Orphan-Drug designation to MN-001 (tipelukast) for treatment of IPF. Orphan-Drug designation will provide seven years of marketing exclusivity for MN-001 (tipelukast) for the treatment of IPF if it is approved for this indication. The FDA has also granted Fast Track designation to MN-001 (tipelukast) for the treatment of patients with IPF.

MN-029 (denibulin)

MN-029 (denibulin) is a novel tubulin binding agent (TBA) under development for the treatment of solid tumors. It exerts its activity through reversible inhibition of tubulin polymerization resulting in disruption of the cell cytoskeleton, which causes the cancer cells to deform in shape and ultimately leads to extensive central necrosis of the solid tumor. We licensed MN-029 (denibulin) from Angiogene Pharmaceuticals, Ltd. (Angiogene) in 2002.

Several preclinical pharmacology studies have assessed the mechanism of action and anti-tumor activity of MN-029 (denibulin) in vivo in rodent models of breast adenocarcinoma, colon carcinoma, lung carcinoma and KHT sarcoma. In these studies, MN-029 (denibulin) damaged poorly formed tumor blood vessels by weakening tumor blood vessel walls and causing leakage, clotting and eventual vascular shutdown within the tumor, in addition to the direct effect over tumor cells. These studies suggest that MN-029 (denibulin) acts quickly and is rapidly cleared from the body, which may reduce the potential for some adverse effects commonly associated with chemotherapy. Shutdown of tumor blood flow in tumor models was confirmed through the use of dynamic contrast-enhanced magnetic resonance imaging. In two Phase I clinical studies we conducted, MN-029 (denibulin) was well-tolerated at doses that reduced tumor blood flow.

The first Phase 1 trial determined the safety, tolerability, and maximum tolerated dose (MTD) level of single doses of MN-029 (denibulin) given every three weeks in 34 subjects with refractory cancer. The MTD was determined to be 180 mg/m² and appeared to be safe as a single i.v. dose administered every three weeks for as many as 25 cycles. There were no clinically significant changes in routine laboratory assessments, vital signs, or

ECG monitoring. The most commonly reported adverse events (AEs) were similar to other chemotherapies—vomiting, nausea, diarrhea, and fatigue. There were a total of nine serious adverse events (SAEs) and study discontinuations due to AEs. In a preliminary evaluation of anti-tumor activity, no patient had a complete response or partial response; however stable disease was seen in 12 patients. MN-029 (denibulin) had a desired vascular effect in seven of 11 patients that were administered drug at dose levels of ≥ 120 mg/m². Nine patients continued into extended cycles of treatment.

The second Phase 1 study was conducted to determine the safety, tolerability and MTD of single doses of MN-029 (denibulin) given every seven days for a total of three doses (Days 1, 8 and 15), followed by 13-day recovery (Days 16-28) in subjects with advanced/metastatic solid tumor cancer. Subjects who tolerated treatment with MN-029 (denibulin) could receive additional cycles. All 20 subjects reported at least one AE related to study drug. The most common AEs considered related to study drug were vomiting, nausea, arthralgia and headache. There were no clinically significant changes in routine laboratory assessments, vital signs or ECG monitoring. There was one SAE considered unrelated to study drug. Consistent with the previous Phase 1 trial, MN-029 (denibulin) up to dose levels of 180 mg/m² appeared to be safe and well tolerated. One subject had a partial response which lasted for 74 days. Stable disease was observed in seven subjects. The results suggested an effect of MN-029 (denibulin) on vascular perfusion; however, a larger sample size is warranted.

In January 2014, we were granted a new patent from the United States Patent and Trademark Office which covers MN-029 (denibulin) di-hydrochloride. The patent, which will expire no earlier than July 2032, has claims that cover a compound, pharmaceutical composition and method of treating certain cell proliferation diseases, including solid tumors, based on denibulin di-hydrochloride. We have filed patent applications based on this U.S. patent in certain foreign countries, and most of them have been granted.

Table 1 Product Candidates and Programs—MN-166 (ibudilast)

Indication	Clinical Study	Principal Investigator /Institution /Funding Agency(s)	Status
Primary Progressive and Secondary Progressive Multiple Sclerosis	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Activity of Ibudilast (MN-166 (ibudilast)) in Subjects with Progressive Multiple Sclerosis	Robert J. Fox, M.D., M.S., FAAN Cleveland Clinic National Institute on Neurological Diseases and Stroke MediciNova, Inc.	Completed

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Amyotrophic Lateral Sclerosis (ALS)	A Single-Center, Randomized, Double-Blind, Placebo-Controlled, Six Month Clinical Trial Followed by an Open-Label Extension to Evaluate the Safety, Tolerability, and Clinical Endpoint Responsiveness of Ibudilast (MN-166 (ibudilast)) in Subjects with Amyotrophic Lateral Sclerosis (ALS)	Benjamin R. Brooks, M.D. Carolinas HealthCare System Neurosciences Institute MediciNova, Inc.	Completed
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ALS / Biomarker	A Biomarker Study to Evaluate MN-166 (ibudilast) (Ibudilast) in Subjects with Amyotrophic Lateral Sclerosis (ALS)	Nazem Atassi, M.D., MMSc Massachusetts General Hospital MediciNova, Inc.	Ongoing
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Degenerative Cervical Myelopathy	A multi-centre, double-blind, randomised, placebo-controlled trial assessing the efficacy of Ibudilast as an adjuvant treatment to decompressive surgery for degenerative cervical myelopathy	Dr. Mark Kotter University of Cambridge National Institute for Health Research (NIHR) in the U.K.	Enrollment expected to begin in mid-2019
Chemotherapy-Induced Peripheral Neuropathy	A pilot study evaluating the impact of ibudilast on prevention of chemotherapy-induced acute neurotoxicity and evaluating pharmacokinetics with oxaliplatin in gastro-intestinal cancer patients receiving oxaliplatin	Dr. Janette Vardy University of Sydney Concord Cancer Centre in Australia	Ongoing
Glioblastoma	Phase 1b/2a Multi-center, Open-label, Dose Escalation Study to Evaluate the Safety, Tolerability and Efficacy of MN-166 (ibudilast) and Temozolomide Combination Treatment in Patients With Recurrent Glioblastoma	Patrick Y. Wen, M.D., Dana-Farber Cancer Institute Kerrie McDonald, Ph.D., University of New South Wales MediciNova, Inc.	Ongoing
Substance Dependence / Addiction:			
Methamphetamine Dependence	Randomized Trial of Ibudilast for Methamphetamine Dependence	Keith Heinzerling, M.D., MPH UCLA National Institute on Drug Abuse	Completed
Methamphetamine Dependence / Biomarker	Effect of Ibudilast on Neuroinflammation in Methamphetamine Users	Milky Kohno, Ph.D. and William Hoffman, M.D., Ph.D. Oregon Health & Science Univ.	Ongoing

