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MARCH 2011

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Opportunity

Biotechnology company Acorda Therapeutics started out with a mission to develop new treatments for spinal cord injuries. But, not all science goes according to plan.

By Cliff Mintz, Ph.D.

THE MS MARKET HAS HISTORICALLY BEEN DOMINATED BY large biotech and pharma companies (e.g. Novartis, Biogen Idec, EMD Serono, Bayer Healthcare Pharmaceuticals, Teva). However, Acorda Therapeutics, a small public biotechnology company in Hawthorne, NY, is trying to change this trend. Early last year, the company received FDA approval of its first product, AMPYRA (dalfampridine), which is designed to improve walking in MS patients.

While AMPYRA is not a disease-modifying drug like other MS treatments, it is the first drug to be approved to specifically treat a bona fide symptom of MS. According to a recent survey conducted by the National Multiple Sclerosis Society, 2/3 of patients with MS experience problems with walking, and 70% of these patients identified walking impairment to be the most challenging symptom of their disease. Rather than developing another marginally effective disease modifying drug for patients with MS, Ron Cohen, M.D., Acorda's founder and

CEO, chose to develop a product that could treat a major symptom of MS and thereby improve the quality of life of patients struggling with the disease.

Cohen, a board-certified internist with a passion to discover cures and drugs to treat patients with chronic, debilitating neurological conditions, founded Acorda in 1995. Prior to founding Acorda, Ron was part of the management team at biotechnology company Advanced Tissue Sciences, Inc. He received his B.A. degree from Princeton University and an M.D. degree from Columbia College of Physicians and Surgeons.

I spoke with Cohen early this year about the challenges of discovering new treatments for CNS (central nervous system) disorders, what it takes to run a small biotechnology company with a newly approved product, and how Acorda expects to be successful in the highly competitive and lucrative MS market.

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WAS ACORDA SPECIFICALLY FOUNDED TO DEVELOP NEW AND INNOVATIVE TREATMENTS FOR MS?

The initial plan for Acorda was to use biotechnology to develop innovative, new treatments for spinal cord injuries. And, by extension, we believed some of these discoveries would lead to treatments for other neurological disorders like MS, Parkinson's, Alzheimer's, and others.

We decided to work on spinal cord injuries mostly because there were no good treatments at the time we formed the company (there still aren't), and very few companies were working in the space. Also, some major fundamental laboratory advances had been made in spinal cord injuries, and I thought the time was right to focus our efforts in this area. In fact, the name Acorda reflects our original, primary focus on developing drugs to treat spinal cord injuries.

The reason why Acorda's MS program is so advanced now is that the drug we decided to develop to treat spasticity in spinal cord injury — which is now AMPYRA — had little clinical benefit to treat spasticity in patients with spinal cord injuries. Meanwhile, because of the mechanism of action of the drug, we quickly realized it may have possible applications in MS. Luckily, we elected to follow the science and data to wherever it took us. This allowed us to develop AMPYRA as a novel treatment to improve walking in persons with MS.

One of the major challenges of running a start-up biotechnology company is resisting the temptation to rationalize your data so that the company cans its next round of financing to stay alive. And, when you find yourself in that box (you almost always do), it means you are trying to make the science fit your preconceived notion of what it is supposed to do, and that is a fatal mistake. Interestingly, the key to Acorda's success was the ability to survive long enough, make our mistakes, and then figure out how to do it correctly as we moved forward. When I think about it, one of the most important things I learned about developing drugs — large or small — to treat neurological diseases is that you have to be almost completely agnostic when it comes to considering possible treatment interventions. In other words, you have to be willing to let the science take you where it may.

DO YOU THINK THE LACK OF STRATEGIC OR FINANCIAL PARTNERSHIPS/ALLIANCES WITH LARGER PHARMA AND BIOTECH COMPANIES WILL HAVE ANY EFFECT ON YOUR COMPANY'S DEVELOPMENT PROGRAMS OR ITS ULTIMATE COMMERCIAL SUCCESS?

Acorda is in the best financial shape it has been since the company was founded. We are generating a positive cash flow and are no longer as dependent on investor capital to determine future research direction. Also, our current financial situation puts us in a much better position to identify and enter into relationships with smaller companies that we think are working on the next big breakthrough in neurodegenerative diseases.

As far as our business relationships go, we do have existing relationships with Elan and Biogen to market and commercialize our approved products. Unfortunately, until AMPYRA and ZANAFLEX

(muscle spasticity in MS and spinal cord injury) were approved, not many companies expressed interest in our preclinical assets. However, this has recently changed, mainly because many big pharma companies have failing pipelines and are facing patent cliffs in the very near future. This has essentially forced many larger companies to begin to consider partnerships and deals with smaller companies like Acorda that have interesting preclinical assets to offer.

