CD377, a Novel Antiviral Fc-conjugate, Demonstrates Potent Viral Burden Reduction Against Influenza A (H1N1) in Mouse and Ferret Models

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Cidara Therapeutics
San Diego, CA
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Abstract 162
All authors are employees and stockholder of Cidara Therapeutics, Inc.
Conventional approaches to prevent and treat influenza

**Prevention**

- **Vaccine**
  - Limited VE

- **Monoclonal Antibody**
  - Limited to Influenza A

- **Small Molecule**
  - Limited to Treatment
Vaccines have limited vaccine effectiveness (VE) against influenza

Source: CDC
Vaccines have limited vaccine effectiveness (VE) - especially in the elderly - against influenza

%VE in high-risk group of >65 is only 30%

Source: CDC
Annual disease burden by influenza in the US (2019-20)

- 39-56M flu illnesses
- 410-740K hospitalizations
- 24-62K deaths

Source: CDC
Antiviral Fc-conjugate (AVC) are a novel approach for prevention and treatment of influenza.
CD377, the first development candidate of the Cloudbreak® AVC platform, for prevention and treatment of influenza

**Antiviral activity**

Potent, universal activity against influenza A and B

**Neuraminidase inhibitor**

Fc domain of human IgG1
CD377, the first development candidate of the Cloudbreak® AVC platform, for prevention and treatment of influenza

**Fc-mediated functions**

- Allows for engagement of immune effector cells
  - Long $T_{1/2}$

**Neuraminidase inhibitor**

**Fc domain of human IgG1**
CD377 has ideal attributes for prevention and treatment of influenza

<table>
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<th>Attribute</th>
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CD377 has universal activity against influenza A and B in vitro

Neuraminidase inhibition assay (median IC$_{50}$ nM)

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<th>Influenza subtype</th>
<th>CD377</th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
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<tbody>
<tr>
<td>A (H1N1, n=9)</td>
<td>1.5</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>A (H3N2, n=6)</td>
<td>4.5</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>B (n=7)</td>
<td>3.1</td>
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\textbf{Cell-based cytopathic effect assay (median EC}_{50} \text{nM)}

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<th>Influenza subtype</th>
<th>CD377</th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
<th>Baloxavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (H1N1, n=10)</td>
<td>1</td>
<td>925</td>
<td>343</td>
<td>3</td>
</tr>
<tr>
<td>A (H3N2, n=6)</td>
<td>1</td>
<td>3,190</td>
<td>112</td>
<td>2</td>
</tr>
<tr>
<td>B (n=6)</td>
<td>3.9</td>
<td>654.8</td>
<td>67</td>
<td>11.5</td>
</tr>
</tbody>
</table>
Lethal challenge with influenza A (H1N1) in mouse model

1. Infection with Influenza
2. Treatment (SC) $t=+2\ h$
3. Health check for 14 days
CD377 has potent efficacy against influenza A (H1N1) in mice
CD377 has potent efficacy against influenza A (H1N1) in mice
CD377 has potent efficacy against influenza A (H1N1) in mice

Single dose at 0.1 mg/kg of CD377 is fully protective
CD377 is superior to oseltamivir against influenza A (H1N1) in mice

Human equivalent dose of oseltamivir = 5 mg/kg BID x 5
CD377 is superior to oseltamivir against influenza A (H1N1) in mice

Human equivalent dose of oseltamivir = 5 mg/kg BID x 5
CD377 is superior to oseltamivir against influenza A (H1N1) in mice

CD377 is superior to oseltamivir at < 1/1,000 the total dose of oseltamivir
Viral burden and cytokine analysis on day 4 after lethal challenge with influenza A (H1N1) in mice.
CD377 demonstrates dose-dependent viral burden reduction against influenza A (H1N1)

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<th>Log reduction</th>
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<tr>
<td>PBS [0]</td>
<td>0.00</td>
</tr>
<tr>
<td>hlgG1 Fc [3]</td>
<td>-0.5</td>
</tr>
<tr>
<td>Oseltamivir [5]</td>
<td>0.8</td>
</tr>
<tr>
<td>Oseltamivir [50]</td>
<td>0.8</td>
</tr>
<tr>
<td>CD377 [0.1]</td>
<td>1.1</td>
</tr>
<tr>
<td>CD377 [0.3]</td>
<td>2.1</td>
</tr>
<tr>
<td>CD377 [1]</td>
<td>3.2</td>
</tr>
<tr>
<td>CD377 [3]</td>
<td>3.6</td>
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Dose-dependent reduction in inflammation by CD377 correlates with viral burden reduction.

