Zacks Small-Cap Research

May 5, 2015
Jason Napodano, CFA
David Bautz, PhD
312-265-9421 / jnapodano@zacks.com

scr.zacks.com
10 S. Riverside Plaza, Suite 1600, Chicago, IL 60606

MediciNova, Inc. (MNOV - Nasdaq)

MNOV: Initiating coverage of MediciNova, Inc. Multiple Shots on Goal with Five Phase 2 Clinical Trials Ongoing…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	05/5/2015
Current Price (05/05/15)	$3.76
Target Price	**$8.00**

INITIATION

We are initiating coverage of MediciNova, Inc. with a Buy rating and a $8.00 price target.

MediciNova is a biopharmaceutical company developing small molecule therapeutics for a number of different indications. MN-166 is being developed for neurological diseases (multiple sclerosis and amyotrophic lateral sclerosis) and substance dependence (methamphetamine, opioid, and alcohol abuse). MN-001 is being developed for fibrotic diseases such as nonalcoholic steatohepatitis (NASH) and idiopathic pulmonary fibrosis (IPF).

The company has $11.6 million in cash, which should fund operations into 2016, and multiple Phase 2 clinical trials ongoing that could provide tremendous upside with positive results.

SUMMARY DATA

52-Week High	**$4.96**
52-Week Low	**$1.74**
One-Year Return (%)	**98.99**
Beta	**0.87**
Average Daily Volume (sh)	**488,355**
Shares Outstanding (mil)	**25**
Market Capitalization ($mil)	**$97**
Short Interest Ratio (days)	**26.43**
Institutional Ownership (%)	**10**
Insider Ownership (%)	**25**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2015 Estimate	**N/A**
P/E using 2016 Estimate	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	0 A	0 A	0 A	0 A	0 A
2015	0 E	0 E	0 E	0 E	0 E
2016					0 E
2017					0 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-$0.10 A	-$0.09 A	-$0.10 A	-$0.09 A	-$0.38 A
2015	-$0.10 E	-$0.10 E	-$0.10 E	-$0.10 E	-$0.39 E
2016					-$0.45 E
2017					-$0.50 E

© Copyright 2015, Zacks Investment Research. All Rights Reserved.

WHAT'S NEW

Initiating Coverage

We are initiating coverage of MediciNova, Inc. (MNOV) with a Buy rating and an $8.00 price target.

MediciNova is a biopharmaceutical company focused on developing small molecule therapeutics for the treatment of serious diseases with unmet medical needs. Currently, the company is focused on the development of MN-166 (ibudilast) and MN-001 (tipelukast).

MN-166 is being developed for the treatment of neurological disorders such as primary and secondary progressive multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and substance dependence (*e.g.*, methamphetamine dependence, opioid dependence, and alcohol dependence). MN-001 is being developed for fibrotic diseases such as nonalcoholic steatohepatitis (NASH) and idiopathic pulmonary fibrosis (IPF). The company's pipeline also includes MN-221 (bedoradrine) for the treatment of acute exacerbation of asthma and MN-029 (denibulin) for the treatment of cancer.

A Phase 2b study investigating the safety and efficacy of MN-166 in patients with progressive MS is currently being conducted by NeuroNEXT, a National Institutes of Health (NIH) funded clinical trial network that conducts studies of treatments for neurological diseases. The study is planning to enroll 250 patients and includes a 96-week treatment phase. As of April 2015, the study had enrolled 228 of the 250 planned subjects. Study results are expected in 2017.

The company is also conducting a single center Phase 2 study in 60 subjects with ALS to evaluate the safety, tolerability, and clinical responsiveness of MN-166 when administered as an adjunct to riluzole, the only U.S. FDA approved ALS treatment. Patients in the study will be randomized 2:1 to receive either MN-166 or placebo in conjunction with riluzole over a six-month time course. As of February 2015 the trial had enrolled 30 of the 60 patients, and an interim safety analysis conducted in April 2015 showed no difference in safety or tolerability between MN-166 and placebo in the first 21 subjects enrolled in the study following three months of treatment. Importantly, the independent safety medical monitor recommended that the study continue as planned.

MN-166 is also being evaluated in three different Phase 2 studies involving methamphetamine, opiate, and alcohol addiction. Each of these trials is being funded through grants obtained from different centers of the National Institutes of Health (NIH).

MN-001 has been studied in preclinical models of nonalcoholic steatohepatitis (NASH) and pulmonary fibrosis (PF). NASH is inflammation and damage in the liver brought on by a buildup of fat and PF is a respiratory disease that occurs when lung tissue becomes damaged and scarred. The FDA has granted Fast Track designation to MN-001 for the treatment of NASH with fibrosis and Orphan Drug designation to MN-001 for the treatment of idiopathic pulmonary fibrosis (IPF). MediciNova has an open investigational new drug (IND) application with the FDA and is currently in the process of finalizing Phase 2 clinical trial designs for both NASH and PF. The FDA has agreed that MediciNova may proceed with Phase 2 protocols in both indications, based on prior safety data.

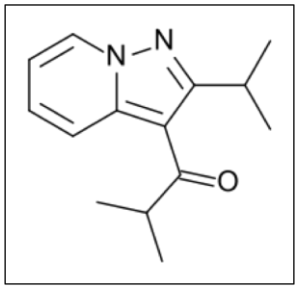
As of December 31, 2014, the company had approximately $11.6 million in cash and cash equivalents. There are currently five clinical trials ongoing testing MN-166 with another two clinical trials being planned for MN-001. Four of those trials are being funded through grants from the NIH. Data readouts from these trials represent a number of potential catalysts for the stock over the next one to two years, with final results from the ALS trial due in the first half of 2016, an interim analysis from the MS trial in the second half of 2016, and final results from the MS trial in the first half of 2017.

INVESTMENT THESIS

MN-166

MediciNova is developing MN-166 (ibudilast) for the treatment of primary and secondary progressive multiple sclerosis (PPMS and SPMS), amyotrophic lateral sclerosis (ALS), methamphetamine (MA) addiction, opioid dependence, and alcohol dependence. The drug is currently being tested in five separate clinical trials in the aforementioned indications.

…Background on MN-166…



Ibudilast. *Source*: medchemexpress.com

MN-166 (ibudilast) is an anti-inflammatory drug that has been utilized for over 20 years in Japan to treat asthma (Rolan *et al*., 2009). It acts as a phophodiesterase (PDE) inhibitor (Suzumura *et al*., 1999) and preferentially inhibits PDE-4 (Huang *et al*., 2006). The drug has shown anti-inflammatory activity in both the peripheral immune system and in the CNS via attenuation of glial cells, which play a role in certain neurological conditions. In addition, delivery of a PDE-4 inhibitor was shown to lead to enhanced differentiation of oligodendrocyte progenitor cells within areas of demyelination and a consequent acceleration of remyelination. (Syed *et al*,, 2013).

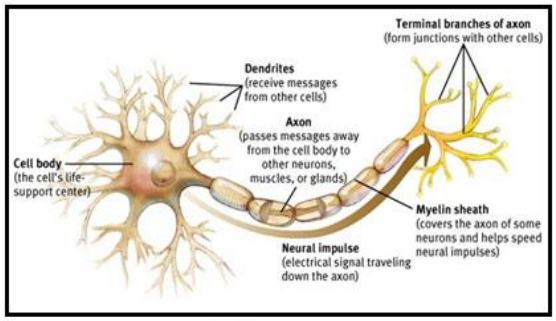
…Neuroprotective Effects of MN-166…

Microglia are a type of glial cell that serve as macrophages in the brain and spinal cord, thus serving as the immune systems first line of defense in the central nervous system. Chronically activated microglia can worsen demyelinating diseases, such as MS. The cells release proinflammatory mediators, such as interleukin (IL)-1, IL-6, tumor necrosis factor-α (TNF-α), and reactive oxygen species. Overproduction of these mediators can lead to the destruction of myelin or oligodendrocytes, producing demyelinating lesions.

Preclinical work performed with MN-166 showed that the compound can suppress neuronal cell death induced by activated microglia (Mizuno *et al*., 2004). MN-166 was shown to suppress the production of TNF-α and IL-6 by microglia as well as enhance the production of the anti-inflammatory cytokine IL-10 and neurotrophic factors such as NGF, GDNF, and NT-4. This data is in agreement with an earlier study of MN-166 in a chronic cerebral hypoperfusion model that showed it could inhibit the activation of microglia cells and prevent the formation of white matter lesions (Wakita *et al*., 2003). This inhibitory effect was shown to be dose dependent and involve the suppression of TNF-α production.

Indication I: Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory disease that affects axons in the central nervous system (CNS). Axons are long, slender projections of nerve cells (neurons) that conduct electrical impulses that transmit information to different neurons, muscles, and glands. Axons are typically insulated with a protective sheath called myelin, which facilitates the proper conductance of nerve signals. When the myelin sheath is damaged there is interference in the communication between the brain, spinal cord, and other areas of the body. This process may also lead to the deterioration of the nerve cells themselves, a condition that is not reversible.



Source: www.majordifferences.com

There is no single diagnostic test for MS, with diagnosis based on the following criteria: 1) at least two different lesions in the white matter of the CNS, 2) at least two different episodes in the disease course, and 3) chronic inflammation of the CNS as determined by analysis of the cerebrospinal fluid (CSF). Having one or more of these criteria allows a general diagnosis of MS.

The pattern and course of the disease is characterized by the following patterns:

- ⇨ Primary progressive (PPMS): Characterized by disease progression from the onset with occasional plateaus and temporary minor improvements. It makes up approximately 10 percent of cases at onset. Patients typically experience a steady decline in function from the beginning and never have acute attacks. There are no currently approved medications for treating primary progressive MS.

- ⇨ Relapsing remitting (RRMS): Relapsing-remitting MS is characterized by clearly defined relapses with full recovery. There is no disease progression during the periods between relapses. This type of MS accounts for approximately 85 to 90 percent of MS cases at onset. However, most patients will then progress into secondary progressive phase.

- ⇨ Secondary progressive (SPMS): Characterized by an initial relapsing-remittance phase followed by progression with or without occasional relapses, minor remissions, and plateaus. Studies suggest that approximately 50% of patients with relapsing-remitting MS will go on to develop secondary progressive MS.

- ⇨ Progressive relapsing (PRMS): Characterized by progressive disease from the onset, with clear acute relapses, with or without full recovery. Disease progression continues to occur during the periods between disease relapses.

There are a host of symptoms associated with MS depending on the location of the affected nerves. Symptoms can include:

- ✓ Optic neuritis: This is the most common type of involvement of the visual pathways. It typically presents as acute eye pain that is followed by variable vision loss affecting mainly central vision.

- ✓ Sensory symptoms: These are common in almost every MS patient at some time during the course of the disease. Symptoms include decreased light touch perception, numbness, tingling, pins-and-needles, and swelling of the limbs or trunk.

- ✓ Vertigo: A relatively common symptom of MS as it is reported in approximately 30 to 50 percent of patients.

- ✓ Tingling or pain in different parts of the body: Pain is a common symptom in patients with MS, with many different types of pain reported such as dysesthetic pain (unpleasant, abnormal sense of touch), back pain, and Lhermitte's sign (an electrical sensation that runs down the back and into the limbs).

