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In Vivo Efficacy of CD388 Against Seasonal Influenza in Prophylaxis in Immune Competent Mice, and in a Severe Immunodeficient (SCID) Mouse Model

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Disclosures

Employee and shareholder of Cidara Therapeutics

A universal influenza prophylactic agent does not yet exist

From the 2018-2019 flu season (USA)

35.5 million
Sick

16.5 million
Seek HCP care

490,600
Hospitalizations

34,200
Deaths

Source: CDC, WHO

Significant healthcare burden and mortality

Significant limitations with existing flu therapeutics

Vaccines
Limited VE

Monoclonal Abs
Type specific

Small molecules
Limited prophylaxis

Need for long-acting flu prevention with potent, universal activity

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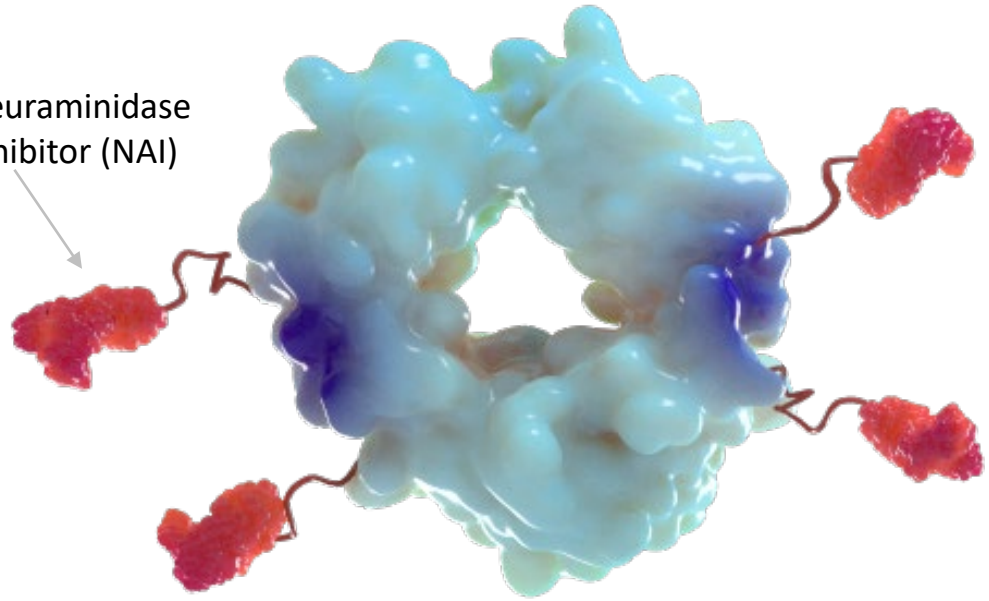
Drug Fc-Conjugates (DFCs) are a novel modality for prevention of Influenza

CD388



hIgG1 Fc fragment

- **The DFC platform is tunable and modular**
  - The inhibitor is a potent, broad spectrum small molecule NA inhibitor
  - The NAI is connected to the Fc fragment by a stable, non-cleavable linker
  - NAI to Fc ratio is tunable for efficacy and physical properties
  - Modified Fc to extend half-life
  - **Multivalent presentation of inhibitor allows for retention of activity against NAI-resistant isolates**

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CD388 outperforms approved small molecule antivirals in CPE assays

Assay: In vitro cell-based assay measuring test article ability to inhibit virus induced CPE*

Influenza subtype	CD388 Median EC_{50} [nM] (EC_{50} [nM] range)	Oseltamivir Median EC_{50} [nM] (EC_{50} [nM] range)	Zanamivir Median EC_{50} [nM] (EC_{50} [nM] range)	Baloxavir Median EC_{50} [nM] (EC_{50} [nM] range)
A/H1N1 (n=16)	**0.80** (0.01 to 11.25)	**185.3** (29.39 to >10,000)	**128.5** (17.22 to 7482)	**1.44** (0.11 to 26.55)
A/H3N2 (n=15)	**1.27** (0.03 to 8.53)	**1166** (2.58 to >10,000)	**2160** (3.06 to >10,000)	**1.62** (<0.00001 to 8.92)
B (n=13)	**1.72** (0.03 to 8.71)	**1483** (151.9 to >10,000)	**401.1** (31.9 to 2991)	**9.99** (0.12 to 40.82)

