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Cardiovascular Devices

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BY STEPHEN LEVIN

Pharmaceutical R&D

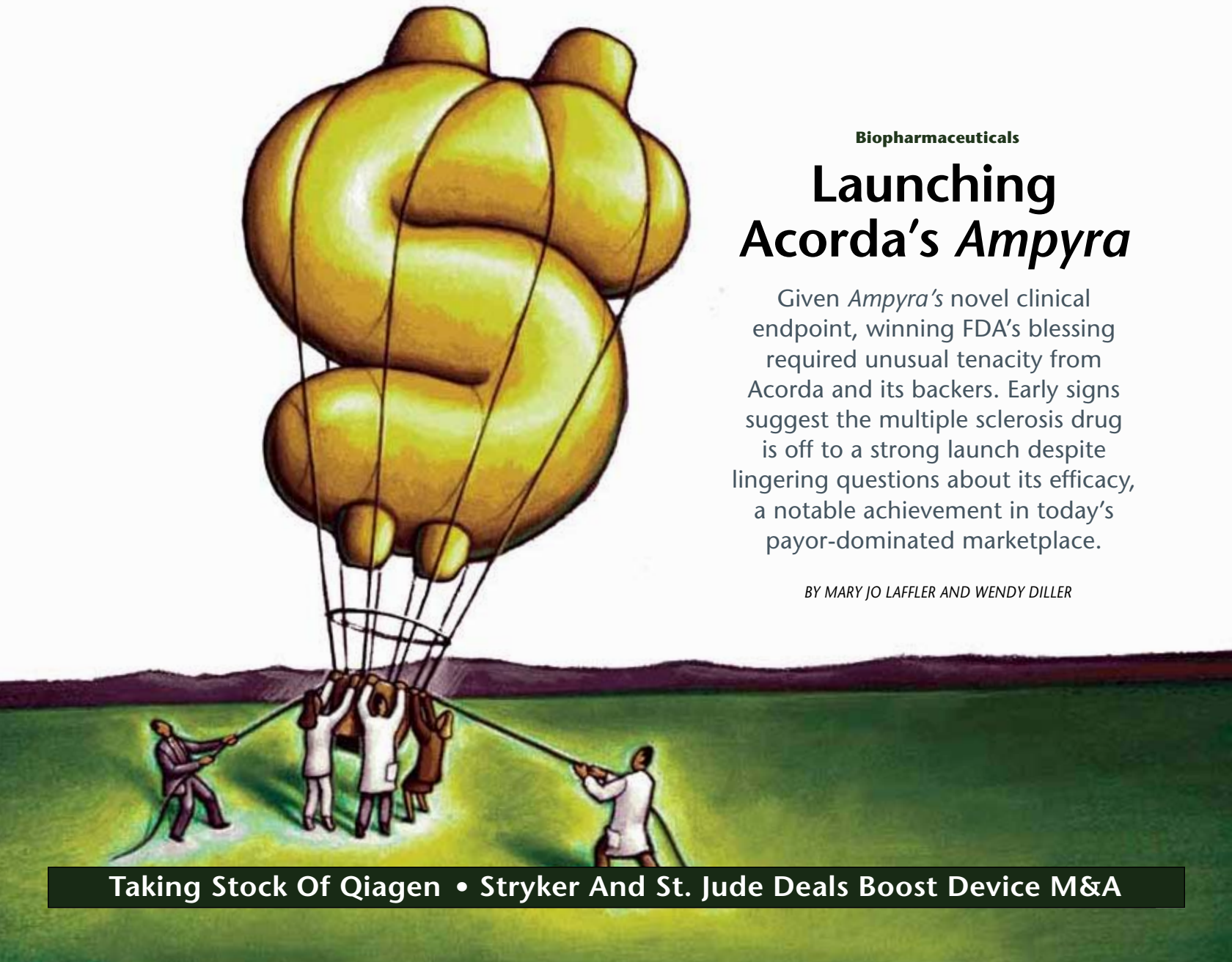
Inside Lilly Research Labs: A Conversation With Jan Lundberg

BY ELLEN FOSTER LICKING

Spinal Devices

NuVasive: Outpacing A Slowing Spine Market

BY DAVID CASSAK



Biopharmaceuticals

Launching Acorda's *Ampyra*

Given *Ampyra's* novel clinical endpoint, winning FDA's blessing required unusual tenacity from Acorda and its backers. Early signs suggest the multiple sclerosis drug is off to a strong launch despite lingering questions about its efficacy, a notable achievement in today's payor-dominated marketplace.