- ✓ Extreme fatigue: typically described as physical exhaustion that is unrelated to the amount of activity performed. Many patients complain of feeling exhausted when waking up, even after a good night's rest.

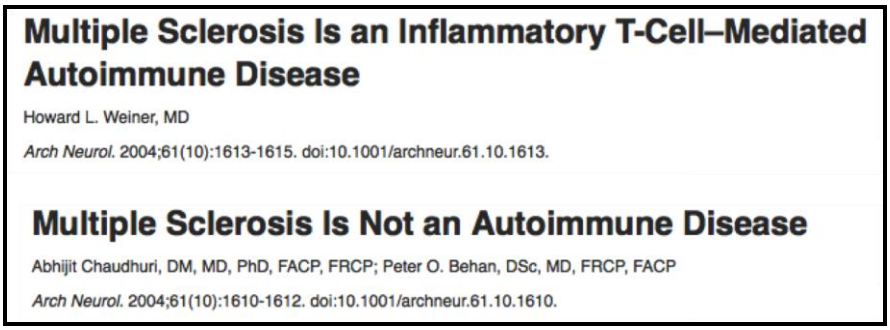
- ✓ Bowel/bladder/sexual function: It is very common for patients with MS to have problems with constipation, urinary incontinence, and sexual dysfunction.

- ✓ Problems with memory or concentration: cognitive dysfunction is rare and is usually only encountered in severely affected individuals, however a larger number of MS patients have cognitive impairment that includes problems with abstract conceptualization, short-term memory, attention, and speed of information processing.

The cause of MS is currently unknown and has been the focus of great attention for more than half a century. The most widely accepted theory at this point states that MS begins as an inflammatory autoimmune disorder mediated by activated lymphocytes (Weiner, 2006). As the disease progresses, it is dominated by microglial (resident macrophages of the CNS) activation and chronic neurodegeneration (Compston *et al*., 2008).

Initially, the inflammation is transient and remyelination occurs but is not durable. This leads to those in the early phase of the disease having episodes of neurological dysfunction that usually resolves. However, over time widespread microglial activation occurs, leading to enhanced pathological changes that lead to a progressive accumulation of disability.

While there is a large amount of data supporting the notion that MS is an autoimmune disorder, direct proof of an autoimmune cause of the disease is lacking as no specific autoantibody or auto-reactive T-cell directed against a self-antigen in the nervous system can passively transfer MS to an experimental animal. The controversy surrounding the cause of MS has been debated for more than 50 years, and leads to articles such as the following that appeared back-to-back in the same issue of JAMA Neurology in 2004:



Multiple Sclerosis Is an Inflammatory T-Cell–Mediated Autoimmune Disease

Howard L. Weiner, MD

Arch Neurol. 2004;61(10):1613-1615. doi:10.1001/archneur.61.10.1613.

Multiple Sclerosis Is Not an Autoimmune Disease

Abhijit Chaudhuri, DM, MD, PhD, FACP, FRCP; Peter O. Behan, DSc, MD, FRCP, FACP

Arch Neurol. 2004;61(10):1610-1612. doi:10.1001/archneur.61.10.1610.

Epidemiological evidence supports the idea that there are certain risk factors for getting MS. One risk factor is sex, with the female to male ratio of MS incidence being approximately 2.3:1 (Alonso *et al*., 2008). The mean age of onset for the disease is 30 years of age, with the peak age of onset approximately five years earlier in women than in men. In support of a possible autoimmune basis for MS, some studies have shown that patients with MS are more likely to have other autoimmune disorders, such as autoimmune thyroid disease.

The incidence and prevalence of MS varies around the world. High frequency areas include Europe, southern Canada, northern U.S., New Zealand, and Australia. The prevalence in the U.S. is approximately 100 per 100,000. There are racial differences in the prevalence as well, which may explain the geographic differences, with white populations, especially those from Northern Europe, being the most susceptible. People of Asian, African, or American Indian origin have the lowest risk. Another possible explanation for the geographic differences in disease prevalence is that sunlight exposure may be protective, either due to an effect of ultraviolet radiation or vitamin D (Ascherio *et al*., 2007).

…Current Treatment Options for MS…

The goal of MS therapy is to shorten the duration of acute exacerbations, decrease their frequency, and provide symptomatic relief. There are no curative therapies currently available; however, there are twelve FDA-approved therapeutic agents that can reduce disease severity and progression in patients with relapsing forms of MS. The only drug that has FDA approval for progressive MS is mitoxantrone, but it is rarely used due to its potential to cause cardiotoxicity.

- ✓ Beta interferons: There are five beta interferons – Avonex® (Biogen), Plegridy® (Biogen), Rebif® (Pfizer), Betaseron® (Bayer), and Extavia® (Novartis). Beta interferons are naturally occurring cytokines secreted by immune cells that act by inhibiting viral replication via a variety of immunomodulating and antiviral activities. The mechanism of action is unknown, but their anti-inflammatory properties are thought to be beneficial.

- ✓ Glatiramer Acetate (Copaxone®, Teva): This is a synthesized copolymer polypeptide mixture consisting of L-glutamic acid, L-lysine, L-alanine, and L-tyrosine. It is recommended as a first line treatment for those patients who cannot tolerate beta interferons. The mechanism of action is unknown, but it appears to activate suppressor T-cells and reduce inflammatory activity.

- ✓ Mitoxantrone (Novantrone®, Merck-Serono): This is a potent inhibitor of topoisomerase II, an enzyme responsible for repairing damaged DNA. Previously used to treat certain cancers, mitoxantrone suppresses the activity of T cells, B cells, and macrophages that are thought to lead the attack on the myelin sheath. This is the only treatment that is approved specifically for treating secondary progressive MS, however its use is limited (2-3 years total) due to the potential for cardiotoxicity (Fox, 2006).

- ✓ Natalizumab (Tysabri®, Biogen): Natalizumab is a humanized monoclonal antibody, and like the beta-interferons its exact mechanism of action in MS patients has yet to be fully elucidated. It binds to the specific receptors on the surface of leukocytes and inhibits adhesion to their counter-receptors.

- ✓ Fingolimod (Gilenya®, Novartis): Fingolimod is a sphingosine-1-phosphate receptor modulator that blocks migration of lymphocytes from lymph nodes, thereby reducing the number of lymphocytes in the blood. The therapeutic mechanism in MS patients is also unknown. Researchers believe it might involve the reduction of lymphocyte migration to the CNS.

- ✓ Alemtuzumab (Lemtrada®, Sanofi): Alemtuzumab is a monoclonal antibody that targets the CD52 receptor on mature lymphocytes. It was previously used to treat certain blood cancers, the drug was approved for the treatment of MS in November 2014. It is approved for patients who have failed two previous MS therapies, and is administered in two treatment courses; the first for five consecutive days and the second 12 months later for three days.

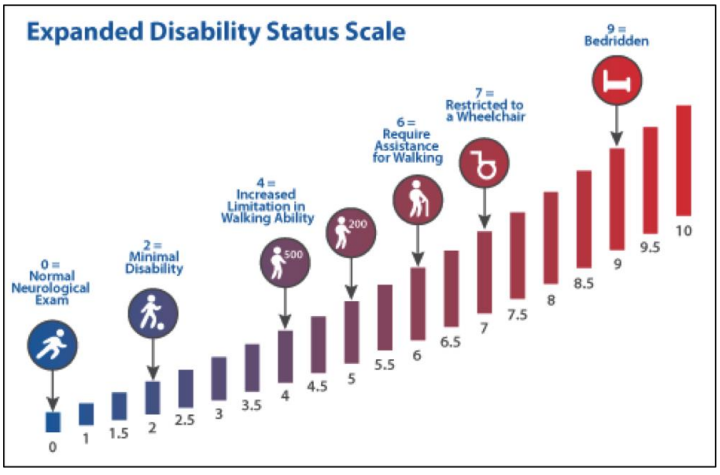
- ✓ Teriflunomide (Aubagio®, Sanofi): Teriflunomide inhibits de novo pyrimidine synthesis and inhibits rapidly dividing cells, including T cells, which are thought to drive the disease process in MS. It was approved for the treatment of relapsing MS in September 2012.

- ✓ Dimethyl fumarate (Tecfidera®, Biogen): DMF (formerly known as BG-12) is an orally administered immune modulator that was approved in March 2013 by the FDA. It appears to have both anti-inflammatory as well as neuroprotective effects. It is quickly becoming the standard of care for relapsing MS.

…MN-166 Phase 2a MS Study…

MN-166 was previously tested in a randomized, double blind, placebo controlled Phase 2a clinical trial to evaluate its safety and effectiveness in MS patients. The study consisted of a total of 297 patients with RRMS or SPMS with continued relapses. Key inclusion criteria consisted of an Expanded Disability Status Scale (EDSS) score of <5.5 along with active disease, defined as at least 1 gadolinium (Gd)-diethylenetriaminepentaacetic acid (DPTA)-enhancing lesion on the screening MRI.

The EDSS is a method of quantifying disability in individuals with MS (Kurtzke, 1983). It allows neurologists to assign a functional system score to each of eight functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other), with the scoring scale depicted in the figure below.



Source: mobilitymattersinms.com

Gadolinium (Gd) is a chemical used in MRI scans that highlights areas of inflammation. It is used to shows areas of active lesions as Gd will only highlight lesions for six weeks or less. This allows physicians to better quantify disease activity.

In the Phase 2a trial, the patients were randomly assigned to receive 10 mg MN-166, 20 mg MN-166, or placebo three times a day (30 mg or 60 mg MN-166 total per day). Patients were treated for 12 months and then offered extended treatment on active medication for an additional 12 months. Those who received placebo during the first 12 months were randomly assigned to receive either 30 mg or 60 mg MN-166 per day in the extension period. The primary outcome of the study was the cumulative number of newly active lesions seen on bimonthly MRI scans over the first 12 months of treatment. Secondary outcomes included the time to first exacerbation, number of relapses, and annualized relapse rate over 12 months, and the cumulative volume of Gd-enhancing lesions over 12 months.

The results showed that there was no difference in the number of newly active lesions or in the cumulative volume of Gd-enhancing lesions between treatment arms. Thus, MN-166 did not appear to have an effect on overt inflammation leading to a suppression of disease activity. However, MN-166 may exert a neuroprotective effect. A preplanned evaluation of brain atrophy showed a statistically significant dose-dependent decrease in atrophy progression in the 60-mg MN-166 group (mean -0.79) compared to placebo (mean -1.20, *P* = 0.04) after only one year of treatment. Brain volume and atrophy measures correlate with measures of disability (Popescu *et al*., 2013) and cognitive function (Yaldizli *et al*., 2014). Changes in brain volume in MS patients is due to the neurodegenerative effect of the disease, thus abrogating brain volume loss may be a means of improving clinical and patient-centered outcomes such as disability progression. An editorial regarding this study was published in the Journal *Neurology* by Dr. Robert Fox, a neurologist at the Mellon Center for Multiple Sclerosis at the Cleveland Clinic and the principal investigator of the company's Phase 2b trial of MN-166. The editorial discussed how MN-166 has the potential to be neuroprotective and that neuroprotection is the "holy grail" in the treatment of progressive MS.

