

# Preclinical Efficacy, Pharmacokinetics, and Safety of CB-012, a Novel Antiviral Fc-Conjugate Against Influenza

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## INTRODUCTION

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 directly inhibit viral dissemination and infection while simultaneously engaging the immune system, providing a multimodal mechanism of action.

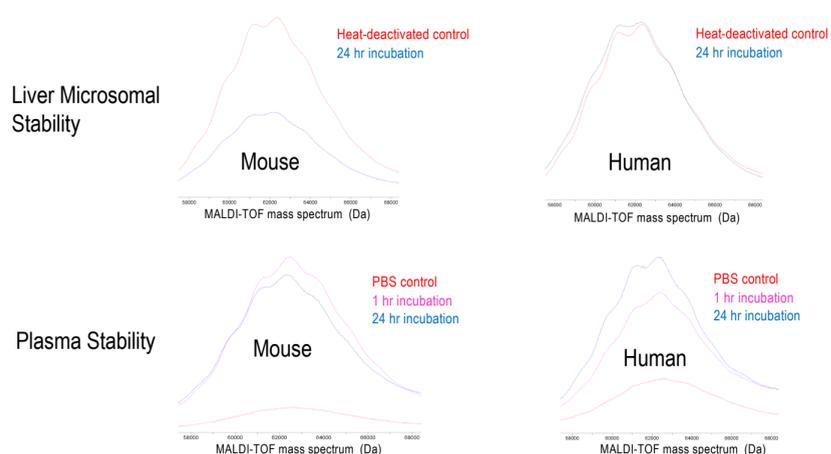
CB-012 is an AVC candidate comprising a potent antiviral agent that directly targets influenza A and B, conjugated to human IgG1. CB-012 has demonstrated robust treatment efficacy in lethal mouse models of influenza. Studies were conducted to assess its pharmacokinetics (PK), safety/tolerability, and efficacy in a prevention (prophylaxis) model.

## METHODS

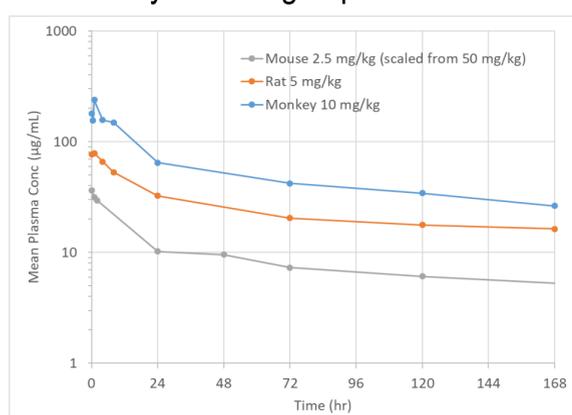
- CB-012 stability was assessed after 0- to 24-hour incubations in mouse/human plasma and liver microsomes at 37 °C using MALDI-TOF mass spectrometry.
- Single-dose PK was studied after dosing in mouse (1 – 50 mg/kg), rat (5 – 50 mg/kg), and monkey (5 – 20 mg/kg). Plasma was at selected times and concentrations were measured using ELISA.
- Efficacy in prevention of influenza infection was studied in a lethal mouse model using a single dose of CB-012 (1.25, 2.5, 5, 10 and 50 mg/kg; n=5/dose) that was administered 28 days prior to intranasal challenge with an LD<sub>90</sub> (~75 PFU/mouse) of A/Texas/36/91 (H1N1).
- Two-week safety/toxicology was evaluated in rats (5, 20, 50 mg/kg) and monkeys (5 & 20 mg/kg) using intravenous (IV) slow bolus on days 1 and 8 with necropsy on day 15; clinical signs, chemistries, hematology, cytokines, and histopathology were evaluated.

## RESULTS

Stability of CB-012 was verified in mouse/human plasma and liver microsomes prior to in vivo studies.



