

Monoclonal antibody to treat *C. difficile* shows promise in clinical trial

September 21 2015, by Mark Shelton

This photograph depicts *Clostridium difficile* colonies after 48hrs growth on a blood agar plate; Magnified 4.8X. *C. difficile*, an anaerobic gram-positive rod, is the most frequently identified cause of antibiotic-associated diarrhea (AAD). It accounts for approximately 15–25% of all episodes of AAD. Credit: CDC

An important new therapeutic for *C. difficile* infection based on discoveries at UMass Medical School will be submitted for regulatory approval based on the results of clinical studies conducted by the international pharmaceutical company Merck. Merck announced that two pivotal Phase 3 clinical studies for a monoclonal antibody licensed from UMass Medical School's MassBiologics met their primary efficacy

endpoint: the reduction in *C. difficile* recurrence through week 12 compared to placebo, when used in conjunction with standard of care antibiotics for the treatment of *C. difficile*.

Based on these results, the company plans to submit new drug applications seeking regulatory approval of the monoclonal antibody, called bezlotoxumab, in the United States, the European Union and Canada in 2015. Currently, there are no therapies approved for the prevention of recurrent disease caused by *C. difficile*.

Bezlotoxumab was developed by researchers at MassBiologics in conjunction with Medarex (now part of Bristol-Myers Squibb), and licensed to Merck in 2009 for development as a potential therapeutic for *C. difficile* infection.

Results from the studies were presented for the first time at the Interscience Conference of Antimicrobial Agents and Chemotherapy and International Congress of Chemotherapy and Infection (ICC) joint meeting in San Diego on Sept. 20.

"Results of these studies showed that a single, one-time infusion of the antitoxin bezlotoxumab given with standard of care *C. difficile* antibiotic treatment significantly reduced the recurrence of *C. difficile* infection compared to standard of care alone, and demonstrated this benefit over a 12-week period," said Mark Wilcox, MD, Leeds Teaching Hospitals and University of Leeds, UK, and a lead investigator for the studies. "These results were also demonstrated in patient subgroups known to be at high risk for *C. difficile* recurrence."

Bezlotoxumab is not an antibiotic; it is a selective, fully-human monoclonal antibody designed to neutralize *C. difficile* toxin B, a toxin that can damage the gut wall and cause inflammation, leading to the symptoms of *C. difficile* enteritis, which include abdominal pain and

watery diarrhea.

MassBiologics has been a pioneer in the development of novel monoclonal antibodies for the treatment and prevention of disease.

"Discovering and developing effective new treatments for significant public health threats is the mission of MassBiologics," said Mark Klempner, MD, UMass Medical School's Executive Vice Chancellor for MassBiologics. "We are pleased that these two pivotal clinical trials form the basis for Merck to submit a new biologics license application seeking regulatory approval in the U.S., as well as applications in Europe and Canada."

"Recurrence is a major challenge with *C. difficile* infection, and novel approaches are needed to help prevent the cycle of *C. difficile* recurrence," said Dale Gerding, MD, professor of medicine, Loyola University Chicago Stritch School of Medicine, and a lead investigator for the studies.

Two global, Phase 3, double-blind studies were conducted to evaluate bezlotoxumab, either alone or in combination with actoxumab (a monoclonal antibody against *C. difficile* toxin A), compared to placebo for the prevention of recurrent *C. difficile* infection in patients on standard of care antibiotics for a primary or recurrent *C. difficile* infection. The MODIFY I study (MONOCLONAL ANTIBODIES FOR *C. DIFFICILE* THERAPY) enrolled 1,452 patients (median age 65 years) in 19 countries and the MODIFY II study enrolled 1,203 patients (median age 67 years) in 17 countries. The studies were conducted in both hospital and outpatient settings, and the primary endpoint for each study was evaluated through 12 weeks following study drug administration.

In both MODIFY I and MODIFY II, the rate of *C. difficile* infection

recurrence through week 12, the primary efficacy endpoint, was significantly lower in the bezlotoxumab arms and the combination bezlotoxumab and actoxumab arms compared to the placebo arms.

The incidence of *C. difficile* infection has risen sharply over the last two decades and today is a leading cause of health care-acquired infections in community hospitals in the United States. According to the U.S. Centers for Disease Control and Prevention, *C. difficile* is estimated to have caused almost half a million infections in the United States in 2011, with 29,000 deaths, often occurring within 30 days of initial diagnosis. In the United States, 8 out of 10 deaths related to *C. difficile* infection occur in patients 65 years of age or older.

C. difficile infection occurs most often in patients staying in health care settings, especially hospitals or nursing homes, who recently took certain antibiotics or other medications. The incidence of *C. difficile* infection is higher in certain patient populations, including people 65 years of age or older, and in patients with compromised immune systems due to an underlying disease or from treatment. Recurrence is a major challenge in *C. difficile* [infection](#), with approximately one in four patients experiencing a recurrence after the initial episode, and more than 40 percent of these patients having further *C. difficile* recurrence.

MassBiologics is the only non-profit, FDA-licensed manufacturer of vaccines in the United States. For over 100 years, MassBiologics has worked to improve public health through applied research, development and production of biologic products, including vaccines, plasma derivatives and most recently, [monoclonal antibodies](#). MassBiologics currently manufactures Tetanus and Diphtheria Toxoids and Adsorbed (Td) vaccine, and distributes nationwide.

Provided by University of Massachusetts Medical School

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