Efficacy of CD377, a Novel Antiviral Fc-Conjugate, Against Seasonal Influenza in Lethal Mouse Infection Models

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Abstract 159
Disclosures

All authors are employees and stockholders of Cidara Therapeutics, Inc.
Cidara’s Cloudbreak AVCs: a new class of long-acting antiviral

Long acting antiviral activity and potential immune engagement

AVC = Anti Viral Conjugate

- Designed for rapid onset, potent activity coupled with 3-6 months of protection
- Not vaccines, monoclonal antibodies, or traditional small-molecule therapeutics

A stable conjugate of a potent neuraminidase inhibitor with a human antibody Fc

TARGETING MOIETY (TM)

- Direct anti-viral activity
- Inhibits essential surface target

Fc MOIETY

- To engage immune system
- To extend PK: 3 – 6 months
The challenges of seasonal influenza
*From the 2018-2019 flu season (USA)*

- **35.5 million** Sick
- **16.5 million** Seek HCP care
- **490,600** Hospitalizations
- **34,200** Deaths

Significant healthcare burden and mortality

Dominant influenza type varies by season and even *within* a season

Need for preventatives with broad, universal activity

Source: CDC, WHO
The challenges of seasonal influenza – incomplete vaccine coverage

Vaccine Effectiveness (2018-19)

Age Group

Vaccine Effectiveness (%)
## FLU AVC profile summary

### Now in IND-enabling studies

| Target Attribute          | AVCs in Preclinical Development                                                                 |
|---------------------------|--------------------------------------------------------------------------------------------------|
| **Indication**            | Universal prevention and treatment                                                                | Data are supportive                           |
| **Spectrum**              | A & B + drug resistant strains, low resistance potential                                           | Potent *in-vivo* activity against all seasonal and pandemic strains |
| **Safety/Tolerability**   | High safety margin for long term prevention                                                       | > 50x exposure margin in 14-day primate toxicity studies |
| **Dosing Frequency**      | 1 to 2x per flu season                                                                            | Estimated 3 to 6-month coverage with single SC or IM dose |
| **Route of Administration** | SubQ, IM and IV dosing                                                                           | Equivalent exposures and efficacy              |
| **Target Populations**    | Higher risk populations where vaccines are not effective                                          | Equally effective in immune compromised & immune competent models at similar doses |

Data available at: [https://ir.cidara.com/presentations](https://ir.cidara.com/presentations)
CD377 mouse efficacy screening models

BALB/c, SCID, Tg32 mice
(ketamine or isoflurane anesthesia)

Dose route (IV, SC, IM)
Single dose (0.03 to 3 mg/kg)

Virus (3x LD_{95})
T+0h

T-28d T-7d T+2h T+72h

14 – 28 days post viral challenge

Survival
Body weight (BW)
Lung burden
Histopathology
Cytokines
Potency of CD377 against an H1N1 pandemic isolate

Lethal infection in BALB/c mice. Single IM dosing at T+2h

CD377 has been tested against 10 H1N1 isolates with fully protective doses between 0.03 and 0.3 mg/kg.
Potency of CD377 against an H3N2 isolate

Lethal infection in BALB/c mice. Single IM dosing at T+2h

Slightly greater potency against H3N2

CD377 dose response evident in daily body weight measurements
Potency of CD377 against influenza B isolates

Lethal infection in BALB/c mice. Single IM dosing at T+2h
A single 0.3 mg/kg dose of CD377 is fully protective against seasonal influenza. Against highly pathogenic influenza (H5N1), 1.0 mg/kg was protective.

CD377 demonstrated exceptional potency against 16 seasonal isolates.

### CD377 efficacy screening against influenza A/B (to date)

| Influenza | Subtype         | n   | Fully protective dose (mg/kg) |
|-----------|-----------------|-----|------------------------------|
| A         | H1N1            | 10  | 0.3                          |
| A         | H3N2            | 1   | 0.1                          |
| A         | H5N1            | 1   | 1.0                          |
| A         | H1N1 (H275Y)    | 2   | 0.3                          |
| B         | Victoria        | 2   | 0.3                          |
| B         | Yamagata        | 1   | 0.1                          |
Activity of CD377 in long-term prevention models

Lethal infection in BALB/c mice. Single, IM dosing at T-28 days

A/California/07/2009 pdm (H1N1)

- Single 1 mg/kg (or less) doses protective against H1N1, H3N2, B (Yamagata/Victoria)
- Data strongly supportive of CD377 use as a long-term preventative
Investigating body weight trends in our LRT screening model

Increasing the translatability of data to the clinic

**Question:** Is the initial BW loss a technical artifact of a severe screening model?

**Virus:** 3x LD$_{95}$
Ketamine anesthesia

**Diagram:**
- Graph titled "28 Day Prevention Study - Body Weights (A/CA/07/09)"
- X-axis: Day post infection
- Y-axis: % Body Weight
- Lines represent:
  - CD377 (3 mg/kg)
  - CD377 (1 mg/kg)
  - CD377 (0.3 mg/kg)
  - Vehicle (PBS)
  - hlgG1 Fc (3 mg/kg)
Improved translational model (upper respiratory tract seeding)
Lethal infection in BALB/c mice. Single IM dosing at T-3d

Isoflurane anesthesia

When virus was introduced in the URT, the model was still lethal, with CD377 fully protective at 0.1 mg/kg

When virus was seeded into the URT the previously observed BW loss was absent for all dose groups (0.1, 0.3, 1 mg/kg)
Oseltamivir was not protective when dosed 72h post-challenge at 20 mg/kg (bid x 5)

A single dose of CD377 at 1 mg/kg was protective

CD377 has significant potential as both a preventative and a **therapeutic treatment** against seasonal influenza
Highly active against seasonal influenza with single doses of 0.3 mg/kg or less

Active against seasonal influenza in 28-Day prevention models @ 1 mg/kg or less

Active against H275Y harboring H1N1 isolates

Effective in immune compromised (SCID) models (see poster 1276)

Superior activity to oseltamivir in therapeutic models

Equivalent potency by IV, SC, or IM dosing routes

Significant reduction in lung burden in mouse and ferret models (see talk 162)
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