❖ *CD388 demonstrates superiority to oseltamivir and zanamivir; on par with baloxavir*

*MOI not optimized to determine a formal resistance profile

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CD388 is a potent antiviral that covers NAI resistant strains

Assay: in vitro cleavage of a neuraminidase substrate by virus in the presence of test articles

Influenza subtype	**CD388** Median IC_{50} [nM] (IC_{50} [nM] range)	**Zanamivir** Median IC_{50} [nM] (IC_{50} [nM] range)	**Oseltamivir** Median IC_{50} [nM] (IC_{50} [nM] range)
H275Y A/Alabama/03/2020 (H1N1)pdm09	**0.98**	**0.16**	**426.80**
H134N B/Laos/0080/2016	**4.66**	**310.80**	**171.80**

❖ *CD388 retains activity against clinically relevant neuraminidase variants*

(CDC NAI Susceptibility Reference Panel; version 2/3)

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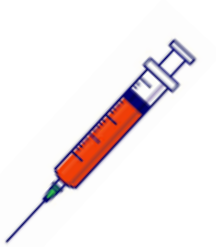
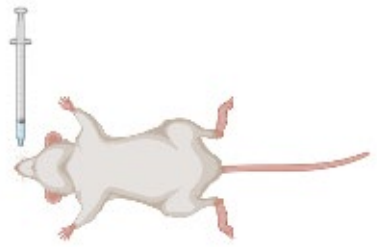
CD388 mouse efficacy screening models - **prevention**

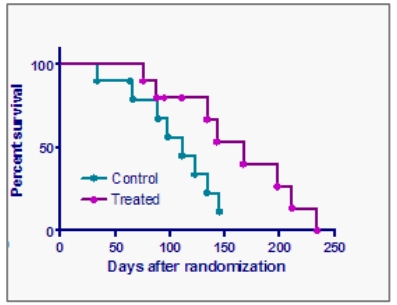


Administration (IM/SC)
(T-7d)



Infection (3x LD_{95})
(T+0d)

Health checks
Body weight
(T+21d)



Kaplan-Meier
Survival curves

Additional in vivo studies:

