Evaluation of CD377, a Novel Antiviral Fc-Conjugate (AVC), In Vitro Activity and In Vivo Efficacy in Immune-Competent and -Deficient (SCID) Lethal Mouse Models

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INTRODUCTION

Cidara Therapeutics is developing a new generation of antivirals that couple potent, small molecule antiviral agents to the Fc domain of human IgG1 antibodies (Fig. 1). These long-acting, antiviral Fc-conjugates (AVCs) have potent antiviral activity and have the potential to engage the immune system. The long half-lives and potent, intrinsic antiviral activities of AVCs make them well suited for use as preventative agents even in patients with significant immunodeficiencies. CD377 is a development candidate with broad-spectrum influenza A/B coverage undergoing evaluation for use in both immune-competent and -deficient populations.

RESULTS (cont.)

CD377 demonstrates potent in vitro activity (Table 1). The TM of CD377 is a neuraminidase inhibitor, therefore its activity was assessed in an NAI assay compared to oseltamivir and zanamivir. All 3 had similar activity with IC50 values in the low nM range, and within ~3-fold of each other. However, in a CPE assay which included baloxavir, CD377 was ~5-fold more active than baloxavir and >1,800-fold more active than oseltamivir or zanamivir.

Table 1. In vitro activity of CD377 and comparators.

| Assay Type | In vitro Activity Against A/Puerto Rico/8/34 (H1N1) (nM) |
|-----------|--------------------------------------------------|
| NAI (EC50) | CD377 | Oseltamivir | Zanamivir | Baloxavir |
| CPE (EC50) | 0.782 | 1480 | 7580 | 3.69 |

Table 2. PK parameters for CD377 and comparators.

| PK Parameter | CD377 | Oseltamivir | Zanamivir |
|--------------|-------|-------------|-----------|
| Tmax (hr)    | 3.2   | 8.5         | 14.4      |
| T1/2 (hr)    | 12.5  | 5.8         | 11.4      |
| Cmax (nM)   | 0.1   | 0.2         | 0.3       |

RESULTS (cont.)

CD377 demonstrates long-lasting protection in a severe model of immunodeficiency (Fig. 4). SCID mice receiving a single IM dose of CD377 as low as 0.1 mg/kg were fully protected for 3 weeks. In contrast, vehicle and Fc-only groups were not protected.

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

CONCLUSIONS

The potent, intrinsic antiviral activity of CD377 is sufficient to protect mice against lethal influenza infection, even in a severely immunodeficient background, at doses identical to those required to protect immune-competent mice. This study underscores the potential of CD377 for prevention and treatment of influenza in immune-competent and -deficient populations.

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