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# NEXT GENERATION ANTIVIRAL CONJUGATE (AVC): STABLE, SAFE, AND SINGLE

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## INTRODUCTION

Cidara Therapeutics is developing a novel class of potent, long-acting antiviral Fc-conjugates (AVCs) against influenza that, in a single molecule, combine a surface-acting antiviral agent with the Fc domain of a human IgG1 antibody. AVCs directly inhibit viral dissemination[1] and infection while simultaneously engaging the immune system, providing a multimodal mechanism of action. CD377 is an AVC candidate comprising a potent antiviral agent that directly targets influenza A and B, conjugated to human IgG1. CD377 has demonstrated robust treatment efficacy[1] in lethal mouse models of influenza. Studies were conducted to assess its pharmacokinetics (PK), safety/tolerability, and efficacy in a prevention (prophylaxis) model.

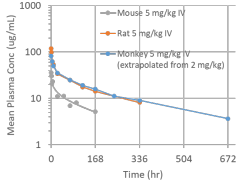
## METHODS

Pharmacokinetics in mouse (1-100 mg/kg), rat (5-50 mg/kg), and monkey (5 and 20 mg/kg) were studied by sampling plasma over 1-4 week interval. Plasma concentrations were measured by a neuraminidase (NA)-capture or Fc-capture with Fc-detection ELISA. The former measures intact molecule while the latter measures total Fc. Two-week safety/toxicology (clinical signs, chemistries, hematology, cytokines, histopathology) was evaluated in monkeys (5 or 20 mg/kg on days 1 and 8). Prophylaxis efficacy was studied in a lethal influenza mouse model using a single dose of CD377 (0.3-3 mg/kg) 28 days prior to IN challenge with 3x the $LD_{95}$ of A/California/07/2009 (H1N1), A/Hong Kong/1/68 (H3N2), or B/Malaysia (Victoria lineage). Treatment efficacy was studied in a similar mouse model using a single dose of CD377 (0.3-3 mg/kg) administered 24 hr after challenge with A/California/07/2009 (H1N1).

## RESULTS

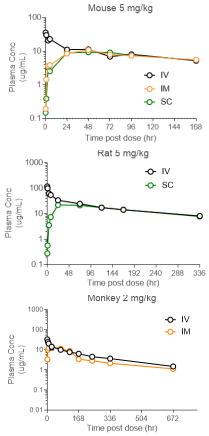
PK studies in the mouse, rat, and monkey, confirmed the low clearance of CD377 in plasma with comparable half-lives of 7 to 10 days depending on sampling time range (**Fig 1;** by NA-capture ELISA).

**Fig 1**




High bioavailability (~77%; **Fig 2;** by NA-capture ELISA) was observed after subcutaneous or intramuscular administration. Dose-proportional increases in exposure were observed in each species.

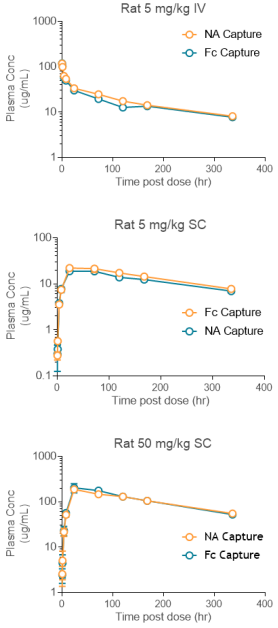
**Fig 2**




## RESULTS (con't)

Following PK studies, plasma exposures from both NA-capture/Fc-detection ELISA as well as Fc-capture/Fc-detection ELISA were comparable (**Fig 3**) regardless of route (IV, SC) or dose (5, 50 mg/kg) tested, confirming that CD377 remained stable in vivo, as former ELISA measures intact molecule while the latter ELISA measures total Fc.

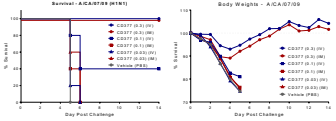
**Fig 3**




## RESULTS (con't)

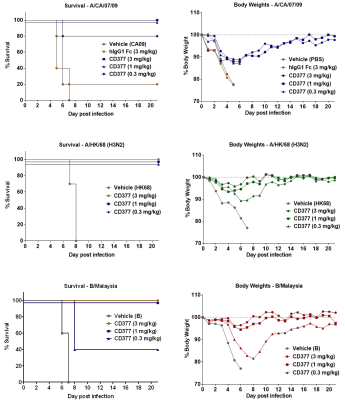
A single dose of 0.3 mg/kg administered 1 day after infection provided 100% protection from death against H1N1 (A/CA/07/09; **Fig 4**).

**Fig 4**



And, due to the long half-life, a single dose of 1 mg/kg given 28 days prior to infection provided 100% protection from death against H1N1 (A/CA/07/09) and B (B/Malaysia) subtypes, while H3N2 (A/HK/68) only required a 0.3 mg/kg dose for full protection (**Fig 5**).

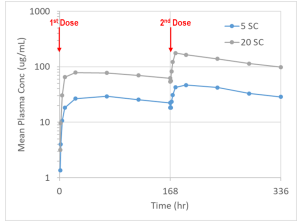
**Fig 5**



## RESULTS (con't)

In the monkey toxicology study, following 2 weekly SC doses, there was no adverse effect on bodyweight, clinical chemistry, hematology, coagulation, cytokines, urinalysis, or histopathology. Furthermore, plasma AUC from just the 2nd 20 mg/kg dose exceeded the plasma AUC from a single 1 mg/kg dose in mouse prophylaxis by >50-fold suggesting a wide safety margin for CD377. It was noted that there was no apparent change in the PK profile (**Fig 6**).

**Fig 6**




## CONCLUSIONS

CD377 was designed and confirmed to be stable in vivo following animal PK studies. CD377 was further found to be safe and well-tolerated. The long half-life of CD377 supports its use as a long-acting and novel antiviral for the prevention of influenza.

## REFERENCES

See related IDWeek 2020 presentations on CD377:

- Levin et al, poster 1276
- Levin et al, oral abstract 159
- Döhrmann et al, oral abstract 162

## ACKNOWLEDGEMENT

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