

Fibromyalgia Trials Successfully Measure Subjects' Pain

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Electronic diaries may significantly improve reporting of subjective, self-reported endpoints such as pain levels.

A Phase 2 trial and subsequent Phase 3 trial of a new treatment for Fibromyalgia Syndrome (FMS) by Cypress Bioscience showed that real time measurements best reflect the type of fluctuating pain and other symptoms reported by patients with FMS. Furthermore, we have found that FMS patients will reliably use electronic diaries to record their pain information. Two to four percent of the population worldwide including 12 million patients in the United States are estimated to have FMS. Yet despite this high prevalence, there are no treatments specifically approved for FMS in the United States or elsewhere. FMS patients have been treated with a variety of medications off-label.

More than five years ago, we at Cypress Bioscience decided to target the development of a pharmaceutical treatment for people suffering from FMS. The need for approved and efficacious therapeutic options for the treatment of this condition seemed to represent an excellent opportunity for a new clinical development program. We began studying FMS, as well as the reasons why therapeutic agents had not been developed nor brought to market previously. Although successful therapeutic approaches appeared to be plausible, several challenges existed including methodological hurdles to ensure the accurate and meaningful assessment of response when dealing almost exclusively with subjective, self-reported endpoints. We became convinced that it would be possible to develop a therapeutic treatment for fibromyalgia, and that innovative techniques to measure symptom severity and response to therapy would be an important part of the clinical program.

During the past five years, Cypress Bioscience has established the clinical and regulatory framework for evaluating compounds targeted at FMS, and we have evaluated the performance of our lead compound, milnacipran, for treatment of the condition. Key to this evaluation has been the development and implementation of real-time methods of tracking patients' pain using electronic diaries.

ABOUT FIBROMYALGIA

FMS is a chronic and debilitating condition characterized by widespread pain and stiffness throughout the body often accompanied by severe fatigue, insomnia, and mood symptoms. Pain associated with FMS is "head to toe," and is often described by patients as a diffuse aching or burning. By some measures, patients with FMS have at least comparable disability and even more pain and lower quality of life than patients with rheumatoid arthritis or osteoarthritis. Most patients are middle-aged women, although the ailment can strike adolescents, the elderly, and men.

HOW TO EVALUATE FIBROMYALGIA?

As we began the planning stages of our clinical program in 2001, we faced a number of challenges. Given that there was no previous treatment targeted at

FMS and therefore, no precedent for regulators, we developed and defended to the FDA a clinical framework for the appropriate evaluation of the treatment of FMS. After working with a number of experts in pain evaluation and FMS, we identified two key issues that needed to be resolved before beginning clinical trials.

AN ACCURATE PICTURE

The first was to determine the most appropriate modality for the measurement of pain experienced by FMS patients. Historically, researchers had asked patients to report on their level of pain at a single moment of time, or patients were asked to complete a retrospective review of their pain over the preceding week, or even a longer period of time. We suspected that FMS pain might fluctuate widely during any given day, or over time, and we were therefore concerned that a single measurement of a patient's current

the most common way to collect such data was using paper and pencil diaries that subjects completed each day, and sometimes at multiple times each day. The superiority of EMA data (vs. retrospective data) hinges on the assumption that patients will be recording their pain in real time, because noncompliance would subject the pain data to the very inaccuracies that motivated the use of the diary in the first place. Studies have shown that patients do not, in fact, tend to complete paper diaries in real time, but instead rely on back-filling, and even forward-filling, of the diary. Therefore, we turned to a relatively new technology (at that time) for clinical trials—the electronic patient diary.

As demanded by good science, we first examined our proposed methodology in a (non-drug) pilot study evaluating electronic patient diaries for the measurement of the real-time pain experienced by FMS patients.

Overall compliance to the electronic diary EMA method was 85 percent.

level of pain would present an inaccurate picture of the overall condition. Retrospective questionnaires on pain tend to focus on average pain over a period of time. However, evidence from a number of studies questioned whether patients could create an accurate mental average of their pain experience over time. Both of these historical methods of pain measurement were deemed inappropriate for our FMS work. A potential solution to this problem lay in a method called Ecological Momentary Assessment (1). This basically means that patients are asked to provide multiple assessments of their current pain in their “natural” environments (ecological) in a real-time fashion (momentary assessment).

