139

IN VITRO POTENCY AND IN VIVO EFFICACY OF CD377, A NOVEL ANTIVIRAL Fc-CONJUGATE, AGAINST HIGHLY PATHOGENIC AVIAN INFLUENZA (HPAI)

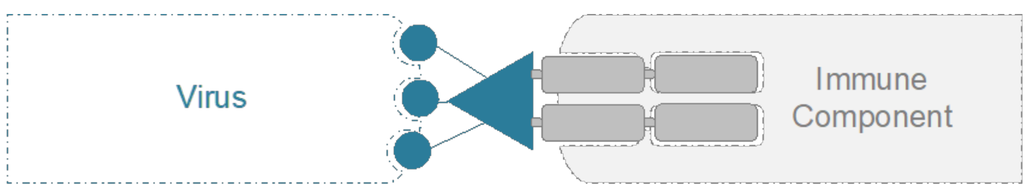
James Levin*, Allen Borchardt, Thanh Lam, Tom Brady, Alain Noncovich, Joanne Fortier, Simon Döhrmann, Voon Ong, and Les Tari

*James Levin, Ph.D.
Cidara Therapeutics, Inc.
6310 Nancy Ridge Drive, Suite 101
San Diego, CA, USA
JLevin@Cidara.com

INTRODUCTION

AVCs (antiviral Fc-conjugates) are long-acting, potent antiviral agents coupled with the Fc domain of human IgG1. CD377 is a novel AVC development candidate for the prevention and treatment of influenza. We evaluated CD377 potency against clinical HPAI (H5N1/H7N9), and efficacy against an H5N1 isolate from Vietnam.

CD377 comprises a stable conjugate of multiple copies of a surface-acting neuraminidase inhibitor with the Fc domain of human IgG1.



Targeting moiety	Fc moiety
Binds conserved surface target *Direct* antiviral activity	Provides prolonged half-life immune engagement potential

METHODS

CD377 in vitro activity was determined by a microneutralization assay (ViroSpot) as previously described (*Baalen et al., 2016. PMID27899226*). Two additional neuraminidase inhibitors, oseltamivir and zanamivir, were also assayed. Efficacy studies used BALB/c mice (n=10) challenged intranasally (1x LD_{90} of A/Vietnam/1203/2004 (H5N1)). CD377 was administered as a single subcutaneous (SC) dose 4 hours after viral challenge. Oseltamivir (10 mg/kg/d) was administered orally (bid x5 days), starting 4 hours post-challenge. Unconjugated Fc (10 mg/kg) was tested as placebo. Body weight (BW) was monitored for 21 days, with ≥20% BW loss recorded as mortality.

RESULTS

In vitro activity of CD377 and comparators in a cell-based assay. In a microneutralization assay CD377 had IC_{50} values between 0.5 and 16.9 nM against HPAI (H5N1 and H7N9; **Table 1**). These values were inline with CD377 activity against a benchmark H1N1 isolate (1.7 nM).

Oseltamivir demonstrated modest activity against two H5N1 isolates (IC_{50}s of ~168 nM) and had no activity against the other isolates in the panel, including H1N1 (≥300 nM). Zanamivir was active against H5N1 (IC_{50} values between 5.3 and 53.3 nM), but was inactive against H7N9 and H1N1 influenza subtypes (≥ 300 nM) (**Table 1**).

Collectively, even though all compounds target the influenza neuraminidase enzyme, only CD377 had potent activity against all tested subtypes. This trend is consistent with cell-based assays conducted at Cidara using larger panels comprising H1N1, H3N2, and influenza B subtypes (data not shown)

Table 1. In vitro activity of CD377 and comparators

Influenza strain	Type	IC_{50} for viral replication (nM)		
		CD377	Oseltamivir	Zanamivir
A/Vietnam/1194/2004	H5N1	5.3	168.7	16.9
A/Indonesia/05/2005	H5N1	16.9	≥ 300	16.9
A/Turkey/turkey/1/2005	H5N1	1.7	168.7	5.3
A/Hong Kong/156/1997	H5N1	0.5	≥ 300	53.3
A/Anhui/1/2013	H7N9	0.5	≥ 300	≥ 300
A/Netherlands/602/2009	H1N1	1.7	≥ 300	≥ 300

RESULTS (CONT)