Not surprisingly, many companies that previously expressed little interest in Acorda are now very interested in talking with us about possible deals. Of course, we are now in a financial position to invest in some of these programs ourselves — at least to get to the next value-creating event which would be proof of concept in Phase 2. That said, we are inclined to assume as much of the preclinical and early stage development risk as possible, because the payoff would be greater if we partner in late stage (Phase 3) clinical development. We feel we can afford to take a year or two to develop more value in our preclinical candidates before we sell an interest in them. At this stage, if we win, we win; if we don't, we don't!

HOW WILL ACORDA COMPETE WITH MUCH LARGER COMPANIES LIKE BIOGEN IDEC, TEVA, MERCK KG, NOVARTIS, AND OTHERS TO BRING NEW MS DRUGS TO MARKET?

Interestingly, Acorda doesn't view itself as a competitor with larger companies in the MS space like Biogen Idec, EMD Serono, and Novartis. Their treatments are disease-modifying immunomodulatory drugs, whereas ours, specifically AMPYRA, was developed to treat a specific functional symptom (walking impairment) of MS. Moreover, AMPYRA can safely be taken by patients receiving immunomodulator therapy like Avonex and Betaseron. At present, roughly 60% of patients treated with AMPYRA also are receiving immunomodulators, whereas 40% are not. With this in mind, we view our products as complementary rather than competing with other MS treatment interventions.

Hypothetically, if someone were to hit a home run (i.e. find a cure for all patients suffering from MS), then companies with disease modification intervention franchises would soon be out of business. However, companies like Acorda with symptomatic or functional treatment franchises would be able to stick around a bit longer because there would be about 400,000 preexisting patients with MS who would likely not be able to benefit from the cure (unless it could completely reverse the disease, which may be a stretch).

The reality is, at present we have no insights into which of the companies currently working on MS is likely to hit the home run. For example, five years ago Biogen Idec looked like it would emerge as the dominant player in MS with Avonex. Unfortunately, Biogen Idec is experiencing problems with PML and Tysabri, Avonex's would-be successor. It now appears that oral medications like Gilenya may be the next big advance to treat patients with MS.

No matter how well-financed or large a biotechnology company may be, it is always at risk of losing leadership or market share in this industry. Conversely, no matter how small you are, you have the potential for taking leadership if your science is good, you develop

good medicines, and your business model makes sense. Of course, the wild card in all of this is whether or not a company's medicines are safer or more efficacious than its competitors'. And, more often than not, it is extremely difficult to predict where the next big advance or innovation is going to come from. Things change very rapidly in this business, and yesterday's perceived "loser" could be tomorrow's big winner!

WHAT ARE SOME OF THE LESSONS LEARNED OR ADVICE YOU WOULD OFFER WOULD-BE ENTREPRENEURS WHO ARE CONSIDERING STARTING UP A COMPANY WITH A CNS FOCUS?

I would tell them if they are not absolutely passionate about what they are attempting to do, then the road ahead will be extremely bumpy and difficult to navigate. Personally, I love what I do, and I am seriously dedicated to making a difference for patients who suffer from chronic, neurodegenerative diseases and spinal cord injuries.

I don't think I would have survived the massive ups and downs over the past 17 years if I didn't have a fire raging deep inside of me that compelled me to come to work every day to butt my head against every possible wall that was put in front of me. Luckily, the walls gave out before my head did!

Perhaps more important than personal conviction, you must surround yourself with people who feel similarly and share your vision. To be successful, there must be a core of individuals on your management team who, by way of analogy, are your perfect "dance partners." That is, persons who may not always necessarily agree with the moves, but who are willing to move with you. Oftentimes you may lead, whereas other times they may lead. But, to succeed, they must share the same passion for the dance that you do!

WHAT DO YOU THINK REPRESENTS THE GREATEST UNMET MEDICAL NEED IN THE TREATMENT OF CNS DISORDERS?

There are several neurological conditions such as Parkinson's disease, epilepsy, and migraines where there are a number of available — albeit not perfect — treatment options that can manage these conditions. And, even within these indications there is still a substantial amount of unmet medical need. Having said that, there are other neurological conditions, including MS, Huntington's disease, and Alzheimer's, where there are very few or no good drugs to treat and manage the disorder.

Based on numbers alone, Alzheimer's represents the greatest unmet medical need and the largest commercial opportunity. Also, traumatic brain and spinal cord injuries represent other areas where patients could benefit from new treatments and medicines. At present, there are no treatment options that can fundamentally alter the functional incapacity that results from these CNS traumas.

Overall, I would have to say most neurological conditions have more unmet medical needs than met ones. Broadly speaking, neurology is a very good place for a company to develop commercially successful new drugs and treatment interventions.

WHAT ARE SOME OF THE MOST CHALLENGING ASPECTS SURROUNDING THE DEVELOPMENT OF DRUGS TO TREAT DISEASES OF THE CNS?

There are two major reasons why developing drugs to treat CNS diseases is so challenging. First, in many cases, such as with MS and Alzheimer's, we simply don't understand the disease mechanisms well enough to identify the correct drug targets. For example, we still don't know what causes MS and why some people get it and others don't. Nor do we understand at the molecular level which specific components of the immune system are responsible for the pathogenesis of the disease.

