Efficacy of CB-012, a Novel Antiviral Fc-Conjugate, in Lethal Mouse Models of Oseltamivir-Sensitive and -Resistant Influenza A H1N1 and H3N2 Isolates

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Introduction
Cidara Therapeutics is developing a new generation of antivirals that couple a neutralizing small molecule to the Fc domain of a human IgG1 antibody. These long-acting, antiviral Fc-conjugates (AVCs) directly attack the virus while simultaneously engaging the immune system. CB-012 is an AVC against influenza that demonstrates robust, broad-spectrum activity and efficacy in lethal mouse influenza models.1,4

Methods
Efficacy studies were conducted in BALB/c mice challenged intranasally with virus (n=5/group). CB-012 was administered as a single dose intravenously at various concentrations 4 hours prior to viral challenge, except in the delayed dosing study. Oseltamivir was dosed orally at 20 mg/kg, bid, for 5 days, which is 4x the humanized dose, starting 8 hours after viral challenge. Body weights (BW) and general health were monitored daily, with 20% BW loss recorded as a mortality.

Results
CB-012 demonstrates potent activity against influenza A (H1N1) in a lethal mouse model. In an initial dose ranging study, CB-012 was administered as a single IV dose between 0.4 and 50 mg/kg. Mice treated with vehicle (PBS) or the Fc alone succumbed to infection by Day 8, as expected. However, mice receiving CB-012 were fully protected even at 0.4 mg/kg, the lowest tested dose in this study.

CB-012 treated mice retain body weight with doses as low as 0.4 mg/kg. All CB-012 dose groups in the study above did not show a significant drop in body weight during the entire course of the study. In contrast, the oseltamivir-treated group showed a significant loss of body weight around days 6 – 10. Despite differences in the dosage and timing of treatments (i.e., higher dose of oseltamivir given 8 hours after viral challenge), the retention of body weight in CB-012-treated animals was striking. (Negative control groups are graphed until the first death occurs within a group).

CB-012 has potent activity against influenza A (H3N2). Based on the significant activity of CB-012 against H1N1, a similar study was conducted against an H3N2 isolate. As before, CB-012 was efficacious at 0.4 mg/kg, and animals demonstrated minimal weight loss (4% for a single day, data not shown).

Conclusions
CB-012 demonstrated robust efficacy in multiple, lethal influenza challenge models of H1N1 and H3N2, and against an important oseltamivir-resistant isolate. In a delayed treatment study, CB-012 was protective up to 72 hours post-infection, whereas oseltamivir was only protective at 24 hours post-infection. These results, in conjunction with additional data being presented at this meeting (see references 1-4 below), support further development of CB-012 as a novel antiviral for the prevention and treatment of influenza.

References