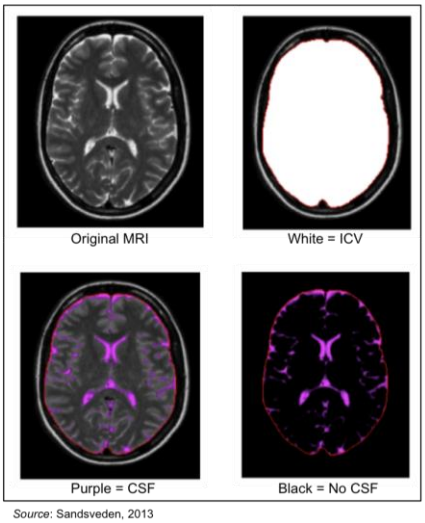
…MN-166 Phase 2b MS Study…

Based on the results of the Phase 2a study, investigators from NeuroNEXT, an NIH funded clinical trial network that conducts studies of treatments for neurological diseases, have initiated the SPRINT-MS trial; a Phase 2b trial evaluating MN-166 in PPMS and SPMS patients titled **"**A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Activity of Ibudilast (MN-166) in Subjects with Progressive Multiple Sclerosis" (NCT01982942).

The study is planning to enroll 250 individuals from 21 to 65 years of age and consists of a screening phase of up to 30 days followed by a treatment phase of 96 weeks and a follow up visit one month after the week 96 visit. Patients will receive either MN-166 (100 mg/day) or placebo twice a day (e.g., MN-166 50 mg or placebo taken once in the morning and once at night). As of April 6, 2015, a total of 228 subjects have been enrolled into the trial. We estimate the final results of the trial will be available by mid 2017.

The primary outcome of the study is the rate of change in brain atrophy over 96 weeks as measured by brain parenchymal fraction (BPF) using MRI. There is a very high degree of variability in skull/brain sizes that leads to a large spread in "normal" values. The BPF was developed to decrease the range of "normal" values and is calculated by dividing the brain parenchymal volume (BPV) by the total intracranial volume (ICV) (Rudick *et al*., 1999).

The brain consists primarily of three parts: white matter (myelinated axons and glial cells), grey matter (neuron cell bodies, dendrites, and unmyelinated axons), and cerebrospinal fluid (CSF). The BPV is the volume of the parenchymal part of the brain (e.g., white matter and grey matter) and does not include the CSF. How the BPF is calculated is best represented by the following MRI images (Sandsveden, 2013)



Source: Sandsveden, 2013

$$BPF = \frac{BPV}{ICV} = \frac{ICV - CSFV}{ICV}$$

The following studies describe brain atrophy rates for SPMS patients and allow us to estimate what would reasonably be expected to occur in the placebo group of the SPRINT-MS trial:

- Study #1: The average rate of brain atrophy (calculated using BPF) in a group of 14 progressive MS patients was found to be -0.62% over a one year time period in a study that took sequential brain MRIs (Guttman *et al*., 2000).

- Study #2: A recent study involving 140 patients (70 active/70 placebo) showed that simvastatin treatment decreased the rate of brain atrophy in SPMS patients compared to those taking placebo (-0.29% vs. -0.58% per year) (Chataway *et al*., 2014).

- Study #3: Another study of 56 subjects with SPMS found whole brain volume change of -0.59% per year (Furby *et al*., 2010).

- Study #4: A recent review article showed the average atrophy rate in MS patients to be approximately 0.5% - 1.3% per year, compared to 0.1% - 0.4% in healthy individuals (Radu *et al*., 2013).

Based on the aforementioned, we would predict a brain atrophy rate calculated using BPF for the control group in the SPRINT-MS study to be -0.6% per year. The reason for the higher rate of brain atrophy seen in the control group in the Phase 2a trial could be based on the majority of patients (92%) having RRMS or the difference in calculating brain volume loss.

We have conducted a power analysis that shows an effect size of 0.38 is necessary for the trial to be 80% powered with an alpha = 0.05 and a total of 250 subjects evenly split between MN-166 and placebo. We estimate this would correspond to an atrophy rate of approximately -0.4% per year in the MN-166 treated group if the rate in the control group is -0.6% per year. Interestingly, the percent difference in rate of brain atrophy seen in the Phase 2a study was approximately -39%. If this same difference were to be seen in the Phase 2b study, given a rate of atrophy in the control group of -0.6%, the treated group would see a rate of decline of -0.366%, which we believe would be a statistically significant effect. Furthermore, the ongoing study is testing a higher dose of MN-166 than the earlier study (100 mg per day vs. 60 mg per day) and the treatment period is longer (96 weeks vs. 52 weeks), both of which increase the likelihood that the ongoing study will achieve the primary endpoint of reducing brain volume loss.

…Market Opportunity in Progressive MS…

MS affects approximately 400,000 people in the U.S. (Tullman, 2013) and 700,000 people in the EU (European MS Platform). As mentioned earlier, approximately 10% of MS patients have the primary progressive form while approximately 85-90% are initially diagnosed with the relapse-remitting form (RRMS). Approximately 50% of those diagnosed with RRMS will go on to develop SPMS, although they still may suffer from relapses.

At the present time there are no approved medications for treating PPMS. Although they are not approved for SPMS (except for mitoxantrone), all of the medications approved to treat RRMS may be used off label in patients who have progressed to SPMS. For example, if a RRMS patient is taking a beta interferon they are likely to stay on treatment even after they have progressed to SPMS, at least until it is determined that the medication is no longer working. At that time, the patient may transition to Merck-KGa's Novantrone® (mitoxantrone), the only FDA approved medication specifically for the treatment of SPMS. However, as per the label, the cumulative lifetime dose is limited to 2-3 years of treatment. In practice, very few patients actually take this medication due to its potential for cardiotoxicity.

In the following figure we have compiled a list of the top selling MS medications and their total sales for 2014. Each of these medications is approved for treating RRMS, and given the fact that half of RRMS patients go on to develop SPMS, there is an enormous market opportunity for an effective SPMS drug to become a blockbuster medication.

Company	Product	WW 2014 Sales (Millions)	YoY Growth
Biogen	Tecfidera	$2,909	232%
Biogen	Tysabri	$1,960	39%
Biogen	Avonex	$3,013	0%
Novartis	Gilenya	$2,477	28%
Merck Serono	Rebif	$2,445	-3%
Sanofi	Aubagio	$575	160%
Bayer	Betaseron	$1,088	-21%
Copaxone	Teva	$4,237	-2%
	TOTAL	$18,704	

Source: Company reports / Zacks SCR (Bautz)

Indication II: Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a rapidly progressing neurodegenerative disease whereby the nerve cells in the brain and spinal cord that control muscle movement degenerate. This rapid degeneration of the motor neurons eventually leads to death, typically in three to five years after patients are first diagnosed. As the motor neurons cease to function properly, they can no longer send signals to the muscle fibers, and thus voluntary muscle action is progressively affected. Eventually, patients in later stages of the disease may become completely paralyzed which includes losing the ability to control their breathing. In the U.S., approximately 30,000 people are currently living with ALS.

Early symptoms of ALS include increasing muscle weakness or stiffness, especially involving the arms and legs. Additional signs of the disease may include difficulty swallowing, cramping, and/or slurred speech. The specific set of neurons that are first affected by the disease dictates what portion of the body will be affected first. Approximately 75% of patients experience "limb onset" ALS. This means they first notice symptoms in their arms and legs. Patients with leg symptoms typically experience difficulty when walking or running, and they may have a tendency to trip or stumble more often. Those patients with arm symptoms may first notice difficulties with buttoning a shirt, opening a can, or writing. The other 25% of cases are "bulbar onset" ALS. These patients first notice difficulty with speaking, swallowing, or their speech. Up to one third of ALS patients may experience "pseudobulbar effect", a neurological disorder which consists of the inability to control certain emotions, such as laughing and crying, which is due to the degeneration of bulbar upper motor neurons.

As the disease progresses all patients will eventually experience increased difficulty swallowing and speaking, with most patients not able to walk or use their arms or hands. The rate at which this occurs varies from patient to patient and is measured utilizing a scoring system called the "ALS Functional Rating Scale Revised" (ALSFRS-R) (Cedarbaum *et al*., 1999). This scoring system consists of a series of 12 questions on basic tasks (speech, salivation, swallowing, handwriting, cutting food, dressing and hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency) that are rated on a five-point scale where 0 = can't do and 4 = normal ability. The individual items are summed to produce a score of between 0 = death and 48 = best.

For the majority of ALS patients (~95%) there is no known cause of the disease. A very small number of cases can be attributed to a genetic component where ALS is known to run in families (familial ALS). Of these familial cases, approximately 20% are associated with a defect in the gene that encodes superoxide dismutase (*SOD1*), with over 100 different *SOD1* mutations described thus far (Andersen, 2006). It is unknown exactly how mutations in *SOD1* lead to neuron degeneration; however, a leading theory is that mutations in superoxide dismutase cause the protein to misfold and aggregate inside the cell. Aggregated proteins are a common pathological feature of both familial and sporadic ALS, and a mouse model of ALS, where the mice harbor a mutation in *SOD1*, showed aggregated protein accumulated only in diseased tissue (Furukawa *et al*., 2006).

Interestingly, mice that lack the *SOD1* gene entirely do not normally develop ALS, although they do tend to exhibit age-related muscle atrophy and a shortened lifespan. These data together suggest that the properties of mutant *SOD1* are not due to a loss of function but rather a gain of function brought on by the mutation.

There is only one drug approved by FDA for treatment of ALS patients. Sanofi's Riluzole® (rilutek) is has been shown to improve survival, but only for two to three months. The compound works by preferentially blocking tetrodotoxin (TTX)-sensitive sodium channels that are associated with damaged neurons (Song *et al*., 1997). This prevents influx of calcium ions and indirectly prevents stimulation of glutamate receptors. Together with direct glutamate receptor blockade, the effect of the neurotransmitter glutamate on motor neurons is greatly reduced. Rilutek does not reverse damage already done to motor neurons, and people taking it must be monitored for liver damage (approximately 10% incidence). Sales of Riluzole® peaked at around $50 million per year. It is now available as a generic.

The remaining treatments for ALS are designed to relieve symptoms and improve quality of life. This supportive care includes a multidisciplinary approach that may include medications to reduce fatigue, control spasticity, reduce excess saliva and phlegm, limit sleep disturbances, reduce depression, and limit constipation. However, none of these treatments reduces disease progression or addresses the underlying cause of the disease.

…MN-166 Phase 2 ALS Study…

In September 2014, MediciNova initiated a Phase 2 study of MN-166 in patients with ALS (NCT02238626). This is a single center, randomized, double blind, placebo controlled six-month study to evaluate the safety, tolerability, and clinical responsiveness of MN-166 (60 mg/day) when administered as an adjunct to riluzole (100 mg/day) in 60 subjects with ALS. Patients in the study will be randomized 2:1 to receive either MN-166 or placebo. The study will consist of a three month screening phase, a six-month double blind treatment phase, and an open label six-month phase and is taking place at the Carolinas Healthcare System in Charlotte, NC. The primary endpoint of the study is the safety and tolerability of MN-166 when administered with riluzole in ALS patients. A number of secondary endpoints are being evaluated including change in ALSFRS-R, respiratory function, muscle strength, and non-invasive ventilation.

