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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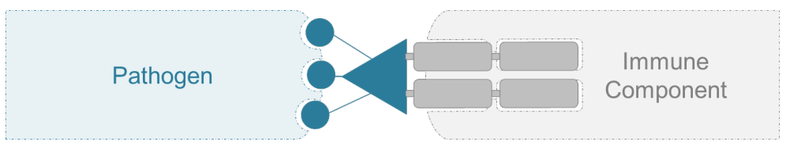
INTRODUCTION

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]



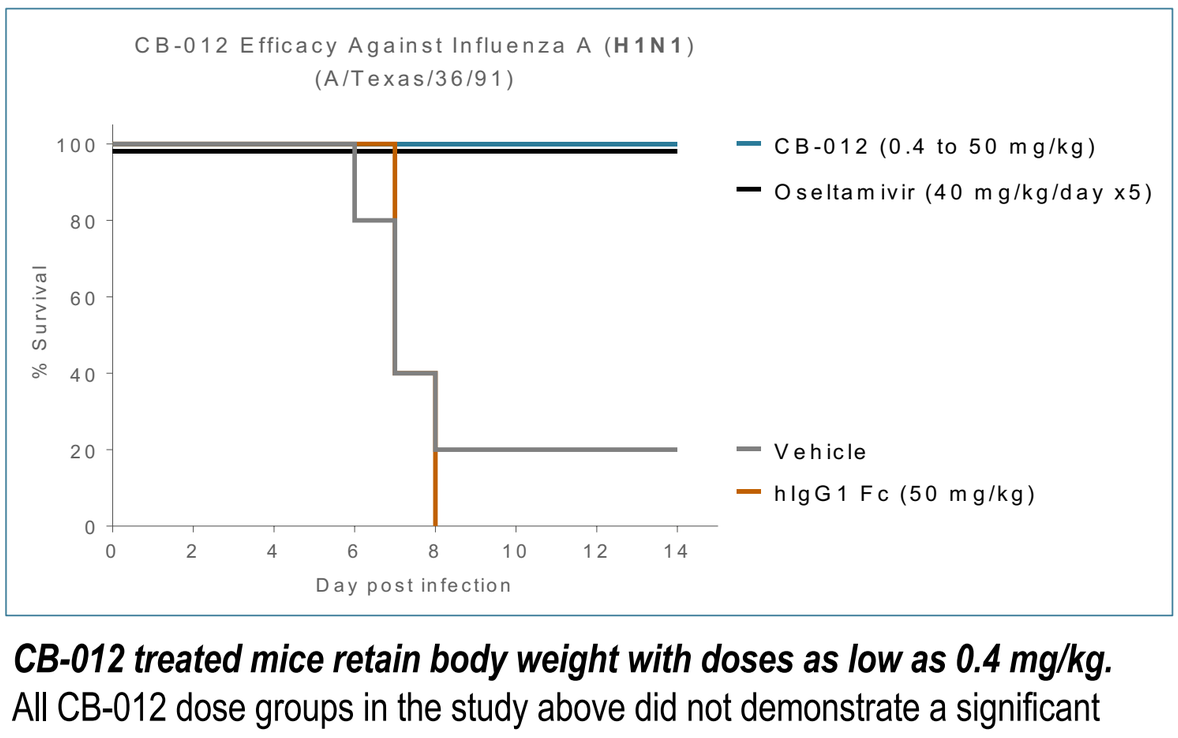
General structure of an AVC, with non-cleavable linker.

METHODS

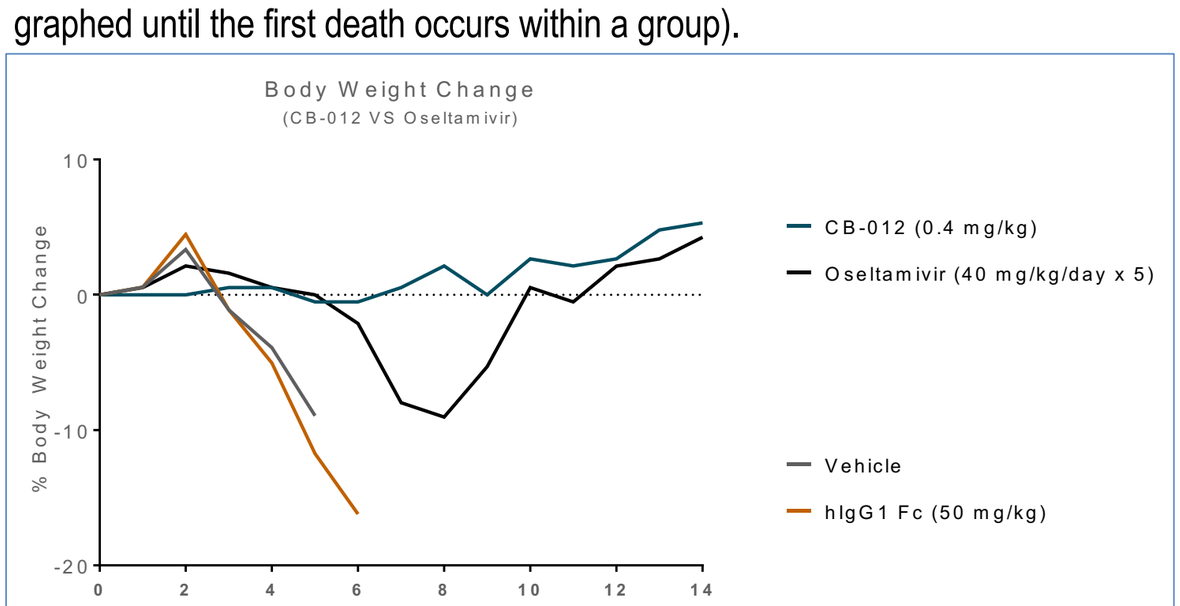
Efficacy studies were conducted in BALB/c mice challenged intranasally with virus (n=5/group). CB-012 was administered as a single dose intravenously at various concentrations 4 hours prior to viral challenge, except in the delayed dosing study. Oseltamivir was dosed orally at 20 mg/kg, bid, for 5 days, 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

