Cloudbreak Influenza

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Influenza – prophylaxis and treatments are available, but have limitations

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Antiviral Treatments</th>
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<tbody>
<tr>
<td>• Vaccines are strain-specific, providing variable coverage</td>
<td>• Short administration window</td>
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<tr>
<td>• 10%-60% effective (2004-2018)¹</td>
<td>• 48 hours from symptom onset²</td>
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<td>• Less effective in elderly &amp; immune compromised</td>
<td>• Drug resistance</td>
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<td>• ~2-week lag time to achieve full protection²</td>
<td>• Effectiveness poorly defined, particularly in high-risk patients</td>
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<td>• Long, complex manufacturing cycle</td>
<td>• Current treatments provide modest effects in reducing symptoms, infectivity</td>
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<td>• Difficult to scale, low antigen yields can limit production capacity</td>
<td>• Insufficient data to demonstrate that they reduce complications</td>
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**Desired Target Product Profile:**
- Long-acting prophylactic agent with full seasonal/pandemic coverage
- Coverage of immune compromised subjects

**Desired Target Product Profile:**
- Broad-spectrum activity, extended treatment window
- Minimize probability of resistance emergence

¹https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm
²https://www.cdc.gov/flu/protect/keyfacts.htm
³https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
Cloudbreak platform – multimodal mechanism of action: intrinsic antimicrobial activity & immune engagement

Pathogen

TARGETING MOIETY

Binds conserved surface target Direct antimicrobial activity

Immune Component

EFFECTOR MOIETY

Engages innate or adaptive immune system
Cloudbreak Antiviral Conjugates (AVCs) are not conventional Antibody-Drug Conjugates (ADCs)

TUMOR CELL

1. Fc recruits immune system

2. Direct Neutralization

3. VIRUS

Tight binding

ONCOLOGY ADC

CLOUDBREAK
Cloudbreak AVCs combine the power of small molecules (SMs) and monoclonal antibodies

- High potency SMs
- Extended half-life
- Broad spectrum (influenza A&B)
- Combining multiple MOAs
Cloudbreak AVCs are highly potent \textit{in vitro}

Plaque Assay (H1N1 WSN/33)

- PBS
- Oseltamivir 1µM
- CB-012 0.01µM
Cloudbreak AVCs are highly potent *in vitro*

3,000-fold greater reduction in viral replication at 1/100 the concentration of oseltamivir
CB-012 outperforms oseltamivir *in vitro*
Plaque reduction in infected A549 cells
CB-012 has highly potent *in vivo* activity

*Lethal influenza model (H1N1: TX/36/91 in mice)*

*Equivalent protection to oseltamivir at 1/500th the dose*

5 mice per cohort CB-012 dosed 4 hours prior to infection, oseltamivir dosed 8 hrs post infection
Body weight data supports robust efficacy & safety

CB-012 Average Body Weights
Influenza A (H1N1; TX/36/91)

CB-012 (0.4 mpk)
Oseltamivir (20 mpk)
CB-012 (50 mpk)

Negative control
CB-012 has highly potent *in vivo* activity

*Lethal influenza model (H3N2: HK/1/68 in mice)*

*Equivalent protection to oseltamivir at 1/1000th the dose*

5 mice per cohort CB-012 dosed 4 hours prior to infection, oseltamivir dosed 8 hrs post infection
CB-012 has potent *in vivo* activity against the dominant oseltamivir$^R$ strain

*Lethal influenza model (H1N1: A/Perth/261/2009 (H275Y))*

**Oseltamivir, 20 mg/kg, 2x/day**

**CB-012, 10 mg/kg, 1 dose**

**CB-012, 2 mg/kg, 1 dose**

**CB-012, 0.4 mg/kg, 1 dose**

5 mice per cohort CB-012 dosed 4 hours prior to infection, oseltamivir dosed 8 hrs post infection
CB-012 improves treatment window versus oseltamivir

Lethal influenza model (H1N1: TX/36/91 in mice)

Single dose of CB-012 improves treatment window vs 10 doses (BID) of oseltamivir

Controls (dosed 4 hrs prior to infection)