On April 21, 2015, MediciNova announced positive interim safety data from the study that showed no difference in safety or tolerability between MN-166 and placebo in the first 21 subjects enrolled in the study following three months of treatment. Importantly, the independent safety medical monitor recommended that the study continue as planned. In February 2015 the company announced that they had enrolled 30 of the 60 patients for the trial. Based on the rate of enrollment thus far, we estimate that the trial will complete enrollment during the second half of 2015, with final results from the 6-month core period of the trial being available in the first half of 2016.

…Market Opportunity in ALS…

ALS is diagnosed in approximately 5,600 people in the U.S. every year and there are an estimated 30,000 patients who are currently living with the disease. With the cost to care for a patient with advanced stage disease estimated to be as high as $200,000, this represents a direct cost of more than $6 billion each year to the healthcare system.

As mentioned previously, there are very limited treatment options for patients with ALS. Riluzole is the only FDA approved medication shown to slow the progress of ALS. It acts by reducing nerve damage and may extend the time before a patient needs a ventilator and could prolong a patient's life by several months. Prior to loss of patent exclusivity, Rilutek® cost approximately $12,000 per year and had sales peak in 2012 of $50 million. This suggests that around 4,200 ALS patients were taking Rilutek® in 2012, or around 15% of the entire U.S. ALS population. Both baclofen and diazepam are used to control muscle spasms, stiffness, or tightening that interfere with daily activities. Trihexyphenidyl and amitriptyline are used to treat patients who have excess saliva and secretions as well as emotional changes. None of the aforementioned drugs alters the course of the diseases.

ALS is a highly complex disease that has multiple pathways of degeneration. Previous ALS drug development efforts have typically focused on one specific mechanism of action, and those have largely been met with failure. MediciNova is attempting to exploit the neuroprotective actions of MN-166 as well as the compounds ability to induce production of neurotrophic factors, which are specialized proteins that promote neuron growth, differentiation, and survival. Given the limited treatment options and high costs associated with patient care, we believe an effective ALS treatment would command a premium price, possibly as high as $100,000 per patient per year. Assuming conservatively that only one third of ALS patients took the drug (10,000 patients), this would generate sales of $1.0 billion per year.

Indication III: Addiction

MN-166 is currently being evaluated in a number of studies having to do with drug dependence, including methamphetamine addiction, opioid dependence, and alcohol addiction. The FDA has granted Fast Track designation for MN-166 for the treatment of methamphetamine dependence. A common mechanism amongst drug addictions appears to be the over-activation of glial cells, thus inhibition of glial cells by MN-166 may be a means to decrease the amount of pro-inflammatory cytokines that are produced by the cells in response to activation by different drugs.

Methamphetamine addiction: Methamphetamine (MA) is a highly addictive stimulant that affects the central nervous system. It was originally developed in the early part of the 20th century as a treatment for nasal congestion and asthma. Effects of the drug include increases wakefulness and physical activity, rapid heart rate, irregular heartbeat, and increased blood pressure and body temperature. Long-term use can lead to memory loss, aggression, psychotic behavior, heart damage, malnutrition, and severe dental problems. It is classified as a Schedule II stimulant, meaning that is has high abuse potential and low therapeutic potential. The SAMHSA 2013 National Survey on Drug Use and Health revealed approximately 595,000 current MA users age 12 and older in the U.S.

Preclinical data showed that MN-166 was able to attenuate footshock - or prime-induced methamphetamine relapse in rats (Beardsley *et al*., 2010). This data was followed up by a Phase 1b trial examining the safety and preliminary efficacy of MN-166 in non-treatment seeking, MA-dependent users, which was completed in 2012. Results showed that in the presence of methamphetamine, there were no significant changes in blood pressure or heart rate in study subjects treated with 40 or 100 mg/day of MN-166. The cardiovascular safety interaction results were a primary objective of the study. In addition, there was a significant improvement in measures of sustained attention in subjects completing a treatment sequence ending with a one-week course of MN-166 dosed at 100 mg/day compared with those treated with placebo.

These results lead to the initiation of a Phase 2 trial of MN-166 that is being funded by the National Institute on Drug Abuse (NIDA), a part of the National Institutes of Health (NIH) with MediciNova responsible for providing drug supply and regulatory support (NCT01860807). The trial will enroll 140 treatment-seeking methamphetamine addicts that will be evenly randomized to receive either MN-166 (100 mg/day) or placebo. During the 12-week outpatient study, subjects will participate in thrice-weekly clinic visits for health checkups, counseling, urine drug screens, and medication adherence monitoring. The primary outcome of the study is methamphetamine abstinence during the final two weeks of treatment, an outcome that is favored by regulatory authorities for addiction medication assessment. Since methamphetamine abuse is often associated with HIV infection, half of the study participants will be HIV positive and the study will assess whether MN-166 also improves HIV outcomes (e.g., medication adherence, CD4 count, and risk behaviors). The trial was initiated in July 2013 and is expected to take approximately four years to complete.

Opioid withdrawal and dependency: The SAMHSA 2013 National Survey on Drug Use and Health reported approximately 1.9 million people over the age of 12 have nonmedical pain reliever dependence or abuse and approximately 517,000 people age 12 and older have heroin dependence or abuse in the U.S. Recent restrictions placed on prescribing opioids have resulted in an increased usage of heroin, which is attractive to opioid abusers because it is cheaper and more readily accessible than prescription opioids. Heroin use is associated with a number of serious health issues, including HIV and Hepatitis C infection, overdose, and death. The economic costs of nonmedical use of prescription opioids in the U.S. in 2006 was estimated to be $53.4 billion with lost productivity and crime accounting for 94% of the total economic burden (Hansen *et al.*, 2011). 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.

A Phase 1b/2a double blind, randomized, placebo controlled study was conducted at Columbia University in 2010 to investigate whether MN-166 could reduce opioid withdrawal symptoms. The study was funded by NIDA. Thirty non-treatment seeking heroin addicts were tested on an in-patient basis over three weeks. The subjects were stabilized with morphine over a two-week period and then the morphine was discontinued during the third week to precipitate a withdrawal. During the second and third weeks of treatment, half the patients were given MN-166 and half were treated with a placebo. If withdrawal symptoms became too severe the subjects were allowed to withdraw at any time. MN-166 at the higher dose reduced each of the withdrawal symptoms that are components of the SOWS (Subjective Opiate Withdrawal Scale) and showed a statistically significantly reduction in two of the withdrawal symptoms (perspiring and hot flashes).

In 2012, MediciNova announced the initiation of a NIDA-funded Phase 2a trial at Columbia University to test MN-166 in patients with prescription opioid dependency (NCT01740414). The trial plans to enroll 24 healthy prescription opioid abusers (OxyContin, Vicodin, Percocet) or heroin abusers. The study will be conducted on an in-patient basis over six weeks. The subjects will be stabilized on morphine for a few days before being slowly tapered off at which time half of the subjects will be treated with MN-166 and half with placebo. As the patients experience withdrawal symptoms they will be given a choice between a dose of oxycodone or money In each subsequent choice session, the amount of money will be doubled from the previous session.

In August 2014, the company announced positive interim results from an interim analysis performed after the first seven patients had completed the study. MN-166 demonstrated a beneficial effect on the subjective, analgesic, and reinforcing effects of oxycodone and significantly decreased the craving for heroin, cocaine, and tobacco ($P < 0.05$ for all three substances).

Alcohol addiction: The SAMHSA 2013 National Survey on Drug Use and Health reported approximately 17.3 million people in the U.S. with alcohol dependence or abuse. There are three FDA approved medicines to treat alcohol dependence including Antabuse®, Vivitrol®, and Campral®. However, there is still a pressing need for a safe and effective treatment for alcohol addiction as the FDA approved compounds have limited efficacy (Witkiewitz *et al*., 2012).

A preclinical study of MN-166 was performed in alcohol-preferring P rats, high-alcohol drinking HAD1 rats, and mice made alcohol dependent through cycles of alcohol vapor exposure (Bell *et al*., 2015). The results showed that MN-166 administered twice daily reduced alcohol drinking in rats by approximately 50% and reduced drinking in mice that were alcohol-dependent in doses that did not affect non-dependent mice.

In August 2013, MediciNova announced that the National Institute on Alcohol Abuse and Alcoholism (NIAAA) would fund a randomized, double blind, placebo controlled Phase 2 clinical trial of MN-166 in 24 non-treatment seeking individuals with either alcohol abuse or dependence (NCT02025998). The trial will randomly assign participants to seven days of MN-166 or placebo treatment during which time the participants will take the study medication, complete an IV alcohol challenge, and take part in laboratory tests of alcohol craving as well as mood surveys and standard safety tests. Following a 7-10 day study break, trial participants will re-enroll for another 7-day period wherein they will cross over to the other treatment condition.

The primary outcomes for the study include safety, tolerability, and preliminary efficacy as indicated by whether MN-166 reduces alcohol craving under controlled conditions. The outcomes of this trial will inform the feasibility of a Phase 2b, regulatory-track, outpatient trial in alcohol dependence.

…Market Opportunity in Addiction Treatment…

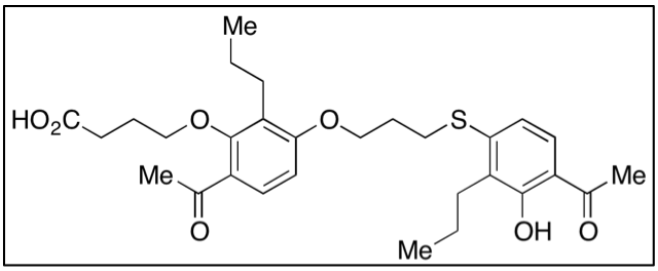
Treatment of addiction represents a sizeable opportunity for MediciNova. For MA addiction, there are no treatments available and there are close to 600,000 MA addicts in the U.S. MA addicts are currently treated with behavioral therapies that typically combine family education, individual counseling, 12-Step support, drug testing, and encouragement for non-drug-related activities. Motivational Incentives for Enhanced Drug Abuse Recovery (MIEDAR), an incentive based program that promotes cocaine and methamphetamine abstinence, has demonstrated efficacy through NIDA's National Drug Abuse Clinical Trials Network.

There are approximately 1.9 million current opioid medicine addicts and an additional 517,000 heroin addicts in the U.S. Current treatment options for opioid addiction include generic methadone, Subutex® (buprenorphine), and Suboxone® (buprenorphine + the opioid antagonist naloxone). Subutex® had U.S. sales of approximately $108 million in 2014 while Suboxone® had sales of $1.1 billion.

In the U.S., there are approximately 17.3 million people addicted to alcohol. There are three FDA approved medications for the treatment of alcohol dependence; Antabuse® (disulfiram), Vivitrol® (naltrexone), and Campral® (acamprosate). Only 20% of eligible patients receive medications to help combat their addiction. In 2014, sales of Vivitrol® totaled $94.2 million, while sales of Antabuse® and Campral® were not disclosed.

