Poster 352

Modeling and Simulation Based on Real-World Data and Phase 2b Results Used to Optimize CD388 Phase 3 Dose Selection for Influenza Prevention

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INTRODUCTION

CD388 is a novel antiviral drug-Fc conjugate with extended half-life sufficient for once per influenza season administration. Designed for broad prevention against both seasonal and pandemic influenza, CD388 recently completed enrollment of over 5000 participants in the ongoing Phase 2b NAVIGATE trial (NCT06609460).

In trials involving community-acquired infections, such as influenza, variations in disease incidence over time may complicate interpretation of drug effect in Phase (Ph) 2 and Ph3 across multiple seasons, especially for a long-acting drug.

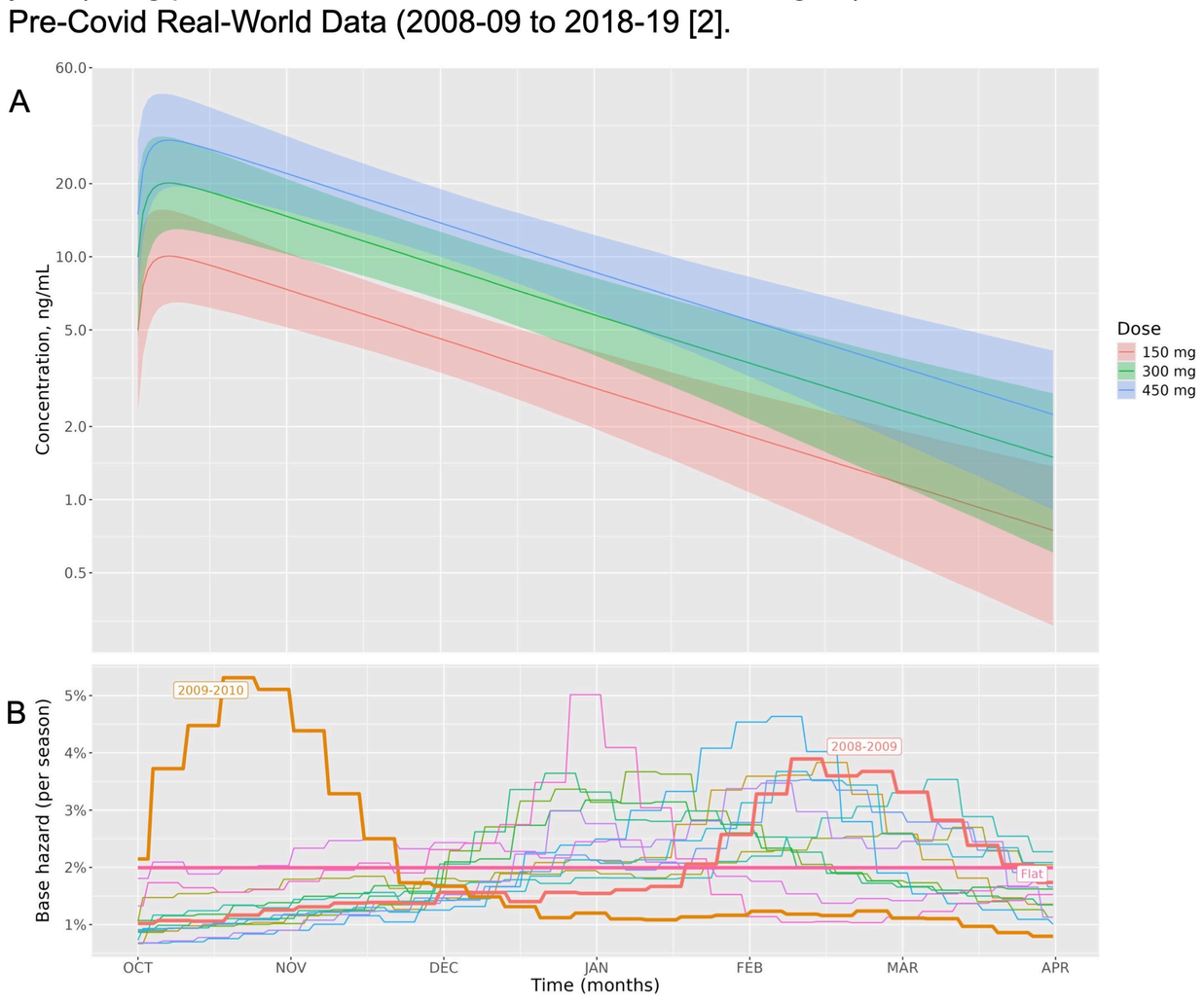
Here we show that an advanced model-based analysis can improve decision power based on Ph2 results.