BY MARY JO LAFFLER AND WENDY DILLER

Taking Stock Of Qiagen • Stryker And St. Jude Deals Boost Device M&A

LAUNCHING ACORDA'S

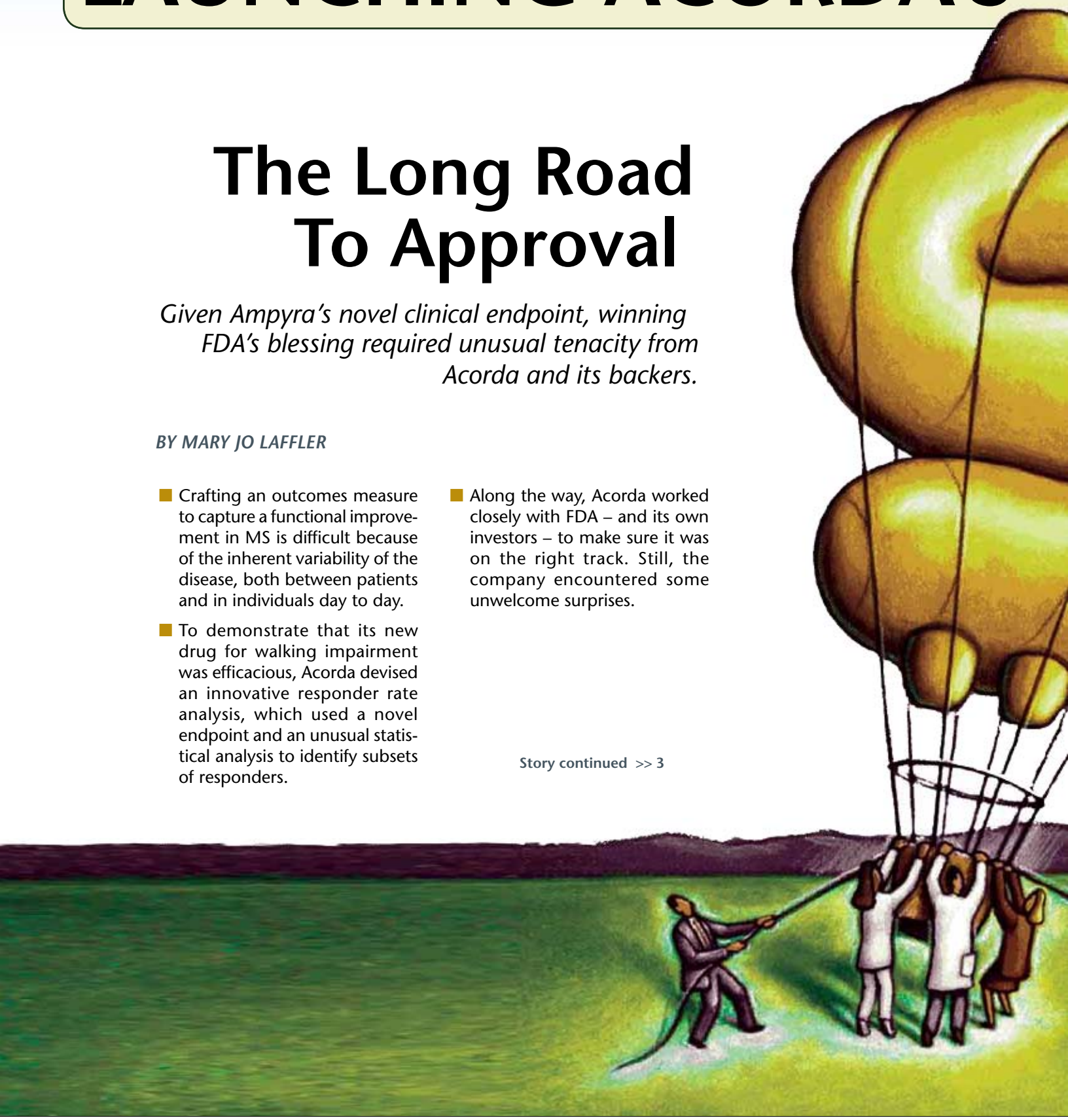
The Long Road To Approval

Given Ampyra's novel clinical endpoint, winning FDA's blessing required unusual tenacity from Acorda and its backers.

BY MARY JO LAFFLER

- Crafting an outcomes measure to capture a functional improvement in MS is difficult because of the inherent variability of the disease, both between patients and in individuals day to day.
- To demonstrate that its new drug for walking impairment was efficacious, Acorda devised an innovative responder rate analysis, which used a novel endpoint and an unusual statistical analysis to identify subsets of responders.
- Along the way, Acorda worked closely with FDA – and its own investors – to make sure it was on the right track. Still, the company encountered some unwelcome surprises.

Story continued >> 3



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AMPYRA

What Drug Companies Can Learn From The Experience

Early signs suggest Acorda's multiple sclerosis drug is off to a strong launch, despite lingering questions about its efficacy. This achievement is even more telling given today's payor-dominated marketplace.

BY WENDY DILLER

- Just months into the Ampyra launch, most payors are allowing patients unrestricted – or nearly unrestricted – access to the medicine.
- Acorda deserves credit for the well-executed launch for which internal preparations began years before Ampyra came to the market.
- The drug's continued traction with payors and physicians will depend on its performance in a real-world setting, including the accuracy of a novel timed walking test, patient adherence, and off-label use.

Story continued >> 7

Story continued >> 28
Executive Summary >> 104

LAUNCHING ACORDA'S *AMPYRA:* THE LONG ROAD TO APPROVAL Continued

The January 2010 approval for **Acorda Therapeutics Inc.**'s oral multiple sclerosis therapy *Ampyra* (dalfampridine) is an impressive accomplishment – by any account.

