CIDARA THERAPEUTICS

Cloudbreak Influenza

Cloudbreak Influenza

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Influenza – prophylaxis and treatments are available, but have limitations

Vaccines

- **Vaccines are strain-specific, providing variable coverage**
  - 10%-60% effective (2004-2018)[1]
  - Less effective in elderly & immune compromised
- **~2-week lag time to achieve full protection[2]**
- **Long, complex manufacturing cycle**
  - Difficult to scale, low antigen yields can limit production capacity

- **Desired Target Product Profile:**
  - Long-acting prophylactic agent with full seasonal/pandemic coverage
  - Coverage of immune compromised subjects

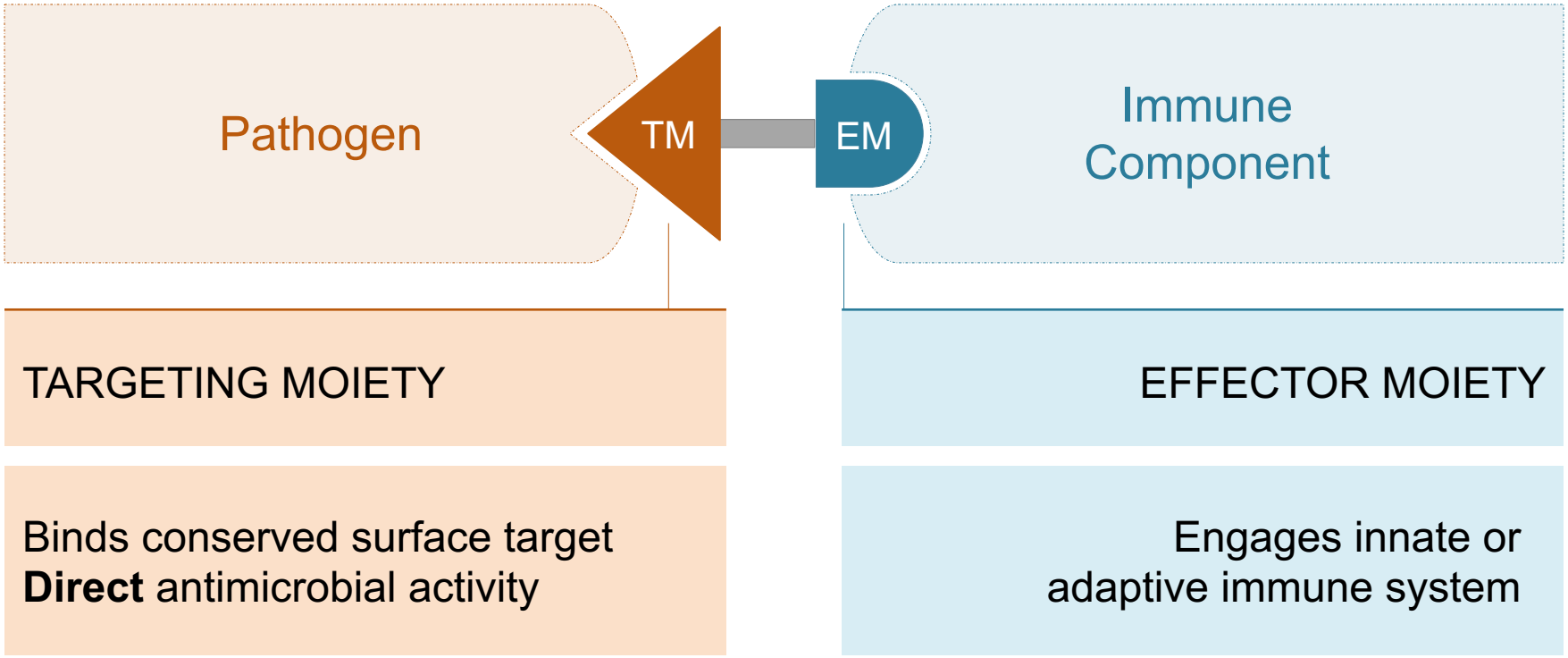
Antiviral Treatments

- **Short administration window**
  - 48 hours from symptom onset[3]
- **Drug resistance**
- **Effectiveness poorly defined, particularly in high-risk patients**
  - Current treatments provide modest effects in reducing symptoms, infectivity
  - Insufficient data to demonstrate that they reduce complications

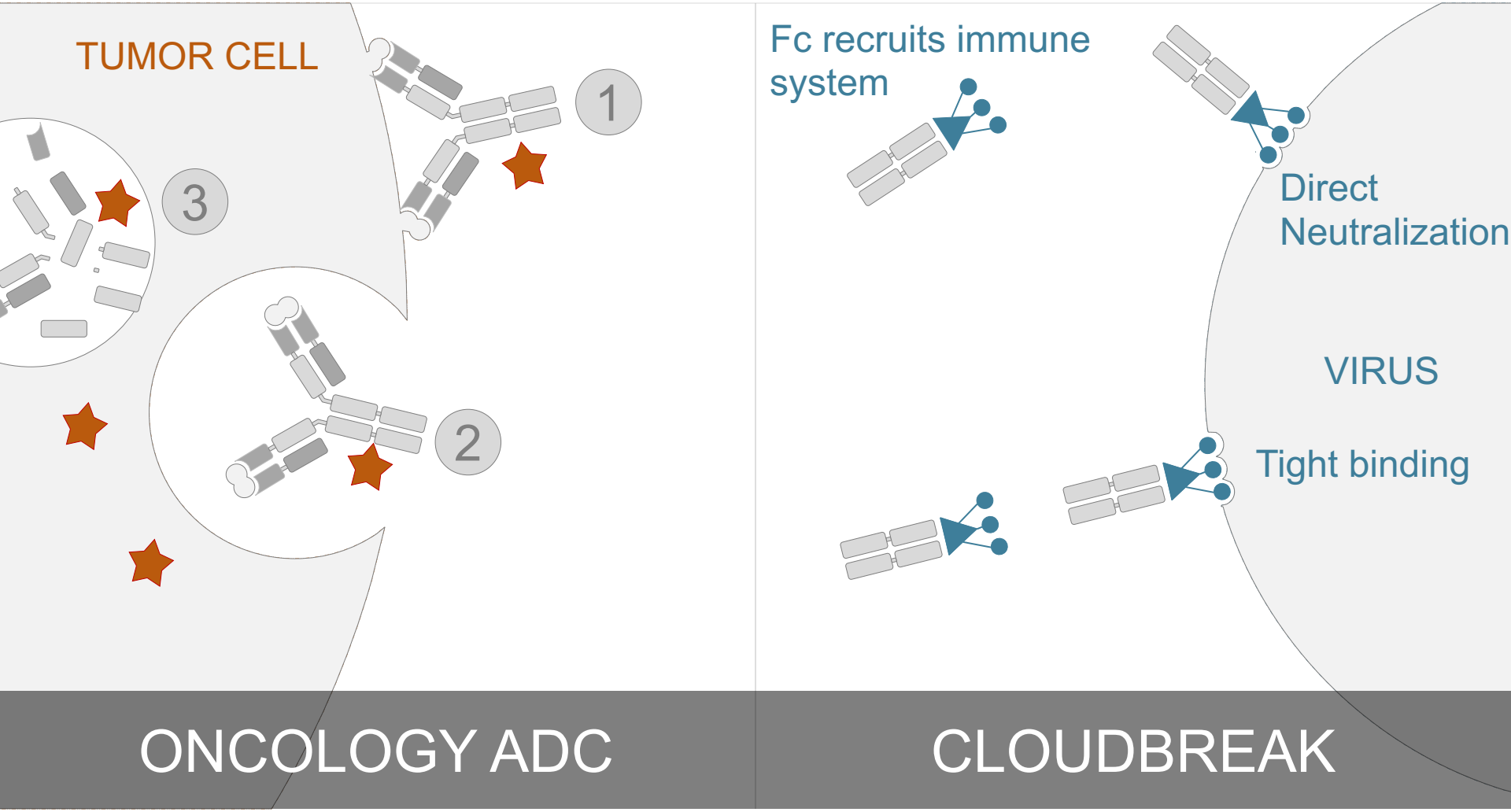
- **Desired Target Product Profile:**
  - Broad-spectrum activity, extended treatment window
  - Minimize probability of resistance emergence

