Poster #689

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Therapeutic Efficacy of CB-012, a Novel Cloudbreak Antiviral Fc-Conjugate (AVC) in Lethal Mouse Models of Influenza A (H1N1) and Influenza B (Victoria)

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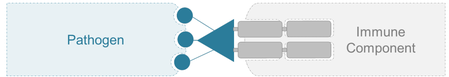
BACKGROUND

In 2018, the World Health Organization estimated that up to 650,000 influenza-related respiratory deaths occur annually. Cidara Therapeutics is developing a novel class of potent, long-acting antiviral Fc-conjugates (AVCs) against influenza that in a single molecule combine a surface-acting antiviral agent with the Fc domain of a human IgG1 antibody. AVCs function by inhibiting viral replication while simultaneously engaging the immune system, providing a multimodal mechanism of action. Here we present efficacy data on an AVC development candidate against influenza A and B.



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

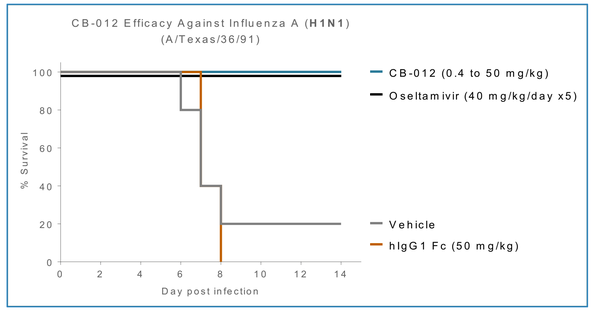
METHODS

Efficacy studies were conducted in female BALB/c mice (6 to 8 weeks old) challenged intranasally with 3x the LD_{95} of influenza A/Texas/36/1991 (H1N1) or B/Malaysia/2506/04. CB-012 or CB-012b (CB-012 with a slightly modified Fc) was administered as a single intravenous (IV) or subcutaneous (SC) dose 2 hours after viral challenge. Oseltamivir was dosed orally, twice daily for 5 days in the influenza A study. Vehicle and appropriate Fc controls were included in both studies. Body weights (BW) and mortality were monitored for 2 weeks; animals found moribund or with 20% BW loss, were scored as a death. BWs are graphed until the time point when the first death occurred within a group.

RESULTS

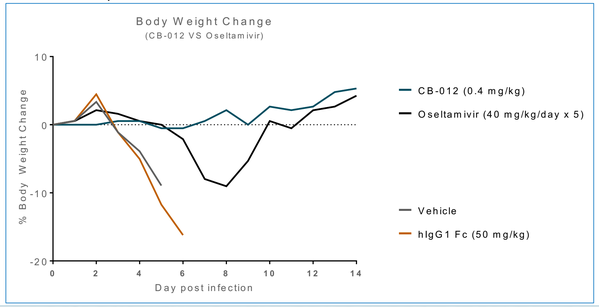
CB-012 demonstrates potent activity against influenza A (H1N1) in a lethal mouse model. In an initial dose-ranging study, CB-012 was administered as a single IV dose between 0.4 and 50 mg/kg. Mice treated with vehicle (PBS) or the Fc alone succumbed to infection by Day 8, as expected. However, mice receiving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

RESULTS (cont.)



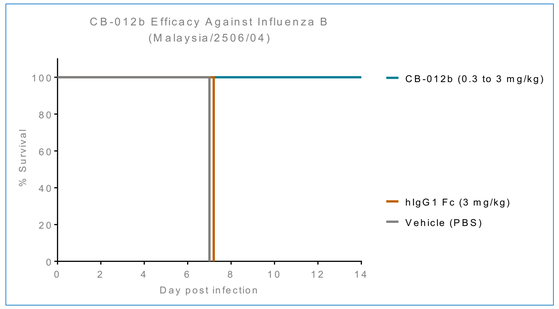
CB-012 treated mice retain body weight with doses as low as 0.4 mg/kg. All CB-012 dose groups in the study above did not demonstrate a significant drop in body weight during the entire course of the study. In contrast, the oseltamivir-treated group showed a significant body weight loss around days 6 – 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 time point when the first death occurred in a group).

In a related study, CB-012 was also found to have similar activity against the H3N2 subtype (A/Hong Kong/1/68) (*data not shown*).

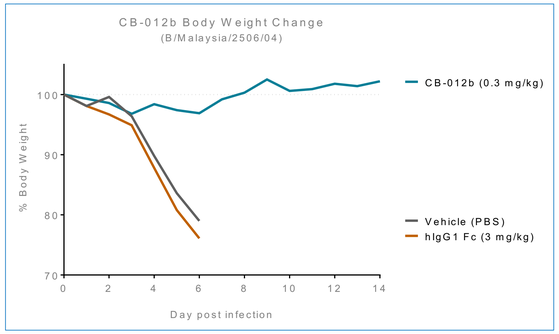


RESULTS (cont.)

CB-012b demonstrates potent activity in a lethal mouse model of influenza B. Having demonstrated activity against H1N1 and H3N2 subtypes, we next determined the susceptibility of influenza B (Victoria lineage) to CB-012. This study was run with CB-012b which has a modified Fc resulting in a shorter half-life. When dosed 2 hours after viral challenge via the SC route, this AVC was fully protective down to 0.3 mg/kg, the lowest concentration tested.



As seen against influenza A, a single dose of CB-012 of less than 1 mg/kg was not only protective against mortality (P = 0.0027), but largely prevented weight loss in challenged mice. The slight weight loss that was seen was transient and less than 4% of the average weight in the group.



CONCLUSIONS

The novel AVC CB-012 demonstrated robust efficacy against the three main seasonal influenza types (H1N1, H3N2, and influenza B). Full protection was achieved with a single IV or SC dose of less than 0.5 mg/kg and was accompanied by minimal body weight loss.

These data contribute to previous findings that established the activity of CB-012 against oseltamivir-resistant mutants (H275Y), engagement of immune components, and activity against a wider selection of influenza types including H5N1 and H7N9[1,3,5]. Furthermore, CB-012 was found to be active in immune-deficient models (SCID) and to possess favorable PK and toxicology profiles[2, 4].

Collectively, these data support the continued development of CB-012 for the prevention and treatment of seasonal and serious influenza infections.

REFERENCES

Additional information on CB-012 and Cidara's Cloudbreak program, as well as the posters below, may be found on the Cidara website:

1. Locke JB, et al. Novel antiviral Fc-conjugate CB-012 demonstrates potent activity in cytopathic effect (CPE) and viral growth inhibition assays against influenza A and B strains. Presented at Options X (2019). Abstract 10974.
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5. Levin J, et al. Efficacy of CB-012, a novel antiviral Fc-conjugate, in lethal mouse models of oseltamivir-sensitive and -resistant influenza A H1N1 and H3N2 isolates. Presented at Options X (2019). Abstract 10979.

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