The company took a drug that failed one development program and resurrected it so that it ultimately won FDA approval and is fast becoming a commercial success. (*See "Launching Acorda's Ampyra: What Drug Companies Can Learn From The Experience," this issue.*) Ampyra is the first drug aimed at relieving walking impairment symptoms in MS patients; as such, it is adjunctive rather than competitive with high profile disease-modifying medications on the market, including **Novartis AG**'s new oral medication *Gilenya* (fingolimod).

Every drug and indication has its challenges, and gaining FDA approval is never simple. But Acorda's challenges were greater than most. MS causes demyelination, which leads to slower nerve conduction; gait problems are one of its most common symptoms. Acorda was first to tackle the walking problem, and it faced the challenge of proving a novel benefit in a disease that is highly debilitating, progressive, and variable. Patients can feel better one day, worse another, for reasons no one entirely understands, making it difficult to discern a drug's impact. Along the way, Acorda also had to contend with the usual complications: development setbacks, edgy investors and negotiations with FDA.

Widespread off-label use gave Acorda confidence that most drug developers don't have - but it still had to put evidence behind the anecdote.

The company's founder and CEO Ron Cohen insists that Ampyra's current success is based on good science and continual communication with important constituents, including the MS community, FDA and investors. "Although there were unique aspects to the approval process for this drug," says Cohen, "my sense is that most, if not all, of that uniqueness pertains to the drug itself."

A DRUG IN NEED OF RESURRECTION

Dalfampridine, previously fampridine, has a long history. A potassium channel blocker, it is thought to restore neurological function by improving nerve condition in demylineated nerve fibers. It is a sustained release formulation of 4-aminopyridine, an unapproved chemical compound available to patients through compounding pharmacies for a variety of neurological disorders. The MS community is familiar with it, and doctors prescribe it to help with a variety of symptoms, including fatigue.

Acorda came to the opportunity mid-stream. Cohen, an MD, was looking for a neurodegenerative compound upon which to build a company and in 1994 teamed up with University of North Carolina neurosurgery researcher Andrew Blight to move forward on the short-acting formulation, fampridine, in spinal cord injury (SCI). The molecule had been studied for 15 years, largely in academia, before Acorda took command. Blight had helped with early initial clinical trials, funded by a Canadian charity. He later became Acorda's chief scientific officer and played a key role in getting Ampyra approved.

In 1997, Acorda signed a deal with **Elan Corp. PLC**, to gain access to Elan's sustained-release formulation of fampridine. That formulation work was critical because the more consistent pharmacokinetics addressed some of drug's noxious side effects, including a risk of seizures. For a while the companies worked in parallel, with Elan running MS studies and Acorda in control of the SCI trials. But in 2003 Acorda took complete control of fampridine development for all indications.

HOMING IN ON THE DRUG'S EFFECT

Because off-label use of 4-AP was widespread, Cohen admits the company had more certainty about activity than most developers of new drugs face. Still, although people were using it to treat a multitude of symptoms, no one had done the clinical studies to support its utility. Acorda's challenges were multifaceted: it needed to identify patient populations most likely to benefit, and develop rigorous methodology to quantify clinical improvements. Early on, two simultaneous Phase III trials testing dalfampridine for spasticity in spinal cord injury patients failed. Emboldened by a promising Phase II trial in MS, the company changed course.

Multiple sclerosis is a protean disease, with myriad impacts on patients' physical abilities, from cognitive and affective functions like motor functions to visual and sensory functions, to spasticity, pain and coordination. The company, intent on demonstrating a physical function improvement in MS, used the Phase II program not only to explore safety and dosing ranges, but also to look for potential outcomes measures for a broad range of function claims.

Leg strength, spasticity, and walking ability all showed potential. Acorda's management tried to make educated guesses, looking for signals and then, as Cohen quips, following Willie Sutton's law. "'Why do you rob banks? Because that's where the money is.' You try to see where the money is in terms of efficacy," he says.

Based on the trial results and conversations with the MS community, Acorda narrowed its target indication to improving walking ability, because that "by far and away" seemed most important to patients," he says. Walking impairment affects roughly 65% of MS patients at any stage of disease, according to a 2008 Harris Poll survey. But it had never been a focus for treatment, so established ways to measure functional improvement directly didn't exist.

Acorda looked to other disease states where walking ability is assessed, such as cardiovascular and pulmonary diseases, for models. "We were able to get some clues from that," Cohen says, such as a timed walk test, though that had never been validated for use in MS clinical trials. Acorda also used other functional outcome measures previously used in the MS field in its final Phase II trial. The study showed a positive trend, compared to placebo, on a timed 25-foot walk, but it was not statistically significant.

"MARVEL AND WONDER": SORTING PATIENTS BY INDIVIDUAL RESPONSES

That failure hit the company hard – especially since the drug had already disappointed in the earlier spinal cord injury program. Encouraged by the positive trend in the walk test, however, Cohen delved further into the data, collecting printouts of the results for the 200 patients in the study. He included their walking tests for each of the nine study visits: four before treatment, four on treatment and one post-treatment. In an ideal world, he says, walking performance would be similar for the first four non-drug visits – with improvements visible as soon as the drug was administered and maintained for the subsequent on-drug visits. At the two-week follow-up visit, however, the gains would disappear. That would show a clear-cut drug effect.

