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Evaluation of the Safety and Pharmacokinetics of Clostridium difficile Toxin A Human Monoclonal Antibody and Clostridium difficile Toxin B Human Monoclonal Antibody Given Alone or in Combination in Healthy Adults

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Background: Clostridium difficile is a common cause of nosocomial infectious diarrhea, and its incidence and associated morbidity and mortality have increased over the past two decades. Pathogenicity of C. difficile, an anaerobic spore-forming gram positive bacillus, is related to production of two exotoxins, toxin A and toxin B, which result in intestinal inflammation and injury. Data from both human and animal studies indicate that antibodies directed against the toxins protect against symptomatic disease and recurrence. Monoclonal antibodies (mAbs) targeted to the toxins may be useful in the treatment of C. difficile associated diarrhea.

Objectives: To assess the safety and tolerability of escalating doses of human mAb to toxin A and human mAb to toxin B given alone or in combination in healthy adults and to determine the pharmacokinetics after a single intravenous infusion.

Methods: Phase I open-label, dose escalation study consisting of six dosing cohorts administered human mAb to C. difficile toxin A and human mAb to C. difficile toxin B as a single intravenous infusion of 200 ml. Doses given ranged from 0.3 mg/kg to 20 mg/kg alone or in combination and were administered over 2 hours. Dose escalation to the next cohort occurred after review of safety data through day 7 for all subjects in the preceding cohort.

Vitals signs, physical examinations, adverse events, and concomitant medication use were assessed at study visits through day 84 post-infusion. Hematology, chemistry and urinalysis samples were also collected as part of the safety evaluation, and values outside the reference range were assessed for clinical significance.

Blood samples for human anti-human antibody detection and pharmacokinetic analysis were collected at fixed time points through day 84 post-infusion. Anti-toxin A and anti-toxin B antibody concentrations were measured using a standard ELISA. Pharmacokinetic analysis was performed using WinNonlin Professional Edition, version 5.0.1.

Results: Sixty subjects ages 18-55 years were enrolled and infusions were well tolerated by all subjects. None of the infusions were interrupted or discontinued. There were no serious adverse events. 172 non-serious adverse events were reported from 50 of 60 subjects. Fifty-three events were assessed to be possibly related to the infusion. No clinically significant laboratory abnormalities were reported. Human anti-human antibodies were not detected in any of the study subjects. Cmax demonstrated dose dependence and was similar when human mAb to toxin A and
human mAb to toxin B were administered alone compared to in combination at the same mg/kg dosing level. Median half life values ranged from 26.16 days to 34.17 days for mAb to toxin A and 19.26 to 27.33 days for mAb to toxin B.

**Conclusions:** Infusions of escalating doses of human mAb to *C. difficile* toxin A and human mAb to *C. difficile* toxin B alone or in combination were safe and well tolerated. The distribution of total adverse events and possibly related adverse events does not suggest a dose-dependent relationship. Pharmacokinetic results do not suggest interference for the monoclonal antibodies administered in combination. A phase II clinical trial is currently underway in patients with *Clostridium difficile* associated disease to evaluate the effect of these human monoclonal antibodies as adjuvant therapy in patients receiving standard of care treatment.