MN-001

Tipelukast (MN-001) is a novel, orally available small molecule compound that works through several mechanisms to produce anti-fibrotic and anti-inflammatory effects in preclinical models. The compound is a leukotriene (LT) receptor antagonist, a PDE inhibitor (mainly 3 and 4), and also inhibits 5-lipoxygenase (5-LO). The 5-LO/LT pathway is though to be a pathogenic factor in fibrosis development (Zeldin *et al*., 2002).



Source: trc-canada.com

MediciNova is developing MN-001 as treatment for nonalcoholic steatohepatitis (NASH) and pulmonary fibrosis (PF). Previously, the company had tested MN-001 as a treatment for asthma and completed a Phase 2 study with positive results. The compound has been tested in over 600 subjects and was considered generally safe and well tolerated.

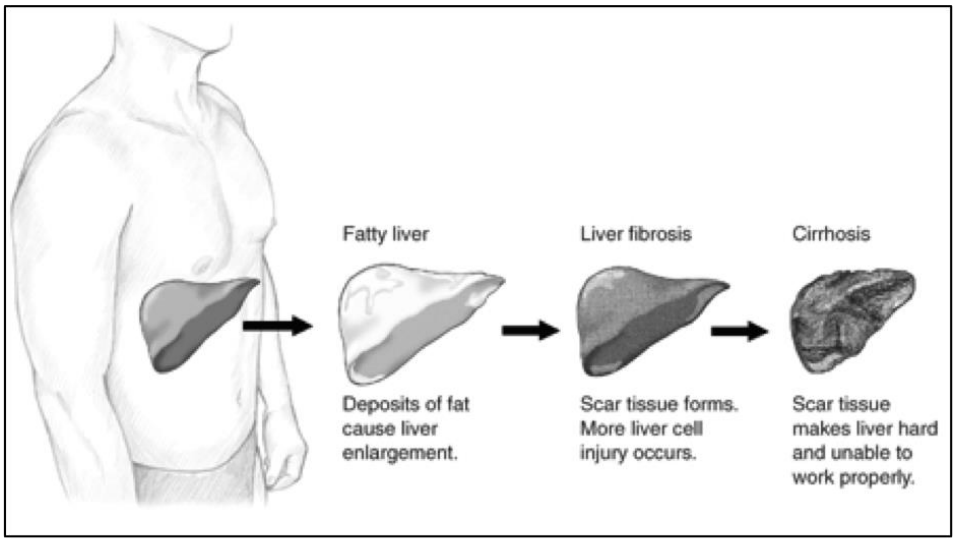
Indication I: NASH

Nonalcoholic steatohepatitis (NASH) is inflammation and damage in the liver brought on by a buildup of fat. The disease is an often "silent" liver disease as most people with NASH feel well and are not aware that they have a liver problem. Nevertheless, NASH can be severe and can lead to cirrhosis, in which the liver is permanently damaged and scarred and no longer works properly.

NASH is the most severe form of nonalcoholic fatty liver disease (NAFLD), a type of fatty liver where there is deposition of fat (steatosis) in the liver brought on by something other than alcohol consumption and is often due to obesity. Approximately 10 to 20 percent of individuals in the U.S. have fat in their liver but no indication of inflammation, while NASH affects two to five percent of people in the U.S (NIDDK).

Both NASH and NAFLD are becoming more common, possibly because of the greater number of Americans with obesity. In the past 10 years, the rate of obesity has doubled in adults and tripled in children. Obesity also contributes to diabetes and high blood cholesterol, which can further complicate the health of someone with NASH.

People with NASH usually have few or no symptoms. Patients generally feel well in the early stages and only begin to have symptoms — such as fatigue, weight loss, and weakness — once the disease is more advanced or cirrhosis develops. The progression of NASH can take years or even decades, can stop on its own and even get better without therapy, or it can slowly worsen and cause fibrosis, or scarring, of the liver. As fibrosis worsens, cirrhosis develops; the liver becomes seriously scarred, hardened, and unable to function normally. Not every person with NASH develops cirrhosis, but once serious scarring or cirrhosis is present there are few treatments that can halt the progression. Liver transplantation is the only treatment for advanced cirrhosis with liver failure, and transplantation is increasingly performed in people with NASH. NASH ranks as one of the major causes of cirrhosis in America, behind hepatitis C and alcoholic liver disease.



Source: NIDDK

Elevated liver enzymes, such as alanine aminotransferase (ALT) or aspartate aminotransferase (AST), are the first sign that a person may have NASH. If further evaluation shows no apparent reason for liver disease (such as medications, viral hepatitis, or excessive use of alcohol) and x-rays or imaging studies of the liver show fat, NASH is suspected. The only means of proving a diagnosis of NASH and separating it from simple fatty liver is a liver biopsy. NASH is diagnosed when examination of liver tissue shows fat along with inflammation and damage to liver cells. If the tissue shows fat without inflammation and damage, simple fatty liver or NAFLD is diagnosed. An important piece of information learned from the biopsy is whether scar tissue has developed in the liver. Currently, no blood tests or scans can reliably provide this information.

While NASH has become more common since it was first diagnosed over 30 years ago (Ludwig *et al*., 1980), its exact cause is still uncertain. Since it is associated with fat accumulation in the liver, it is not surprising that many patients with NASH have elevated blood cholesterol and triglycerides. However, some patients with NASH are not overweight, do not have diabetes, and have normal blood cholesterol and triglyceride levels. Thus, while they are contributory factors, NASH is not simply a consequence of obesity or elevated blood lipid levels.

…Current Treatment Options for NASH…

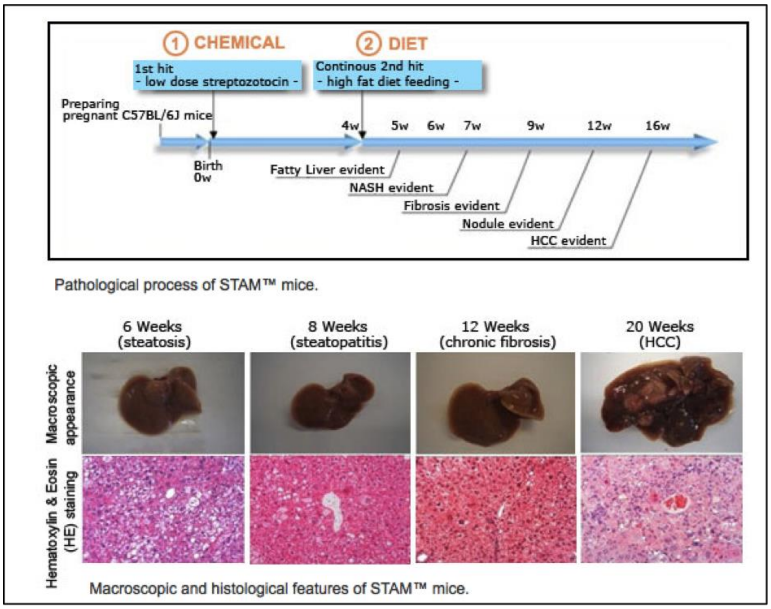
There are currently no treatment options available for those that develop NASH. Physicians typically advise NASH patients to lose weight (if they are overweight or obese), get more exercise, eat healthy, and avoid alcohol and unnecessary medications. While these are simply standard recommendations for maintaining a healthy lifestyle they can make a difference in patients with NASH. Losing weight typically leads to improved liver tests and may possibly reverse the disease, but usually only to a certain extent.

Experimental approaches currently under development include the use of antioxidants, such as Vitamin E, selenium, and betaine. There is usually an increased oxidative stress in the livers of NASH patients, thus these medications may work to lower the amount of oxidative species. Another experimental approach under development is the use of antidiabetic medications, even for those NASH patients who are not diabetic. Many NASH patients are insulin resistant, thus medicines such as metformin, rosiglitazone, or pioglitazone may increase patients sensitivity to insulin and reduce liver injury by better enabling a patient to control blood glucose and lipid levels. Additional therapies under development include experimental medications obeticholic acid (Intercept Pharmaceuticals), RP103 (Raptor Pharmaceuticals), GR-MD-02 (Galectin Therapeutics), and LJPC-1010 (La Jolla Pharmaceuticals).

…Pre-clinical Data Supports MN-001 for the Treatment of NASH…

Two separate studies in mouse models of NASH have shown MN-001 to have both anti-NASH and anti-fibrotic activity.

Study #1: MN-001 was administered orally once daily (10, 30, or 100 mg/kg) for three weeks in the STAM™ (NASH-HCC) mouse model of NASH. The model is created by a combination of chemical and dietary interventions in a standard laboratory mouse strain, as shown below.



Source: PsychoGenics.com

Treatment with MN-001 resulted in a dose-dependent reduction in liver fibrosis as demonstrated by a reduction in liver hydroxyproline content ($P < 0.01$). In addition, there was a significant improvement ($P < 0.01$) in the NAFLD activity score (NAS), which is a summation of the separate scores for steatosis (0–3), hepatocellular ballooning (0–2) and lobular inflammation (0–3). Concurrently, MN-001 was shown to significantly down-regulate ($P < 0.01$) the expression of MCP-1, CCR2, collagen type-1, and TIMP-1; all of which are genes associated with the formation of fibrosis.

Study #2: In a second study, the same STAM™ (NASH-HCC) mouse model of NASH was utilized, however the mice were at a more advanced stage of NASH. MN-001 was administered orally once daily (10, 30, or 100 mg/kg) beginning at eight weeks of age for four weeks.

Once again, treatment with MN-001 resulted in a statistically significant decrease in NAS score ($P < 0.001$), owing mostly to a decrease in hepatocyte ballooning score and lobular inflammation score. Fibrosis area was also significantly reduced in the MN-001 treated group ($P < 0.01$). MN-001 was once again shown to decrease expression levels of the previously tested genes along with LOXL2, a gene shown to be upregulated in fibrotic livers (Barry-Hamilton *et al*., 2010). Importantly, treatment with MN-001 had no effect on body weight or general condition of the mice compared to placebo.

Indication II: Pulmonary Fibrosis

Pulmonary fibrosis (PF) is a respiratory disease that occurs when lung tissue becomes damaged and scarred. As the disease progresses patients gradually become more short of breath. The disease can be caused by a number of factors, however in most cases there is no known cause. When a specific cause can't be found, it is referred to as idiopathic pulmonary fibrosis (IPF). A diagnosis of PF carries a grim prognosis, as most patients diagnosed with the disease typically die within three to five years of diagnosis (Frankel *et al*., 2009).

Most cases of PF will come on gradually, with patients typically first experiencing symptoms at least six months prior to a diagnosis. Symptoms of the disease include dyspnea (shortness of breath), a dry cough, fatigue, weight loss, and aching muscles and joints. Risk factors for developing PF include age (most cases are diagnosed in older adults), smoking, working in mining, farming, or construction, and certain cancer treatments.