Cohen tried that approach to break down the data. He organized the patient records by the number of on-drug visits showing improvement. Four visits with improvement constituted a clear response and three visits were deemed a likely drug effect, accounting for a fluke reading or bad day for the patient. He stacked those up against the lower scores (two, one or zero on-drug visits with improved walking performance). After the statistician unblinded the data, Cohen still remembers the look on her face: "Marvel and wonder," he says. Almost all the patients in the three and four group were on drug, and the p-value for that was less than 0.00001.

Even after FDA accepted that the novel methodology showed an effect, more work was needed to show that it mattered to patients.

The casual sorting worked, but for FDA, Acorda needed a more rigorous methodology. Andy Blight and Acorda's lead statistician Lawrence Marinucci created a statistical algorithm to sort the data. They ultimately did a statistical proof to give it rigor, which they are preparing to publish.

Acorda's methodology is a means of assessing a data set based on rates of individual response instead of average response across the cohort. "It's a very powerful statistical tool for identifying response when the great majority of the group is not actually responding," Cohen notes. Instead of succumbing to the "tyranny of the means" – whereby a signal of effect in a subset is lost when the results are averaged out over the entire population – the responder rate analysis winnows out the subset of responders. The company believes it can license its method for other companies to use.

For the Ampyra program, they applied the homegrown methodology to the intent-to-treat population – the data slice FDA generally prefers. "Lo and behold, about 35% of the drug patients were responders, and about 8% of the placebo group also met that definition," Cohen notes, with a statistically significant p-value. Acorda presented the responder finding at an end-of-Phase II meeting with FDA in July 2004, bringing along an expert clinician as a consultant. "The neurology division poured cold water on our enthusiasm," Cohen reports. Agency officials found the responder analysis interesting, but remained focused on the trial's overall failure. "It was the low point for us in the program," Cohen recalls.

But Acorda saw some dim signs for optimism. The division appeared to be generally comfortable with using a responder analysis; it described Acorda's approach as a different "flavor," but found it a valid responder analysis, Cohen says. That encouragement presented another challenge, however. While the agency accepted that the drug was showing an effect based on the novel methodology, the data didn't clarify what that meant to the patient.

CLEARING THE CLINICAL MEANINGFULNESS BAR

That's where Acorda ran up against one of the trickiest requirements for FDA approval. Because the agency's criteria for what is clinically meaningful vary among and even within diseases, sponsors must work on a case-by-case basis to determine a particular therapy's clinical impact, based on evolving precedent. For example, progression-free survival (PFS) may be clinically meaningful in certain cancers, but in others, FDA will only accept an overall survival advantage. **AstraZeneca PLC** withdrew regulatory filings for its oncologic *Zactima* (vandetanib) for lung cancer in 2009 when it became clear that PFS was no longer acceptable for that setting.

FDA often asks companies for additional assessments to show clinical meaningfulness of an effect. In neurology, such verification is standard for functional improvement assessments in depression and Alzheimer's disease, for instance. A formal scale used in depression or dementia is often supplemented by a global impression score, an assessment by a patient or clinician that overall the patient is doing better.

Acorda had done global impressions in the Phase II study, using the MSWS-12, a well-known and validated patient-reported outcome measure that asks patients to rate their recent level of disability, including on walking. The problem was that the results weren't significant under the original pre-specified analysis, before Acorda had come up with the stratification as responders or non-responders.

Heading home on Amtrak after the disheartening end-of-Phase II meeting, the Acorda team had a Eureka moment – one that paved the way for a valid Phase III trial: it could marry the MSWS-12 global impression data and the responder analysis. "That was the light-bulb moment," Cohen says. "We were pretty much chest bumping on the train – which is a bit embarrassing for a bunch of doctors and scientists."
Acorda's analysis showed that responders scored higher than non-responders on self-ambulation in the MSWS-12. "That was a gamble on our part, because we had very little data on MSWS-12, but it was the best that we could come up with in terms of validation within the study," Blight notes.

Here, however, they met another roadblock: impatient investors, who were "getting to the end of their ropes," after two failed Phase III trials for spinal cord injury and the problematic Phase II MS trial, Cohen said. The venture backers, including respected funds such as MPM Capital and Forward Ventures, hesitated to commit more funds, dragging out discussions for almost a year. During that time, Acorda's management almost walked away.

But compromise saved them. Both sides agreed to form

a committee to vet the company's prospects consisting of company management, VC representatives (both physicians), and an outside expert. The process succeeded, with the group concluding that the company's analytic approach could work. One requisite in exchange for additional financing, however, was that Acorda secure a Special Protocol Assessment with FDA – a consultative process in which the trial protocol is agreed upon, in writing, with the agency up front. Though SPAs are common in pharma, investors don't typically use them as a bargaining chip.

The delays cost Acorda at least a year and a half of development time. Acorda wanted to run two Phase III trials in parallel to make up for lost time, but the VCs refused to fund simultaneous trials. So the trials ran sequentially. Once the first trial came back positive, "everyone was happy to fund the next trial, obviously," Cohen adds.