[1]https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm
[2]https://www.cdc.gov/flu/protect/keyfacts.htm
[3]https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

Cloudbreak platform – multimodal mechanism of action: instrinsic antimicrobial activity & immune engagement

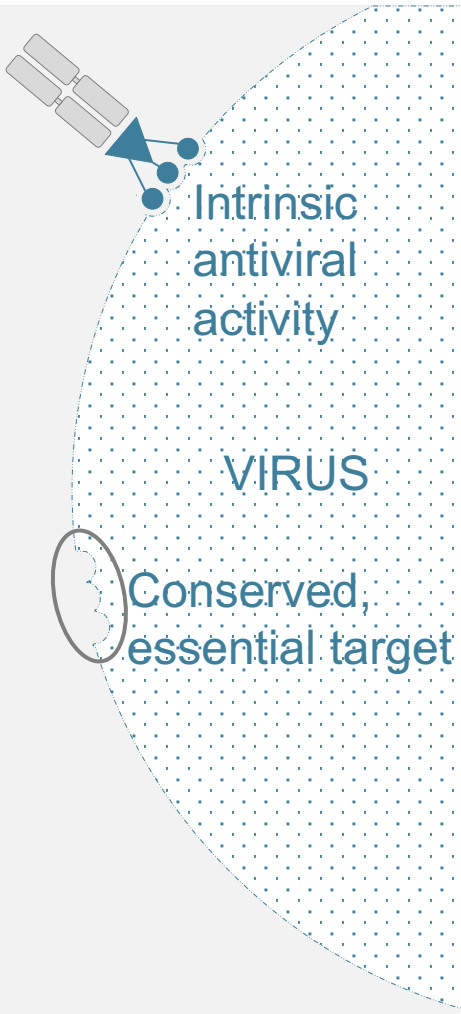


Cloudbreak Antiviral Conjugates (AVCs) are not conventional Antibody-Drug Conjugates (ADCs)

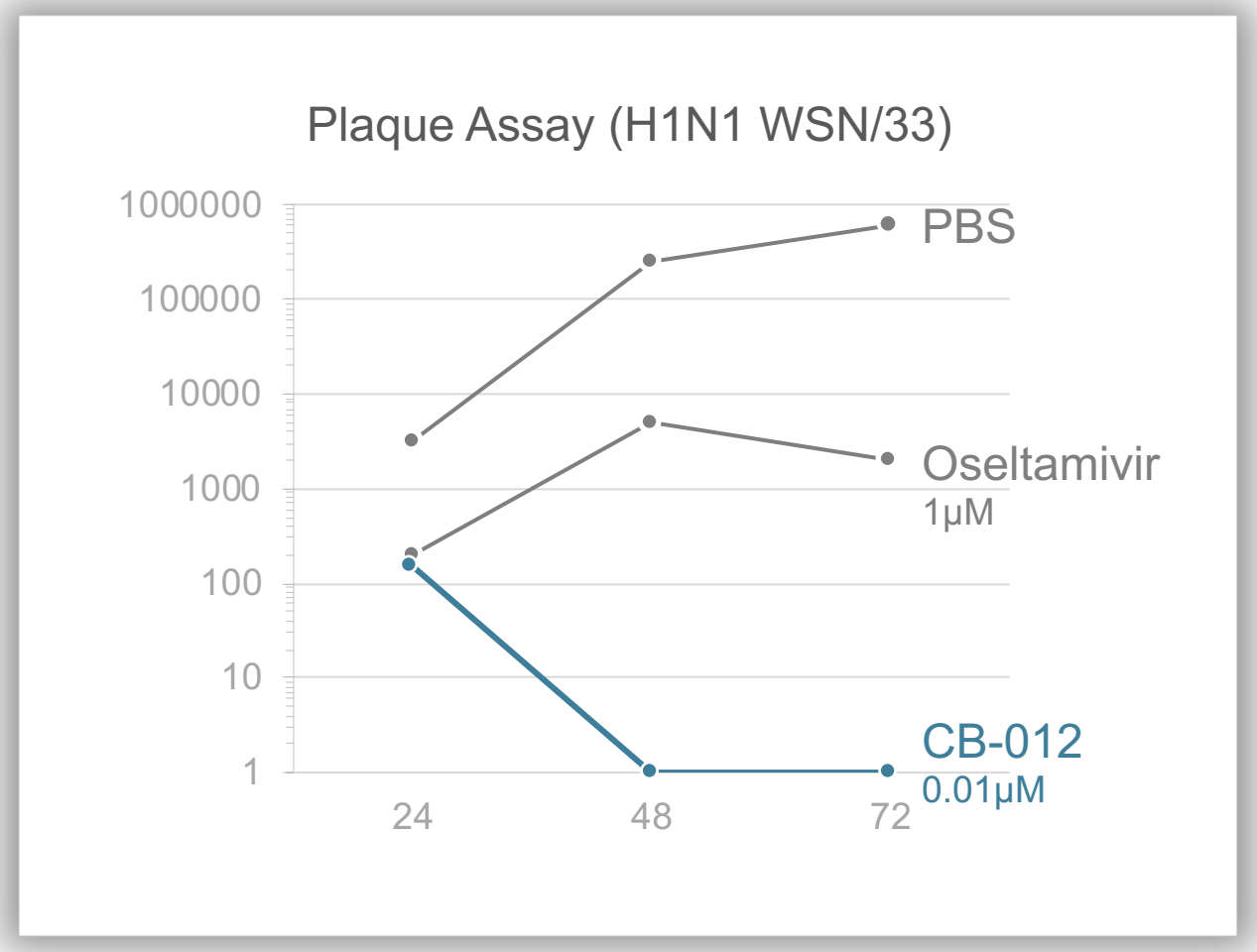


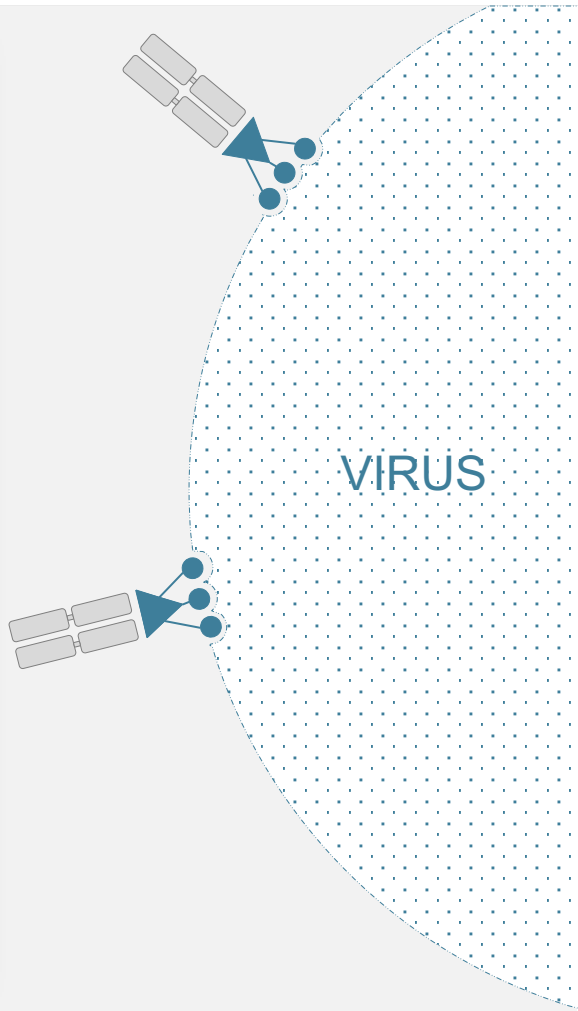
Cloudbreak AVCs combine the power of small molecules (SMs) and monoclonal antibodies

- High potency SMs
- Extended half-life
- Broad spectrum (influenza A&B)
- Combining multiple MOAs