- **IL-6**
  - Graph showing concentration ranges from 0 to 2000 pg/mL.
  - Significant reduction in IL-6 levels across different treatment groups compared to uninfected controls.

- **MIP-1α**
  - Graph showing concentration ranges from 0 to 5000 pg/mL.
  - Significant reduction in MIP-1α levels across different treatment groups compared to uninfected controls.

- **KC**
  - Graph showing concentration ranges from 0 to 10000 pg/mL.
  - Significant reduction in KC levels across different treatment groups compared to uninfected controls.

- **MCP-1**
  - Graph showing concentration ranges from 0 to 25000 pg/mL.
  - Significant reduction in MCP-1 levels across different treatment groups compared to uninfected controls.
High-challenge dose, transient infection with influenza A/CA/07/2009 (H1N1)pdm in ferret model
CD377 reduces viral burden in dose-dependency against influenza A (H1N1)

### Day 2

<table>
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<tr>
<th>Test article [mg/kg]</th>
<th>Log reduction</th>
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<tbody>
<tr>
<td>PBS [0]</td>
<td>0</td>
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<tr>
<td>hIgG1 Fc [15]</td>
<td>-0.3</td>
</tr>
<tr>
<td>Oseltamivir [5]</td>
<td>0.5</td>
</tr>
<tr>
<td>CD377 [0.3]</td>
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</tr>
<tr>
<td>CD377 [1]</td>
<td>0.5</td>
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<tr>
<td>CD377 [3]</td>
<td>1.3</td>
</tr>
<tr>
<td>CD377 [10]</td>
<td>1.9</td>
</tr>
<tr>
<td>CD377 [30]</td>
<td>1.9</td>
</tr>
</tbody>
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CD377 reduces viral burden in dose-dependency against influenza A (H1N1)

**Day 2**

- Untreated
- IgG1 Fc (30 mg/kg)
- Oseltamivir (5 mg/kg, BIDx4)
- CD377 (0.3 mg/kg)
- CD377 (1 mg/kg)
- CD377 (3 mg/kg)
- CD377 (10 mg/kg)
- CD377 (30 mg/kg)

**Day 4**

- Untreated
- IgG1 Fc (30 mg/kg)
- Oseltamivir (5 mg/kg, BIDx4)
- CD377 (0.3 mg/kg)
- CD377 (1 mg/kg)
- CD377 (3 mg/kg)
- CD377 (10 mg/kg)
- CD377 (30 mg/kg)

**Day 6**

- Untreated
- IgG1 Fc (30 mg/kg)
- Oseltamivir (5 mg/kg, BIDx4)
- CD377 (0.3 mg/kg)
- CD377 (1 mg/kg)
- CD377 (3 mg/kg)
- CD377 (10 mg/kg)
- CD377 (30 mg/kg)

Below LOD
Summary of AVCs against influenza

- CD377 has universal, broad-spectrum activity against influenza A and B
- CD377 at 0.3 mg/kg or lower is protective in lethal mouse models against influenza A and B (Talk #159 presented by James Levin, PhD)
- CD377 has superior efficacy as compared SOC, Oseltamivir, in mice
- CD377 demonstrates dose-dependent reduction in viral burden and inflammation in mice
- CD377 demonstrates dose-dependent reduction in viral burden in ferrets

→ CD377 has true universal activity against influenza with potential to transform the prevention and treatment of influenza
Cidara Cloudbreak® AVC platform: Expansion to other viruses

Influenza
Cidara Cloudbreak® AVC platform: Expansion to other viruses

- Influenza
- RSV
- HIV
- hCoV
Acknowledgements

- Cidara Team
- Charles River Laboratories (Histopathology)
- IITRI (Ferret study)
- Link to Website https://www.cidara.com/cloudbreak/