Dosed 8 hrs post infection

Dosed 24 hrs post infection

Dosed 48 hrs post infection

Dosed 72 hrs post infection

Dosed 96 hrs post infection

5 mice per cohort oseltamivir dosed BID for 5 days in each cohort
CB-012 rapidly distributes to lung, supporting treatment applications

10 mg/kg IV dose, evaluation of levels in whole lung

CB-012 plasma and lung levels

Reaches Cmax in lung by 1 hr

Lung levels track with plasma levels at ~10% relative to plasma
CB-012 demonstrates extended half-life

Mouse PK 50 mg/kg IV injection

Mean Plasma Conc (ug/mL)

7-12 days: Half-life in mouse, rat, cyno
PK is dose linear across wide dose range
Extended half-life translates to long duration of action

Lethal influenza model (H1N1: TX/36/91 in mice)

CB-012 dosed once 28 days prior to viral challenge

Oseltamivir 20 mg/kg, 2x/day starting 8 hrs post infection

CB-012, 50 mg/kg, 1 dose

CB-012, 10 mg/kg, 1 dose

CB-012, 5 mg/kg, 1 dose

CB-012, 2.5 mg/kg, 1 dose

CB-012, 1.25 mg/kg, 1 dose

5 mice per cohort
Efficacy is observed using multiple dosing routes

Lethal influenza model (H1N1: TX/36/91 in mice)

CB-012 dosed once 4 hours prior to viral challenge

Oseltamivir 20 mg/kg, 2x/day starting 8 hrs post infection

CB-012, 1 dose, IV

CB-012, 1 dose, IM

CB-012, 1 dose, SC

5 mice per cohort
Preclinical safety results consistent with a high therapeutic index

CB-012 14-day, dose-range finder toxicity study in rat

- Compounds dosed twice - day 0 & day 7
- 5, 20 and 50 mpk doses tested (IV)
- No significant effects on body weight gain, organ weights or food consumption at any dose

![Graph showing averaged body weights](image)
Preclinical safety results consistent with a high therapeutic index

**Summary: CB-012 14-day, dose-range finder toxicity study in rat**

- TK: Plasma exposures/AUC increase proportionally with dose, and PK scales from mouse to rat to cyno approximately by BW
- Exposure margins >15X - based on 28 day mouse prophylaxis model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Findings at highest dose (50 mpk) vs vehicle</th>
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</thead>
<tbody>
<tr>
<td>Clinical observations</td>
<td>No findings</td>
</tr>
<tr>
<td>Hematology</td>
<td>No change from vehicle</td>
</tr>
<tr>
<td>Clinical Chemistry</td>
<td>No change from vehicle</td>
</tr>
<tr>
<td>Coagulation</td>
<td>No change from vehicle</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>No change from vehicle</td>
</tr>
<tr>
<td>Histopathology</td>
<td>No observations</td>
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14-day dose-range finder toxicity study in cyno complete
Cloudbreak AVCs are being advanced to IND-enabling studies

CB-012 has demonstrated robust proof of concept

- Superior \textit{in vitro} activity vs standard of care antivirals & coverage of Inf A and Inf B strains
- Activity with single, low doses in efficacy models vs multiple strains
- Efficacy via IV, SC and IM dosing
- 28-day protection with a single 2.5 mg/kg dose in mice
- Expanded treatment window in mice vs oseltamivir
- Exposure margins (rat) >15X - based on 28-day mouse prophylaxis model

Optimized molecules are being advanced

- 1-2 log improvements in \textit{in vitro} potency (CB-038)
- Fc engineering underway to extend half-life
- \textbf{Goal}: Extend protection to entire flu season with a single dose

<table>
<thead>
<tr>
<th>Molecule</th>
<th>EC$_{50}$ (nM)</th>
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<tbody>
<tr>
<td>Oseltamivir</td>
<td>390</td>
</tr>
<tr>
<td>CB-012</td>
<td>4.0</td>
</tr>
<tr>
<td>CB-038</td>
<td>0.6</td>
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