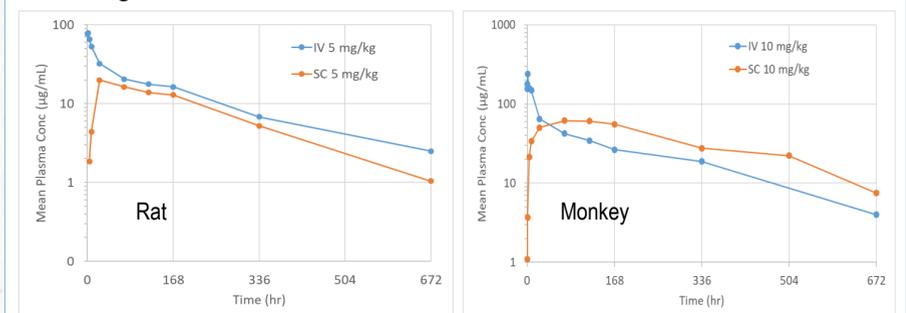
Subsequently, PK studies in the mouse, rat, and monkey, confirmed the low clearance of CB-012 in plasma with effective half-lives of 7 to 10 days in all 3 groups.



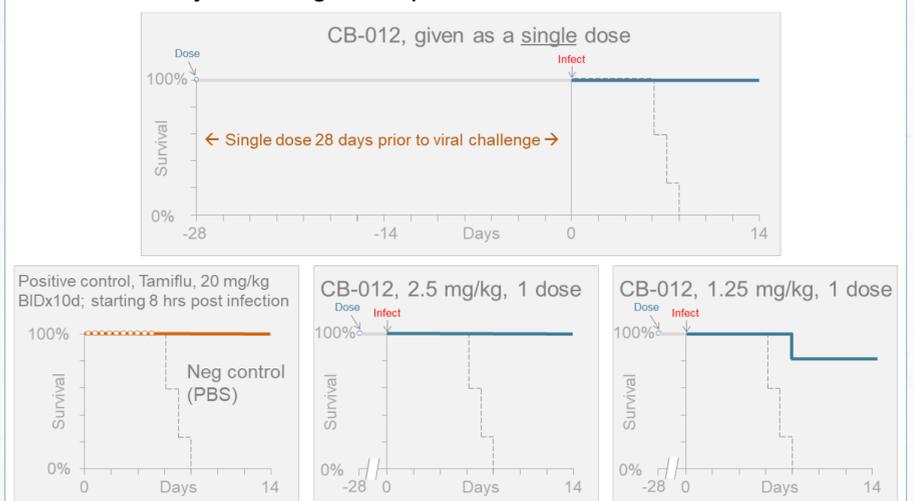
Across all doses tested to date, dose-proportional increases in exposure has been observed in each species: mouse, 1–50 mg/kg; rat, 5–50 mg/kg; monkey, 5–20 mg/kg.

## RESULTS (cont'd)

High bioavailability (>65%) was observed in the rat and monkey after subcutaneous administration allowing for more dosing flexibility. Further, CB-012 plasma elimination after IV dosing remained linear for at least a month post-dose with no evidence of anti-drug antibodies.



A single IV dose of 2.5 mg/kg given 28 days prior to infection resulted in 100% protection (all 5 mice survived), while a single 1.25 mg/kg dose showed 80% protection (4/5 mice survived). Oseltamivir (Tamiflu®), as positive control, was given PO 20 mg/kg BID for 10 days starting 8 hrs post-infection.



In rat and monkey toxicology studies, animals were administered CB-012 once weekly for 2 weeks by IV (slow bolus) injection. Toxicokinetic parameters were measured and exposures were confirmed to be at least 10-fold higher than needed for efficacy. In rats and monkeys, CB-012 was well tolerated and there was no effect on bodyweight, clinical chemistry, hematology, coagulation, cytokines, or urinalysis. Histological findings related to CB-012 were absent at all doses tested (rat up to 50 mg/kg, monkey up to 20 mg/kg).

## CONCLUSIONS

CB-012 displayed extended systemic exposure in animals that translated to long duration of action and efficacy in an influenza prophylaxis mouse model. Its safety and prolonged half-life underscore the potential of CB-012 as a long-acting, novel antiviral for prevention and treatment of influenza in humans.

These findings demonstrate the benefit of AVCs as a new multimodal strategy against influenza.

## REFERENCES

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