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Opioid Dependence	Effects of Ibudilast (MN-166 (ibudilast)), a Glial Activation Inhibitor, on Oxycodone Self-Administration in Opioid Abusers	Sandra D. Comer, Ph.D. Columbia University/NYSPI National Institute on Drug Abuse	Completed
Alcohol Dependence	Development of Ibudilast (MN-166 (ibudilast)) as a Novel Treatment for Alcoholism	MediciNova, Inc. Lara Ray, Ph.D. UCLA National Institute on Alcohol Abuse and Alcoholism	Completed

Alcohol Dependence and Withdrawal	Ibutilast (MN-166 (ibutilast)) and Withdrawal-Related Dysphoria	Lara Ray, Ph.D.	Ongoing
		UCLA	
		National Institute on Drug Abuse	
Alcohol Dependence	Ibutilast (MN-166 (ibutilast)) for the Treatment of Alcohol Use Disorder	Lara Ray, Ph.D.	Ongoing
		UCLA	
		National Institute on Alcohol Abuse	
		and Alcoholism	

Sales and Marketing

We currently have no marketing and sales capabilities and we expect to rely on strategic partners to commercialize our products.

Manufacturing

We rely on third parties to manufacture bulk active pharmaceutical ingredients (API) and finished investigational products for research, development, preclinical and clinical trials. We expect to continue to rely on third-party manufacturers for the manufacture of the API and finished products for our clinical and any future commercial production requirements. We believe that there are several manufacturing sources available at commercially reasonable terms to meet our clinical requirements and any future commercial production requirements for the API of our products and the finished drug products.

For the MN-166 (ibutilast) development program, we have historically sourced and imported delayed-release ibutilast capsules, marketed in Japan as Pinatos[®], from Taisho Pharmaceutical Co., Ltd. (Taisho). In addition, we have begun using contract manufacturers to manufacture API and finished product for the MN-166 (ibutilast) development program.

Pursuant to the terms of our license agreement with Kissei for MN-221 (bedoradrine), Kissei has the exclusive right to manufacture the commercial supply of the API for MN-221 (bedoradrine). If we enter into a supply agreement with Kissei, we will purchase from Kissei all API that we require for the commercial supply of MN-221 (bedoradrine), if this product candidate is approved for commercial sale by the FDA or other regulatory authorities.

Intellectual Property and License Agreements

Since our inception in September 2000, we have entered into license agreements with pharmaceutical companies which cover our current product candidates. We have also entered into license agreements with universities which cover additional intellectual property related to our product candidates. In general, we seek to procure patent protection for our anticipated products, or obtain such protection from the relevant patents owned by our licensors. Although the majority of our licensed patents have expired, we hold licensed rights to one issued foreign patent that is not expired. In addition to these licensed rights, we hold 24 issued U.S. patents and have filed nine additional U.S. patent applications. We also hold 36 issued foreign patents and 40 pending foreign patent applications corresponding to these U.S. patents and patent applications. We are not aware of any third-party infringement of the patents owned or licensed by us and are not party to any material claims by third parties of infringement by us of such third parties' intellectual property rights. The following is a description of our existing license agreements and intellectual property rights for each of our product candidates.

MN-166 (ibudilast)

On October 22, 2004, we entered into an exclusive license agreement with Kyorin for the development and commercialization of MN-166 (ibudilast). Kyorin is a fully integrated Japanese pharmaceutical company and is listed on the First Section of the Tokyo Stock Exchange. We obtained an exclusive, worldwide (excluding Japan, China, South Korea and Taiwan), sub-licensable license to the patent rights related to MN-166 (ibudilast) for the treatment of MS, except for ophthalmic solution formulations. MN-166 (ibudilast) is not covered by a composition of matter patent. The United States method of use patent for MN-166 (ibudilast) in MS underlying the license expired on August 10, 2018. Corresponding method of use patents in certain foreign countries also expired on August 10, 2018. Under the terms of the agreement, we granted to Kyorin an exclusive, royalty-free, sub-licensable license to use the preclinical, clinical and regulatory databases to develop ophthalmic products incorporating the MN-166 (ibudilast) compound anywhere in the world and non-ophthalmic products incorporating the MN-166 (ibudilast) compound outside of our territory.

The license agreement may be terminated by either party following an uncured breach of any material provision in the agreement by the other party. We may terminate the agreement for any reason with 90 days' written notice to

Kyorin or, in the event that a third party claims that MN-166 (ibudilast) infringes upon such third party's intellectual property rights, with 30 days' written notice.

The term of this agreement is determined on a country-by-country basis and extends until the later of the expiration of the obligation to make payments under the agreement or the last date on which the manufacture, use or sale of the product would infringe a valid patent claim held by Kyorin but for the license granted by the agreement or the last date of the applicable market exclusivity period. In the absence of a valid patent claim and generic competition in a particular country, the agreement will expire on the earlier of five years from the date of the first commercial sale of the product by us or the end of the second consecutive calendar quarter in which generic competition exists in such country.

Under the license agreement, we have paid Kyorin \$700,000 to date, and we are obligated to make payments of up to \$5.0 million based on the achievement of certain clinical and regulatory milestones. We are also obligated to pay a royalty on net sales of the licensed products.

