Positive results in Phase 2 trial of treatment of C-difficile-associated diarrhea

November 3 2008

Medarex, Inc. and The Massachusetts Biologic Laboratories (MBL) of the University of Massachusetts Medical School (UMMS) today announced that a Phase 2 trial of an anti-*C. difficile* antibody combination treatment in patients with *C. difficile* Associated Diarrhea (CDAD) successfully met its primary objective.

The top-line results from the recently completed multi-center, randomized, double-blind, placebo-controlled Phase 2 trial indicated a statistically significant reduction in recurrences of CDAD when compared with placebo. In the study, 200 patients symptomatic with CDAD receiving standard of care antibiotics (metronidazole or vancomycin) were randomized to receive either intravenous placebo or intravenous administration of a combination of MDX-066 (CDA-1) and MDX-1388 (CDB-1), two fully human antibodies that neutralize *C. difficile* toxins A and B, respectively.

Consistent with the published literature, the recurrence rate in the placebo-treated group exceeded 20 percent for patients following successful treatment with standard of care antibiotics. In comparison with placebo, MDX-066/MDX-1388 treatment reduced recurrence rates by approximately 70 percent ($p=0.0004$ on the intent-to-treat population). The antibody combination treatment was generally safe and well-tolerated. Full results from this Phase 2 trial are planned to be presented at a future scientific meeting.

The incidence and mortality associated with CDAD has been increasing ,

with estimates of over 500,000 cases in the United States, and approximately 15,000 deaths caused or contributed by *C. difficile*. The emergence of a highly virulent epidemic strain that produces much higher levels of toxins A and B has also been associated with morbidity and mortality in younger, healthier, and non-hospitalized patients.

"We are delighted with these dramatic results. CDAD is a growing and serious epidemic, with twenty to fifty percent of hospitalized patients relapsing after receiving antibiotic treatment," said Donna Ambrosino, MD, Executive Director of the MBL and Professor of Pediatrics at UMMS. "The demonstration of significant protection from relapse indicates that treatment with monoclonal antibodies against the toxins could reduce this significant and costly public health problem."

"These results highlight the exquisite specificity of monoclonal antibodies and their important role to save lives," said Howard H. Pien, President and CEO of Medarex. "We believe that the strength of our antibody technology platform for generating potentially important treatment options, such as the *C. difficile* program antibodies, will continue to shape the future of medicine. Furthermore, Medarex's strategy of proving the utility of potentially promising candidates for development by well-designed and well-executed studies is amply demonstrated."

About *Clostridium difficile* Acquired Diarrhea (CDAD)

C. difficile is a spore forming bacterium that is common in the environment and can colonize the gastrointestinal (GI) tract. It can be easily spread among hospitalized patients and residents of long term care facilities, but also can be found in otherwise healthy individuals in the community. The origin of disease is believed to develop in the presence of antibiotics administered for other infections, in which the complex microbial make up of the GI tract is altered, and *C. difficile* spores may

germinate, grow, and produce toxins A and B. The toxins cause damage to the GI tract lining in the colon, resulting in severe diarrhea, and may lead to perforations of the colon and/or death. Treatment of severe disease requires administration of additional antibiotics to kill the *C. difficile* bacteria, but because of the persistence of spores, as well as the difficulty for the intestinal flora to re-normalize in the setting of antibiotics, relapse/recurrence of CDAD is common, and is estimated to occur in 20 percent of cases, with post-therapy recurrence rates as high as 60 percent. Recurrence can be difficult to manage and is a challenging complication of CDAD; however, the use of non-antibiotic based approaches to neutralization of *C. difficile* toxins may be important options needed to facilitate recovery of the GI flora.

Source: University of Massachusetts Medical School