PF appears to be a relatively rare disease; however, no large-scale studies of the incidence or prevalence are currently available. According to the Coalition for Pulmonary Fibrosis, IPF affects approximately 128,000 individuals in the U.S., with about 48,000 new cases diagnosed annually. Approximately two-thirds of people diagnosed with PF are above the age of 60 at the time of diagnosis (Raghu *et al*., 2006).

…Current Treatment Options for PF…

There is no cure for PF, thus currently used medications are aimed at preventing additional lung scarring, relieving symptoms, and helping patients stay active and healthy. Patients with PF typically present with a number of comorbid conditions, including chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, gastroesophageal reflux disease (GERD), and coronary artery disease (CAD). GERD is particularly prevalent amongst patients with PF and a retrospective analysis showed that of 204 patients, 34% reported symptoms of GERD, 45% had a history of GERD, and 47% reported use of medications for GERD. In addition, the use of GERD medications was associated with longer survival time (Lee *et al*., 2011). Additional medications that have been utilized to treat PF include prednisone, cyclophosphamide, azathioprine, and mycophenolate mofetil. Oxygen therapy is typically prescribed when lung function begins to deteriorate and blood oxygen levels fall too low. Lastly, lung transplant may be recommended if a patient is younger than 65, has no other medical problems, and are not responding to other medications.

There are currently two agents that are FDA-approved for the treatment of PF: pirfenidone (Esbriet®) and nintedanib (Ofev®), both of which were approved in October 2014.

- **Pirfenidone** was approved based on the results of the ASCEND and CAPCITY 1 and 2 Phase 3 clinical trials. The CAPACITY program included two clinical trials (study 004 and study 006) of 345 pirfenidone-treated patients and 347 placebo-treated patients where a pooled analysis of pirfenidone dosed at 2403 mg/day showed a significant reduction in decline of forced vital capacity (FVC), a measure of lung capacity (Noble *et al*., 2011). The ASCEND study included 555 patients randomized 1:1 to receive pirfenidone or placebo (King Jr. *et al*., 2014). Results showed that after one year of treatment, 16.5% of patients in the pirfenidone-treated group experienced an FVC decline of 10% or more compared to 31.8% in the placebo group. In addition, 22.7% of patients in the pirfenidone group experienced no decline in FVC compared with 9.7% in the placebo group. Analysts estimate peak sales of Esbriet® are approximately $1.1 billion; Roche acquired the drug by purchasing InterMune for $8.3 billion in August 2014.

- **Nintedanib** was approved based on the results of two Phase 3 clinical trials (INPULSIS-1 and INPULSIS-2) conducted in parallel in 1066 patients randomized 3:2 to receive either 150 mg nintedanib or placebo twice daily (Richeldi *et al*., 2014). Results showed a significantly lower annual rate of change in FVC in nintedanib-treated patients compared to placebo-treated patients. In addition, a smaller proportion of patients in the nintedanib groups than in the placebo groups had an absolute decline in FVC or more than 5 percentage points.

…Clinical Development Pathway for MN-001…

MediciNova currently has an investigational new drug (IND) application open with the FDA to initiate a Phase 2 trial of MN-001 in both NASH and IPF. In October 2014, the company announced they had received feedback in regards to the study protocol for the Phase 2 trial of MN-001 in NASH. That same month, the company announced that the FDA granted Orphan Drug designation to MN-001 for the treatment of IPF. Orphan drug designation carries a number of incentives for the company, including increased feedback from the FDA regarding clinical trial design, seven years of market exclusivity following approval for the treatment of IPF, tax credits, and a waiver of PDUFA fees. In February 2015, MediciNova announced that FDA has approved the protocol for a Phase 2 study in moderate to severe IPF. The company is currently in discussions with investigators to initiate trials in NASH and IPF.

Other Programs

MediciNova has additional compounds/programs that do not have clinical trials ongoing currently. These programs include:

MN-221 (Bedoradrine): MN-221 is a highly selective β2-adrenergic receptor agonist that has previously been tested for the treatment of acute exacerbations of asthma. The drug is designed to be delivered to patients via intravenous infusion, thus bypassing constricted airways where drug delivery to the lungs would be restricted. Preclinical studies showed that MN-221 has high selectivity for the β2-adrenergic receptor, primarily found in the lungs, compared to the β1-adrenergic receptor found primarily in cardiac tissue. A Phase 2b randomized, double blind, placebo controlled clinical trial was previously conducted in 175 patients with acute exacerbations of asthma in the emergency department setting. MN-221 did not meet the primary endpoint of the study, improvement in forced expiratory volume in one second (FEV1) compared to placebo. However, MN-221 did show a significant benefit over placebo for FEV1 area under the curve of change from baseline along with a reduction in hospital admissions when MN-221 was added to standard drug treatments. In October 2012, the company met with the FDA to review future development of MN-221. The FDA identified the risk/benefit profile of MN-221 as a focal point for development and advised that a clinical outcome, such as reduction in hospitalizations, would need to be included as a primary endpoint in a pivotal trial.

MN-029 (Denibulin): MN-029 is a novel tubulin binding agent (TBA) that is under development for the treatment of solid tumors. It inhibits tubulin polymerization that results in a disruption of the cell cytoskeleton, thus causing cancer cells to deform in shape and ultimately leading to necrosis. Preclinical work with the compound shows that it weakens tumor blood vessel walls, resulting in leakage, clotting, and eventual vascular shutdown within the tumor. A Phase 1 trial was performed with 34 subjects with refractory cancer. Side effects were similar to other chemotherapeutic agents – vomiting, nausea, diarrhea, and fatigue. No patient had a complete or partial response; however stable disease was noted in 12 patients. A second Phase 1 study was performed with 20 subjects with advanced/metastatic solid tumors. One subject had a partial response that lasted 74 days and stable disease was observed in seven subjects.

Financial Position and Capital Structure

As of December 31, 2014, MediciNova was well capitalized with approximately $11.7 million in cash and cash equivalents, which we estimate is enough to fund operations through the first quarter of 2016. As of December 31, 2014, the company had approximately 3.66 million warrants outstanding with exercise prices ranging from $3.15 to $3.56. If all warrants were exercised, they would bring in an additional $11.9 million in gross proceeds.

In addition, MediciNova currently has an at-the-market equity distribution agreement with Macquarie Capital (USA), Inc. (MCUSA) pursuant to which the company may sell common stock through MCUSA from time to time up to an aggregate of $10 million. As of December 31, 2014, the company had generated gross and net proceeds of $5.1 million and $4.4 million, respectively, on the sale of 2,082,500 shares of common stock under the agreement. The company is likely to sell additional shares under the agreement during 2015.

The company currently has approximately 24.6 million shares outstanding. In addition, there are 220,000 shares of Preferred stock outstanding, with each share of preferred stock convertible to 10 shares of common stock. There are also 3.66 million warrants outstanding and 3.45 million stock options outstanding, so the fully diluted share count is approximately 33.9 million.

MANAGEMENT PROFILES

Yuichi Iwaki, MD, PhD – President and Chief Executive Officer
Dr. Iwaki holds three professorships at the University of Southern California School of Medicine in the Departments of Urology, Surgery, and Pathology and has been Director of the Transplantation Immunology and Immunogenetic Laboratory since 1992. He is also a visiting professor at the Nihon University School of Medicine, Kyushu University and Toho University, School of Medicine in Japan. Prior to joining the faculty at the University of Southern California School of Medicine, Dr. Iwaki held professorships at the University of Pittsburgh School of Medicine in the Departments of Surgery and Pathology from 1989 through 1991. He received both his M.D. and Ph.D. degrees from Sapporo Medical School in Sapporo, Japan. Dr. Iwaki is the author of 200 peer-reviewed publications and more than 40 books. He has been advising pharmaceutical companies and venture capital funds regarding research and investment strategies for over 30 years and is a board member of several biotechnology companies.

Masatsune Okajima – Vice President
Mr. Okajima joined MediciNova in September 2006. Before joining MediciNova, Mr. Okajima served as Deputy General Manager, Daiwa Securities SMBC Co., Ltd. From 1999 through 2002, Mr. Okajima served as Manager, Daiwa Securities' SB Capital Markets Co., Ltd. (currently Daiwa Securities SMBC Co., Ltd.). As Deputy General Manager, Mr Okajima was involved in pivotal phases of initial public offerings, subsequent public offerings, corporate bond issuances, and mergers & acquisitions. In addition, he handled Investors Relations and stock trading. From 1996 to 1999, Mr. Okajima served as Manager, Sumitomo Capital Securities Co., Ltd. Mr. Okajima served in various positions at Sumitomo Bank, Ltd. (currently Mitsui Sumitomo Bank) between 1991 and 1996. Mr. Okajima graduated with a B.S. Degree from the Department of Science and Technology, Tokyo Science University.

Kazuko Matsuda, MD, PhD – Chief Medical Officer
Dr. Matsuda has served as Vice President of Clinical Development for MediciNova since 2010 and is responsible for all clinical development. Previously, Dr. Matsuda was a clinical advisor to MediciNova for its MN-221 and MN-166 development programs. Prior to joining MediciNova, Dr. Matsuda was assistant professor, University of Southern California, Keck School of Medicine after an appointment at the Children's Hospital Los Angeles. Dr. Matsuda commenced her residency in internal medicine/pediatrics at Michigan State University and completed a pediatric residency at Loma Linda University. She is a board certified pediatrician in both the United States and Japan. Dr. Matsuda received her M.D. and Ph.D. from Sapporo Medical School and MPH from Harvard University, School of Public Health.

Geoffrey O'Brien – Vice President
Mr. O'Brien joined MediciNova in June 2009. Prior to joining MediciNova, Mr. O'Brien worked on Wall Street for 10 years as an equity research analyst and investment banker covering pharmaceutical and biotechnology companies at UBS, DLJ/Credit Suisse First Boston, Nomura, and Punk Ziegel, and was a Vice President from 2004-2008. During his career as a senior equity research analyst on the sell side and buy side, he focused on clinical, scientific, financial, strategic and competitive analysis of development programs and marketed products. He used this analysis to predict the future prospects of both development-stage and established pharmaceutical and biotechnology companies. At UBS, Mr. O'Brien worked on the specialty pharmaceuticals team, which was ranked #2 in Institutional Investor magazine's All-America Research Team survey. He executed acquisitions and equity offerings as a health care investment banker at DLJ/Credit Suisse First Boston. Prior to graduate school, Mr. O'Brien worked on the successful development of a biotechnology product at The Liposome Company. Mr. O'Brien received a B.S. in chemistry, cum laude, from the University of Delaware and completed his J.D. and M.B.A. simultaneously at Vanderbilt Law School and Owen Graduate School of Management at Vanderbilt University.

Esther van den Boom – Chief Financial Officer
Ms. van den Boom was appointed Chief Financial Officer in 2014 and is responsible for Accounting and Finance. Ms. van den Boom brings over thirteen years of accounting and auditing experience to MediciNova, including most recently having worked with Ernst & Young LLP as a Senior Manager in their San Diego office's audit practice where she was responsible for accounting and auditing matters and helping public and private biotechnology companies. Ms. van den Boom has worked closely with many early stage, venture backed companies, as well as seasoned public companies. Esther received a B.A. in Economics from University of California, San Diego and a M.S. in Accountancy from San Diego State University and is a licensed CPA.