We own, co-own or hold licenses to seven issued U.S. patents and eight pending U.S. patent applications as well as 22 issued foreign patents and eleven pending foreign patent applications covering MN-166 (ibudilast) and its analogs. These patents and patent applications are related to our development portfolio and are primarily directed to methods of treating various indications using MN-166 (ibudilast) and its analogs.

We have been granted a U.S. patent which covers the use of MN-166 (ibudilast) for the treatment of progressive forms of MS. This patent will expire no earlier than November 2029, not including a potential extension under patent term restoration rules, and covers a method of treating PPMS or SPMS by administering MN-166 (ibudilast). Counterparts of this patent application have been granted in certain foreign jurisdictions. We have been granted a U.S. patent which covers the use of MN-166 (ibudilast) for the treatment of amyotrophic lateral sclerosis (ALS) and it expires no earlier than January 2029. We have been granted a patent which covers the use of MN-166 (ibudilast) for the treatment of drug addiction or drug dependence or withdrawal syndrome in the United States and it expires no earlier than January 2030. Counterparts of this patent application have been granted in certain foreign jurisdictions. We have been granted a patent which covers the use of MN-166 (ibudilast) for the treatment of neuropathic pain in the United States and it expires no earlier than December 2025.

MN-221 (bedoradrine)

On February 25, 2004, we entered into an exclusive license agreement with Kissei for the development and commercialization of MN-221 (bedoradrine). Kissei is a fully integrated Japanese pharmaceutical company and is listed on the Tokyo Stock Exchange. We obtained an exclusive, worldwide (excluding Japan), sub-licensable license to various patent rights and know-how related to MN-221 (bedoradrine) and other compounds disclosed or included in, or covered by, these patent rights, for all indications. This license includes an exclusive license under one U.S. patent and certain corresponding patents in foreign countries and is sub-licensable upon receipt of the written consent

of Kissei. The United States composition of matter patent underlying the license issued on October 17, 2000 and it expired on February 18, 2017. Most of the corresponding composition of matter patents in various other countries also expired on February 18, 2017.

In addition to the licensed patents, we have filed patent applications in the United States and certain foreign countries regarding additional uses and formulations of MN-221 (bedoradrine). We have been granted a U.S. patent which covers the use of MN-221 (bedoradrine) for the treatment of acute exacerbations of asthma and it expires no earlier than November 2030. This patent includes claims covering the use of MN-221 (bedoradrine) in combination with a standard of care treatment regimen and covers different routes of administration, including intravenous, oral and inhalation. We have been granted a U.S. patent that covers the use of MN-221 (bedoradrine) for the treatment of irritable bowel syndrome and it expires no earlier than April 2031.

The license agreement may be terminated by either party following an uncured breach of any material provision in the agreement by the other party, and we may terminate the agreement for scientific or commercial reasons upon 100 days' prior written notice to Kissei during the development phase and 180 days' prior written notice to Kissei during the commercialization phase.

The term of the agreement is determined on a country-by-country basis and extends until the expiration of the last Kissei patent (or equivalent) under license to expire or in the event that a valid claim does not exist or, if a valid claim expired more than ten years from the date of first commercial sale, ten years from the date of first commercial sale. In either case, the term of the agreement would not extend for any particular country past the date on which generic competition exists in such country.

Under the license agreement, we have paid Kissei \$1.0 million to date, and we are obligated to make payments of up to \$17.0 million based on the achievement of certain clinical and regulatory milestones. We are also obligated to pay a royalty on net sales of the licensed products. Under the terms of a letter agreement we entered into with Kissei in September 2011, we agreed to renegotiate in good faith with Kissei the existing levels of the milestone payment amounts and royalty rates.

MN-001 (tipelukast)

On March 14, 2002, we entered into an exclusive license agreement with Kyorin for the development and commercialization of MN-001 (tipelukast). We obtained an exclusive, worldwide (excluding Japan, China, South Korea and Taiwan) sub-licensable license to the patent rights and know-how related to MN-001 (tipelukast) and its active metabolite, MN-002, disclosed and included in, or covered by, these patents, in all indications, except for ophthalmic solution formulations. This license included an exclusive, sub-licensable license under two U.S. patents and certain corresponding patents in foreign countries. The United States composition of matter patent for MN-001 (tipelukast) underlying the license expired on February 23, 2009, and the United States composition of matter patent for MN-002 underlying the license expired on December 30, 2011. Foreign composition of matter patents for MN-001 (tipelukast) and MN-002 have also expired. We have been granted 14 U.S. patents covering certain compositions, uses and manufacturing processes associated with MN-001 (tipelukast) and MN-002. Uses covered by these patents include nonalcoholic steatohepatitis (NASH), advanced NASH with fibrosis, nonalcoholic fatty liver disease (NAFLD), steatosis, hypertriglyceridemia, hypercholesterolemia, hyperlipoproteinemia, fibrosis, ulcerative colitis, interstitial cystitis, and irritable bowel syndrome. Patent applications corresponding to these U.S. patents have been filed in certain foreign countries and some of the foreign patents have issued.

Under the terms of the agreement, we granted to Kyorin an exclusive, royalty-free, sub-licensable license to use the preclinical, clinical and regulatory databases to develop ophthalmic products incorporating MN-001 (tipelukast) anywhere in the world and non-ophthalmic products incorporating MN-001 (tipelukast) outside of our territory. The license agreement may be terminated by either party following an uncured breach of any material provision in the agreement by the other party, and we may terminate the agreement for any reason with 90 days' written notice to Kyorin or, in the event that a third party claims that the licensed patent rights or know-how infringe upon such third party's intellectual property rights, with 30 days' written notice.