Looking back at the process, using the SPA for the Phase III trials was one of Acorda's best decisions, Cohen and Blight agree. Creating that development roadmap gave them reason for discussions with FDA and a chance to gain its buy-in. SPAs aren't water-tight; although they are written agreements, the agency can change or even rescind them based on evolving knowledge. But the process wasn't a tremendous burden because the company already had been working closely with FDA on trial design. All told, the back-and-forth negotiating covered six to seven months, but the formal SPA process took only a couple months, Cohen says. "I would recommend to anybody in a similar circumstance that they absolutely make use of the SPA process," he says.

FIGURING OUT THE ENDPOINT

As the SPAs spelled out, the primary endpoint for each of the two Phase III trials was the timed 25-foot walk test, analyzed by Acorda's responder rate methodology. The MSWS-12 was included as a means of assessing the clinical meaningfulness of the walk test results.

In a memo summarizing the review decision, FDA Office of Drug Evaluation I Director Robert Temple notes the choice of endpoint was not the "most obvious" measure. More typical, he wrote, would have been "average walking speed in the drug and placebo groups or increase in baseline on drug vs. increase on placebo." But Cohen and Blight believed such an approach would not work, because only certain patients responded to the medication.

Crafting an outcome measure to capture a functional improvement in MS is difficult because of the inherent variability of the disease, both between patients and in individuals day to day. With most drugs in most diseases, one expects to see a quantifiable, vertical improvement – that a patient improved 15% from baseline, for instance. But in an MS patient, baselines shift unpredictably. A patient could do well – or poorly – regardless of treatment. He or she could exhibit a 20% improvement in walking ability while receiving treatment, but separating out the drug's effect from the disease's variability is tough, Blight explains.

That's where Acorda's eccentric responder analysis was critical, because it identifies patients who actually respond to the drug. By looking at the difference between the periods before and after treatment and during treatment, it was clearer to see that when responders were on the drug they got better and when they came off they got worse. That eliminated a lot of the background noise caused by variation over time, Blight points out. "For a very variable condition," he says, "really homing in on the consistent improvement over time I think is a very valuable way to look at the data. It's just hard for people to think about, because they're not used to it."

The low rate of responders in the placebo arm – 8% and 9% – is evidence that the approach works, he explains. If the data is examined just on the level of improvement, however, like a threshold 15% improvement, then around 15 to 16% of placebo patients reached that mark. Looking at an improvement in the walking speed itself would also be a difficult measure, "because statistically it looked like you would need a fairly large study to show a treatment effect on the walking speed," Blight notes.

The company also submitted as secondary endpoints more typical measures of average walking speed improvement, leg strength and spasticity, and FDA review documents indicate the agency was reassured by having that traditional evidence to back up the primary analysis. (*See "Acorda's Novel Primary Endpoint Was Made Possible By A Supporting Scaffolding Of Secondary Analyses,"* Pharmaceutical Approvals Monthly*, April 2010.*)

The agency also found reassurance in an alternate analysis of the responder rate data, which is included in the FDA-approved label as a cumulative distribution showing how many patients achieved various levels of improvement in walking speed. Acorda didn't plan on submitting that data but Temple responded positively to its presentation at the Advisory Committee review, and it showed up in the label. In his review memo, Temple cites the difference between Ampyra and placebo in the patients that had a 30% increase in walking speed: 15 to 20% versus 3%. "That is a minority of patients, of course, but it would seem to be an obvious benefit," he concludes.

The responder analysis may actually be a more modern type of measurement of drug effect. While traditional endpoints can be statistically and scientifically satisfying from a perspective of quantification, they may not be the most relevant to clinical practice. "FDA likes responder approaches because it gets you away from this concept of measuring a small statistically significant change that doesn't really mean anything" in the clinic, Blight observes. "You don't care to the infinitesimal place what is the average change, you want to know how many people saw benefit that was actually worth having," he says.

FDA's Temple and the agency's neurology division, among others, certainly agree. "Responder analysis may be particularly useful where response is confined to a subset," Temple wrote in his review memo. He has since advanced that argument in other disease states. At a March 2 meeting on clinical trials for hypertension, he discussed how the distribution of positive results for individual patients can be helpful in discerning a drug's effect, especially when there isn't a mean benefit across the entire population – e.g. when there is a small subset of patients who have a strong response. He pointed to Ampyra as an example where the distribution of results supported efficacy in the absence of an average benefit. (*See "FDA's Temple Discusses How To Measure Drug Efficacy When Mean Effect Is Limited,"* "The Pink Sheet" DAILY*, March 4, 2010.*)

Working with FDA to gain acceptance and approval, however, appears easier in hindsight. "It wasn't as much fun to live through," Cohen recounts.

SURPRISES FROM FDA

From the beginning of its review, FDA took a critical approach to the data. In particular, there was "considerable discussion of the meaningfulness of the study endpoint," Temple reported. The primary clinical reviewer argued the endpoint and unusual sequential analysis of the responder rate measurement was an intermediate variable, not a true endpoint, and allowed statistical significance without clear clinical significance. "The responder variable ignores the importance of the extent of improvement in walking speed," the reviewer, Kachikwu Illoh, said. That meant that a small benefit in a relatively large number of patients on the active drug could result in a positive trial, "even when the benefit is not clinically significant or meaningful for the patient." Illoh concluded the analysis was not appropriate to support approval, and recommended a "complete response" letter.

