Efficacy of CB-012, a Novel Antiviral Fc-Conjugate, Against Influenza A (H1N1) in a Lethal Mouse Model of Severe Combined Immunodeficiency (SCID)

J. Levin, T. Lam, A. Borchardt, K. Amundson, J. Donatelli, J. Fortier, S. Döhrmann, E. Abelovski, J. Cole , V. Ong, L. Tari

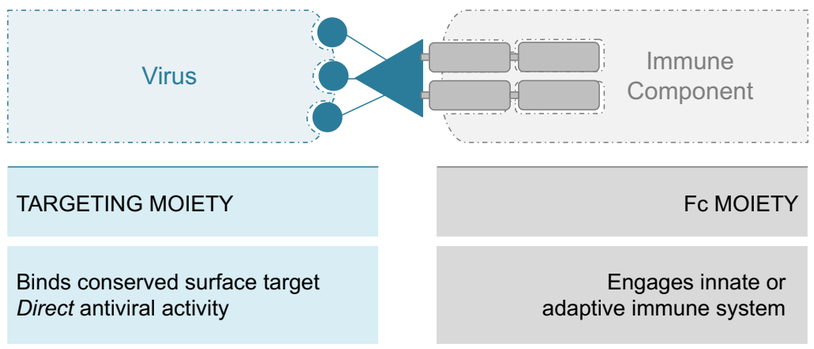
Cidara Therapeutics, San Diego, CA, USA

Les Tari, PhD
Cidara Therapeutics, Inc.
6310 Nancy Ridge Drive, Suite 101
San Diego, CA, USA
ltari@cidara.com

INTRODUCTION

Cidara Therapeutics is developing a new generation of antivirals that couple potent, small molecule antiviral agents to the effector domain (Fc) of a human IgG1 antibody (Fig. 1). These long-acting, antiviral Fc-conjugates (AVCs) inhibit the viral replication cycle while simultaneously engaging the immune system. The long half-lives and potent, intrinsic antiviral activities of AVCs make them well suited for potential use as preventative agents in patients with significant immunodeficiencies. CB-012 is an AVC candidate with broad-spectrum influenza A/B coverage undergoing evaluation for use in both immune-competent and -deficient populations.

Figure 1. CB-012 comprises a stable conjugate of multiple copies of a surface-acting antiviral agent with the Fc domain of human IgG1



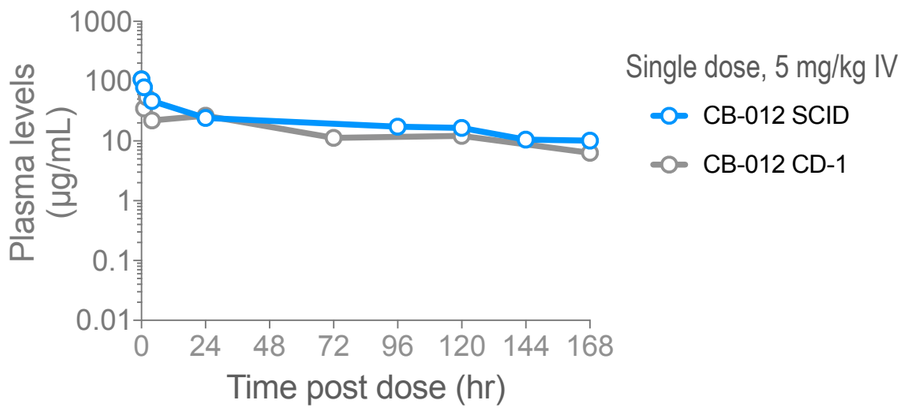
METHODS

- Single-dose pharmacokinetics were studied after dosing in mouse (5 mg/kg, IV). Plasma samples were collected at selected times and concentrations were measured using ELISA.
- Efficacy was evaluated in male BALB/c *scid* mice (~7 wks) (Jackson Labs, #001803) challenged intranasally with 3x the LD_{95} of influenza A/Puerto Rico/8/1934 (H1N1). CB-012 was administered intravenously as a single IV dose: 0.3, 1, or 3 mg/kg two hours after viral challenge. Body weights (BW) were monitored daily for 5 weeks, with 20% BW loss recorded as mortality.