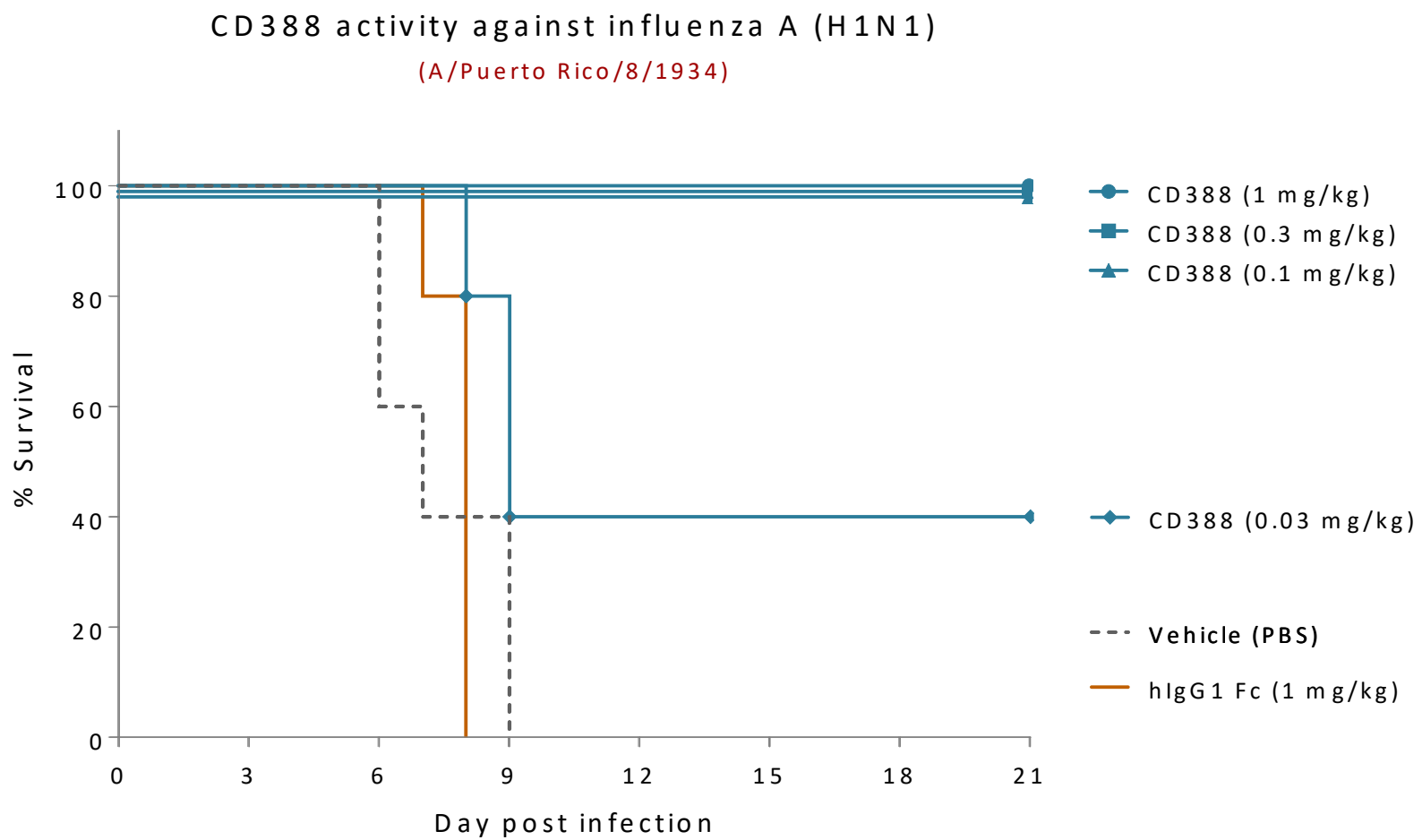
BALB/c, SCID*, Tg32, and Fcer1g-/- mice*
Dose schedules (T-7d to T+72h)

Additional readouts:

Cytokine profile
Lung burden

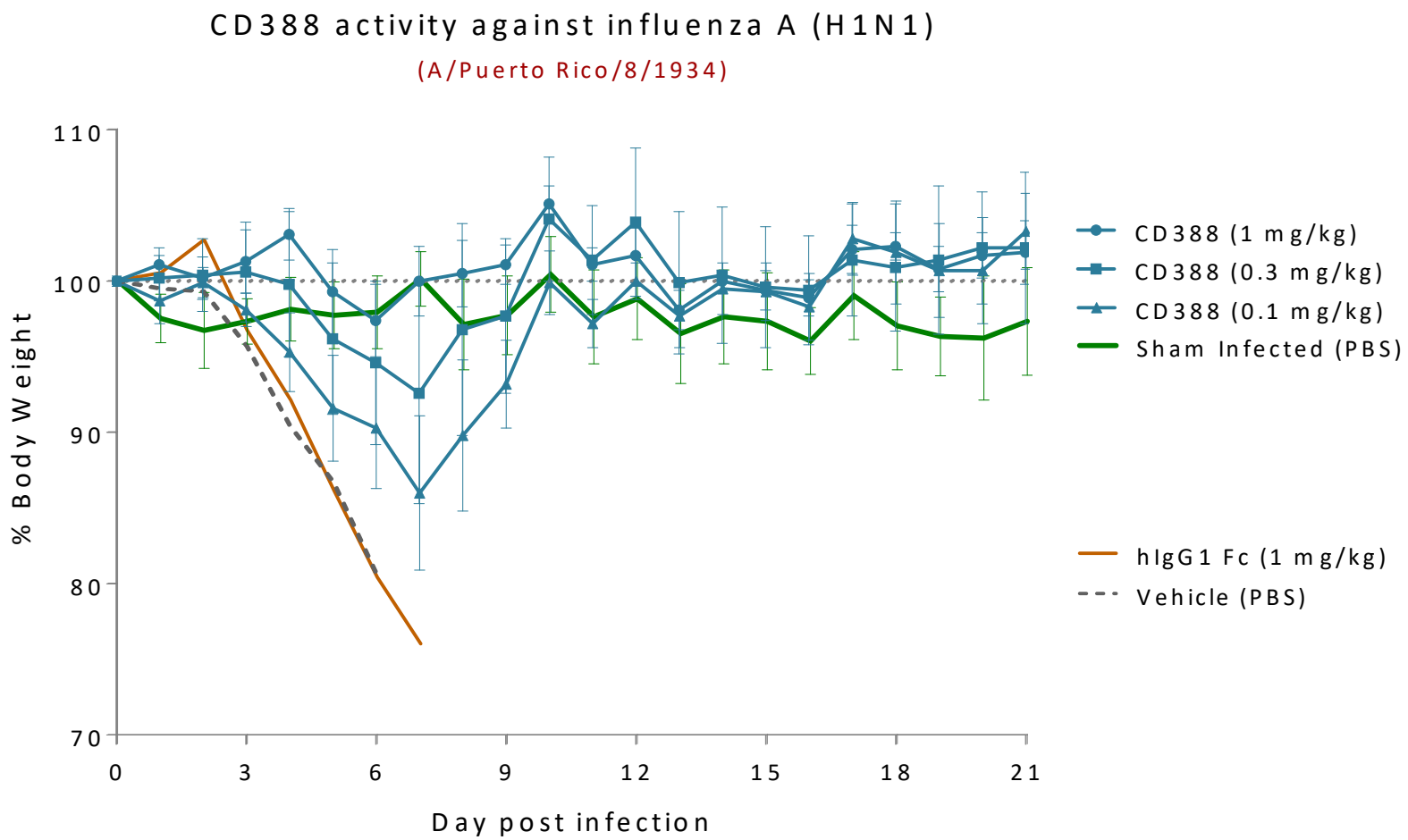
In vitro potency translates to efficacy in lethal challenge models

Model: T-7d prophylaxis against H1N1 (single dose)



Minimal body weight reduction with low doses of CD388

Model: T-7d prophylaxis against H1N1 (single dose)



CD388 is a potent antiviral in both prevention and treatment models

Prevention (T-7d)

Subtype	Number of isolates tested	Fully protective dose required for complete subtype coverage (mg/kg)
A (H1N1)	7	**1**
A (H3N2)	1	**0.3**
B (Victoria)	2	**1**
B (Yamagata)	1	**0.3**

Treatment (T+2h)

Subtype	Number of isolates tested	Fully protective dose required for complete subtype coverage (mg/kg)
A (H1N1)	8	**1**
A (H3N2)	1	**0.3**
B (Victoria)	2	**0.3**
B (Yamagata)	1	**0.3**

- ***1 mg/kg fully protective @ T+72h in a delayed treatment model***

- **A single dose of CD388 at 1 mg/kg is fully protective against lethal challenge by seasonal isolates**
- **This includes H275Y and H134N isolates resistant to oseltamivir and zanamivir, respectively**