Temple also noted that the speed differences were numerically small, and FDA indeed brought the question of the meaningfulness of the effect to an advisory committee for interpretation by experts in the field. Leading up to the panel review, Acorda was confident, figuring any uncertainties had to do with how to craft labeling and potential conditions around use.

That changed when they saw the briefing documents. "We were surprised," Cohen says. "It seemed to come completely out of left field and it did not in our minds at all reflect what we thought we had understood from our ongoing dialog with FDA, up to and including the SPA agreements." After five months of work, the biotech had just 14 days to rejigger its strategy in advance of the meeting. Even worse, Illoh's negative review introduced new doubt and fear as to whether Ampyra would be cleared at all.

However, at the meeting, FDA Division of Neurology Products Director Russell Katz and Temple made clear that they stood by the SPA agreement and the company's analyses, and that the briefing documents should be considered alternate ways of looking at the data. Much of the meeting focused on the clinical meaningfulness of the signal, which the MS practitioners helped address. They led the panel to an overwhelming 12-1 vote that dalfampridine was effective at improving mobility.

LESSONS LEARNED

Though Acorda's gamble on using a primary endpoint based on an unusual responder analysis ultimately succeeded, it was still a risky play. Agency review documents reveal dissension among the review team, though it was overturned by higher level officials. It took a great deal of willingness and flexibility from FDA to appreciate the unique evidence and accept the drug's effect. In a less debilitating disease or a condition without unmet medical need, such an approach might not be a good bet.

> **"It seemed to come completely out of left field and it did not in our minds at all reflect what we thought we had understood from our ongoing dialog with FDA."**
>
> **– Ron Cohen**

Acorda's experience underscores how frequent communication with FDA along the way is essential. "If we went in, talked straight, gave the data the good and the bad, and had an objective, science-based discussion, [it] was very productive," says Cohen. Much of Acorda's success with FDA is due to its head of regulatory affairs, Brian Walter, who came on board in January 2006 from **Boehringer Ingelheim GMBH**, where he had many years of experience across multiple products. Cohen believes that experience proved particularly helpful because FDA speaks its own nuanced language. He recalls numerous examples where companies have interpreted the agency's comments to their detriment, inferring something as a suggestion when regulators really meant it as a requirement. Despite the ongoing back and forth during the Ampyra review, the surprise of the primary reviewer's negative assessment in the briefing documents still rankles. "The review document itself was so different from what we had expected based on all of the cumulative discussions with FDA, that's what threw us." He believes that "if it were possible to give companies more advance notice of those sorts of issues, that would be all to the good." The limiting factor may not be FDA's willingness, he points out, but the lack of resources. Whether that comes from user fees or appropriations, it's a message that both industry and FDA keep repeating. "From an industry standpoint of getting safe and effective drugs to the patients who need them," Cohen concludes, "more [FDA] resources would be better, more opportunities for communication would be better and more transparency would be better."

Acorda's extensive preparation with a range of evidence in support of its drug also smoothed Ampyra's path to approval. The company didn't rely on the primary findings alone; it had more traditional endpoints as secondary evidence. And it was prepared to defend its choices. "If you're going after a novel endpoint, the onus is on you to demonstrate that what you're doing passes muster," Cohen notes.

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COMMENTS: *Email the author: M.Laffler@Elsevier.com*

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LAUNCHING ACORDA'S *AMPYRA:* WHAT DRUG COMPANIES CAN LEARN FROM THE EXPERIENCE Continued

Acorda Therapeutics Inc.'s risky regulatory strategy paid off at FDA, but it also has ramifications in the commercial world. As of September 30, seven months after *Ampyra* (dalfampridine) launched on March 1, the drug had generated sales of more than $85 million, well above the company's forecasts and most Wall Street analysts' expectations.

Most major payors have reviewed the drug and have decided to allow it relatively unrestricted coverage. That means any MS patient who is ambulatory and wants the drug is likely to get it (it is not indicated for wheelchair-bound patients). But given the novelty of the drug and its clinical endpoints, its launch has also presented challenges. FDA approved Ampyra despite a mixed Advisory Committee reaction, and what some perceive to be poorly defined clinical endpoints, questionable responder rates, and a safety risk of seizures. The key regulatory controversy revolved around two pivotal trials, in which patients were evaluated based on an unvalidated timed walking test and the data were analyzed using a novel responder rate analysis that Acorda designed. (*See "Launching Acorda's Ampyra: The Long Road To Approval," this issue.*)

> **"As of September 30, about 75% of commercially-covered lives have either limited or no restrictions on use of *Ampyra.*"**
>
> **– Lauren Sabella**

As a result, doctors, payors, and patients must be educated about the science behind Ampyra. Some wonder if its stellar launch trajectory can continue, given what they perceive to be the drug's low efficacy for most people and lack of data correlating walking speed and improved quality of life or functionality. Furthermore, in the increasingly pressurized environment of reimbursement, payors are reviewing evidence on their own and may not come to the same conclusions as FDA. While the payor community appears to be swiftly embracing the drug, its reaction in reality is more nuanced. Health plans, in general, are finding it challenging to define Ampyra's value. The interplay among payors, providers and patients in MS highlights interesting dynamics in what is an increasingly payor-dominated commercial environment.

