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Aventis Pharmaceuticals, Inc.

Making Pharmaceutical History with Arava®

Background

In March 2003, Aventis Pharmaceuticals Inc. and the Food and Drug Administration (FDA) made history. The FDA and its Arthritis Drugs Advisory Committee reviewed two-year, controlled, clinical trial data and allowed Aventis to make the claim that its drug, Arava® (leflunomide), improves physical function in rheumatoid arthritis (RA) patients. On the same day, the FDA also accepted a new approach that pharmaceutical companies could use in the future to validate such a claim.

Leading factors influencing the FDA's decision were the results from studies employing two health outcome measures — the SF-36® Health Survey (SF-36) and the Health Assessment Questionnaire (HAQ). The SF-36 is a patient-reported, 36-question, generic measure of health-related quality of life developed by John E. Ware, Jr., PhD, co-founder of QualityMetric Incorporated, now part of Optum. The HAQ was developed by James F. Fries, MD, and colleagues at Stanford University, and was one of the first functional status (disability) measures.

The SF-36 is the established "gold standard" of patient-reported outcome (PRO) measurement used to prove efficacy in clinical trials and to substantiate product marketing and label claims. It has been cited in more than 450 peer-reviewed studies of rheumatoid arthritis and included in more than 100 randomized controlled trials for rheumatoid arthritis.

Meanwhile, the HAQ has become the dominant instrument in many disease areas, including arthritis. Widely used throughout the world, it has become a mandated outcome measure for clinical trials in rheumatoid arthritis and some other diseases.

Faced with a Challenge

Before Aventis was able to celebrate success in 2003, there was a long path to travel. In 1998, Aventis submitted a New Drug Application (NDA) to the FDA and received approval for Arava on the basis that the drug improved the signs and symptoms of, and impeded the structural damage from, rheumatoid arthritis. Prior to submitting the NDA, Aventis had conducted clinical trials including both the SF-36 and the HAQ.

"The tests mirrored each other. They could not have been in more harmony in terms of the results," says Karen Simpson, MD, Arava Medical Product Leader at Aventis. "This is of particular interest because at the time the SF-36 was included it was not believed to be sensitive to change in a musculoskeletal disease such as RA. These data were the first to demonstrate the harmony between a rheumatology-specific measure and a generic measure."

"You gain much more information out of the patient-reported outcomes than you do out of some of the other measures."
– Lee S. Simon, MD, Former Division Director, Office of New Drugs, FDA

The application Aventis submitted in 1998 also included a proposed claim of improved physical function, supported by one-year data using the SF-36 and the HAQ. At the time of the Arava NDA, the FDA was in the process of developing a guidance document for the treatment of rheumatoid arthritis. The document redefined the claim of improvement in physical function and disability, and required two to five years of clinical data to support the claim. It also recommended that any study include a validated measure of physical function — the HAQ or AIMS — and a validated generic, health-related, quality-of-life (HRQOL) measure — the SF-36.

Because Aventis only had one year of data at the time of the NDA submission, Arava was approved for the treatment of active rheumatoid arthritis, but could not yet claim improved physical function.

The Solution

In 2002, Aventis submitted a supplemental NDA to the FDA, with two-year physical function and HRQoL data from the Arava controlled clinical trials. In essence, the company was requesting that Arava's indication be expanded to include improved physical function in rheumatoid arthritis patients.

Aventis proposed to the committee that 12 months of data is adequate to establish a claim for improvement in physical function. "We saw statistically significant improvement at six or 12 months in the study data, and benefits were maintained at 24 months in most patients who continued to use Arava," says Simpson.