The term of this agreement is determined on a country-by-country basis and extends until the later of the expiration of the obligation to make payments under the agreement or the last date on which the manufacture, use or sale of the

product would infringe a valid patent claim held by Kyorin but for the license granted by the agreement or the last date of the applicable market exclusivity period. In the absence of a valid patent claim and generic competition in a particular country, the agreement will expire on the earlier of five years from the date of the first commercial sale of the product by us or the end of the second consecutive calendar quarter in which generic competition exists in such country.

Under the license agreement, we have paid Kyorin \$4.0 million to date, and we are obligated to make payments of up to \$5.0 million based on the achievement of clinical and regulatory milestones. We are also obligated to pay a royalty on net sales of the licensed products.

MN-029 (denibulin)

On June 19, 2002, we entered into an exclusive license agreement with Angiogene for the development and commercialization of the ANG-600 series of compounds. Angiogene is a privately held, British drug discovery company. We obtained an exclusive, worldwide, sub-licensable license to the patent rights and know-how related to

the ANG-600 series of compounds disclosed in and included or covered by these patents for all indications. MN-029 (denibulin) is one of the ANG-600 series compounds covered by this license. We have been granted a U.S. patent which covers MN-029 (denibulin) di-hydrochloride and expires no earlier than July 2032. The allowed claims cover a compound, pharmaceutical composition and method of treating certain cell proliferation diseases, including solid tumors, based on denibulin di-hydrochloride. Patent applications corresponding to this U.S. patent were filed in certain foreign countries and patents have been granted or allowed in some of those countries.

The license agreement may be terminated by either party following an uncured breach of any material provision in the agreement by the other party, and we may terminate the agreement at any time by giving 30 days' advance written notice to Angiogene.

The term of this agreement is determined on a country-by-country basis and extends until the earlier of the expiration of the last Angiogene patent (or equivalent) under license which has a valid claim to expire or 15 years from the date of first commercial sale.

Under the license agreement, we have paid Angiogene \$1.4 million to date and are obligated to make payments of up to \$16.5 million based on the achievement of clinical and regulatory milestones. We are also obligated to pay a royalty on net sales of the licensed products.

General

Our proposed commercial activities may conflict with patents which have been or may be granted to competitors, universities and/or others. Third parties could bring legal action against us, our licensors or our sub-licensees claiming patent infringement and could seek damages or enjoin manufacturing and marketing of the affected product or its use or the use of a process for the manufacturing of such products. If any such actions were to be successful, in addition to any potential liability for indemnification, damages and attorneys' fees in certain cases, we could be required to obtain a license, which may not be available on commercially reasonable terms or at all, in order to continue to manufacture, use or market the affected product. We also rely upon unpatented proprietary technology because, in some cases, our interests would be better served by reliance on trade secrets or confidentiality agreements than by patents. However, others may independently develop substantially equivalent proprietary information and techniques or gain access to or disclose such proprietary technology. We may not be able to meaningfully protect our rights in such unpatented proprietary technology. We may also conduct research on other pharmaceutical compounds or technologies, the rights to which may be held by, or be subject to patent rights of, third parties. Accordingly, if products based on such research are commercialized, such commercial activities may infringe patents or other rights, which may require us to obtain a license to such patents or other rights. We are not aware of any third-party infringements of patents we hold or have licensed and have not received any material claims by third parties of infringement by us of such parties' intellectual property rights.

There can be no assurance that patent applications filed by us or others, in which we have an interest as assignee, licensee or prospective licensee, will result in patents being issued or that, if issued, any of such patents will afford protection against competitors with similar technology or products or could not be circumvented or challenged. For example, we have U.S. patents covering the method of treating progressive MS with MN-166 (ibudilast), the method of treating ALS with MN-166 (ibudilast), the method of treating drug addiction or drug dependence with MN-166 (ibudilast), and the method of treating neuropathic pain with MN-166 (ibudilast), but we do not have any composition of matter patent claims for MN-166 (ibudilast) because that patent has expired. As a result, unrelated third parties may develop products with the same API as MN-166 (ibudilast) so long as such parties do not infringe our method of use patents, other patents we have exclusive rights to through our licensors or any patents we may obtain for MN-166 (ibudilast).

In addition, if we develop certain products that are not covered by any patents, we will be dependent on obtaining market exclusivity under the new chemical entity exclusivity provisions of Hatch-Waxman Act for such products in the United States and/or data exclusivity provisions in Europe. If we are unable to obtain strong proprietary protection for our products after obtaining regulatory approval, competitors may be able to market competing generic products by taking advantage of an abbreviated procedure for obtaining regulatory clearance, including the ability to demonstrate bioequivalency to our product(s) without being required to conduct lengthy

clinical trials. Certain of our license agreements provide for reduced or foregone royalties in the event of generic competition.

Competition

The development and commercialization of new drugs is extremely competitive and characterized by extensive research efforts and rapid technological progress. Competition in our industry occurs on a variety of fronts, including developing and bringing new products to market before others, developing new products to provide the same benefits as existing products at lower cost and developing new products to provide benefits superior to those of existing products. We face competition from pharmaceutical and biotechnology companies, as well as numerous academic and research institutions and governmental agencies in the United States and abroad. Some of these competitors have products or are pursuing the development of drugs that target the same diseases and conditions that are the focus of our product development programs. Many of our competitors have products that have been approved or are in advanced development and may succeed in developing drugs that are more effective, safer, more affordable or more easily administered than ours or that achieve patent protection or commercialization sooner than our products. Our competitors may also develop alternative therapies that could further limit the market for any products that we are able to obtain approval for, if at all.

In many of our target disease areas, potential competitors are working to develop new compounds with different mechanisms of action and attractive efficacy and safety profiles. Many of our competitors have substantially greater financial, research and development resources (including personnel and technology), clinical trial experience, manufacturing, sales and marketing capabilities and production facilities than we do. Smaller companies also may prove to be significant competitors, particularly through proprietary research discoveries and collaboration arrangements with large pharmaceutical and established biotechnology companies.