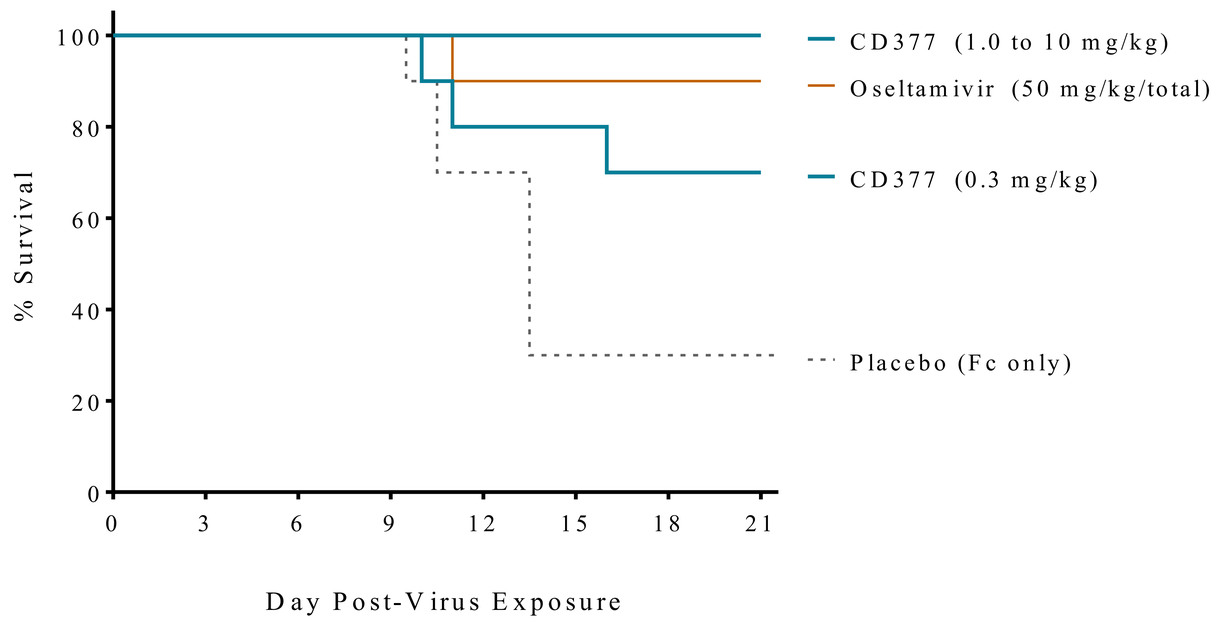
Efficacy of CD377 in a lethal mouse model of influenza A (H5N1). Previously, we have shown CD377 to be highly active in lethal mouse models against seasonal influenza. Against 16 influenza A/B types, no isolates required more than a single administration of CD377 at 0.3 mg/kg (IM or SC) for full protection. Here we wished to extend that data set to include HPAI.

In this study, 10 mice/group were used with treatment initiated 4 hours after viral challenge. The placebo group was dosed (SC) with Fc lacking the targeting moiety; as expected, it was not protective, reaching 70% mortality (**Figure 1**). Oseltamivir at the humanized dose was nearly fully protective (90% survival). In contrast, a single 1 mg/kg SC dose of CD377 (1/50th the oseltamivir dose) was fully protective (P<0.01 vs placebo) (**Figure 1**).

BWs mirrored survival, with transient BW loss of ~0.5% at the lowest, fully-protective CD377 dose (data not shown). BWs in this CD377 group and uninfected controls were not significantly different. In contrast, BWs of surviving oseltamivir-treated mice were significantly lower than control animals (P<0.0001).

Figure 1: CD377 efficacy against A/Vietnam/1203/2004 (H5N1)

(T+4h Dosing)



CONCLUSIONS

- **CD377 demonstrated potent in vitro activity against a panel of HPAI isolates (IC_{50} range 0.5 nM to 16.9 nM). Oseltamivir and zanamivir were significantly less active, with several IC_{50} values beyond testing limits (≥ 300 nM).**
- **A single dose of CD377 at 1 mg/kg demonstrated greater protection than oseltamivir (50 mg/kg total) against H5N1 in a lethal mouse treatment model.**
- **These data underscore CD377's potential for treatment and prevention of HPAI with pandemic potential.**

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