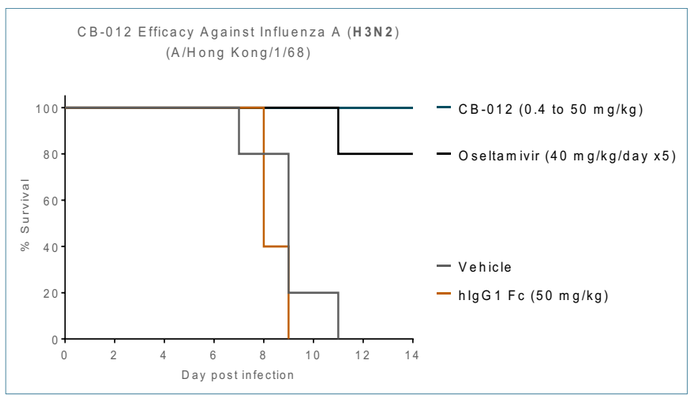
CB-012 demonstrates potent activity against influenza A (H1N1) in a lethal mouse model. In an initial dose ranging study, CB-012 was administered as a single IV dose between 0.4 and 50 mg/kg. Mice treated with vehicle (PBS) or the Fc alone succumbed to infection by Day 8, as expected. However, mice receiving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



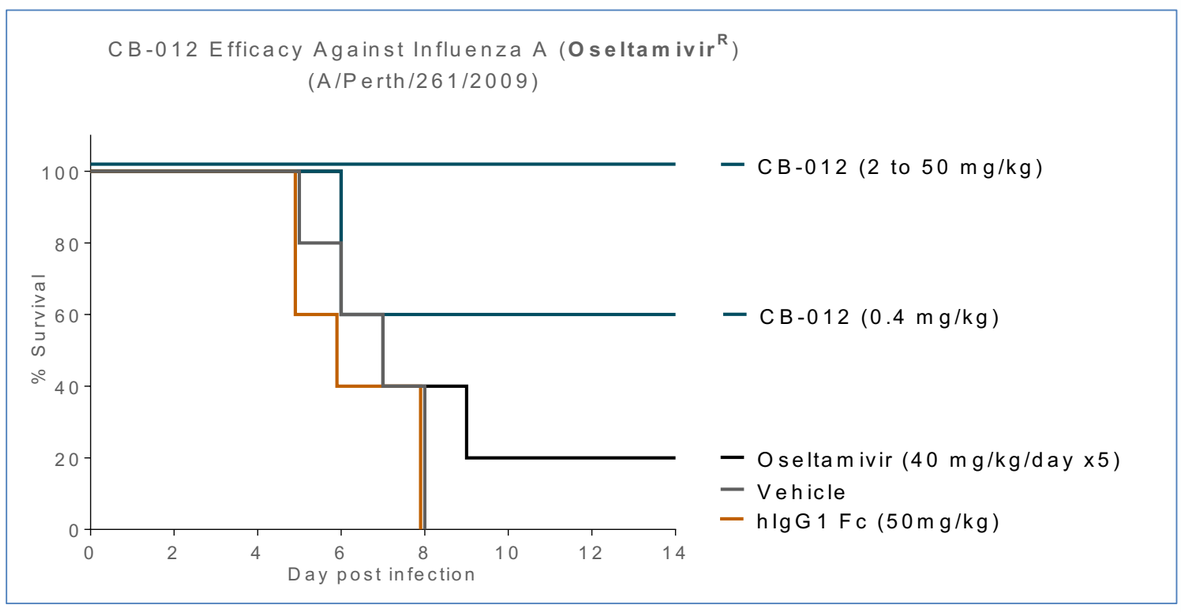
CB-012 has potent activity against influenza A (H3N2).