METHODS

A linear, one-compartment disposition population pharmacokinetic (PopPK) model with first-order absorption was previously developed from Ph1 data (CD388 First in human study NCT05285137) [1]. CD388 plasma concentration versus time data generated from this PopPK model showed single dose subcutaneous (SC) administrations would provide >1-Log range of exposures (**Figure 1A**) over the course of the influenza season with C_{max} to $C_{6months}$ range of approximately 10 to 0.75 µg/mL, 20 to 1.5 µg /mL, and 30 to 2.25 µg/mL for CD388 doses of 150, 300, and 450 mg, respectively.

Clinical trial results from a single influenza season may misrepresent efficacy of that dose when evaluated in a subsequent (pivotal) trial under a different influenza season. (**Figure 1B**).

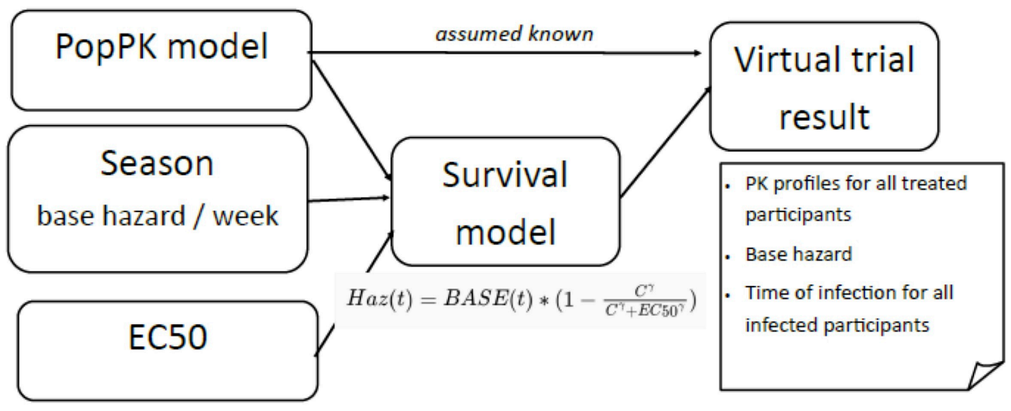
Figure 1. (A) Simulated concentration-time profile (median, 95% PI) of CD388 plasma concentrations after a single SC dose of 150, 300, and 450 mg. **(B)** Weekly hazard for influenza infection in the US population, scaled to 2% overall cumulative hazard per year (using percent influenza like infection visits as surrogate), based on Most Recent Pre-Covid Real-World Data (2008-09 to 2018-19 [2].



Using methods previously described [3], the probability of influenza infection was simulated through a survival model (**Figure 2**), where

hazard $\mathrm{Haz(t)} = \mathrm{BASE(t)} * (1 - \frac{C^{\gamma}}{C^{\gamma} + EC50^{\gamma}})$, with $\gamma = 3$ and base hazard 2% / year.

Figure 2. Schematic overview of simulation approach for a single trial



Simulations of a virtual Ph2 trial of single dose of placebo or CD388 150 mg, 300 mg, and 450 mg prior to start of influenza season (early October) were performed using known PopPK and a survival model based on publicly available data on incidence of influenza [2], assuming drug concentrations reduce this hazard. Scenarios with different drug potency and timing of peak viral transmission (early peak 2009-10, late peak 2008-9, or a flat constant rate) were simulated.

500 virtual trials were simulated per assumed drug EC_{50}, evaluating virtual dose arms (150 mg, 300 mg, 450 mg, placebo) at N=1250 virtual patients per arm. The incidence of infection per arm in each virtual trial was analyzed by a proportions test, comparing each arm independently to placebo. The lowest dose reaching superiority to placebo ($p<.05$) was selected to continue into Ph-3 (**Figure 3**).