RESULTS

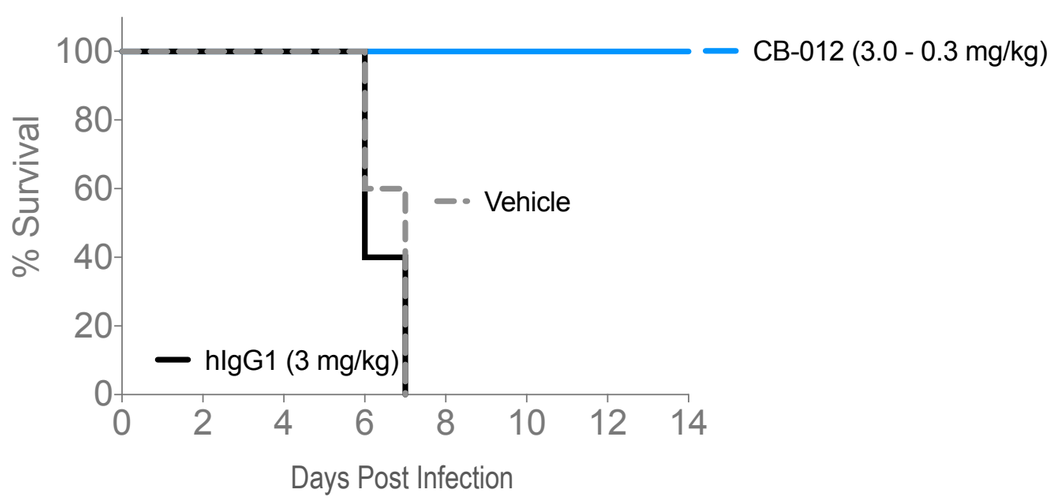
***CB-012 displays comparable PK profiles in immune competent and immune compromised mice* (Fig. 2).** CB-012 administered intravenously to SCID and CD-1 (immune competent) mice at 5 mg/kg demonstrated similar PK profiles. The two-phase PK profiles comprise 24-hour distribution phases followed by a shallow elimination phase. CB-012 plasma levels remained high (~10 µg/ml) relative to C_{max} levels over the one week course of the study.

Figure 2. Pharmacokinetics of CB-012 in BALB/c *scid* mice and CD-1 immune competent mice



***CB-012 is effective in preventing mortality in immune competent mice challenged with a lethal dose of influenza, using a single, low IV dose* (Fig. 3).** *In vivo* activity of CB-012 was determined in wild-type BALB/c mice. Animals receiving a single IV dose of CB-012 two hours post viral challenge were fully protected at doses as low as 0.3 mg/kg out to 40 days (only 14-day survival is shown).

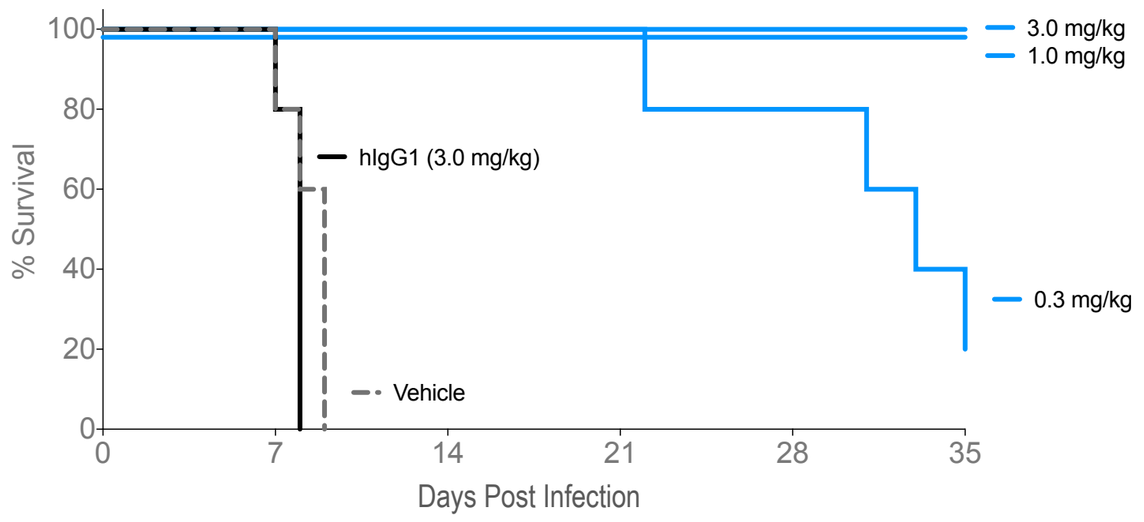
Figure 3. CB-012 efficacy in a lethal model of influenza A (H1N1) in immune competent BALB/c mice.