VALUATION AND RECOMMENDATION

We are initiating coverage of MediciNova, Inc. (Nasdaq: MNOV) with a Buy rating and a price target of $8.00. MediciNova is a biopharmaceutical company focused on developing small molecule therapeutics for the treatment of serious diseases with unmet medical needs. Currently, the company is focused on the development of MN-166 (ibudilast) and MN-001 (tipelukast).

MN-166 is Both an Anti-inflammatory and Neuroprotective Agent

MN-166 (ibudilast) is an anti-inflammatory compound that exerts its effects through attenuation of the peripheral immune system and in the CNS via attenuation of glial cells, which play a role in certain neurological conditions. The compound also has neuroprotective qualities through inhibition of glial cell activation and enhances the production of the anti-inflammatory cytokine IL-10 and neurotrophic factors such as NGF, GDNF, and NT-4.

MediciNova is currently testing MN-166 in five separate Phase 2 clinical trials; one for progressive MS, one for amyotrophic lateral sclerosis (ALS), and three for addiction.

…Targeting a Huge Unmet Medical Need in Progressive Multiple Sclerosis…

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory disease that affects axons in the central nervous system (CNS). MS is associated with a wide range of debilitating symptoms brought on by the deterioration of the myelin sheath that surrounds axons, which are long, slender projections of nerve cells (neurons) that conduct electrical impulses that transmit information to different neurons, muscles, and glands. When the myelin sheath is damaged there is interference in the communication between the brain, spinal cord, and other areas of the body. This process may also lead to the deterioration of the nerve cells themselves, a condition that is not reversible.

Approximately 85% of MS cases are relapse-remitting MS (RRMS) at onset. This form of MS is characterized by clearly defined relapses with full recovery. Fifty percent of patients with RRMS go on to develop secondary progressive MS (SPMS), which occurs when the disease steadily progresses following an initial relapsing-remitting phase. Approximately 10% of patients have primary progressive MS (PPMS), which is characterized by disease progression from the time of onset with no acute attacks. The least common form is progressive relapsing MS (PRMS), which is characterized by progressive disease with occasional relapses.

There are twelve compounds that are FDA approved for the treatment of RRMS, but only one of which (mitoxantrone) is approved for the treatment of SPMS. There are no drugs approved for the treatment of PPMS. Due to cumulative cardiotoxicity, patients may not take mitoxantrone for longer than two to three years, however very few people actually take mitoxantrone due to its toxicity. Thus, there is a significant, unmet need for new treatments that are effective in treating the progressive forms of MS.

The top seven best-selling MS drugs in 2014 each generated revenues in excess of $1 billion, with the total MS market size being greater than $18 billion. Each of those drugs is only approved for the treatment of RRMS, thus we believe an effective treatment for progressive MS would most likely generate peak revenues in excess of $2-3 billion per year.

…ALS Represents Another Large Opportunity with Blockbuster Potential…

Amyotrophic lateral sclerosis (ALS) is a rapidly progressing neurodegenerative disease whereby the nerve cells in the brain and spinal cord that control muscle movement degenerate. This rapid degeneration of the motor neurons eventually leads to death, typically in three to five years after patients are first diagnosed. For the vast majority of patients (~95%) there is no known cause while a very small number of cases can be attributed to a genetic component where ALS is known to run in families.

Riluzole is the only compound that has ever been approved to treat ALS, and it only increases lifespan in patients by two to three months. The remaining treatments for ALS are designed to relieve symptoms and improve quality of life. However, none of these treatments reduces disease progression or addresses the underlying cause of the disease. MN-166 would appear to be a natural choice for testing in ALS patients due to its neuroprotective effects and ability to incite production of neurotrophic factors.

Any treatment that affected the progression of ALS would likely be a blockbuster opportunity given the limited treatment options and high costs associated with patient care. We believe an effective ALS treatment would command a premium price, possibly as high as $100,000 per patient per year. Assuming conservatively that only one third of ALS patients took the drug (10,000 patients); this would generate sales of $1.0 billion per year.

…Treatment of Addiction Has Shown Success in Early Testing…

A common mechanism amongst drug addictions appears to be the over-activation of glial cells, thus inhibition of glial cells by MN-166 may be a means to decrease the amount of pro-inflammatory cytokines that are produced by the cells in response to activation by different drugs. While not as large a market as for MS or ALS, the treatment of different addiction disorders represents another sizeable opportunity for the company.

The company has already reported positive results from the study of MN-166 in opioid withdrawal and inattention associated with methamphetamine abuse. In addition, positive results were recently released from an interim analysis performed after the first seven patients in an opioid dependency study had completed treatment. MN-166 demonstrated a beneficial effect on the subjective, analgesic, and reinforcing effects of oxycodone and significantly decreased the craving for heroin, cocaine, and tobacco ($P < 0.05$ for all three substances).

Importantly, each of the three Phase 2 clinical trials currently ongoing for methamphetamine, opioid, and alcohol addiction is being funded through grants from the National Institutes of Health. Thus, the company is spending no money on the trials outside of supplying drug product and supporting regulatory filings.

MN-001 Targeting Two Blockbuster Opportunities

Tipelukast (MN-001) is a novel, orally available small molecule compound that works through several mechanisms to produce anti-fibrotic and anti-inflammatory effects. The compound is a leukotriene (LT) receptor antagonist, a PDE inhibitor (mainly 3 and 4), and also inhibits 5-lipoxygenase (5-LO). The 5-LO/LT pathway is though to be a pathogenic factor in fibrosis development.

The compound was previously tested for its potential clinical efficacy in treating asthma patients in a Phase 2 study that gave positive results. Over 600 individuals have been exposed to the drug, which was considered to be generally safe and well-tolerated.

Currently, MediciNova is targeting MN-001 for the treatment of two diseases: nonalcoholic steatohepatitis (NASH) and idiopathic pulmonary fibrosis (IPF). NASH is inflammation and damage in the liver brought on by a buildup of fat while IPF is a respiratory disease that occurs when lung tissue becomes damaged and scarred. There are currently no treatment options available for NASH patients, while the first medications for treating IPF (pirfenidone and nintedanib) were approved in October 2014. NASH affects between two and five percent of Americans while analysts have estimated peak sales of the recently approved IPF drugs at over $1 billion.

Comparative Valuations

There are a number of companies developing treatments for MS, ALS, addiction, NASH, and IPF. The following table lists some of these companies, the compounds under development, and the valuations currently assigned to them.

Company	Symbol	Indication	Product	Development Stage	Current Market Cap
Active Biotech	ATVBF	Progressive MS	Laquinimod	Phase 2	$130 million
AB Science	ABSCF	Progressive MS	Masitinib	Phase 3	$580 million
Brainstorm Cell Therapeutics	BCLI	ALS	NurOwn	Phase 2	$70 million
Neuralstem	CUR	ALS	NSI-566	Phase 2	$168 million
AB Science	ABSCF	ALS	Masitinib	Phase 2/3	$580 million
Titan Pharmaceuticals	TTNP	Opiod addiction	Probuphine	Phase 3	$78 million
La Jolla Pharmaceuticals	LJPC	NASH	LJPC-1010	Phase 1	$300 million
Intercept	ICTP	NASH	OCA	Phase 2b	$6,400 million
FibroGen	FGEN	IPF	FG-3019	Phase 2	$1,450 million

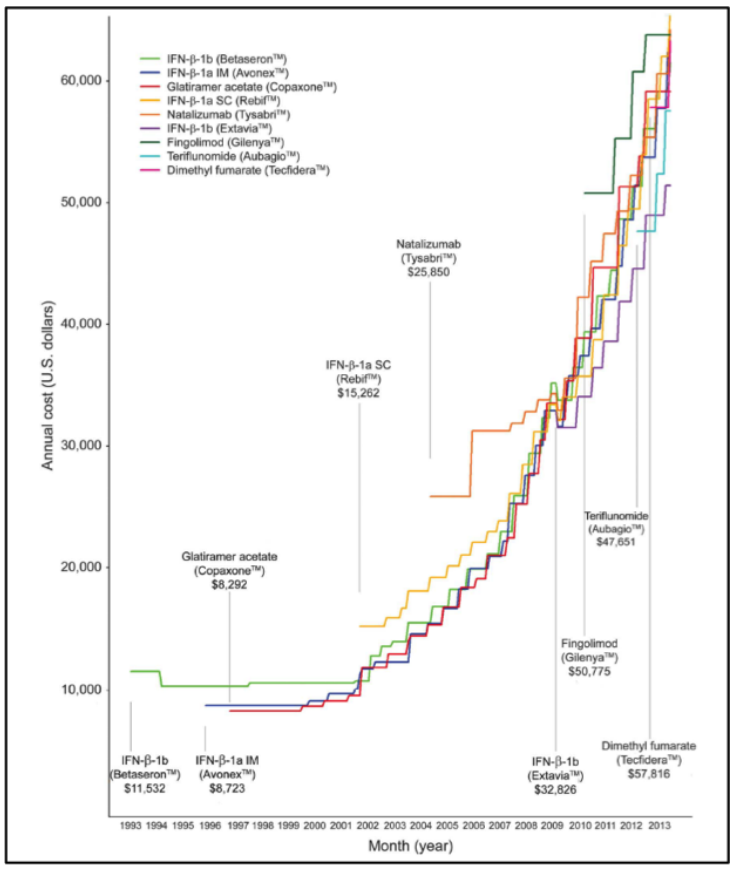
Source: Company information / Zacks SCR

While it is very difficult to make an “apples to apples” comparison, as most of these companies have additional compounds under development, one company that may serve as a useful proxy is AB Science, which is developing masitinib for both progressive MS and ALS and has a current market cap of approximately $580 million. AB Science is also developing masitinib for multiple oncology indications, thus the entire market cap of the company cannot be attributed to the MS and ALS indications. However, we believe that MediciNova’s $95 million market cap is low in comparison, particularly given that the company is also developing MN-001 for NASH and IPF, two indications that appear to command premium valuations based on the market caps of Intercept Pharmaceuticals and FibroGen, Inc.

…Our Valuation Methodology…

For MN-166, the vast majority of its value lies in the potential for treating progressive MS. An interim analysis for the MS trial is set to occur after half of the 250 patients targeted for enrollment in the study have received 96 weeks of treatment. The trial hit 125 enrollees in Aug. 2014, thus we anticipate an interim analysis in the second half of 2016 with the full data available in the first half of 2017. Positive interim and/or full data is very likely to lead to a partnership deal before the initiation of a Phase 3 study, which we estimate would begin in 2018, leading to an NDA filing in 2021 and approval in 2022.

A recent article in the journal *Neurology* shows that pricing for MS medications has increased at a very high rate since the first treatments were approved in the early 1990’s (Hartung *et al*., 2015). As the following figure shows, yearly MS drug prices now range between $45,000 and $65,000, even for those drugs that were approved more than twenty years ago. This means that a successful MS drug is likely to command at least $50,000 per year, which we are using for valuation purposes.