Right now, there are a couple of moderately effective immunotherapies such as the beta-interferons and Copaxone that slow down MS relapses (with minimal long-term side effects), but they don't stop disease progression. The more potent, newer agents like Tysabri and Gilenya may actually act to slow disease progression, but they are such powerful immune inhibitors that the risk of much more severe adverse events like progressive multifocal leukoencephalopathy (PML) and certain cancers are much greater.

What is really needed to develop safe and effective new drugs to treat MS is a clearer understanding of what specifically is causing the immune system to go haywire and attack the central nervous system. The same can be said about developing new drugs to treat Parkinson's, Huntington's, and Alzheimer's. For example, people are still arguing on a fundamental level whether or not the amyloid plaque hypothesis for the etiology of Alzheimer's is correct. And, when there is still debate at such a basic level, it suggests we still don't know enough about a disease to design an effective intervention. Unfortunately, drug discovery in these areas is still a "hit-or-miss" process and is currently the state of the industry when it comes to developing treatments for progressive neurodegenerative disorders.

Second, delivery of a pharmacologically active small molecule drug or biologic across the blood brain barrier can be extremely challenging. That said, there are a variety of biotechnology and medical devices companies that have recently developed novel strategies to deliver pharmacologically active molecules (large and small) across the blood brain barrier. Consequently, the delivery of therapeutic agents to CNS targets is becoming less of a problem than it has been in the past. Again, the challenge in this business is identifying the correct target(s), which in turn will facilitate development of the "right" drugs.

AFTER 17 YEARS IN THE BUSINESS, WHAT DO YOU CONSIDER TO BE THE "HOLY GRAIL" FOR DEVELOPING DRUGS TO TREAT MS?

To date, none of the so-called disease-modifying drugs developed to treat MS actually cure or prevent the progression of the disease. For me, slowing disease progression or curing MS has and will continue to be the Holy Grail for developing drugs to treat MS. Sadly, I don't think we understand the biology of MS well enough to develop these types of drugs just yet. But, I think the industry as a whole is making progress in that direction.

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Ron Cohen, M.D., founder and CEO, Acorda

While everyone's goal is to cure or slow the progression of MS, we can't allow the quest for the "best be the enemy of the good." What I mean is that we can't allow the search for better disease-modifying drugs to stand in the way or prevent development of drugs (like AMPYRA) that can improve the quality of life for patients with MS. Improving a critical function like walking is a massive benefit for MS patients, and it should not be overlooked or ignored by companies working in this area.

One product in our pipeline that we are very excited about is rhlgM22, a monoclonal antibody that acts as a signaling molecule and stimulates oligodendrocytes (myelin-producing cells in the CNS) to produce myelin and remyelinate nerve cells in three experimental animal models of MS. At present, there are no other molecules that we are aware of that induce or promote remyelination of damaged nerves in MS. This is a potential disease-modifying agent that we are extremely eager to take into the clinic as soon as possible.

WHY ARE THE PRICE TAGS FOR THESE DRUGS SO HIGH? HOW WILL U.S. HEALTHCARE REFORM AFFECT DRUG PRICING AND YOUR BUSINESS GOING FORWARD?

I believe drug pricing is the single most pressing issue, not only for the life sciences industry but for society in general. The basic issue is that drug development costs a lot, and it takes a very long time to bring innovative new drugs to market. This is because we, as a society, have chosen to use very precise and stringent regulatory standards for drug development to ensure new drugs are safe and efficacious.

Unfortunately, most Americans have absolutely no concept of what is risky or not or how drug risk is measured in the life sciences

industries. Recent missteps with drugs like Vioxx and Avandia have contributed to the hysteria and increased focus on drug safety by the media, U.S. government, and Americans in general. This increased scrutiny has, in turn, caused new drug development costs to skyrocket in recent years. Americans must realize that someone has to pay for these increases. And, the most obvious way for companies to increase development costs is to charge higher prices for their drugs. Like it or not, life sciences companies are obligated (to investors and stakeholders) to garner a sufficient ROI on their products to generate sufficient revenue to invest in new product development.

The downside to this model is that high drug prices can limit patient access to potentially life-saving or -altering drugs. For example, AMPYRA costs \$12,850 per patient, per year, whereas many disease-modifying MS drugs like Gilenya cost in excess of \$45,000 per year, and some cancer biologics cost well over \$100,000 per patient. At Acorda, we are very torn by the drug pricing and patient access issue. To that end, whenever we are allowed by law, we pay down a patient's copays for AMPYRA to no more than \$40 per month (Medicare and the State of Massachusetts prohibit it). Further, roughly 10% of the drug we ship is free (for patients who are either uninsured or lack adequate medical insurance).

As a company, we are trying to strike as good a balance as possible with the obvious competing imperatives of ROI and patient access to drugs. This is an incredibly complicated issue and, quite frankly, may very well put future medical innovation in the United States at risk. ●