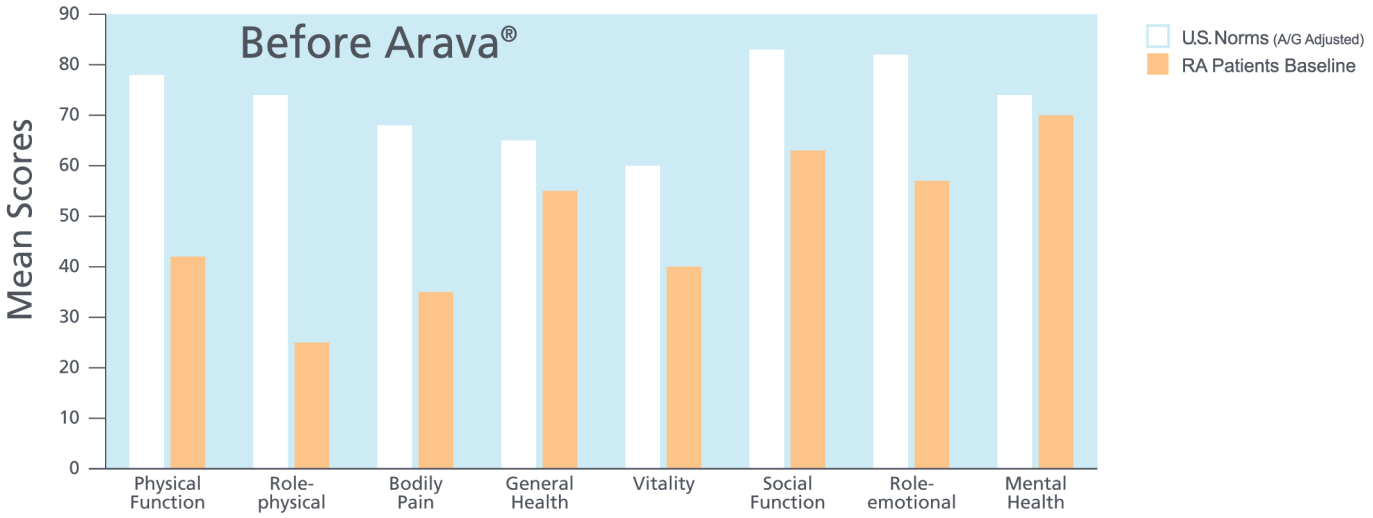
The data was reviewed at a March 2003 FDA Arthritis Drugs Advisory Committee meeting. Lee S. Simon, MD, a rheumatologist and former associate professor at Harvard Medical School, was Division Director for Analgesic, Auto-inflammatory, and Ophthalmologic Drug Products within the Office of New Drugs at the FDA.

"The problem I faced when I came to the Agency in 2001 was the word 'disability,'" Simon says. "It has a huge impact, and it has multiple definitions. But it is not exactly what we want to measure when we consider physical function, which is measurable by an HAQ, or even by inference from the SF-36. We began a debate at the agency as to whether [the language] needed to be changed from 'disability' to 'physical function.'"

The other issue Simon and the FDA faced was the requirement that pharmaceutical companies demonstrate sustained improvement in patients for at least two years. According to Simon, "Our perspective [at the FDA] was that we were between a rock and a hard place, because a clinical trial that requires two years of data is very hard to generate. We wanted to start a debate at the [March 2003] Advisory Committee meeting that would allow us to move forward with this change of the wording to 'physical function' and, recognizing the exigencies of doing a trial over a two-year period, say, 'could we make it be a one-year period?' If you had evidence, why couldn't that evidence stand?"