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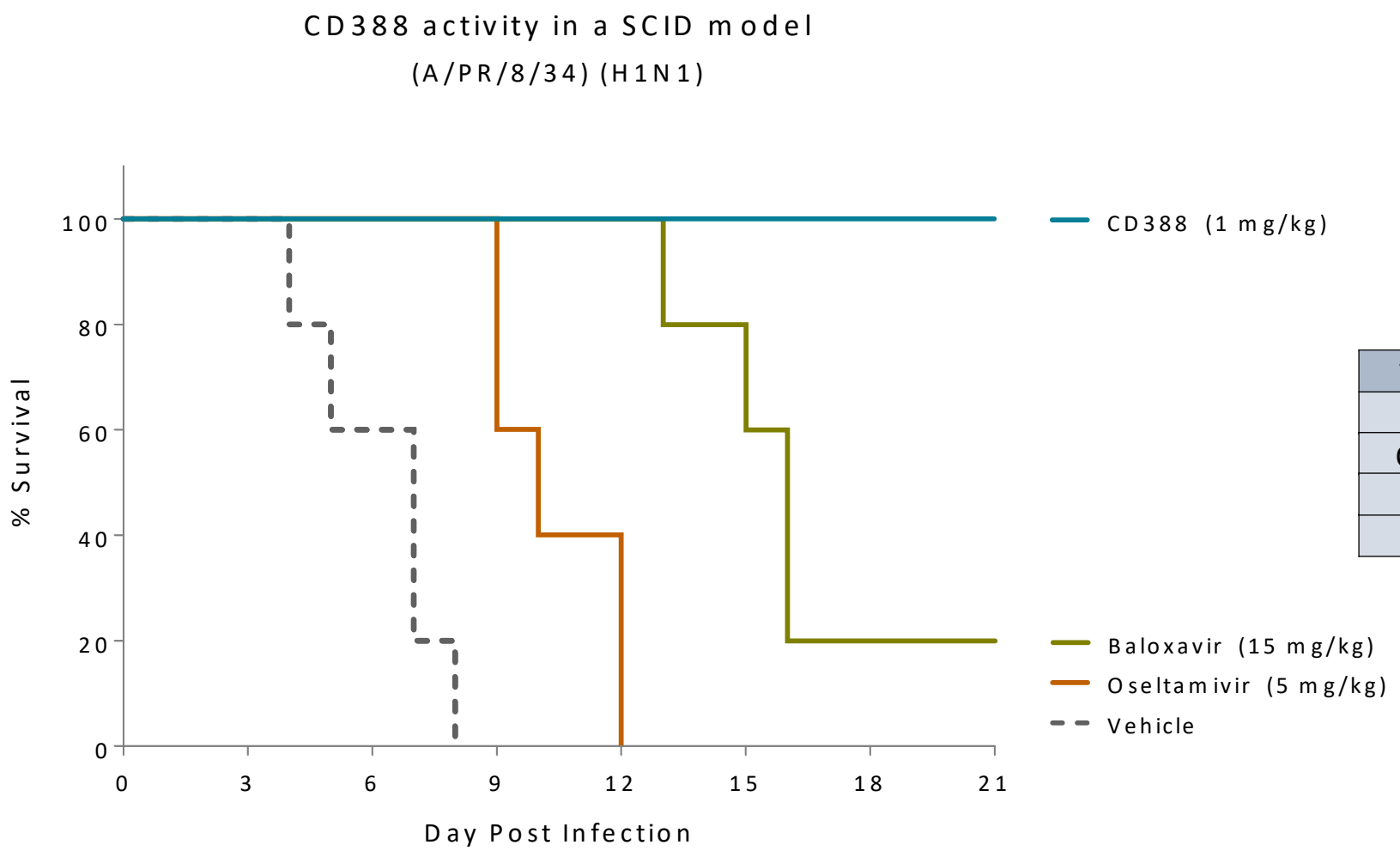
CD388 is more active than approved drugs in an immune-compromised model

