

DRUG TESTING

Massive Trial of Celebrex Seeks to Settle Safety Concerns

Since the COX-2 inhibitor Vioxx was yanked off the market more than a year ago, the remaining anti-inflammatory painkillers have been under a cloud of suspicion. Which are the safest, the least likely to contribute to heart attacks and strokes? And which are the most dangerous?

Pfizer, maker of the COX-2 inhibitors Celebrex and Bextra (which was pulled in April), is placing a \$100 million bet on a 20,000-person, international trial led by the Cleveland Clinic in Ohio. But some experts are concerned that the design of the trial, announced last week, could load the dice in Celebrex's favor and put patients at risk. European Union (E.U.) countries have declined to participate because of their concerns about Celebrex's safety.

The clinical trial is unusual for focusing on patients with heart disease, including those who recently underwent bypass surgery and those at risk of cardiac problems. The approach is meant to mirror conditions in the real world. "If you have arthritis and you have heart disease, we can't ask you to tolerate the pain. So what do I give you?" says Steven Nissen of the Cleveland Clinic, who's leading the trial. "In the absence of knowledge, we're just guessing." Nissen has criticized Vioxx and other COX-2 drugs, although at a U.S. Food and Drug Administration (FDA) meeting last February, he voted to keep Bextra on the market.



Three-way race. Pfizer is putting up at least \$100 million for Celebrex to take on naproxen (above, right) and ibuprofen.

Patients in the Celebrex trial will be randomly and blindly assigned to receive either Celebrex or one of two older anti-inflammatory drugs—ibuprofen or naproxen. The trial will end after 715 "events"—heart attacks, strokes, or deaths—have occurred, says Nissen. That's expected to take roughly 4 years.

But some scientists wonder whether the study will really resolve questions about the drug's safety. "The important thing in science is to make sure you've controlled all your variables," says Alastair Wood, a drug-safety expert and associate dean of Vanderbilt University School of Medicine in Nashville, Tennessee. "Here, there's another variable in the room that potentially could affect some of the outcomes."

That variable is aspirin, used by heart

disease and at-risk patients to reduce clotting. Previous trials have often excluded those on aspirin, which will be given in low doses to all the volunteers in the Pfizer trial because they're at higher risk.

The catch, says Garret FitzGerald, a pharmacologist and cardiologist at the University of Pennsylvania, is that aspirin reduces clotting by acting on COX-1. That's one of the molecules targeted by ibuprofen and naproxen, but mostly ignored by Celebrex. Previous studies in animals and humans have suggested that both ibuprofen and naproxen, but not COX-2 inhibitors, "can interfere to undermine the cardiovascular protection of aspirin," says FitzGerald. If so, a finding that heart attacks and strokes are the same in all three drug groups might actually mean that Celebrex is less safe, because the cardiovascular benefits of aspirin may be decreased for those taking ibuprofen or naproxen but not for those in the Celebrex group.

The solution, say both FitzGerald and Wood, is to banish aspirin from the study and give patients clopidagrel, or Plavix, a more expensive drug made by Bristol-Myers Squibb that has cardiovascular benefits similar to aspirin but doesn't work through COX molecules. Nissen disputed that approach in an e-mail, noting that clinically, chronic clopidagrel use isn't indicated for heart disease patients, and its effects are not known. He also said the interaction between aspirin and ibuprofen remains speculative.

The ethics of the new trial are also getting mixed reviews. Although some clinical trials are faulted for relying on the healthiest patients, this one has garnered criticism for planning to enroll the sickest. "Why take the highest-risk people?" asks Curt Furberg, an epidemiologist at Wake Forest University School of Medicine in Winston-Salem, North Carolina, who suggests instead tracking them through health databases of hun- ▶

DEEP-SEA DRILLING

Scientific Drill Ship to Be Reborn

SAN FRANCISCO, CALIFORNIA—The *JOIDES Resolution* ends its 20-year career as the world's lone deep-sea scientific drilling ship next week. But the National Science Foundation (NSF) hopes that \$115 million will bring her back into the water, better than ever.

An NSF-funded group has contracted with the ship's owner to rebuild and upgrade the *Resolution*, beginning next fall. When the work has been completed, it would join the Japanese behemoth *Chikyu* late in 2007, ending an 18-month drilling hiatus and beginning the most ambitious ocean drilling ever attempted.

The renamed ship will be more capable and comfortable, NSF's Assistant Director

for Geosciences Margaret Leinen told an audience last week at the American Geophysical Union meeting here. The ship, representing the U.S. contribution to the International Ocean Drilling Program, will have 50% more shipboard laboratory space, an enhanced drilling system, and a greater variety of analytical instrumentation. But the biggest applause greeted her description of the improved creature comforts: No more four-person staterooms or eight-person bathrooms, Leinen promised, and there will be a sauna. To stay on schedule, however, NSF needs \$42 million from Congress in its next budget to complement what it has received in the past 2 years.

The half-billion-dollar *Chikyu*, which during a shakedown cruise this month retrieved its first sediment core, will become fully operational in September 2007. Its first challenge will be a series of holes working up to a superdeep hole into the fault that generates great earthquakes off the coast of Japan. But more work lies beyond that 6-year project, Y. Tatsumi of the Japan Drilling Earth Science Consortium reminded the audience. He urged the community to begin planning other ambitious projects, including drilling through the ocean's rocky crust. An ill-fated attempt to pierce the ocean crust (*Science*, 18 April 2003, p. 410) 40 years ago gave rise to modern scientific drilling.

—RICHARD A. KERR