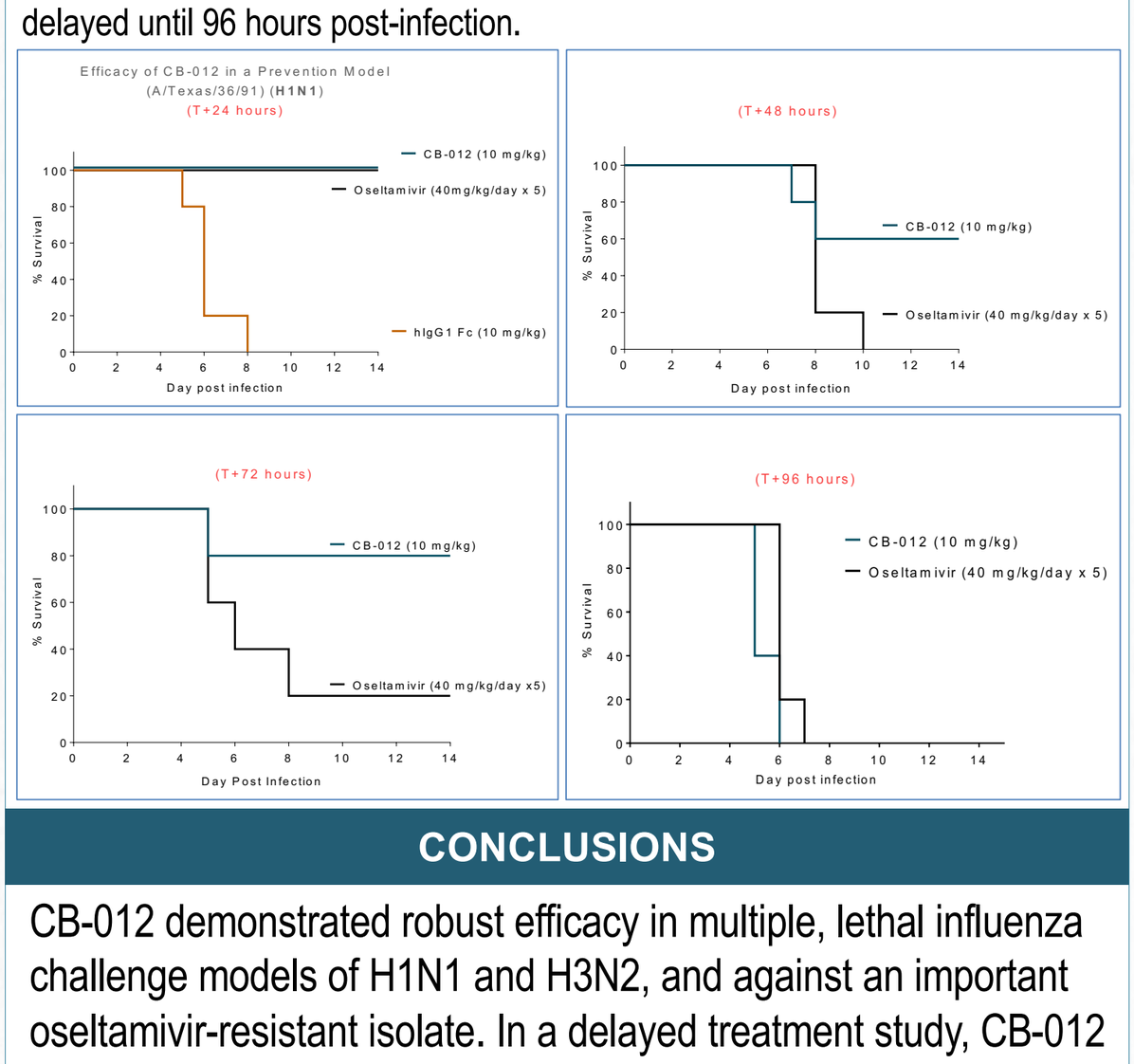
Based on the significant activity of CB-012 against H1N1, a similar study was conducted against an H3N2 isolate. As before, CB-012 was efficacious at 0.4 mg/kg, and animals demonstrated minimal weight loss (4% for a single day, *data not shown*).

RESULTS (cont'd)

CB-012 is efficacious against the dominant oseltamivir^R mutation. The H275Y substitution is the most prevalent, clinically relevant mutation conferring resistance to oseltamivir in N1 subtypes[5]. Because of this, CB-012 activity against this mutation was highly desired. As shown below, the effective CB-012 dose shifted moderately against this strain, with full protection at doses as low as 2 mg/kg. A transient loss of body weight occurred at this dose but was less than 6% and resolved within several days. As expected, oseltamivir was not effective against the H275Y-carrying isolate.



CB-012 demonstrates improved activity relative to oseltamivir in a delayed treatment model (H1N1). Influenza A is generally noted for having a short treatment window after the onset of symptoms. To investigate the intervention window of CB-012 at 10 mg/kg (IV), dosing was delayed for 24 to 96 hours. In this study, oseltamivir (dosed at 4x its humanized dose) was only efficacious when dosed at T+24 hours. In contrast, CB-012 demonstrated at least partial protection out to T+72 hours. Neither test article was effective when dosing was delayed until 96 hours post-infection.



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.

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