



Alicaforsen Significantly Improves Symptoms and Produces Durable Responses in Patients With Ulcerative Colitis

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Company to Host Webcast to Review Results and Provide Additional Data Today at 7:30 AM ET

CARLSBAD, Calif., Dec 2, 2004 /PRNewswire-FirstCall via COMTEX/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today the results of three Phase 2 studies of alicaforsen enema to treat patients with ulcerative colitis (UC). In these Phase 2 clinical trials, alicaforsen enema produced significant and long-lasting disease improvement, as measured by changes in Disease Activity Index (DAI) scores and other indicators of disease. In particular, a substantial number of patients treated with alicaforsen enema experienced mucosal healing, as well as decreases in rectal bleeding and in stool frequency; manifestations of the disease that cause considerable discomfort, inconvenience and pain to patients. In all three trials, alicaforsen enema was well-tolerated.

"For clinicians, new drugs that are safe and produce long-term disease improvement are critical. The prolonged responses of UC patients treated with alicaforsen enema are impressive, lasting much longer than those observed with currently available enemas," said Philip B. Miner, Jr., M.D., Clinical Professor of Medicine at the University of Oklahoma, President and Medical Director of The Oklahoma Foundation for Digestive Research, and a clinical investigator in the Phase 2 studies. "Based on data from these trials, as well as positive data from previously reported studies, alicaforsen enema has the potential to be an important development in the treatment of UC."

"We have met all of our objectives for our Phase 2 program in ulcerative colitis. We have confirmed that alicaforsen enema produces, when compared to either placebo or the enema standard of care, responses that can last six months or longer, identified a dose and schedule for Phase 3 clinical trials and established that alicaforsen enema can be a local treatment for a local disease. The durability of treatment benefit with alicaforsen enema is a key competitive advantage in the commercial profile of this drug," said Mark Wedel, M.D., J.D., Isis' Vice President of Development and Chief Medical Officer. "Our next steps will be to use the results from our broad Phase 2 experience to design effective Phase 3 clinical trials, and to discuss these data and our plans for Phase 3 clinical trials with the U.S. Food and Drug Administration."

Phase 2 Clinical Trials of Alicaforsen in Ulcerative Colitis: Designed to Measure Activity and Duration of Response

To support the Phase 3 development of alicaforsen enema for UC, Isis conducted four Phase 2 trials involving more than 300 UC patients. Today, the company is reporting results from the three most recent studies. The goals of these trials were to characterize the safety profile of alicaforsen enema, identify the dose and dose regimen for Phase 3 trials, and to compare the activity of alicaforsen enema to mesalamine enema, the enema standard of care for the treatment of UC.

- The objectives of the placebo-controlled study were to determine a dose and dose regimen for Phase 3 clinical studies and to confirm the drug's ability to produce durable responses.
- The primary objective of the mesalamine enema comparison study was to compare the drug's safety, efficacy and durability of response to that of mesalamine enema.
- The objective of the pharmacokinetics study was to determine if the drug was systemically absorbed. In addition, safety and efficacy of alicaforsen enema were also assessed.

As a result of these trials, the company has selected the best performing dose and dose regimen of 240mg nightly for Phase 3 clinical trials.

Key results from each study on the top performing alicaforsen enema dose of 240mg nightly are reported below:

Placebo-Controlled Study

Once-nightly administration of 240mg alicaforsen enema for six weeks produced greater and more durable responses, as measured by DAI, than placebo. In addition, alicaforsen enema-treated patients had improved mucosal healing, decreased rectal bleeding and decreased stool frequency. Alicaforsen enema was well-tolerated. Specifically:

- Based on an intent-to-treat analysis, 59% (13/22) of patients treated with 240mg alicaforsen enema achieved a response, as measured by DAI. Six months later, the end of the study, 77% (10/13) of these patients continued to respond.
- Patients treated with alicaforsen enema who achieved a response maintained their response, on average, for longer than

six months compared to a duration of response of less than 3 months for placebo-treated patients.

- Alicaforfen enema-treated patients achieved a mean 51% reduction in DAI at week 18 and 50% at week 30, compared to 18% and 11% at weeks 18 and 30, respectively, for patients treated with placebo ($p=0.04$ and $p=0.03$, respectively). Disease improvement observed with alicaforfen enema was more pronounced in patients with moderate disease than in patients with mild UC.
- Mean improvement in DAI demonstrated strong trends in favor of the drug or statistical significance compared to placebo. The improvement was confirmed by analyses of mucosal healing, reduction in rectal bleeding, reduction in stool frequency, and by the Physician Global Assessment, the doctor's assessment of all aspects of a UC patient's health. Responses to alicaforfen enema were durable.

Mesalamine Comparison Study

Patients treated with 240mg alicaforfen enema nightly for six weeks achieved improvements in disease equal to or better than patients treated with mesalamine enema. Alicaforfen enema was well-tolerated. Responses in patients receiving alicaforfen enema were substantially more durable than those of mesalamine enema-treated patients. Specifically:

- The acute response to alicaforfen enema was comparable to that of mesalamine enema.
- Many patients treated with alicaforfen enema who achieved a response maintained their response for six months or longer compared to an average duration of response of less than 3 months for mesalamine enema-treated patients.
- Across all time points following treatment in the 54-week study, patients treated with alicaforfen enema demonstrated greater improvement in DAI than patients treated with mesalamine enema.
- Improvements in mucosal healing, decreases in rectal bleeding and decreases in stool frequency also demonstrated strong trends in favor of alicaforfen enema or statistical significance compared to mesalamine enema. These data confirm the benefits of alicaforfen enema, as assessed by DAI and numerous other measures.

Pharmacokinetics Study:

Patients receiving once nightly doses of 240mg alicaforfen enema for six weeks achieved significant improvements in DAI, demonstrated little to no systemic absorption of the drug, and achieved mucosal healing by the end of the trial. Specifically:

- Patients treated with 240mg alicaforfen enema experienced minimal to no systemic absorption of drug (