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

Voon Ong1, James Levin1, Allen Borchardt1, Thanh Lam1, Wanlong Jiang1, Zhi-Yong Chen1, Duyen-Quyen Do1, Tom Brady1, Alain Noncovich1, Joanne Fortier1, Makia Nakamura1, Karin Amundson1, Jeffrey Locke1, Amanda Almaguer1, Nicholas Dedeic1, Grayson Hough1, Jason M. Cole1, Simon Döhrmann1, Rajvir Grewal1, Elizabeth Abelovski1, James M. Balkovec1, Michael Schlosser1, Ken Bartizal1, Leslie W. Tari*1

1Cidara Therapeutics, San Diego, United States

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 LD50 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 t1/2 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=0.0002; 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

Presenter email address: ltari@cidara.com