A WELL-EXECUTED LAUNCH REAPS REWARDS

Acorda deserves credit for a well-executed launch. The drug's status as a first-in-class molecule with a unique indication for an unmet medical need in a debilitating chronic disease is certainly an advantage when talking to physicians and payors. The biotech has also been able to leverage the MS community's long-standing awareness of Ampyra's active ingredient, fampridine, a compound neurologists prescribe to address disease symptoms.

Credit, however, is also due to Acorda's disciplined planning. As early as 2004, President and CEO Ron Cohen, MD, sought to re-balance Acorda's intense focus on R&D to one that also encompassed the commercial world. That year, the company in-licensed *Zanaflex* (tizanidine hydrochloride), a spasticity drug developed by **Elan Corp. PLC**, which it never expected to be its main growth driver. Zanaflex's sales were only $13.6 million in the third quarter of 2010, five years after Acorda launched it, but selling that niche medication generated cash flow and gave Acorda real-world commercial experience.

In late 2009 – several months after the company filed an NDA for Ampyra – it brought on Lauren Sabella, a former VP of sales at **Boehringer Ingelheim GMBH**, first as a consultant and, beginning January 2010, as EVP, commercial development. Sabella had helped to launch Boehringer's best-selling respiratory drug *Spiriva* (tiotropium bromide), and more recently was CEO of the biotech **Altus Pharmaceuticals Inc.** The opportunity at Acorda intrigued her because "the company had done a great job planning prior to the launch of its flagship product," she says. "They had the infrastructure in place from Zanaflex, and everything was scalable. But they did not push the button until Ampyra got FDA approval."

As soon as FDA approved Ampyra, the company moved to double the size of its 50-rep commercial organization, so that it had all territories covered by the March 1 launch. Plans also called for Acorda to distribute the drug through a closed specialty pharmacy network. Although Ampyra is an oral medication, taken twice daily as a pill, Acorda opted for the specialty pharmacy network, in part to manage an FDA-required risk evaluation and mitigation program and in part because MS patients are accustomed to receiving disease-modifying agents through such networks. The network structure also enables Acorda to collect additional data on patient utilization.

The network includes the managed care organization Kaiser Permanente, a move that generated some controversy, because Kaiser is the only payor in Acorda's specialty pharmacy network. Kaiser's participation is necessary to gain access to that managed care organization's large membership, because Kaiser insists on doing its own distribution, says Sabella. But Kaiser has used Acorda to make a public point about how drug companies use REMS to control access to their products; in December 2009, it filed a Citizen's Petition related to the subject, citing Acorda specifically. (*"Kaiser Pushes Back on REMS: Acorda Listens; Will FDA?,"* The RPM Report, *February 2010.*)

On November 1, Acorda executives had evidence of how their advanced planning had paid off. Through the first seven months of launch, approximately 6,300 physicians, including almost 90% of the company's initial top-target specialists, prescribed Ampyra at least once, Sabella said in an earnings call. Thus far, about 31,000 patients, or 8% of the MS population in the US, have received Ampyra – a figure that could be the tip of the iceberg, since a 2008 Harris poll found 64% of people with MS reported walking impairment.

New data, which researchers presented at the *European Committee for Treatment and Research in Multiple Sclerosis* (*ECTRIMS*)

conference in October 2010, show even further the potential demand: the researchers found that 28% of MS patients have walking impairment two years following initial diagnosis – whereas physicians generally assume that walking difficulties begin later in the course of the disease.

Given the drug costs about $13,000 a year, Ampyra's position on managed care formularies is critical to its overall commercial success. Importantly, as of September 30, about 75% of commercially covered lives have either limited or no restrictions on use of Ampyra, Sabella said in the earnings call. This includes UnitedHealth Group, the nation's largest insurer, which in September put the drug on Tier 2 status with what Timothy Heady, CEO of UnitedHealth Pharmaceutical Solutions, has described as a "modest" notification criteria requirement. UnitedHealth, which covers 21 million lives, doesn't have direct control over other plans, but Cohen told analysts in the November 1 call that, "When our team goes out, we certainly consider it more helpful than not that UnitedHealth made that decision and that we can refer to it."

A minority of plans have more restrictions, such as prior authorizations or higher tier placement, and a small percentage in the low single digits have declined to cover the drug. Acorda says it is working to educate the holdouts about how it designed the clinical trials and the benefits of the drug to convince them to revisit their decisions. In addition, where permitted by law (almost all states except for Massachusetts), it pays the difference for any co-pay greater than $40 per month.

So far, Sabella says, the biggest challenge has been responding to pent-up demand. Because call centers collaborating with the specialty pharmacies weren't staffed efficiently, processing scripts initially took weeks. The problem was resolved by early September, but it frustrated patients and skewed the sales trajectory, which was low early in the launch and shot up in the third quarter, executives say. Now the company is working off a more normal base, and, while it isn't forecasting specifics, it warned analysts that fourth-quarter sales may be less than third-quarter sales based on the backlog bolus.