RESULTS (cont'd)

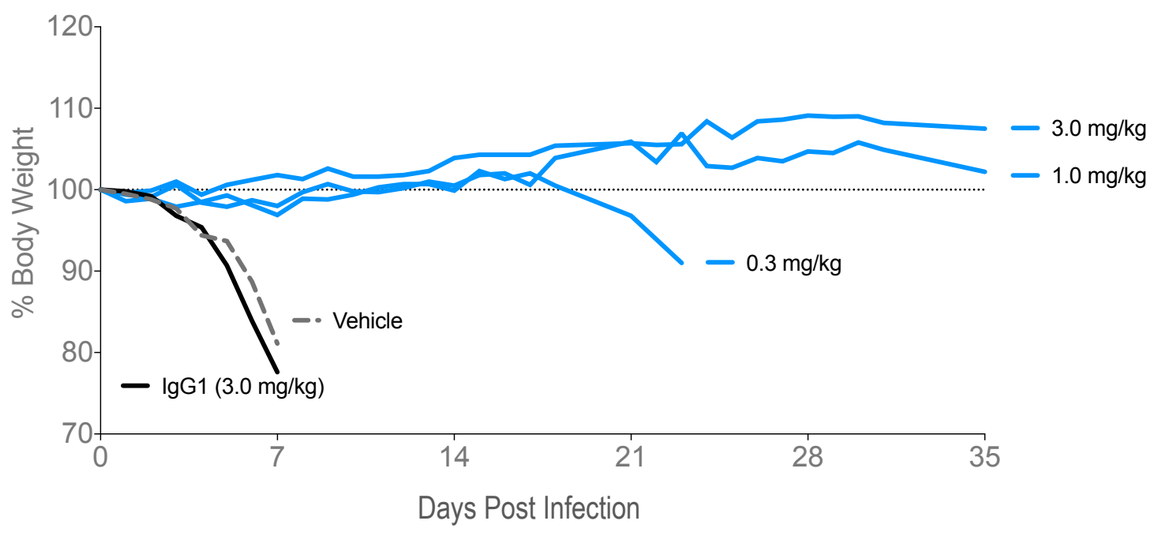
***CB-012 demonstrates long lasting protection in a severe model of immunodeficiency* (Fig. 4).** SCID mice receiving a single IV dose of CB-012 as low as 1 mg/kg were fully protected out to 35 days.

Figure 4. Survival of SCID mice lethally challenged with influenza A.



***CB-012 demonstrates long lasting protection in a severe model of immunodeficiency* (Fig. 5).** SCID mice receiving a single IV dose of CB-012 as low as 1 mg/kg retained their body weights throughout the course of the experiment.

Figure 5. Body weights of SCID mice lethally challenged with influenza A.



CONCLUSIONS

- CB-012 displays long systemic exposure in SCID mice that translates to a long duration of action and efficacy in a treatment model.
- The potent, intrinsic antiviral activity of CB-012 is sufficient to protect mice against lethal influenza infection, even in a severely immunodeficient background, at doses similar to those required to protect immune competent mice.
- This study underscores the potential of CB-012 for prevention and treatment of influenza in immune-senescent and immune-compromised subjects.

REFERENCES

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ACKNOWLEDGEMENTS

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