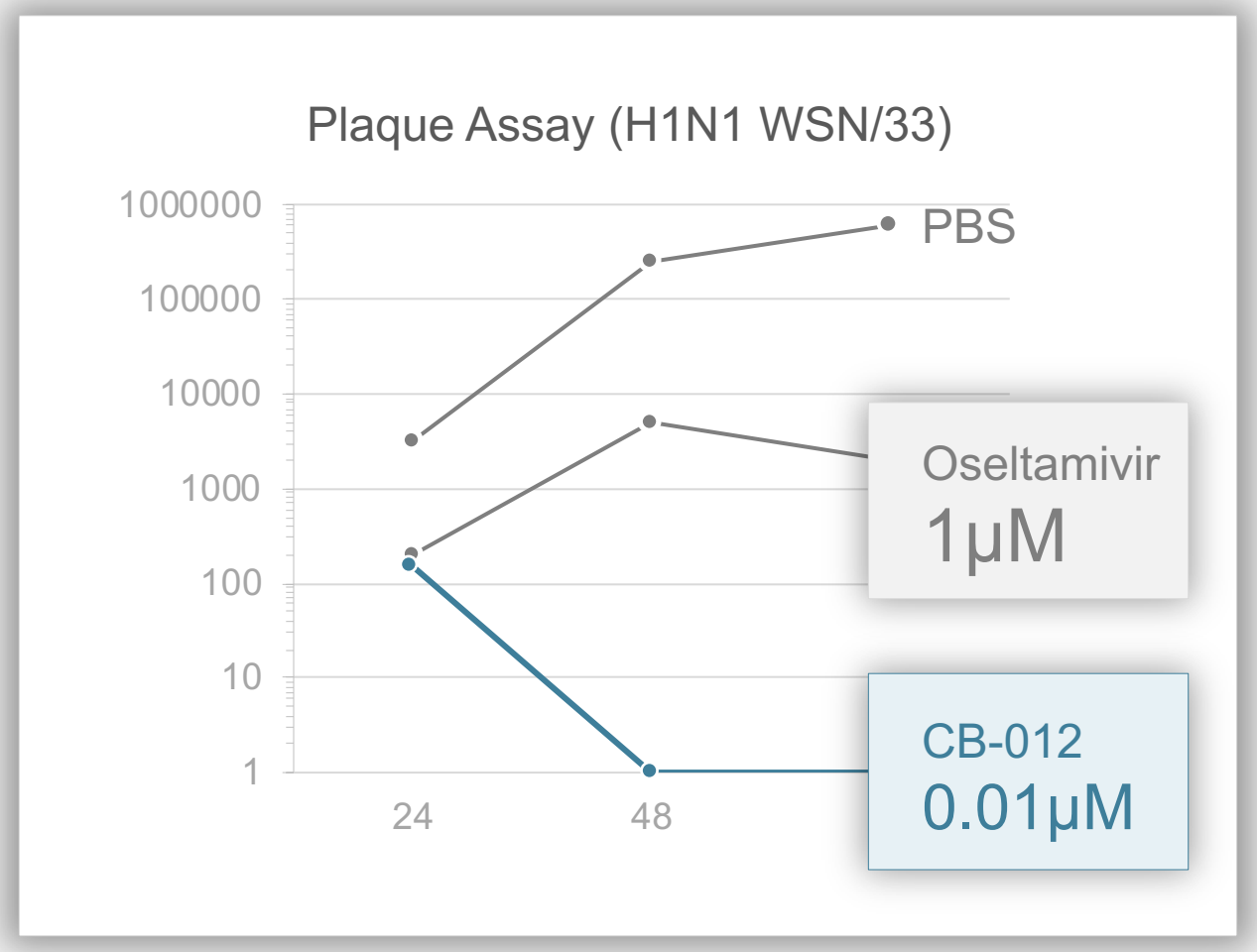
Cloudbreak AVCs are highly potent *in vitro*

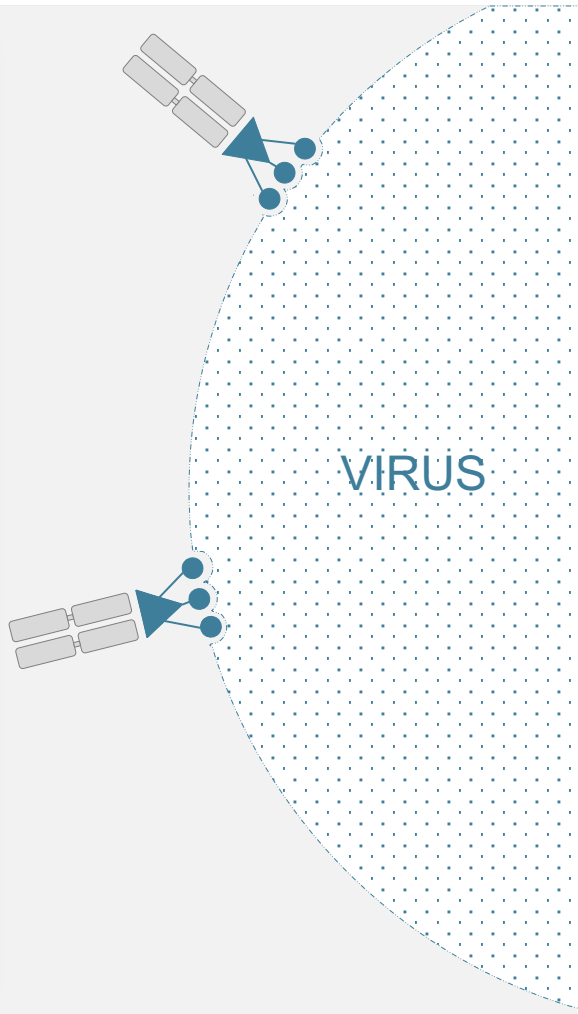




Cloudbreak AVCs are highly potent *in vitro*

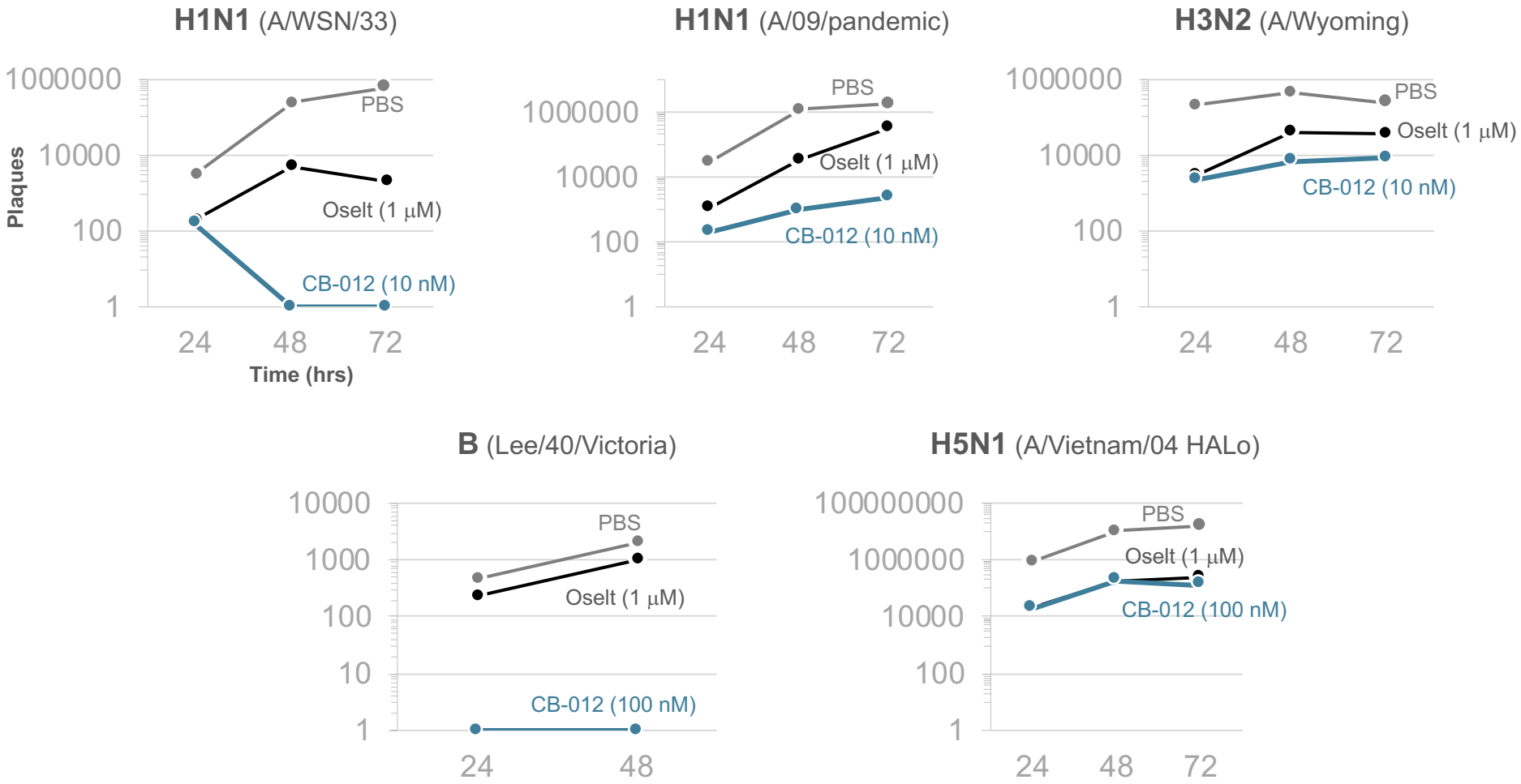
3,000-fold greater reduction in viral replication at 1/100 the concentration of oseltamivir