Model: Severe Combined Immunodeficient (SCID) - Mice lacking B and T lymphocytes

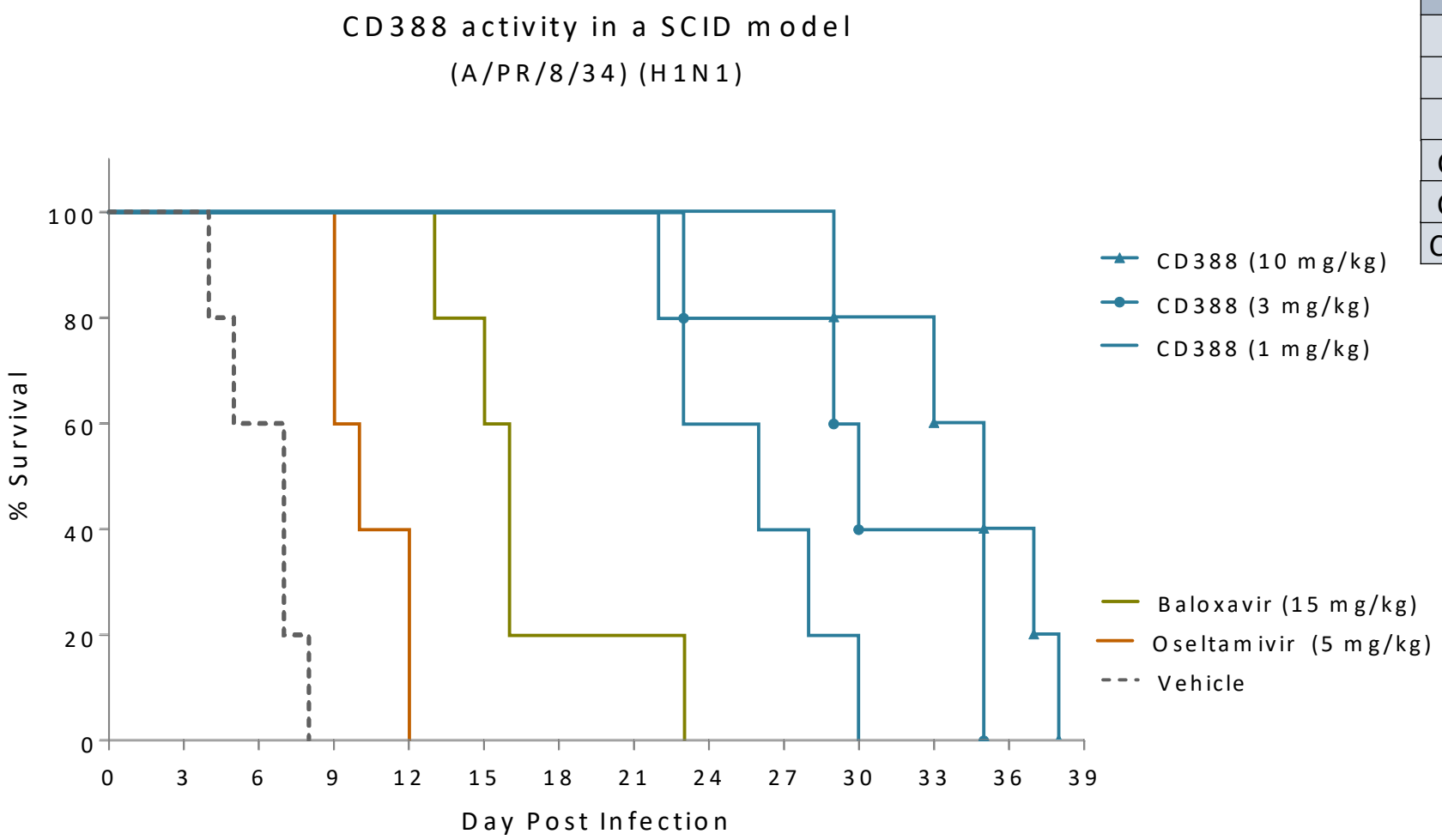


Dosing (n=5/group):
Oseltamivir (5 mg/kg, bid x5d)
Baloxavir (15 mg/kg, bid x1d)
CD388 (1, 3, & 10 mg/kg, single)

Test article	Median time of death (d)
Vehicle	7
Oseltamivir	10
Baloxavir	16
CD388	>21