MN-166 (ibudilast) for Progressive Multiple Sclerosis (Progressive MS)

Our MN-166 (ibudilast) product candidate is in development for the treatment of progressive MS. Only one drug, mitoxantrone, is approved for the treatment of secondary progressive MS. However, mitoxantrone cannot be used on a long-term basis because of the potential for cardiac toxicity. Only one drug, Ocrevus (ocrelizumab) is approved for the treatment of primary progressive MS. Other programs in clinical development for progressive MS include Novartis's BAF312 (siponimod), MedDay's MD1003, and AB Science's masitinib.

MN-166 (ibudilast) for Amyotrophic Lateral Sclerosis (ALS)

Our MN-166 (ibudilast) product candidate is also in development for the treatment of ALS. Riluzole and Radicava (edaravone) are approved for the treatment of ALS. We are aware of additional compounds in clinical development

for the treatment of ALS at other companies including Cytokinetics, BrainStorm Cell Therapeutics Inc., AB Science, Mallinckrodt, Biogen, and Amylyx Pharmaceuticals.

MN-166 (ibudilast) for Substance Dependence and Addiction

Our MN-166 (ibudilast) product candidate is also in development for the treatment of opioid dependence, methamphetamine addiction, and alcohol dependence. Current treatments for opioid withdrawal symptoms include narcotics such as generic methadone and Indivior, Inc.'s Suboxone[®] Film (buprenorphine + the opioid antagonist naloxone). Other products approved for opioid dependence include Alkermes's Vivitrol[®] (naltrexone monthly injection), Orexo's Zubsolv[®] (buprenorphine and naloxone), BioDelivery Sciences's Bunavail[®] (buprenorphine and naloxone), Titan Pharmaceuticals Inc.'s Probuphine (buprenorphine) implant, and Indivior's Sublocade[™] (buprenorphine extended-release injection). In December 2018, Braeburn announced tentative FDA approval of BRXADI, an extended-release weekly and monthly injectable buprenorphine product, for the treatment of moderate to severe opioid use disorder. Limited non-narcotic drug candidates for opioid withdrawal symptoms exist. US WorldMeds, LLC's Lucemyra[™] (lofexidine) is a central alpha-2 adrenergic agonist approved for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation. There are no pharmaceuticals currently approved for the treatment of methamphetamine addiction. Approved treatments for alcohol dependence include Antabuse[®] (disulfiram), Vivitrol[®] (naltrexone), and generic acamprosate. We are aware of additional treatments in

development for the treatment of alcohol dependence at other companies including Indivior and Opiant Pharmaceuticals.

MN-166 (ibudilast) for Chemotherapy-Induced Peripheral Neuropathy

Our MN-166 (ibudilast) product candidate is also in development for the treatment of chemotherapy-induced peripheral neuropathy. There are no pharmaceuticals currently approved for the treatment of chemotherapy-induced peripheral neuropathy. Duloxetine is sometimes used off-label for this indication.

MN-166 (ibudilast) for Degenerative Cervical Myelopathy

Our MN-166 (ibudilast) product candidate is also in development for the treatment of degenerative cervical myelopathy. There are no pharmaceuticals currently approved for the treatment of degenerative cervical myelopathy.

MN-166 (ibudilast) for Glioblastoma

We have initiated clinical development of our MN-166 (ibudilast) product candidate for the treatment of glioblastoma. Surgery, radiation, and chemotherapy with the drug temozolomide is the current standard of treatment for glioblastoma. GLIADEL® WAFER (carmustine implant) and AVASTIN® (bevacizumab) are also approved for the treatment for glioblastoma. We are aware of additional compounds in development for the treatment of glioblastoma at companies including AbbVie, Celgene and Amgen.

MN-221 (bedoradrine) for Acute Exacerbations of Asthma

Our MN-221 (bedoradrine) product candidate has been developed for the treatment of acute exacerbations of asthma in the emergency room setting. The current standard of care for acute exacerbations of asthma is inhaled albuterol (a β_2 -adrenergic receptor agonist), inhaled ipratropium (an anticholinergic) and oral or injected corticosteroids. In addition, subcutaneously administered terbutaline (a β_2 -adrenergic receptor agonist) is sometimes used to treat this condition, particularly in pediatric patients.

MN-001 (tipelukast) for Nonalcoholic Steatohepatitis (NASH)

Our MN-001 (tipelukast) product candidate is being developed for the treatment of NASH. There are currently no therapeutic products approved for the treatment of NASH. We are aware of compounds in clinical development for the treatment of NASH at other companies including Intercept Pharmaceuticals, Genfit, Galectin Therapeutics, Gilead Sciences, Allergan (which acquired Tobira Therapeutics), Galmed Pharmaceuticals, Bristol-Myers Squibb and Conatus Pharmaceuticals.

MN-001 (tipelukast) for Idiopathic Pulmonary Fibrosis (IPF)

Our MN-001 (tipelukast) product candidate is also being developed for the treatment of IPF. Products approved in the United States for treatment of IPF include Roche's (formerly InterMune) Esbriet® (pirfenidone) and Boehringer Ingelheim's OFEV® (nintedanib). Companies working on clinical development programs for treatment of IPF include Biogen and FibroGen.

MN-029 (denibulin) for Solid Tumor Cancer

Our MN-029 (denibulin) product candidate is being developed for the treatment of solid tumor cancers. Roche's Kadcyla®, a HER2-targeted antibody and microtubule inhibitor conjugate, is approved for treatment of patients with HER2-positive metastatic breast cancer who previously were treated with trastuzumab and a taxane. Bayer's Stivarga®, a kinase inhibitor approved for metastatic colorectal cancer, was also approved for patients with advanced, unresectable (not subject to surgical removal) or metastatic gastrointestinal stromal tumor. Other drugs approved for solid tumor cancers include Roche's Avastin and Xeloda, Amgen's Xgeva, Pfizer's Sutent, and Novartis's Afinitor. We are aware of additional compounds in development for the treatment of solid tumor cancers at companies including Eli Lilly, Roche, Novartis, Pfizer, Amgen and Celgene.