CB-012 outperforms oseltamivir *in vitro*

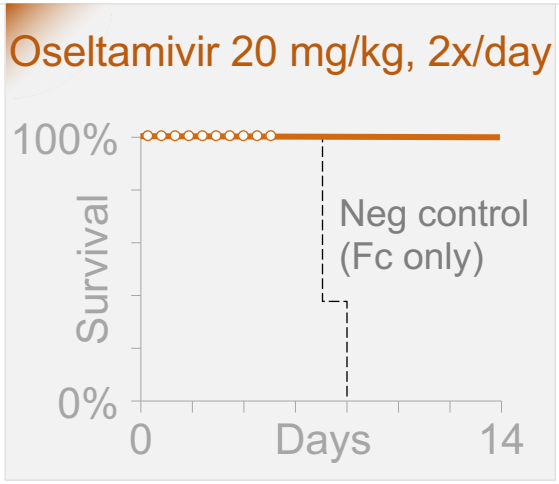
Plaque reduction in infected A549 cells

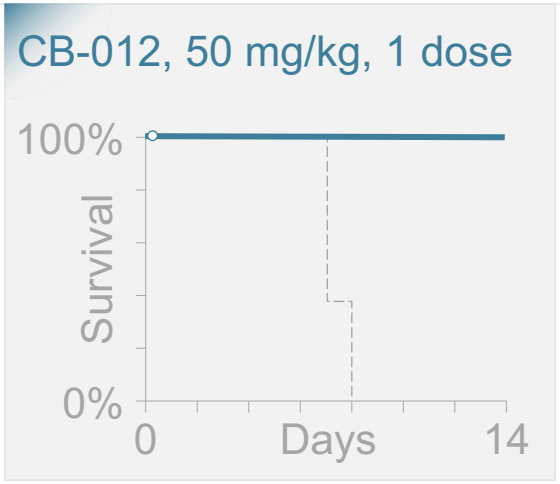


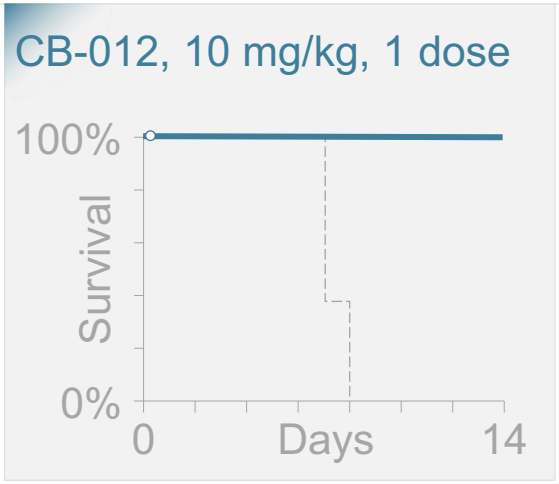
CB-012 has highly potent *in vivo* activity

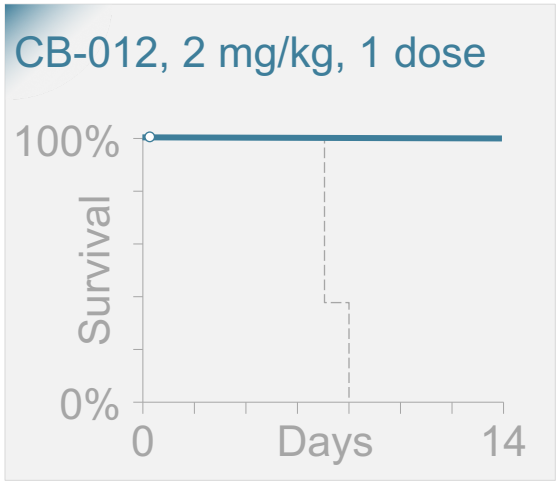
Lethal influenza model (H1N1: TX/36/91 in mice)

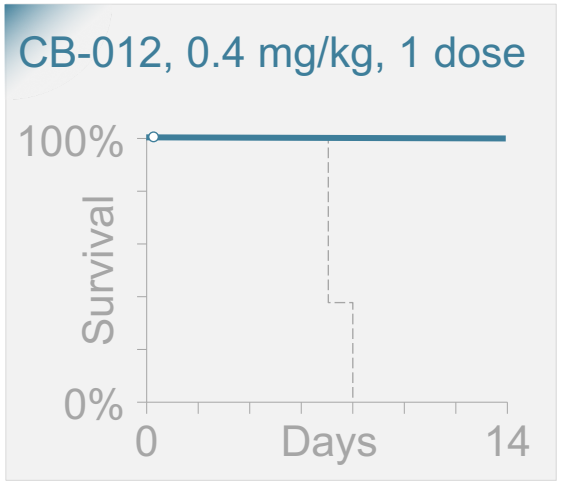
Equivalent protection to oseltamivir at 1/500th the dose

