Preclinical efficacy, pharmacokinetics and safety of CD377, a novel antiviral Fc-conjugate against influenza

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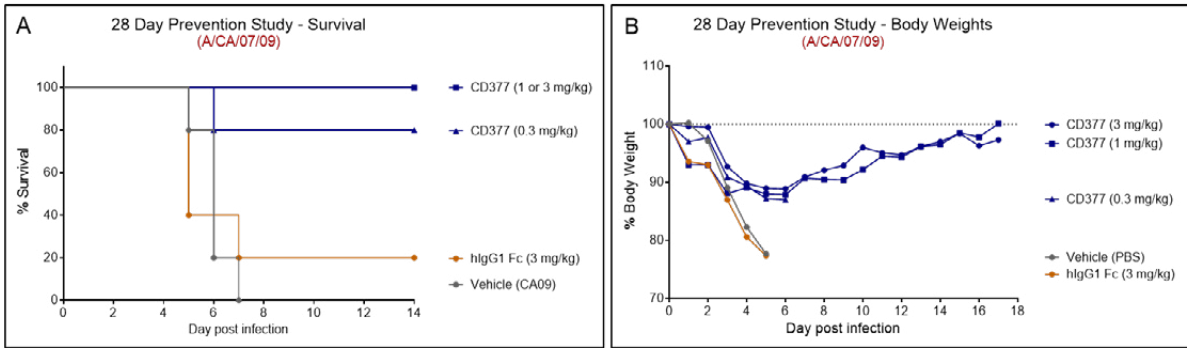
Background: CD377 is a novel antiviral Fc-conjugate (AVC) comprising a potent small-molecule antiviral and the Fc domain of human IgG1. CD377 is long-acting and demonstrates robust efficacy in lethal mouse models of influenza. Studies were conducted to confirm its stability and characterize CD377 pharmacokinetics, safety/tolerability, and efficacy in a mouse influenza prevention model.

Materials/methods: CD377 stability was assessed after 0-24 h incubations at 37°C in mouse/human plasma and human liver hepatocytes using MALDI-TOF mass spectrometry. Single-dose pharmacokinetics/tolerability were studied in the mouse (1-100 mg/kg), rat (5-50 mg/kg), and monkey (5-20 mg/kg). Plasma concentrations were measured by a neuraminidase (NA)-capture or Fc-capture with Fc-detection ELISA. In this case, Fc-capture/Fc-detection measured the total concentration of Fc-related species while NA-capture/Fc-detection measured the concentration of intact NA-linked–Fc species. Two-week safety/toxicology was evaluated in monkeys (5-20 mg/kg SC) on days 1 and 8 with necropsy on day 15; clinical signs, chemistries, hematology, cytokines, and histopathology were evaluated. Preventative efficacy was studied in a lethal influenza mouse model using a single dose of CD377 (0.3–3 mg/kg) 28 days prior to intranasal challenge with 3x the LD_{95} of A/California/07/2009 (H1N1) (3E4 pfu), A/Hong Kong/1/68 (H3N2) (3.6E4 pfu), or B/Malaysia (Victoria lineage) (1E4).

Results: CD377 was stable after incubations in plasma and liver hepatocytes. Further, plasma exposures from both Fc-capture/Fc-detection and NA-capture/Fc-detection were comparable, indicating that the molecule remained intact *in vivo*. In the mouse, rat, and monkey, CD377 $t_{1/2}$ was 5–10 days. Dose-proportional increases in exposure were observed in each species, notably from 1–100 mg/kg in mouse. High bioavailability (77%) was observed after subcutaneous or intramuscular administration. A single SC dose of 1 mg/kg administered 28 days prior to infection provided 100% protection from death against H1N1 (P=0.0020; Figure 1) and B (P=0.0031) subtypes. H3N2 required only a 0.3 mg/kg dose for 100% protection (P=0.0007). The 2-week monkey toxicology study showed no adverse effect on bodyweight, clinical chemistry, hematology, coagulation, cytokines, or urinalysis.

Conclusions: CD377 was well-tolerated and stable *in vitro* and *in vivo*; its extended half-life support its potential as a long-acting, novel AVC for prevention of influenza.

Figure 1. Efficacy of CD377 in a 28 Day Prevention Model. A, survival; B, body weight



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