Government Regulation

Government authorities in the United States and other countries extensively regulate the research, development, testing, manufacture, labeling, promotion, advertising, distribution, sampling, marketing and import and export of pharmaceutical products and biologics such as those we are developing. In the United States, the FDA, under the Federal Food, Drug and Cosmetic Act, as amended, and other federal statutes and regulations, subjects pharmaceutical products to extensive and rigorous review. Any failure to comply with applicable requirements, both before and after approval, may subject us, our third-party manufacturers, contractors, suppliers and partners to administrative and judicial sanctions, such as a delay in approving or refusal to approve pending applications, fines, warning letters, product recalls, product seizures, total or partial suspension of manufacturing or marketing, injunctions and/or criminal prosecution.

United States Regulatory Approval

Overview. In the United States, drugs and drug testing are regulated by the FDA under the Federal Food, Drug and Cosmetic Act, or FDCA, as well as state and local government authorities. All our product candidates in development will require regulatory approval by government agencies prior to commercialization. To obtain approval of a new product from the FDA, we must, among other requirements, submit data supporting safety and efficacy, as well as detailed information on the manufacture and composition of the product and proposed labeling. Our product candidates are in the early stages of testing and none has been approved. The steps required before a drug can be approved generally involve the following:

- completion of nonclinical laboratory, animal studies, and formulation studies;
- submission of an IND which must become effective before human clinical trials may begin in the United States;
- completion of adequate and well-controlled human clinical trials to establish the safety and efficacy of the product candidate for each indication for which approval is sought;
- submission to the FDA of a New Drug Application (NDA) accompanied by a substantial user fee;
- development of manufacturing processes which conform to FDA-mandated commercial good manufacturing practices (cGMPs) and satisfactory completion of FDA inspections to assess cGMP compliance and clinical investigator compliance with good clinical practices; and
- FDA review and approval of an NDA, which process may involve input from advisory committees to the FDA and may include post-approval commitments for further clinical studies and distribution restrictions intended to mitigate

drug risks.

The testing, collection of data, preparation of necessary applications and approval process requires substantial time, effort and financial resources. Additionally, statutes, rules, regulations and policies may change and new regulations may be issued that could delay approvals of our drugs. The FDA may not act quickly or favorably in reviewing our applications, and we may encounter significant difficulties and costs in our efforts to obtain FDA approvals that could delay or preclude us from marketing our product candidates.

Preclinical Tests. Preclinical tests include laboratory evaluation of the product candidate, its chemistry, toxicity, formulation and stability, as well as animal studies to assess the potential safety and efficacy of the product candidate. The results of the preclinical tests, together with manufacturing information, analytical data and other available information about the product candidate, are submitted to the FDA as part of an IND. Preclinical tests and studies can take several years to complete and, despite completion of those tests and studies, the FDA may not permit clinical testing to begin.

The IND Process. An IND must be effective to administer an investigational drug to humans. The IND will automatically become effective 30 days after its receipt by the FDA unless the FDA, before that time, places the

IND on clinical hold. At any time thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold if the FDA deems it appropriate. In such case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin or continue. The IND application process may become extremely costly and substantially delay development of our product candidates. Moreover, positive results in preclinical tests or prior human studies do not necessarily predict positive results in subsequent clinical trials.

Annual progress reports detailing the results of the clinical trials must be submitted to the FDA and written IND safety reports must be promptly submitted to the FDA and the investigators for serious and unexpected adverse events or any findings from tests in laboratory animals that suggest a significant risk for human subjects.

Clinical Trials. Human clinical trials are typically conducted in three sequential phases that may overlap:

Phase 1: The drug candidate is initially introduced into a small number of healthy human subjects or patients and tested for safety, dosage tolerance, absorption, distribution, excretion and metabolism. If the investigational product is considered inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in the target population.

Phase 2: The drug candidate is introduced into a limited patient population to assess the efficacy of the drug in specific, targeted indications, assess dosage tolerance and optimal dosage, and to identify possible adverse effects and safety risks.

Phase 3: The drug candidate is introduced into an expanded patient population at geographically dispersed clinical trial sites to further evaluate clinical efficacy and safety. The purpose of the Phase 3 trial is to conduct a risk/benefit analysis of the potential drug and provide an adequate basis for product labeling. It is common to have two adequate and well-controlled Phase 3 trials for the FDA to approve an NDA.

Prior to initiation of each clinical trial, an independent Institutional Review Board (IRB) for each medical site proposing to conduct the clinical trials must review and approve the study protocol and study subjects must provide informed consent for participation in the study.

We cannot be certain that we will successfully complete Phase 1, 2 or 3 testing of our drug candidates within any specific time period, if at all. Clinical trials must be conducted in accordance with the FDA's good clinical practices (GCP) requirements. The FDA may order the partial, temporary or permanent discontinuation of a clinical trial at any time or impose other sanctions if it believes that the clinical trial is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. The IRB may also require the clinical trial at that site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions. In addition, we may suspend or discontinue a clinical trial at any time for a variety of reasons, including a finding that the research subjects or patients are being exposed to an unacceptable health risk.

During the development of a new drug, we may request to meet with the FDA at times such as prior to submitting an IND, at the End-of-Phase 2 meeting, and before an NDA is submitted, and meetings are not limited to these certain times. The purpose of the End-of-Phase 2 meeting is to discuss the Phase 2 clinical trial results and present plans for a pivotal Phase 3 trial that, in our opinion, will support the approval of the new drug. Additional animal safety studies, formulation studies and pharmacology studies are concurrently conducted with the ongoing clinical trials. Also, in compliance with cGMP requirements, the process for manufacturing commercial quantities of the new drug is finalized, with the expectation that the quality, purity, and potency of the drug will meet standards. A sponsor may also request a Special Protocol Assessment (SPA), the purpose of which is to reach agreement with the FDA on the Phase 3 clinical trial protocol design and analysis that will form the primary basis of an efficacy claim.

Fast track designation: The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs and biological products that meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to

the combination of the product and the specific indication for which it is being studied. Unique to a Fast Track product, the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA.