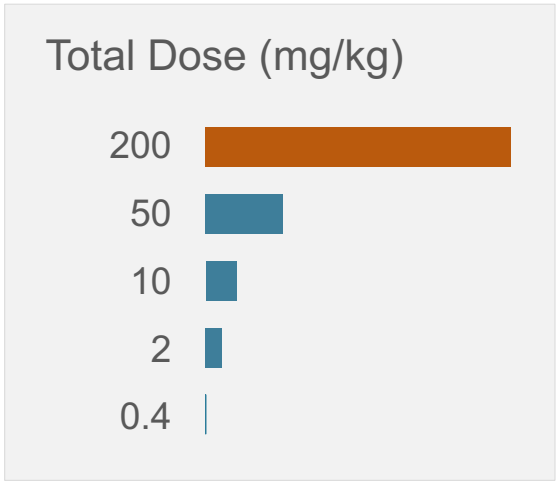






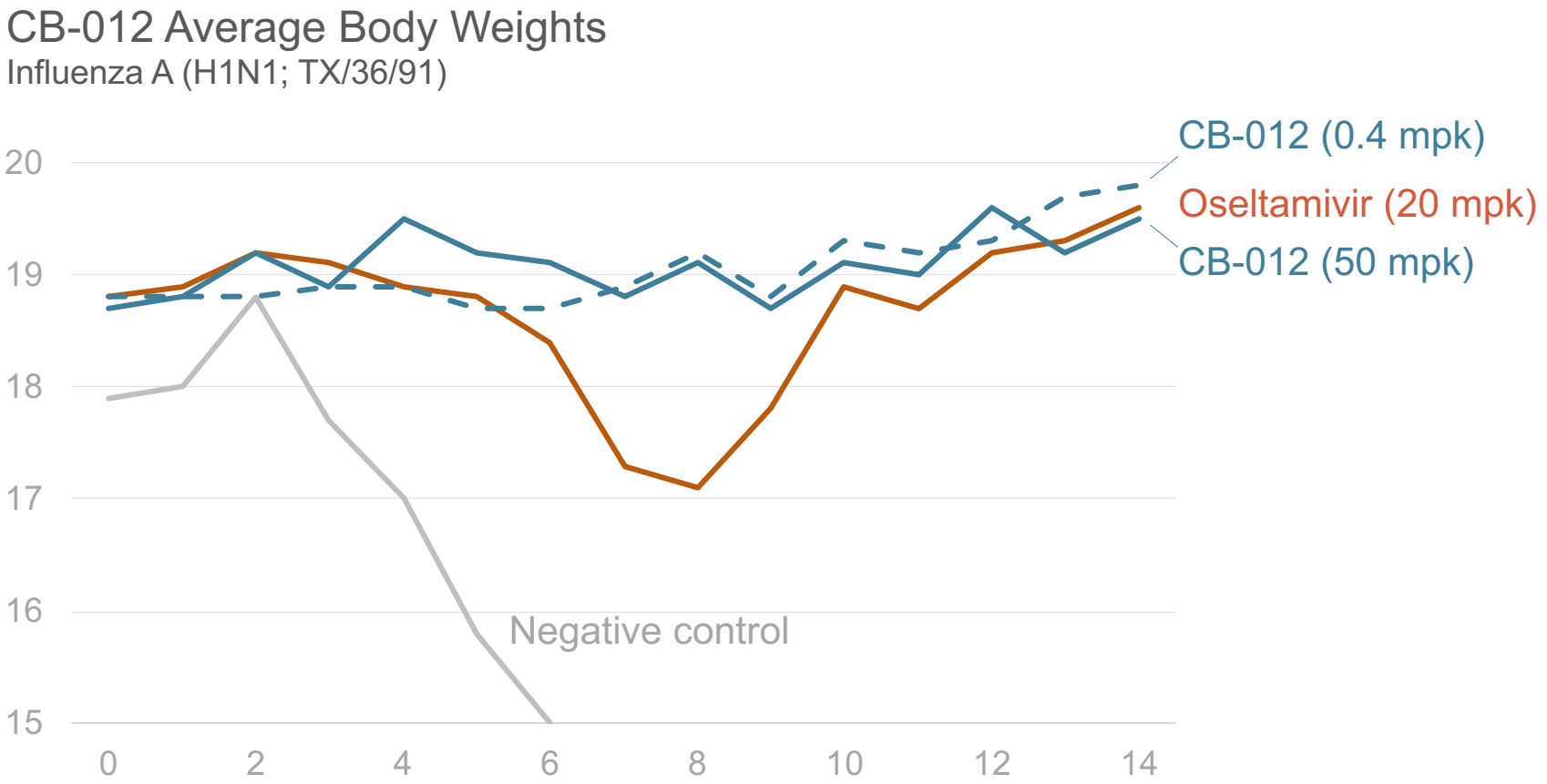






5 mice per cohort CB-012 dosed 4 hours prior to infection, oseltamivir dosed 8 hrs post infection

Body weight data supports robust efficacy & safety

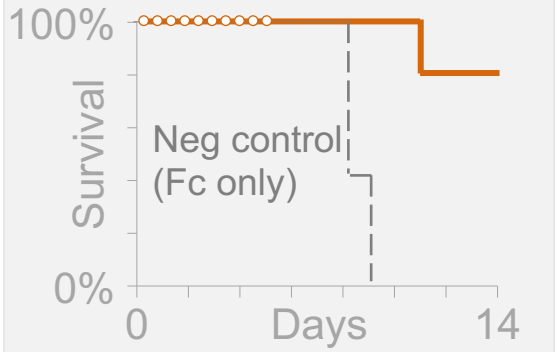


CB-012 has highly potent *in vivo* activity

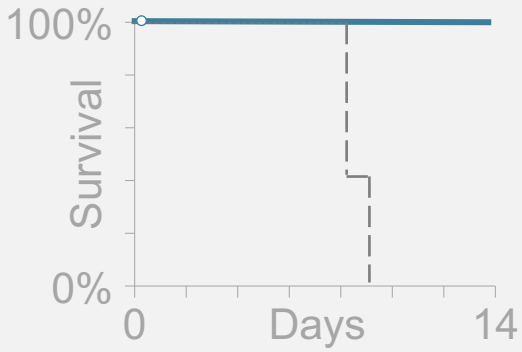
Lethal influenza model (H3N2: HK/1/68 in mice)

Equivalent protection to oseltamivir at 1/1000th the dose

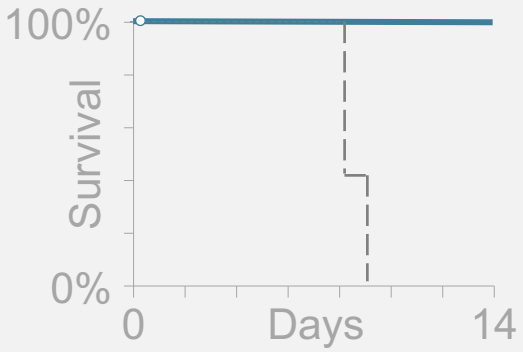
Oseltamivir, 20 mg/kg, 2x/day



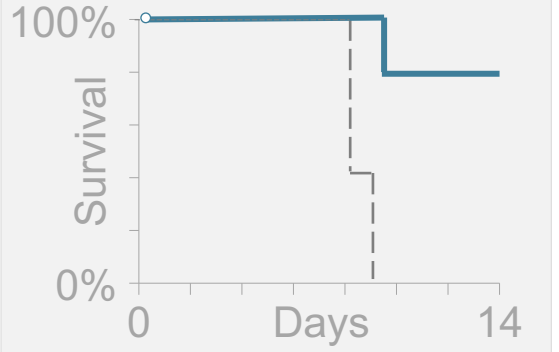
CB-012, 2 mg/kg, 1 dose



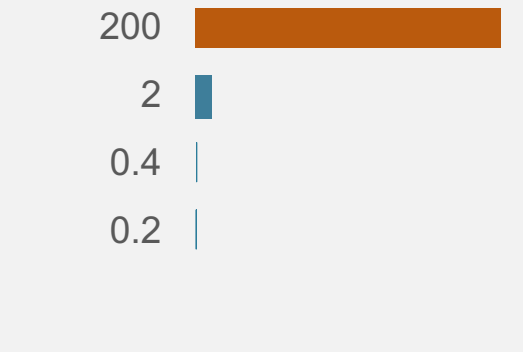
CB-012, 0.4 mg/kg, 1 dose



CB-012, 0.2 mg/kg, 1 dose



Total Dose (mg/kg)

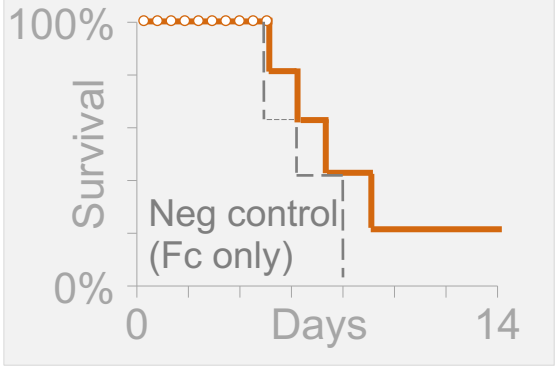


5 mice per cohort CB-012 dosed 4 hours prior to infection, oseltamivir dosed 8 hrs post infection

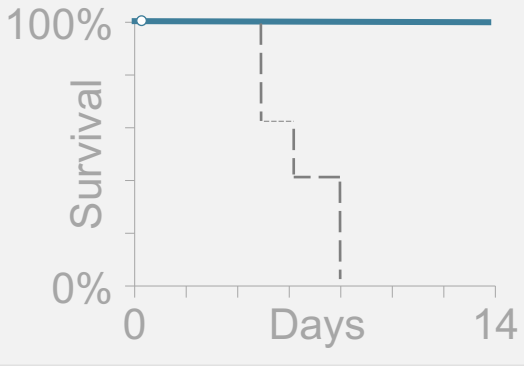
CB-012 has potent *in vivo* activity against the dominant oseltamivir^{R} strain