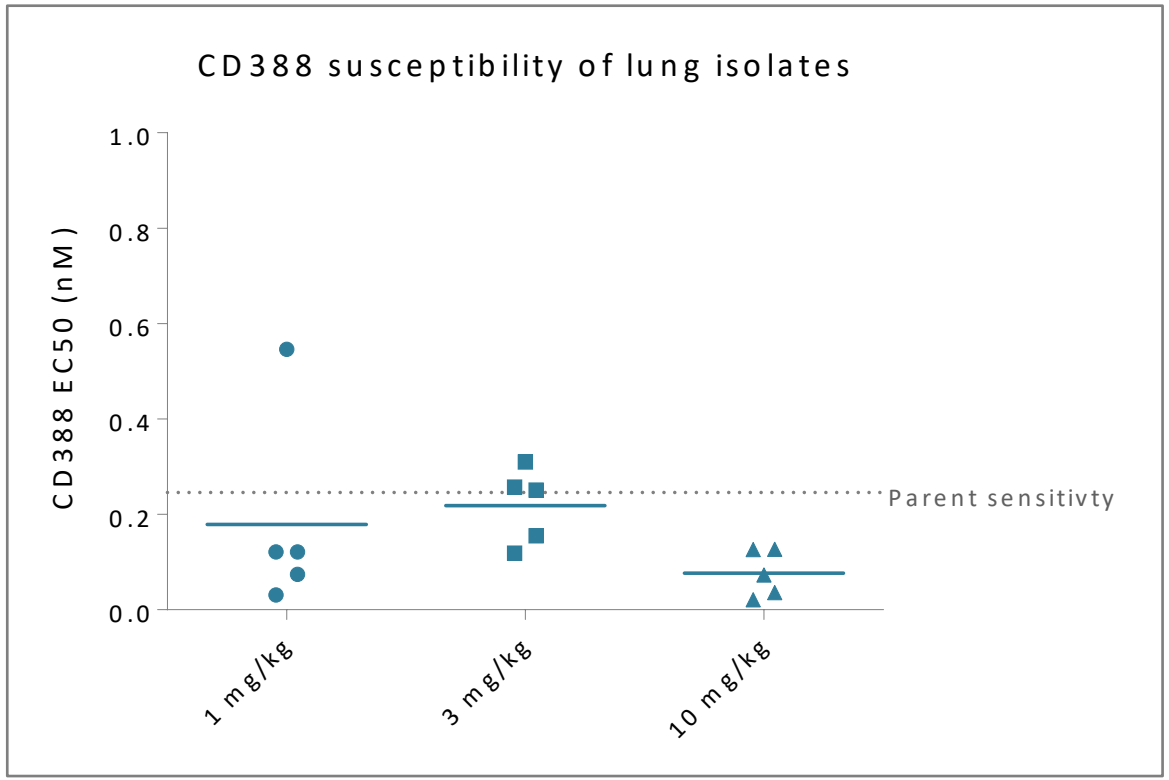
CD388 achieves prolonged protection in a murine SCID model

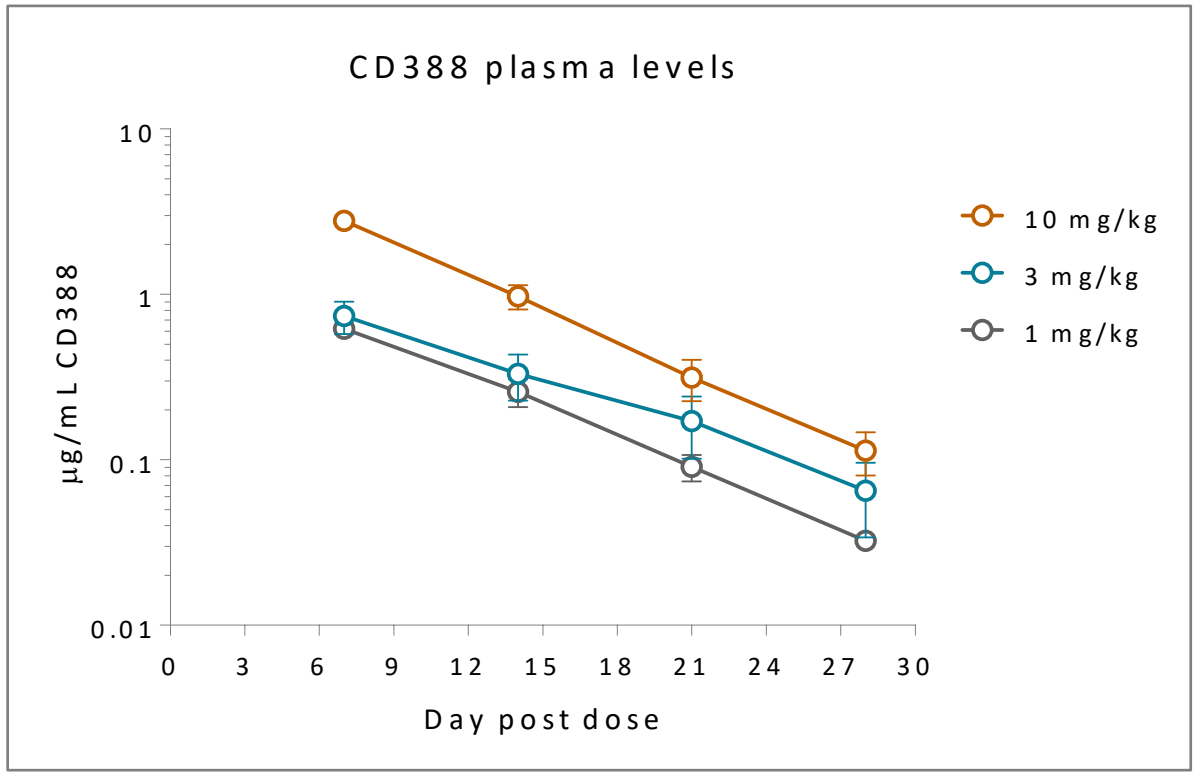
Model: Severe Combined Immunodeficient (SCID) - Mice lacking B and T lymphocytes