AMPYRA SEES STRONG DEMAND NOW, BUT UNCERTAIN FUTURE

Despite the broad acceptance, analysts, payors and others are still on edge about the launch. The large backlog initially distorted prescription data and added to many variables that have made it difficult to predict uptake of the medicine. In addition, some analysts believe that IMS Health, because of technical glitches, was not capturing the sales data accurately.

From a Wall Street perspective, analysts have been mildly concerned by a slight downward trend in prescription volume. Therefore, they are closely watching the refill rate, which is a surrogate indicator of whether users see enough benefit to continue taking the medicine. Acorda's Sabella says the data are still limited on refill rates because the launch is in its early stages, and the way the drug is dispensed makes accurate measurement hard. But about 67% of the 17,500 patients who have received a one-month supply have already refilled their prescriptions. It's not clear what minimum refill rates Ampyra needs to get to analysts' consensus estimates of peak sales, which now stand at $740 million.

Thus, while most major plans have generous coverage policies for Ampyra, the nuances seem important. A sizable minority of plans require follow-up assessments at six months and/or yearly to determine if they should allow individual patients to continue the therapy. But they use a variety of evaluation criteria, some of which are quite lenient. Some ask doctors merely to check a box on a form to confirm a patient has MS and walking impairment; others may want to know how patients perform on the Expanded Disability Status Scale (EDSS), which is already standard of care for MS patients and therefore readily accessible for doctors. Their opinion of the walking test criteria, which Acorda invented as a helpful tool for assessing clinical efficacy, is at best mixed, mostly because doctors aren't familiar with it but also because it is subjective.

Health plans, in general, are finding it challenging to define *Ampyra's* value.

Before reimbursing for Ampyra, UnitedHealth, for example, requires a patient to have an EDSS score of less than or equal to 7, or, if EDSS is not measured, the patient can not be wheelchair-bound or have a history of seizures or renal impairment. It doesn't currently require the more onerous walking test, says Suzanne Tschida, VP, specialty pharmacy. Although UnitedHealth has a generous policy toward the drug, it is highly interested in the rate at which patients stop taking the drug, adherence ratios, and other signs of efficacy, she says. "We will all be learning from it," she says of the drug's commercial uptake. "It's up in the air to put a measurement on how well this drug will perform outside clinical trials."

UnitedHealth may be open-minded, but a minority of payors are taking a harder line and requiring follow-up visits with physicians, which may include the walking test as an option and quantitative limits on the number of pills pharmacies can dispense to patients at any one time. A key reason: they remain skeptical of the clinical data supporting the drug, which only provides symptomatic relief. "When I look at the numbers for Ampyra, the drug increases walking speed by one second. For $13,000 a year, does it translate into a better quality of life?" asks the head of pharmacy at one regional plan. Right now, any improvement on the walking test is defined as efficacious, she points out, but a precise quantitative cutoff would more clearly define demonstrable improvement.

These uncertainties could cause plans to revisit their decisions on the drug, once they have a clearer idea of its real-world effectiveness, the accuracy of the walking test, patient adherence rates, and off-label use. Ultimately, however, that may not happen, no matter how the drug performs, experts say. First, plans aren't likely to stand firm against a vocal patient advocacy community for a drug that, while expensive, comprises such a small part of their pharmacy budgets.

Furthermore, the trend in managed care in recent years has been to remove restrictions in access to medicines, relying instead on higher co-pays and premiums to manage demand. That pendulum seems to be shifting back toward greater restrictions, some say, but not in the case of MS.

Plans aren't interesting in managing MS therapy utilization and don't often restrict disease-modifying MS therapies, although it is a competitive, expensive category, says Robert

Lipsy, PharmD, an assistant professor at the **University of Arizona College of Pharmacy**. Instead, they may wait to review uptake after they put it on an open formulary. If the drop-out rate is high, or the utilization rate is low, they may not bother to implement formal programs to reign in utilization. Nor will they implement formal programs to restrict access if they ultimately believe the majority of denial coverage will be overturned on appeal. "Plans don't want to get into PR battles over drugs that aren't having a major impact on their budgets," Lipsy says.

Indeed, these days, plans are much more concerned with *Gilenya* (fingolimod), and other novel, oral disease-modifying agents in development. At $48,000, **Novartis AG**'s oral drug for modifying the progression of MS is likely to be a much bigger budget buster – however, currently, managed care seems resigned to paying for it, even as first-line therapy (*"Novartis' Gilenya: Efficacy, Patient Assistance, Lie At Heart Of Marketing Push,"* "The Pink Sheet," *October 11, 2010.*)

As is so often the case in the early days of a launch, Acorda currently holds the stronger hand when it comes to negotiating with payors because of its wealth of clinical trial data. Company executives say they aren't planning new trials that tease more data out of Ampyra's impact on walking impairment, though they plan to expand the franchise by studying the drug in other indications, developing new formulations, and applying to get a key patent extended. (The drug has orphan drug exclusivity until 2017, but a critical patent expires in the US in 2013.)

In a few years, payors will have sufficient data about the drug to establish its real-world efficacy. That may lead them to reevaluate their decision to cover Ampyra. As disciplined as Acorda has been in launching its most important product, it still has a substantial job ahead of it to convince payors, patients and physicians of the value of the drug and of the outcome measures used to support it.

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