Source: Hartung *et al*., 2015

For MS, we estimate that MN-166 will have peak worldwide sales of approximately $5 billion. This may seem like an unrealistically high number, however we feel it is justified based on the pricing of MS drugs, the fact there is only one treatment for progressive MS that is not widely used, and a patient population of approximately 210,000 in the U.S. In addition, seven different MS drugs had greater than $1 billion in sales in 2014. We apply a 20% discount rate and a 33% probability of success to arrive at a probability adjusted net present value for MN-166 in MS of $115.5 million.

Results from the company's Phase 2 study of MN-166 in ALS should be available in the first half of 2016. Positive results could lead to the initiation of a Phase 3 trial in 2017, an NDA filing in 2019 and approval in 2020. Given the limited treatment options and small patient population (we estimate a target population of 18,000 in the U.S.), we believe a successful ALS drug could command $100,000 per year. Thus, we model peak worldwide sales of approximately $2.5 billion for MN-166 in ALS. Due to the fact that only one drug has ever been approved to treat ALS we model a 10% probability of success and apply a 20% discount rate. This gives a probability adjusted net present value for MN-166 in ALS of $35.8 million.

The addiction indications are not as large of an opportunity as for MS and ALS, however early results from those studies have been quite encouraging and there are few if any treatment options currently available. Treatments for addiction are capable of being blockbuster medications, as exemplified by Suboxone®, a treatment for opioid addiction, which had sales of $1.1 billion in 2014.The timelines for the addiction indications are not known at this point, thus instead of a detailed financial model, we assign a current valuation based on potential peak sales of approximately $750 million for the three indications with a discount rate of 20% and a 25% probability of success. This gives a net present value for MN-166 in addiction of $31.6 million.

The company should begin Phase 2 studies of MN-001 in both NASH and IPF in 2015. We model for a Phase 3 study in each indication in 2017 and an NDA filing and approval in 2020 and 2021, respectively. We estimate peak worldwide sales for MN-001 in NASH and IPF of $3 billion and $2 billion, respectively, and apply a 20% discount rate and a 20% probability of success. This gives a probability adjusted net present value for MN-001 in NASH and IPF of $70.8 million and $44.4 million, respectively.

Summing up the valuations for each indication, the cash on the books, and an expected $40 million in capital requirements gives a net present value for the company of approximately $270 million. Dividing this by the company's current fully diluted share count gives a target price of $8 per share, and we are assigning a 'Buy' rating to the stock.

PROJECTED FINANCIALS

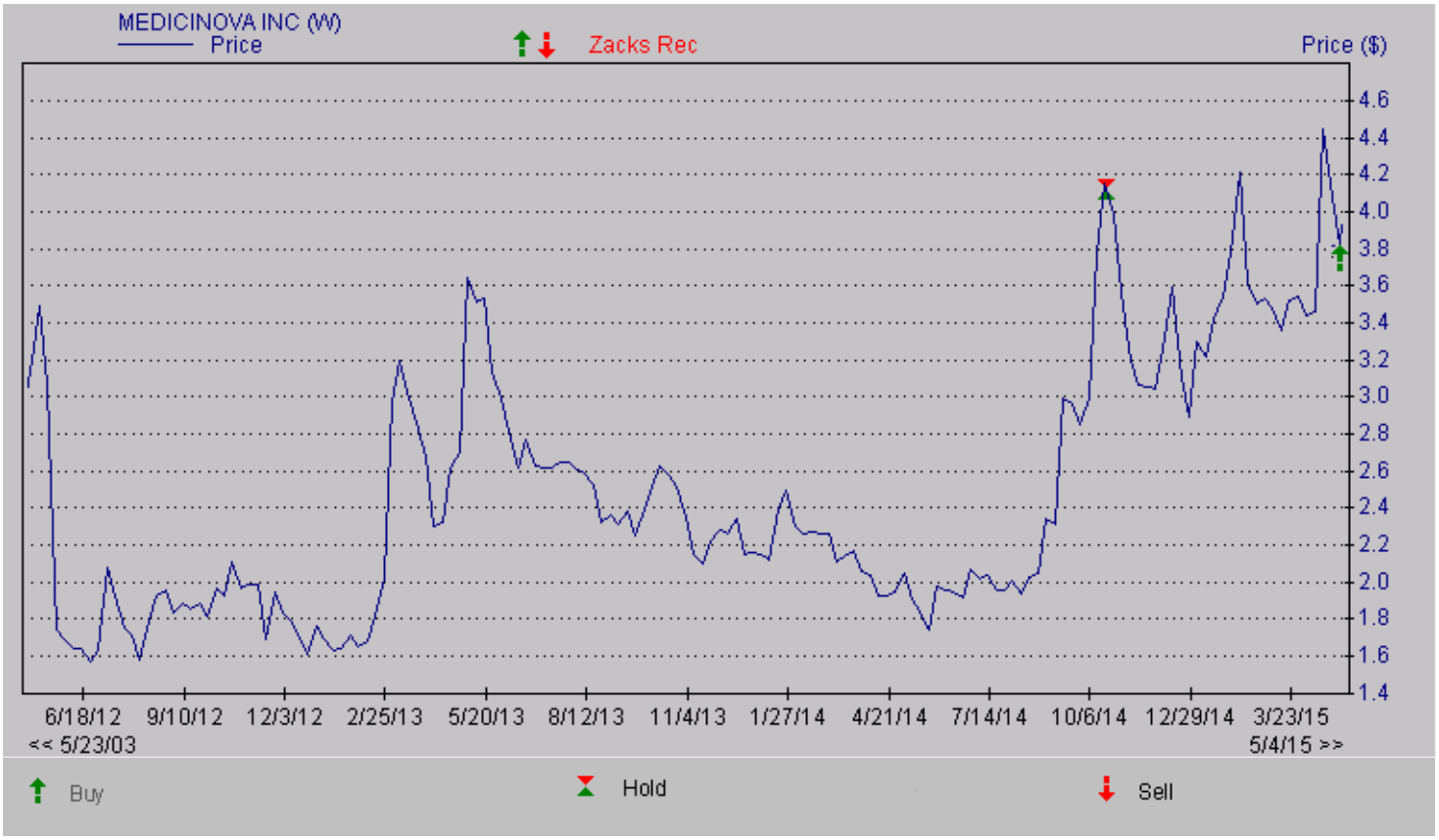
MediciNova Inc.
Income Statement

MediciNova, Inc.	2014 A	Q1 E	Q2E	Q3 E	Q4 E	2015 E	2016 E	2017 E
MN-166 (Multiple Sclerosis)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
MN-166 (ALS)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
MN-166 (Addiction)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
MN-001 (NASH)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
MN-001 (IPF)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$3.260	$0.800	$0.900	$0.950	$1.000	$3.650	$5.000	$7.000
General & Administrative	$5.963	$1.500	$1.600	$1.650	$1.700	$6.450	$8.000	$10.000
Other Expenses	$0	$0	$0	$0	$0	$0	$0	$0
Operating Income	($9.223)	($2.300)	($2.500)	($2.600)	($2.700)	($10.100)	($13.0)	($17.0)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$0.028	($0.100)	($0.100)	($0.100)	($0.1)	($0.4)	($0.5)	($0.5)
Pre-Tax Income	($9.195)	($2.4)	($2.6)	($2.7)	($2.8)	($10.5)	($13.5)	($17.5)
Income Taxes Paid	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($9.195)**	**($2.4)**	**($2.6)**	**($2.7)**	**($2.8)**	**($10.5)**	**($13.5)**	**($17.5)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($0.38)**	**($0.10)**	**($0.10)**	**($0.10)**	**($0.10)**	**($0.39)**	**($0.45)**	**($0.50)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	24.068	25.000	25.500	28.000	29.000	26.875	30.000	35.000

Source: Zacks Investment Research, Inc. *Jason Napodano, CFA*

© Copyright 2015, Zacks Investment Research. All Rights Reserved.

HISTORICAL ZACKS RECOMMENDATIONS



© Copyright 2015, Zacks Investment Research. All Rights Reserved.

DISCLOSURES

The following disclosures relate to relationships between Zacks Small-Cap Research ("Zacks SCR"), a division of Zacks Investment Research ("ZIR"), and the issuers covered by the Zacks SCR Analysts in the Small-Cap Universe.

ANALYST DISCLOSURES

I, Jason Napodano, CFA, hereby certify that the view expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the recommendations or views expressed in this research report. I believe the information used for the creation of this report has been obtained from sources I considered to be reliable, but I can neither guarantee nor represent the completeness or accuracy of the information herewith. Such information and the opinions expressed are subject to change without notice.

INVESMENT BANKING, REFERRALS, AND FEES FOR SERVICE

Zacks SCR does not provide nor has received compensation for investment banking services on the securities covered in this report. Zacks SCR does not expect to receive compensation for investment banking services on the Small-Cap Universe. Zacks SCR may seek to provide referrals for a fee to investment banks. Zacks & Co., a separate legal entity from ZIR, is, among others, one of these investment banks. Referrals may include securities and issuers noted in this report. Zacks & Co. may have paid referral fees to Zacks SCR related to some of the securities and issuers noted in this report. From time to time, Zacks SCR pays investment banks, including Zacks & Co., a referral fee for research coverage.

Zacks SCR has received compensation for non-investment banking services on the Small-Cap Universe, and expects to receive additional compensation for non-investment banking services on the Small-Cap Universe, paid by issuers of securities covered by Zacks SCR Analysts. Non-investment banking services include investor relations services and software, financial database analysis, advertising services, brokerage services, advisory services, investment research, investment management, non-deal road shows, and attendance fees for conferences sponsored or co-sponsored by Zacks SCR. The fees for these services vary on a per client basis and are subject to the number of services contracted. Fees typically range between ten thousand and fifty thousand per annum.

POLICY DISCLOSURES

Zacks SCR Analysts are restricted from holding or trading securities in the issuers which they cover. ZIR and Zacks SCR do not make a market in any security nor do they act as dealers in securities. Each Zacks SCR Analyst has full discretion on the rating and price target based on his or her own due diligence. Analysts are paid in part based on the overall profitability of Zacks SCR. Such profitability is derived from a variety of sources and includes payments received from issuers of securities covered by Zacks SCR for services described above. No part of analyst compensation was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in any report or article.

ADDITIONAL INFORMATION

Additional information is available upon request. Zacks SCR reports are based on data obtained from sources we believe to be reliable, but are not guaranteed as to be accurate nor do we purport to be complete. Because of individual objectives, this report should not be construed as advice designed to meet the particular investment needs of any investor. Any opinions expressed by Zacks SCR Analysts are subject to change without notice. Reports are not to be construed as an offer or solicitation of an offer to buy or sell the securities herein mentioned.

ZACKS RATING & RECOMMENDATION

ZIR uses the following rating system for the 1047 companies whose securities it covers, including securities covered by Zacks SCR:
Buy/Outperform: The analyst expects that the subject company will outperform the broader U.S. equity market over the next one to two quarters.
Hold/Neutral: The analyst expects that the company will perform in line with the broader U.S. equity market over the next one to two quarters.
Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

The current distribution is as follows: Buy/Outperform- 16.5%, Hold/Neutral- 77.7%, Sell/Underperform – 5.1%. Data is as of midnight on the business day immediately prior to this publication.