Any product submitted to the FDA for marketing, including a Fast Track program, may also be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an NDA designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Drug products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug product receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast Track designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

United States patent term restoration and marketing exclusivity: Depending upon the timing, duration and specifics of the FDA approval of a drug candidate, some U.S. patents covering the product candidates may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The United States Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may apply for restoration of patent terms for one or more of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA.

Market exclusivity provisions under the FDCA can also delay the submission or the approval of certain applications of other companies seeking to reference another company's NDA. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application (ANDA) or a 505(b)(2) NDA submitted by another company for another version of such drug where the applicant does not own or have a

legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. The FDCA also provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the original active agent. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness. Pediatric exclusivity is another type of regulatory market exclusivity in the

United States Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued “Written Request” for such a trial.

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

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a clinical trial application (CTA) must be submitted to each country’s national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country’s requirements, clinical trial development may proceed.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational drug under European Union regulatory systems, we or our strategic alliance partners must submit a marketing authorization application. The application used to file the NDA in the United States is similar to that required in the European Union, except for, among other things, country-specific document requirements.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

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

Employees

We have assembled an experienced and cohesive management and support team, with core competencies in general management, clinical development, regulatory affairs and corporate development. We have nine full-time employees as of the date of this report. We believe that our relations with our employees are good, and we have no history of work stoppages.

Company Information

We were originally incorporated in the State of Delaware in September 2000. Our principal executive offices are located at 4275 Executive Square, Suite 300, La Jolla, CA 92037. Our telephone number is 858-373-1500. Our website is www.medicinova.com, which includes links to reports we have filed with the Securities and Exchange Commission, or SEC. The information contained in, or that can be accessed through, our website is not part of, and is not incorporated into, this Annual Report on Form 10-K.

Item 1A. Risk Factors

We operate in a dynamic and rapidly changing environment that involves numerous risks and uncertainties. Certain factors may have a material adverse effect on our business, financial condition and results of operations, and you should carefully consider them. Accordingly, in evaluating our business, we encourage you to consider the following discussion of risk factors, in its entirety, in addition to other information contained in this Annual Report on Form 10-K and our other public filings with the SEC. Other events that we do not currently anticipate or that we currently deem immaterial may also affect our results of operations and financial condition.

Risks Related to Our Business and Industry

We have incurred significant operating losses since our inception and expect that we will incur continued losses for the foreseeable future.

We have incurred significant net losses since our inception. For the year ended December 31, 2018, we had a net loss of \$14.7 million. At December 31, 2018, from inception, our accumulated deficit was \$356.1 million. We expect to incur substantial net losses for the next several years as we continue to develop certain of our existing product development candidates, and over the long-term if we expand our research and development programs and acquire or in-license products, technologies or businesses that are complementary to our own. As of December 31, 2018, we had available cash and cash equivalents of \$62.3 million and working capital of \$60.6 million. There can be no assurances that there will be adequate financing available to us in the future on acceptable terms, or at all. If we are unable to obtain additional financing, we may have to out-license or sell one or more of our programs or cease operations.

Our future cash requirements will also depend on many factors, including:

• progress in, and the costs of future planned clinical trials and other research and development activities;

- the scope, prioritization and number of our product development programs;

• our obligations under our license agreements, pursuant to which we may be required to make future milestone payments upon the achievement of various milestones related to clinical, regulatory or commercial events;

• our ability to establish and maintain strategic collaborations, including licensing agreements and other arrangements;

• the time and costs involved in obtaining regulatory approvals;

• the costs of securing manufacturing arrangements for clinical or commercial production of our product candidates;

•the costs associated with any expansion of our management, personnel, systems and facilities;

•the costs associated with any litigation;

•the costs associated with the operations or wind-down of any business we may acquire;

•the costs involved in filing, prosecuting, enforcing and defending patent claims and other intellectual property rights;
and

•the costs of establishing or contracting for sales and marketing capabilities and commercialization activities

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if we obtain regulatory approval to market our product candidates.

We expect our research and development expenses to increase in 2019 relative to 2018 as we continue our focus on the development of MN-166 (ibudilast) and MN-001 (tipelukast) in 2019. Our estimate of cash requirements for future operating expenses assumes that we do not incur significant additional new clinical development expenditures unless we raise additional capital and/or enter into one or more strategic alliances. We do expect to continue to incur significant operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing drug products, we are unable to predict the extent of any future losses or when we will become profitable, if at all.

If we have taxable income in the future, utilization of the net operating losses, or NOL, and tax credit carry-forwards will be subject to a substantial annual limitation under Sections 382 and 383 of the Internal Revenue Code of 1986, and similar state provisions due to ownership change limitations that have occurred. These ownership changes will limit the amount of NOL and tax credit carry-forwards that can be utilized to offset future taxable income and tax, respectively.

If we fail to obtain the capital necessary to fund our operations, we will be unable to develop and commercialize our product candidates.

We have consumed substantial amounts of capital since our inception.

Our business will continue to require us to incur substantial research and development expenses. We believe that without raising additional capital from accessible sources of financing, we will not otherwise have adequate funding to continue our operations and to complete the development of our existing product candidates or the commercialization of any products we successfully develop. There is no guarantee that adequate funds will be available when needed from debt or equity financings, arrangements with partners, or from other sources, on terms attractive to us, or at all. The inability to obtain sufficient additional funds when needed to fund our operations would require us to significantly delay, scale back, or eliminate some or all of our clinical or regulatory activities and reduce general and administrative expenses.

We do not have any products that are approved for commercial sale and therefore do not expect to generate any revenues from product sales in the foreseeable future, if ever.

To date, we have funded our operations primarily from sales of our securities and, to a lesser extent, debt financing. We do not expect to receive any revenues from the commercialization of our product candidates for at least the next several years, if at all. We anticipate that, prior to our commercialization of a product candidate, out-licensing upfront and milestone payments will be our primary source of revenue if we can enter into collaborations, strategic alliances or other agreements that would provide us with such revenues. To obtain revenues from sales of our product candidates, we must succeed, either alone or with third parties, in developing, obtaining regulatory approval for, manufacturing and marketing drugs with commercial potential. We may never succeed in these activities, and we may not generate sufficient revenues to continue our business operations or achieve and maintain profitability.