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

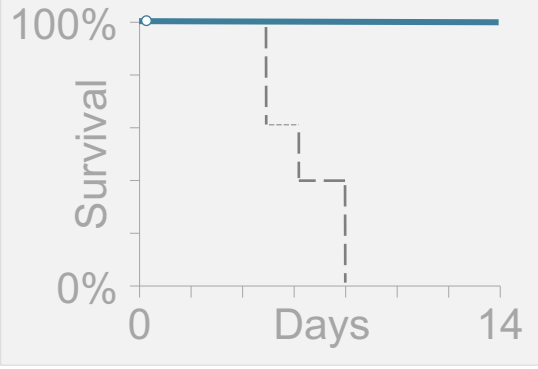
Oseltamivir, 20 mg/kg, 2x/day



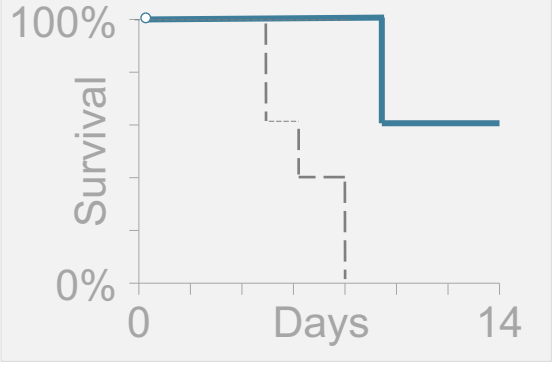
CB-012, 10 mg/kg, 1 dose



CB-012, 2 mg/kg, 1 dose



CB-012, 0.4 mg/kg, 1 dose



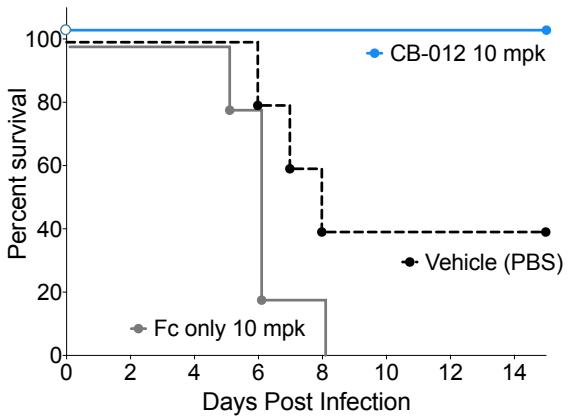
5 mice per cohort CB-012 dosed 4 hours prior to infection, oseltamivir dosed 8 hrs post infection

CB-012 improves treatment window versus oseltamivir

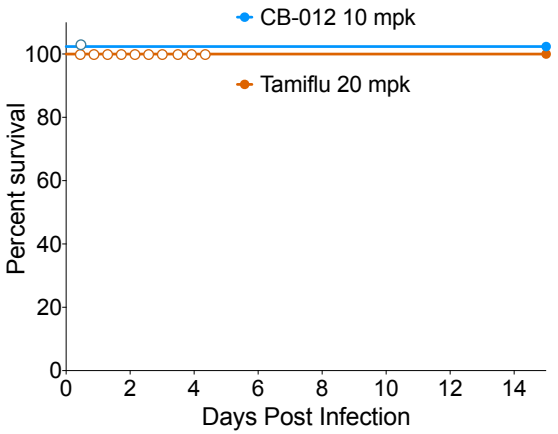
Lethal influenza model (H1N1: TX/36/91 in mice)

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

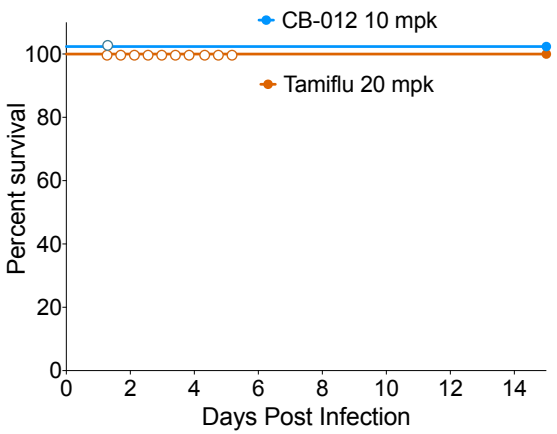
Controls (dosed 4 hrs prior to infection)



