BUSINESS & REGULATORY NEWS

Crohn's trial shows the pros of antisense

In the past, it was assumed that an antisense drug could never be delivered systemically. But recent clinical results have shown that it can be effective when delivered systemically and not just locally. This good news may be significant, not only for the drug and the disease concerned, but for the prospects of antisense drugs in general. Isis Pharmaceuticals (Carlsbad, CA) announced in February that its phosphorothioate oligonucleotide drug, ISIS 2302, had been successful in treating 20 Crohn's disease patients systemically. In a randomized, placebo-controlled trial, the drug controlled disease symptoms and reduced steroid dependency by a statistically significant amount in 75% of patients. Ten patients reported a remission of disease for several months.

"We are encouraged by the efficacy of this drug," says Frank Bennett, vice president of biology at Isis. He says the drug was well tolerated and the pharmacokinetics seen in humans could have been predicted from earlier results obtained in animal tests. Completion of the trial and initiation of large, pivotal phase IIb clinical trials triggered a $10 million milestone payment from Boehringer Ingelheim (Ingleheim, Germany), Isis' partner in a cell adhesion drug discovery and development joint venture since 1995.

The efficacy of antisense drugs given systemically is regarded as a notable milestone. ". . .the systemic delivery of the antisense drug [ISIS 2302] directed against a human gene product now suggests a greater utility across several disease targets," says David Stone, managing director and biotechnology analyst at Cowen & Co. (Boston, MA). Andy Grinstead, chairman and CEO of Isis' rival, Hybridon (Cambridge, MA), agrees that the Isis trial result is important. "Systemic delivery and more importantly oral delivery is a critical milestone toward a broad use of oligonucleotides as drugs, particularly for chronic therapy," he says.

Hybridon's own clinical trials are showing some promise. In January, Philippe Guinot, general manager of Hybridon Europe, reported that its first "advanced chemistry" oligonucleotide, GEM 132, completed a 14-patient phase I safety clinical trial. GEM 132 is a "hybrid" oligonucleotide containing phosphorothioate DNA and 2′ O-methyl RNA. Compared with Hybridon's first-generation antisense drugs, GEM 132 showed improved pharmacokinetics and no dose-limiting side effects.

The drug is designed to treat cytomegalovirus (CMV) retinitis and therefore is administered not systemically, but by intravitreal injections. However, Grinstead predicts that "hybrid" drugs will increase the time between injection from two weeks to four months and could allow systemic administration. Hybridon is currently enrolling patients in GEM 132 phase I/II clinical trials. The company also expects to file an investigational new drug application with the US Food and Drug Administration (Rockville, MD) before the end of 1997 for GEM 92, the "hybrid" version of its HIV antisense drug, GEM 91.

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Isis is endeavoring to capitalize on the clinical success of ISIS 2302 in Crohn's disease by testing the same drug in four other inflammatory indications—rheumatoid arthritis, psoriasis, ulcerative colitis, and acute renal transplantation. "Drugs fail in human beings despite working in animal models for one of three reasons: Pharmacokinetics, toxicology, or pharmacology," says Stanley Crooke, chairman and CEO of Isis. The Crohn's disease trial result indicates that the toxicology and pharmacokinetics of ISIS 2302 are acceptable, and that limits the risk of failure to questions of pharmacology.

Despite seeing activity in all the relevant animal models, Crooke "does not expect ISIS 2302 to be active in all four indications being tested." The drug acts by selectively directing the degradation of mRNA encoding the intercellular adhesion molecule, ICAM-1, which is produced during inflammatory responses. But Crohn's disease and other inflammatory indications are multifactorial diseases: ISIS 2302 will only work if a particular manifestation of the disease is due to upregulation of ICAM-1.

Crooke believes that the clinical performance of ISIS 2302 gives grounds for optimism about other antisense molecules of the same chemical class, the phosphorothioates. Databases of clinical data developed by antisense companies demonstrate that antisense drugs exhibit class-generic pharmacokinetic and toxicological properties. "We are not going to lose new drugs due to unexpected pharmacokinetic reasons or unfavorable toxicological profile," says Crooke.

Zofie E. Dziewanowska, senior vice president of clinical affairs at Genta (San Diego, CA) agrees, but only in part: "There appear to be class effects with antisense drugs." But, she says, researchers are starting to see "some differences in pharmacokinetics and toxicology between individual phosphorothioate oligonucleotides depending on route and frequency of administration."

In one sense, some critics would argue, the recent Isis trial changes nothing: The pharmacokinetic properties of antisense drugs have always been predictable—"predictably bad,"—with limited stability and oral availability. But Stone believes that things are getting better. "I have no doubt with continued investment in the chemistry, the stability and [very limited] oral availability of antisense drugs will improve."

Debra Robertson

Debra Robertson is a freelance writer working in San Diego, CA.