We are largely dependent on the success of our MN-166 (ibudilast) and MN-001 (tipelukast) product candidates and we cannot be certain that these product candidates will receive regulatory approval or be successfully commercialized.

We currently have no products for sale, and we cannot guarantee that we will ever have any drug products approved for sale. The research, testing, manufacturing, labeling, approval, sales, marketing and distribution of drug products are subject to extensive regulation by the FDA and comparable regulatory authorities in other countries. We are not permitted to market any of our product candidates in the United States until we submit and receive approval of a New Drug Application, or NDA, for a product candidate from the FDA or its foreign equivalent from a foreign regulatory authority. Obtaining FDA approval is a lengthy, expensive and uncertain process. The success of our business currently depends primarily on the successful development and commercialization of our MN-166 (ibudilast) and

MN-001 (tipelukast) product candidates. These product candidates have not completed the clinical development process, and therefore we have not submitted an NDA or foreign equivalent or received marketing approval.

The clinical development program for our product candidates may not lead to commercial products for a number of reasons, including our clinical trials' failure to demonstrate to the FDA's satisfaction that the product candidate is safe and effective, or our failure to obtain necessary approvals from the FDA or similar foreign regulatory authorities for any reason. We may also fail to obtain the necessary approvals if we have inadequate financial or other resources to advance our product candidates through the clinical trial process or are unable to secure a strategic collaboration or partnership with a third party. Any failure or delay in completing clinical trials or obtaining regulatory approval for our product candidates in a timely manner would have a material and adverse impact on our business and our stock price.

Because the results of early clinical trials are not necessarily predictive of future results, our product candidates we advance into clinical trials in any indication may not have favorable results in later clinical trials, if any, or receive regulatory approval.

Our product candidates are subject to the risks of failure inherent in drug development. We will be required to demonstrate through well-controlled clinical trials that our product candidates are safe and effective for use in a diverse population for its target indications before we can seek regulatory approvals for their commercial sale. Success in early clinical trials does not mean that later clinical trials will be successful because product candidates in later-stage clinical trials may fail to demonstrate sufficient safety or efficacy despite having progressed through initial clinical testing, even at statistically significant levels.

Companies frequently suffer significant setbacks in advanced clinical trials, even after earlier clinical trials have shown promising results. Any of our planned clinical trials for our product candidates may not be successful for a variety of reasons, including the clinical trial designs, the failure to enroll a sufficient number of patients, undesirable side effects and other safety concerns and the inability to demonstrate sufficient efficacy. If a product candidate fails to demonstrate sufficient safety or efficacy, we would experience potentially significant delays in, or be required to abandon, development of such product candidate.

Our attempts to develop MN-001 (tipelukast) in NASH and IPF may detract from our efforts to develop other product candidates and may limit the effectiveness of our product development efforts as a whole.

We have decided to pursue development of MN-001 (tipelukast) in NASH and IPF. These activities will divert financial and management resources from our other product development activities and may limit our ability to complete or continue those other programs.

In order to commercialize a therapeutic drug successfully, a product candidate must receive regulatory approval after the successful completion of clinical trials, which are long, complex and costly, have a high risk of failure and can be delayed or terminated at any time.

Our product candidates are subject to extensive government regulations related to development, clinical trials, manufacturing and commercialization. The process of obtaining FDA and other regulatory approvals is costly, time-consuming, uncertain and subject to unanticipated delays. To receive regulatory approval for the commercial sale of any of our product candidates, we must conduct, at our own expense, adequate and well-controlled clinical trials in human patients to demonstrate the efficacy and safety of the product candidate. Clinical testing is expensive, takes many years and has an uncertain outcome. To date, we have obtained regulatory authorization to conduct clinical trials for our product development programs. INDs were approved by the FDA and are active for our product candidates.

It may take years to complete the clinical development necessary to commercialize a drug, and delays or failure can occur at any stage, which may result in our inability to market and sell any of our product candidates that are ultimately approved by the FDA or foreign regulatory authorities. Our clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical and/or non-clinical testing. Interim results of clinical trials do not necessarily predict final results, and success in preclinical

testing and early clinical trials does not ensure that later clinical trials will be successful. A number of companies in the pharmaceutical industry have suffered significant setbacks in advanced clinical trials even after obtaining promising results in earlier clinical trials. In addition, any delays in completing clinical trials or the rejection of data from a clinical trial by a regulatory authority will result in increased development costs and could have a material

adverse effect on the development of the impacted product candidate.

In connection with the conduct of clinical trials for each of our product candidates, we face many risks, including the risks that:

• the product candidate may not prove to be effective in treating the targeted indication;

• clinical trial participants and/or patients may experience serious adverse events or other undesirable drug-related side effects;

• the results may not confirm the positive results of earlier trials;

• the FDA or other regulatory authorities may not agree with our proposed development plans or accept the results of completed clinical trials; and

- our planned clinical trials and the data collected from such clinical trials may be deemed by the FDA or other regulatory authorities not to be sufficient, which would require additional development for the product candidate before it can be evaluated in late stage clinical trials or before the FDA will consider an application for marketing approval.

If we do not complete clinical development of our product candidates successfully, we will be unable to obtain regulatory approval to market products and generate revenues from such product candidates. We may also fail to obtain the necessary regulatory approvals if we have inadequate financial or other resources to advance our product candidates through the clinical trial process. In addition, even if we believe that the preclinical and clinical data are sufficient to support regulatory approval for a product candidate, the FDA and foreign regulatory authorities may not ultimately approve such product candidate for commercial sale in any jurisdiction, which would limit our ability to generate revenues and adversely affect our business. In addition, even if our product candidates receive regulatory approval, they remain subject to ongoing FDA regulations, including obligations to conduct additional clinical trials, changes to the