REAL TIME

The second issue emerged after the selection of EMA as the optimal approach. EMA requires capturing data from patients in their natural environments, over time. Historically,

ELECTRONIC DIARY DELIVERS

In order to evaluate electronic diaries and EMA, we examined three different strategies for assessing pain during a 12-week non-drug study involving 14 FMS patients (2): 1) real-time pain reports (EMA) using an electronic patient experience diary (from Inivodata Inc.; 2) end-of-week reports of average pain over the preceding seven days using the electronic diary; and 3) monthly in-clinic reports of average pain over the preceding week using a traditional paper and pencil format. The real-time pain assessments were performed both as “random-prompt” assessments, where the device beeped and the patient rated their pain at that moment in time (true EMA), and also as morning recall pain, where each morning upon awakening the patient was asked to rate her average level of pain for the preceding 24 hours. Overall compliance to the electronic diary EMA method was 85 percent. Eight out of 14 patients had



Compliance using the electronic diary was superior to that of recall methods.

compliance rates exceeding 90 percent, while three patients had rates below 70 percent; no patient had a compliance rate below 50 percent. In contrast, compliance with follow-up clinic visits for the completion of paper and pencil measures was 72 percent, and only 49 percent of these were within the scheduled window for the visit. In summary, the compliance using the electronic diary for pain monitoring was superior to compliance with the recall measures completed during the clinic visits.

We also examined the actual pain scores derived from the various methods. The baseline scores at the beginning of the study were higher for the two seven-day recall methods as compared to EMA, as shown in “Baseline Pain Scores Using Different Recall Methods.” This was unexpected, because patients were randomly placed into each of the three different groups.

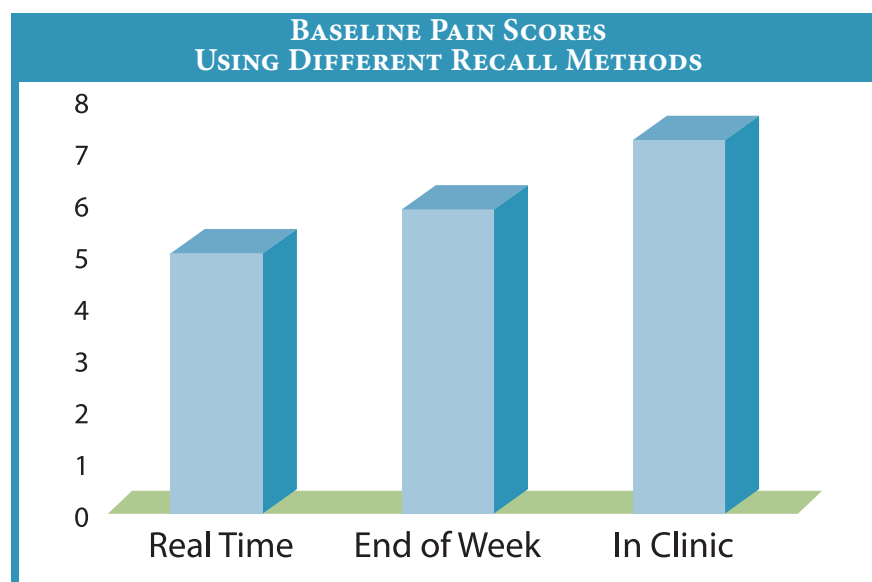
At the end of 12 weeks, patients in the recall methods groups had an apparent improvement because of these higher baseline pain scores. In other words, the patients in the recall groups apparently improved *in the absence* of an intervention; such an effect is considered to be equivalent to a placebo response. This finding along with the higher rate of compliance with the protocol convinced us to use electronic diaries employing EMA methods for our clinical program.

Further support for our decision was derived from a study published concurrent with our pilot study in which patient adherence with paper

diaries completed at home was explicitly examined (3). A hidden electronic device was used to track the time and date of paper pain diary entries during a three-week non-drug study. Twelve patients were asked to make three pain reports per day, at fixed times. Although patients submitted 90 percent of their paper diary cards with date and time entries indicating compliance with the protocol, the electronic device indicated that only 11 percent of ratings were actually completed within 30 minutes of the appointed time and that 74 percent to 78 percent of the completed diary