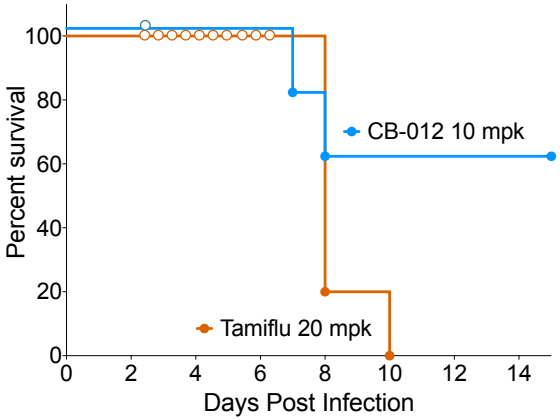
Dosed 8 hrs post infection



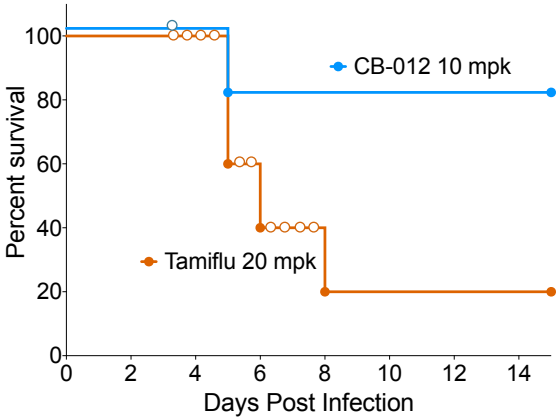
Dosed 24 hrs post infection



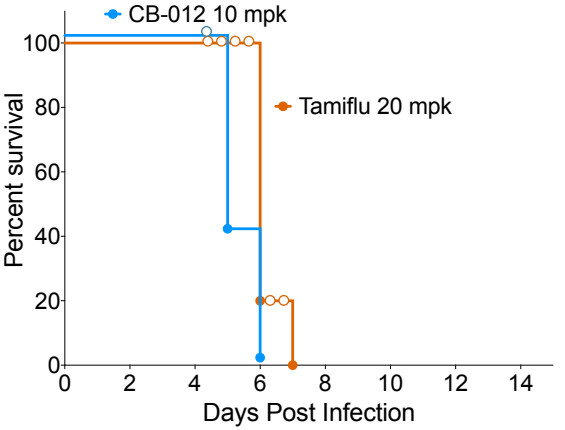
Dosed 48 hrs post infection



Dosed 72 hrs post infection



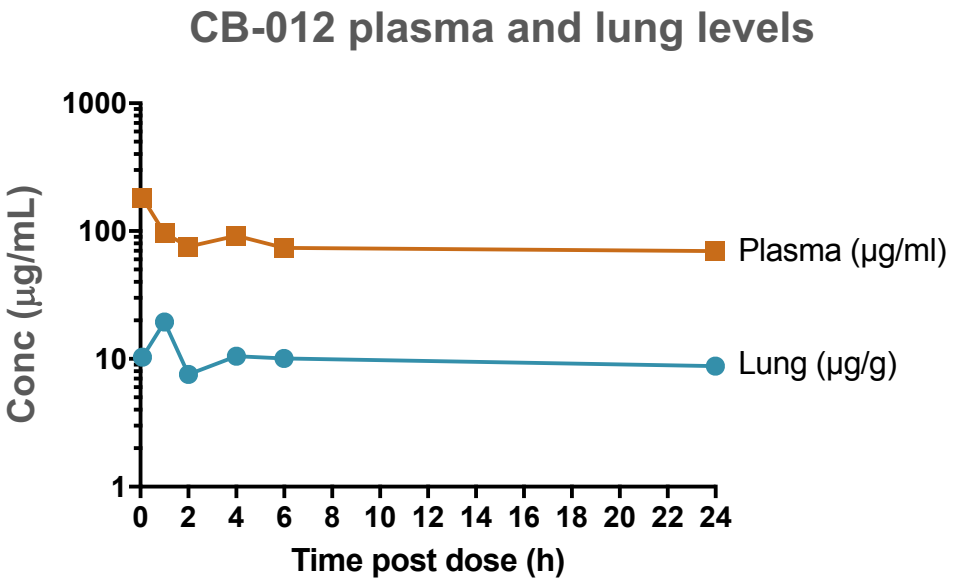
Dosed 96 hrs post infection



5 mice per cohort oseltamivir dosed BID for 5 days in each cohort

CB-012 rapidly distributes to lung, supporting treatment applications

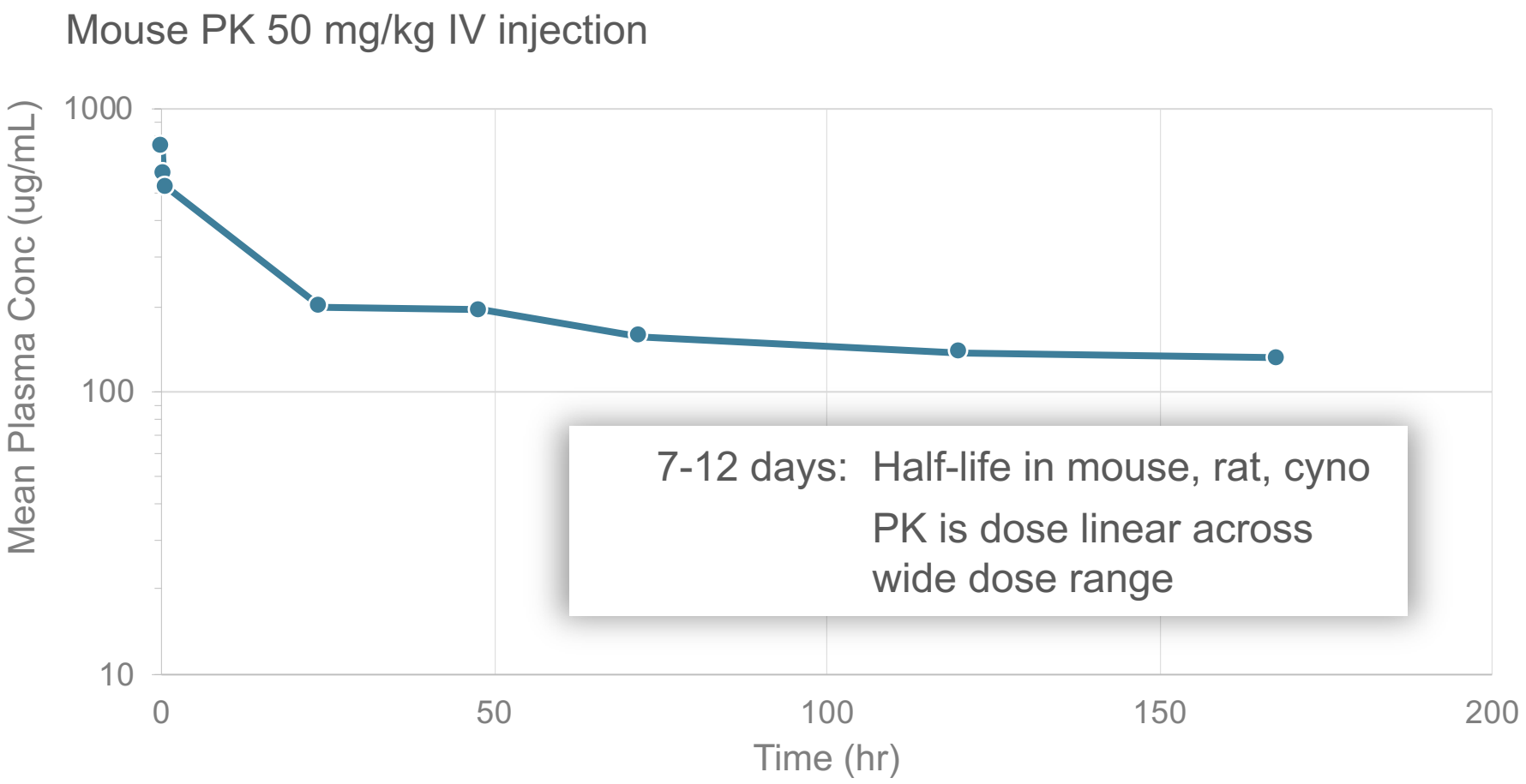
10 mg/kg IV dose, evaluation of levels in whole lung



Reaches Cmax in lung by 1 hr

Lung levels track with plasma levels at ~10% relative to plasma

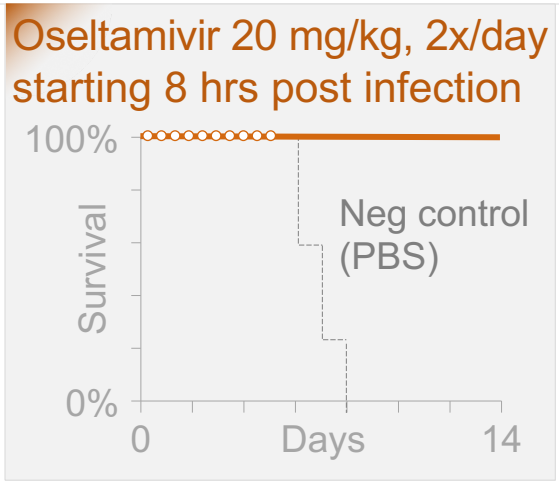
CB-012 demonstrates extended half-life

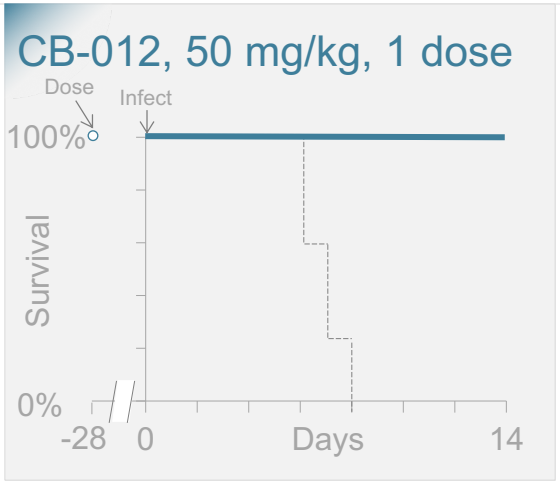


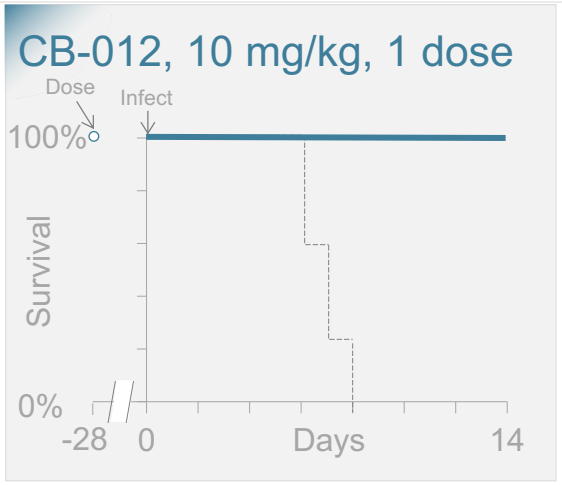
Extended half-life translates to long duration of action

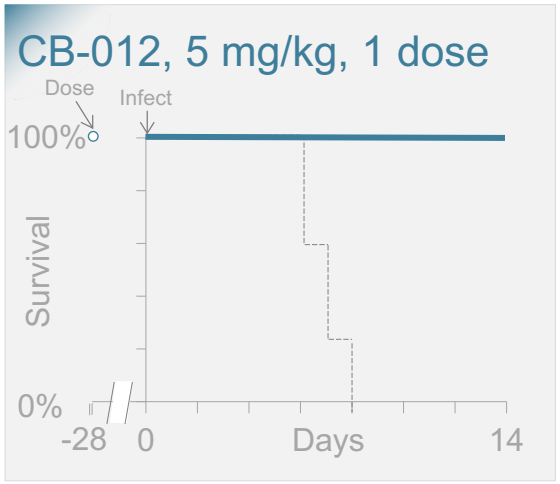
Lethal influenza model (H1N1: TX/36/91 in mice)

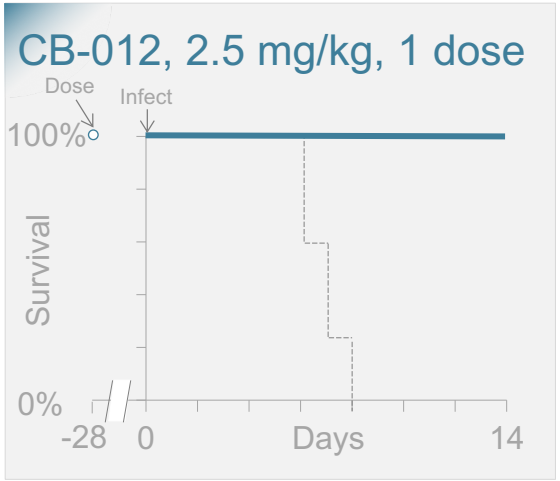
CB-012 dosed once 28 days prior to viral challenge

