

Case Study

Drug Z-2 for Prevention of *C. difficile* Infection by Minimizing Disruption of the Gut Microbiome

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Development of Non-Traditional Therapies for Bacterial Infections
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Principles of Therapy

- Antibacterial use disrupts the gut microbiome, reduces its α -diversity, and reduces colonization resistance
- Extent of disruption is dependent on concentrations of antibacterial drugs achieved in the gut, degree of local inactivation and duration of therapy
- Selective pressure from antibacterial drugs inhibits susceptible members of indigenous flora, and facilitates overgrowth of antibacterial-resistant flora, including *C. difficile*.
- Drug Z-2 reduces the concentration of β -lactam drugs in the gut thereby potentially decreasing the incidence of *C. difficile* infection (CDI) and potentially decreasing the disruption of the gut microbiome

Non-Clinical Studies

- In vitro:
 - Rapid and complete dissolution and release of Drug Z-2 from oral delayed-release formulation to be used in clinical and pharmacological studies was studied
 - Stability of Drug Z-2 in gut environment at different levels (at the action site, in intestinal chyme, and with intestinal contents) has been evaluated
- In vivo:
 - 28-day dog safety study with placebo vs. varying doses of Drug Z-2 (15, 30 and 60 mg/kg/dose - 3 times daily [max. 180 mg/kg/d]). Drug Z-2 was well-tolerated.
 - 14-day dog study with Drug Z-2 and β -lactam drugs: no interaction, no significant effect on the plasma PK of β -lactams. Drug Z-2 was well-tolerated.

Phase 1 Studies

- Healthy volunteers
- Single- and multiple-ascending dose PK studies
 - single oral doses of 10-1000 mg and multiple oral doses of 10-200 mg every 6 hours for a week
 - Drug Z-2 is not systemically bioavailable except at the highest dose (1000 mg) where systemic concentrations of 6-8 ng/mL could be detected.
 - Most plasma concentrations were below the LLOQ (1.5 ng/mL) for the assay.

Phase 1b/2a Studies

- Clinical studies were done to confirm mechanism of action in the human intestine
- Healthy subjects with functioning ileostomies were administered Drug Z-2, with serial sampling of intestinal chyme to ascertain levels of Drug Z-2 and a variety of β -lactam drugs.
 - Plasma PK of β -lactam drugs were unchanged.
 - Intestinal concentration of β -lactam drugs decreased significantly.
- DDI studies were done with drugs that alter pH of gut (e.g. proton-pump inhibitors), or composition of gut microbiome (e.g. probiotics)

Phase 2

- Prevention of CDI can be used as an easily measurable clinical endpoint.
- Study Design: Parallel-group, DB, PC, MC trial was conducted to evaluate the effectiveness of Drug Z-2 vs. placebo for prevention of CDI in hospitalized patients receiving β -lactam drugs for various non-GI infections.
- Duration of treatment with Drug Z-2: 3x daily, concomitant with, and for 72 hours after, course of therapy with β -lactams; patients followed for 6-8 weeks
- Efficacy endpoint: Prevention of CDI for 4 weeks following start of treatment with β -lactam drugs.

Phase 2

- Study Population: 300 patients per study arm; 55% male; mean age: 67 years
- Results: The following were observed in the Drug Z-2 vs. placebo arms:
 - Lower incidence of CDI: 3% (n=9) vs. 5% (n=15).
 - Reduction of colonization with *C. difficile* and Vancomycin-resistant Enterococci [VRE] (5% vs. 9% at 72 hours)
 - In addition:
 - Colonization with ESBL-GNB was similar between the groups and no different from baseline
 - No effect on incidence of antibiotic-associated diarrhea (AAD) without CDI



Questions for the panel...

- What are some important clinical trial considerations for such products with respect to trial design and endpoints?
- How does the expected higher mortality in the population that might be at greater risk for CDI factor into the endpoint? Is being alive and free of CDI an appropriate endpoint?
- Besides reduction in CDI, are there other appropriate clinical endpoints?
- Are there other measurable benefits of such products?
- Are study results from such trials generalizable to populations beyond those evaluated in clinical trials e.g., to individuals on other antibacterial drugs?



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