overall efficacy and safety of milnacipran in this population of FMS patients. The primary endpoint was based on improvement in patient-reported pain collected on the electronic diaries. Patients in this study demonstrated more than 90 percent compliance with the various EMA requirements of the trial. With respect to clinical efficacy, 37 percent of milnacipran-treated patients randomized to the twice a day dosing group reported at least a 50 percent reduction in pain intensity (which means that their reported pain was half as intense as it was at the beginning of the study), compared with 14

responsibility for the ultimate commercialization of the treatment, and is working closely with us to facilitate approval by the FDA. We completed our first Phase 3 trial evaluating milnacipran for the treatment of FMS in summer 2005, and we now have two additional Phase 3 trials underway. The first Phase 3 trial was a six-month, randomized, double-blind, placebo-controlled pivotal study involving 888 FMS patients who were randomized to either milnacipran treatment or placebo. Again, the primary endpoint of this trial was a composite response rate of an assessment of pain as measured by the electronic diary and an assessment of overall impression of patient well-being as measured by the Patient Global Impression of Change. The pain data collected via the electronic diary system again employed EMA methods by which patients document their levels of daily pain at several random times each day as well as each morning and evening. There was also a weekly pain assessment on the electronic diary. The patients in the first Phase 3 trial also displayed very high rates of compliance (more than 90 percent) with the electronic diaries. This study showed that milnacipran can lead to reductions in pain over long periods of time in patients who were compliant with the dosing protocol.



The three baseline values differed significantly from one another.

entries could not have been made at the times claimed by the patients. This study found substantial evidence of both forward filling (recording estimates of future pain before it was actually experienced) and back filling (completing missed “current” pain ratings at a later time using recall), which degrades the veracity of the pain ratings captured using paper diaries.

REAL-TIME METHODS

Subsequently, we used electronic diaries to capture pain data as the primary endpoint in a Phase 2 trial, and several subsequent Phase 3 pivotal trials. Our Phase 2 trial, completed in the fall of 2002, was a three-month, randomized, placebo-controlled study involving 125 FMS patients who were randomized to either milnacipran treatment or placebo. The study evaluated the

percent of placebo patients. The reduction in pain intensity was statistically significant. Further, 75 percent of all milnacipran-treated patients reported an impression of overall improvement compared with 38 percent in the placebo group, which was also statistically significant. We were pleased with the clinical impact of milnacipran, and we had a high degree of confidence and trust in our findings because of the rigorous EMA methods we had developed and employed with the electronic diaries used in the Phase 2 trial.

As we prepared for our Phase 3 clinical program, we met with the FDA and worked out a clinical program that they agreed would be satisfactory for eventual approval of a new treatment for fibromyalgia. We later entered into a partnership with Forest Laboratories, Inc., which will take lead

ADVANTAGES AND LIMITATIONS

Our experience implementing real-time EMA methods using electronic diaries has convinced us that it was the correct decision for the milnacipran clinical program. Our early pilot work, followed by the Phase 2 and 3 trials, has confirmed that the pain of FMS is best evaluated in the context of patients’ day-to-day lives. The pain measures we captured with EMA appear to be free from many of the biases that would have been introduced with assessments that require the recollection of the pain experienced over extended periods of time. Further, these measures appear to truly reflect the patients’ experience of their FMS.

During the pilot study, we observed a large amount of missing and late information when paper and pencil forms were used at the investigative site. Other researchers have found

that most data captured using paper and pencil diaries do not comply with protocol requirements. In contrast, the electronic diary can be set to prompt patients to enter information according to a specified protocol; it can also capture the date and time of each patient record for verification of protocol compliance, and it has credibility as a 'scientific tool' to capture data (as anecdotally reported by patients).

Although we have been pleased with the performance of the electronic diaries, they do have some limitations. It is necessary to invest time, money, and resources into the development of the diary's software. Investigative site staff must be trained in teaching patients to use the diaries and in interpreting the daily data uploads from patients in the field. That does increase the overall burden on the investigative sites, although we believe such activity is essential to support patient compliance. Additionally, as with any electronic product, it is possible for patients to damage the hardware or for the software to fail. Fortunately, we found that hardware problems were surprisingly rare. Although software

'glitches' did occasionally occur; they were dealt with by a 24-hour help desk that provided immediate responses to problems encountered in the field. With appropriate planning and diligence, we have been able to effectively manage these limitations. With regard to cost, we maintain that the high quality of data—critical in our evaluation of milnacipran for this entirely new therapeutic area—is our return on investment.

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