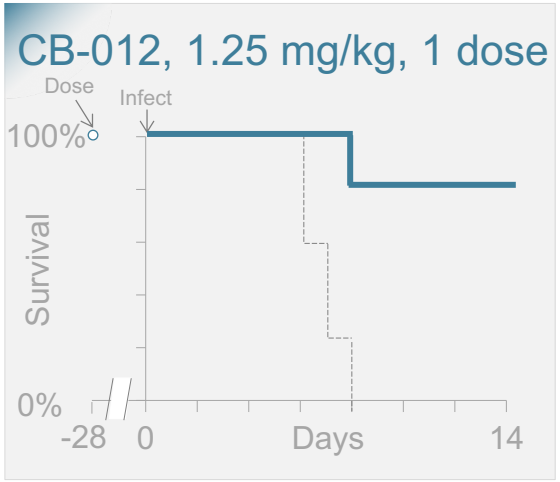












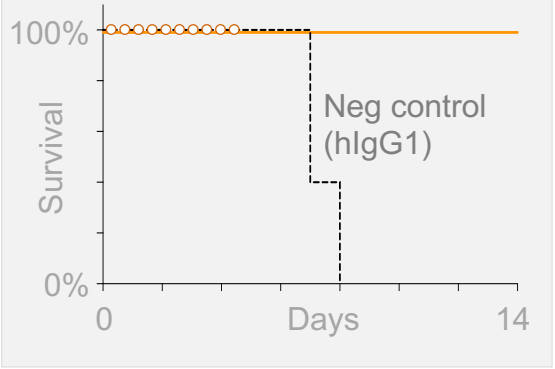
5 mice per cohort

Efficacy is observed using multiple dosing routes

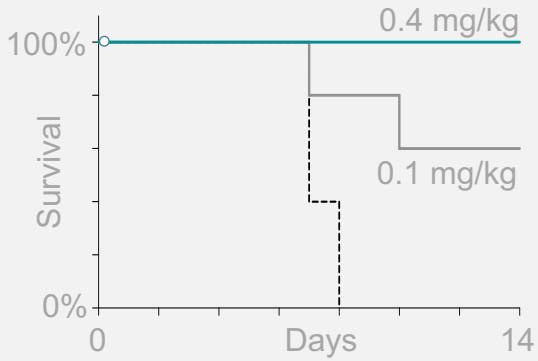
Lethal influenza model (H1N1: TX/36/91 in mice)

CB-012 dosed once 4 hours prior to viral challenge

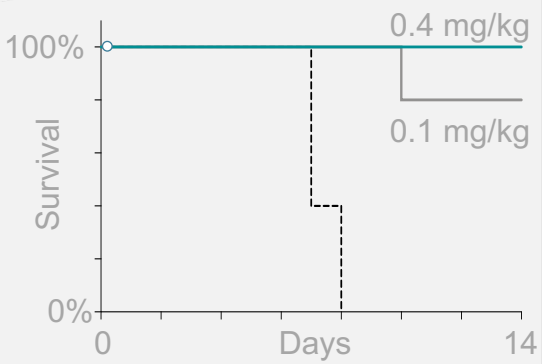
Oseltamivir 20 mg/kg, 2x/day starting 8 hrs post infection



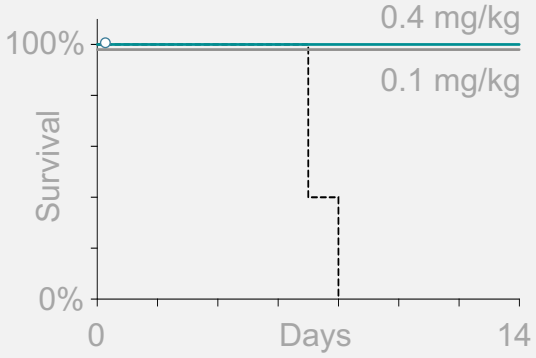
CB-012, 1 dose, IV



CB-012, 1 dose, IM



CB-012, 1 dose, SC

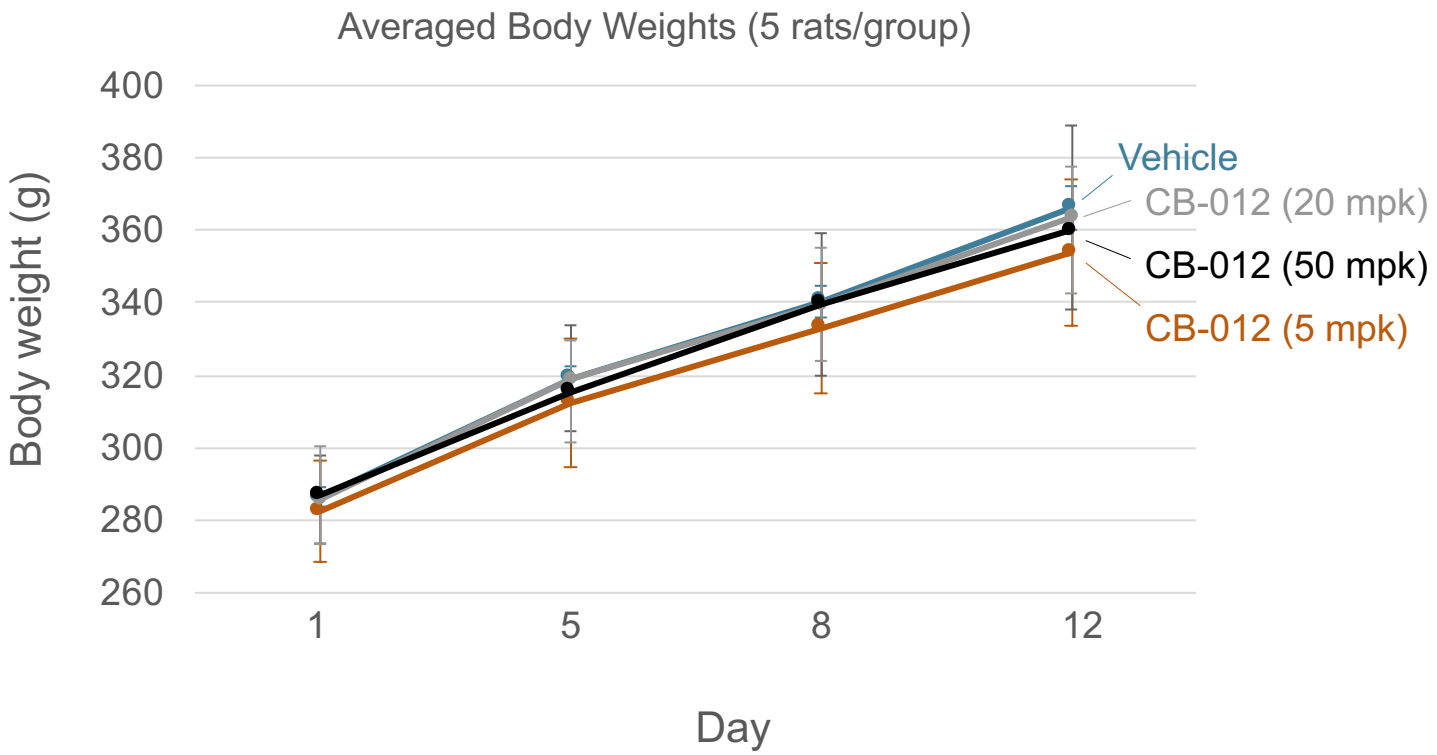


5 mice per cohort

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



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

Parameter	Findings at highest dose (50 mpk) vs vehicle
Clinical observations	No findings
Hematology	No change from vehicle
Clinical Chemistry	No change from vehicle
Coagulation	No change from vehicle
Urinalysis	No change from vehicle
Histopathology	No observations

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 *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 *in vitro* potency (CB-038)
- Fc engineering underway to extend half-life
- **Goal**: Extend protection to entire flu season with a single dose

Cytopathic Effect based microneutralization assay (H1N1 CA/09) in MDCK cells

Molecule	EC_{50} (nM)
Oseltamivir	390
CB-012	4.0
CB-038	0.6

Acknowledgements

Cidara Research Team

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Voon Ong
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Joanne Fortier
Makia Nakamura
Dan Bensen
Jim Balkovec

Sanford Burnham

Sumit Chanda
Paul De Jesus
Laura Martin-Sancho

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