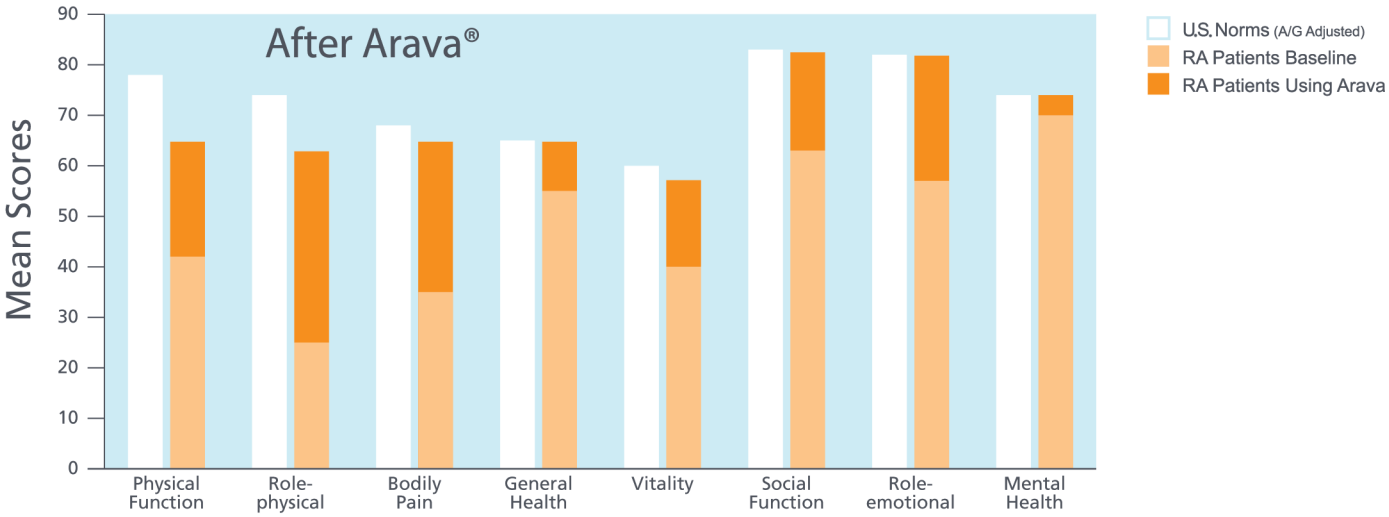
Results

At the end of the day, "We were ready to give a new indication for Arava for improvement in physical function," Simon notes. Ware, who provided testimony before the committee regarding interpretation of the SF-36 data on behalf of Aventis, adds, "It was a big day for outcomes measurement tools, both in regard to the FDA allowing for the indication of improvement in physical function, and in determining to grant future approvals based on 12 months of collected data."



Source: Adapted from FDA Arthritis Advisory Committee, March 5, 2003.

Optum's generic health surveys show the burden of rheumatoid arthritis, as well as the benefits of using the rheumatoid arthritis medication Arava.



Source: Adapted from FDA Arthritis Advisory Committee, March 5, 2003.

"This was the first time within a discussion at the Agency that a patient-reported outcome measure, such as the SF-36 or the HAQ, was considered as a free-standing indication," Simon says. "We had looked at all the data and we were pretty convinced that if you look at the Arava data set... you gain much more information out of the patient-reported outcomes than you do out of some of the other measures. That's very powerful data."

After the 2003 Advisory Committee meeting, Aventis worked with the FDA on the language the company could include in the prescribing information for the rheumatoid arthritis drug. On the Aventis website, and in the Arava prescribing information, the company now states, "The improvement in physical function demonstrated at six and 12 months was maintained over two years. In those patients continuing therapy for a second year, this improvement in physical function as measured by HAQ and SF-36 was maintained."

Never before had a pharmaceutical company referred directly to an outcome measure in its product literature. In stating its claim, Aventis, with data collected from the SF-36 and HAQ, made history.

Moving Forward

When Simon left the FDA in 2003, he left a legacy that includes strong support for the importance of patient-based outcome measures in drug trials.

"There's a movement at the Agency on patient-related outcomes," he says. "Within the Office of New Drugs, [they have] created a sub-office on patient-related outcomes and how to validate them. At my previous division, almost 100 percent of everything we looked at had patient-reported outcomes."

"The whole field is moving toward specific/generic combinations of patient-reported outcomes — using physical function and generic, health-related, quality-of-life measures in tandem," confirms Aventis' Simpson.

About Optum

Optum is a leading information and technology-enabled health services business platform serving the broad health marketplace. Optum specializes in improving the performance of the health system by providing analytics, technology and consulting services that enable better decisions and results. We integrate workflow solutions that deliver data in real time and create actionable insights — processing health information that relates directly to and affects one in four patients in the United States, one in every three Medicaid dollars, and one in every five emergency room visits.