Test article	Median time of death (d)
Vehicle	7
Oseltamivir	10
Baloxavir	16
CD388 (1 mg/kg)	26
CD388 (3 mg/kg)	30
CD388 (10 mg/kg)	35

CD388 has a low resistance potential and is active at low [plasma]





- No significant change in CD388 susceptibility over time in this model
- Re-emergence of infection when plasma levels drop below ~0.2 µg/mL (0.091 – 0.171)

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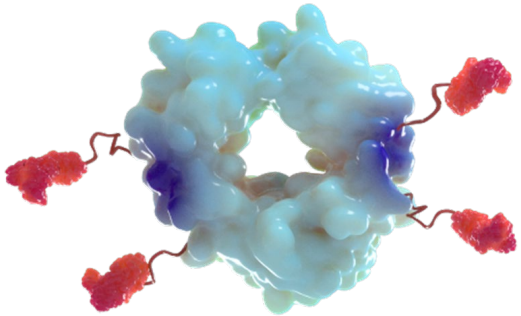
CD388 is a potent antiviral superior to existing therapeutic options

CD388



CD388 demonstrates:

- **Exceptional activity against seasonal influenza in prevention and treatment models**
- **Activity against naturally occurring neuraminidase variants**
- **Superior protection in an immune-deficient model of influenza**
- **A low resistance potential and activity at low plasma concentrations**

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Acknowledgements – *Preclinical development of CD388*

Cidara Therapeutics
Les Tari (CSO) and the rest of the management team
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Department of Protein Chemistry
Department of Microbiology
Department of Immunology
Department of Preclinical Development

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External Collaborators
Stacey Schultz-Cherry, PhD (St. Jude's)
Sumit Chanda, PhD (TSRI)
Laura Martin-Sancho, PhD (Imperial College)
Paul DeJesus (TSRI)

Efficacy of CD388, a Novel Drug Fc-Conjugate (DFC), is Driven by the Small Molecule Neuraminidase Inhibitor (NAI)

Simon Döhrmann, PhD
Session Title: Antimicrobial Novel Agents
Session Date: Saturday October 14, 2023
Session Time: 12:15 PM - 1:30 PM
Session Location: BCEC Poster Hall

Single Ascending Dose Safety, Tolerability, and Pharmacokinetics of Subcutaneous and Intramuscular CD388, a Novel Long-acting Drug-Fc Conjugate for Universal Prevention of Seasonal and Pandemic Influenza

Shawn Flanagan, PhD
Session Title: New Antimicrobial Drug Development
Session Date: Saturday, October 14, 2023
Session Time: 12:15 PM – 1:30 PM
Session Location: Hall B + C