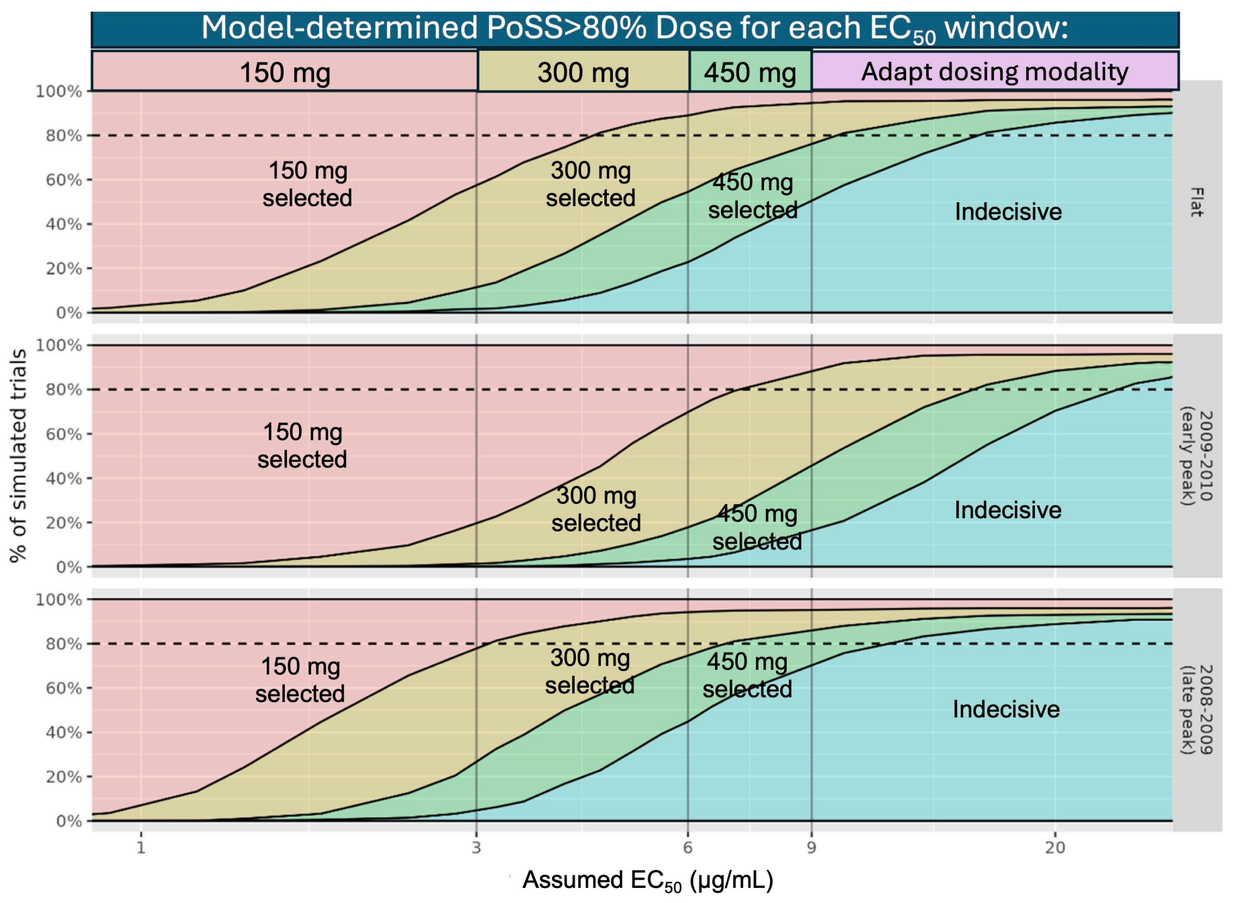
Alternatively, the Ph-3 dose was selected using a model: First, the drug potency EC_{50} was estimated by optimizing the overall log-likelihood of the data for both uninfected and infected participants across all dose arms, characterizing the most likely EC_{50} and 95% CI (based on Chi-squared distribution where $EC_{50,WorstCase}$= 95%, $EC_{50,BestCase}$= 5%). Then, based on the $EC_{50,WorstCase}$ from Ph2b, the lowest dose predicted to be successful in Ph3 was selected (**Figure 4**), defined as >80% probability of study success (PoSS>80%) demonstrating superiority to placebo at N=6000 1:1 sample size in a Flat season. The model-derived dose to achieve PoSS>80% in Ph3 was 150 mg for EC_{50} <3µg/mL, 300 mg for EC_{50} between 3 and 6 µg/mL, 450 mg for EC_{50} between 6 and 9 µg/mL, and >450mg for EC_{50} above 9 µg/mL.

RESULTS

<u>Each dose group compared to placebo separately</u>:

Sensitive to shape of influenza season

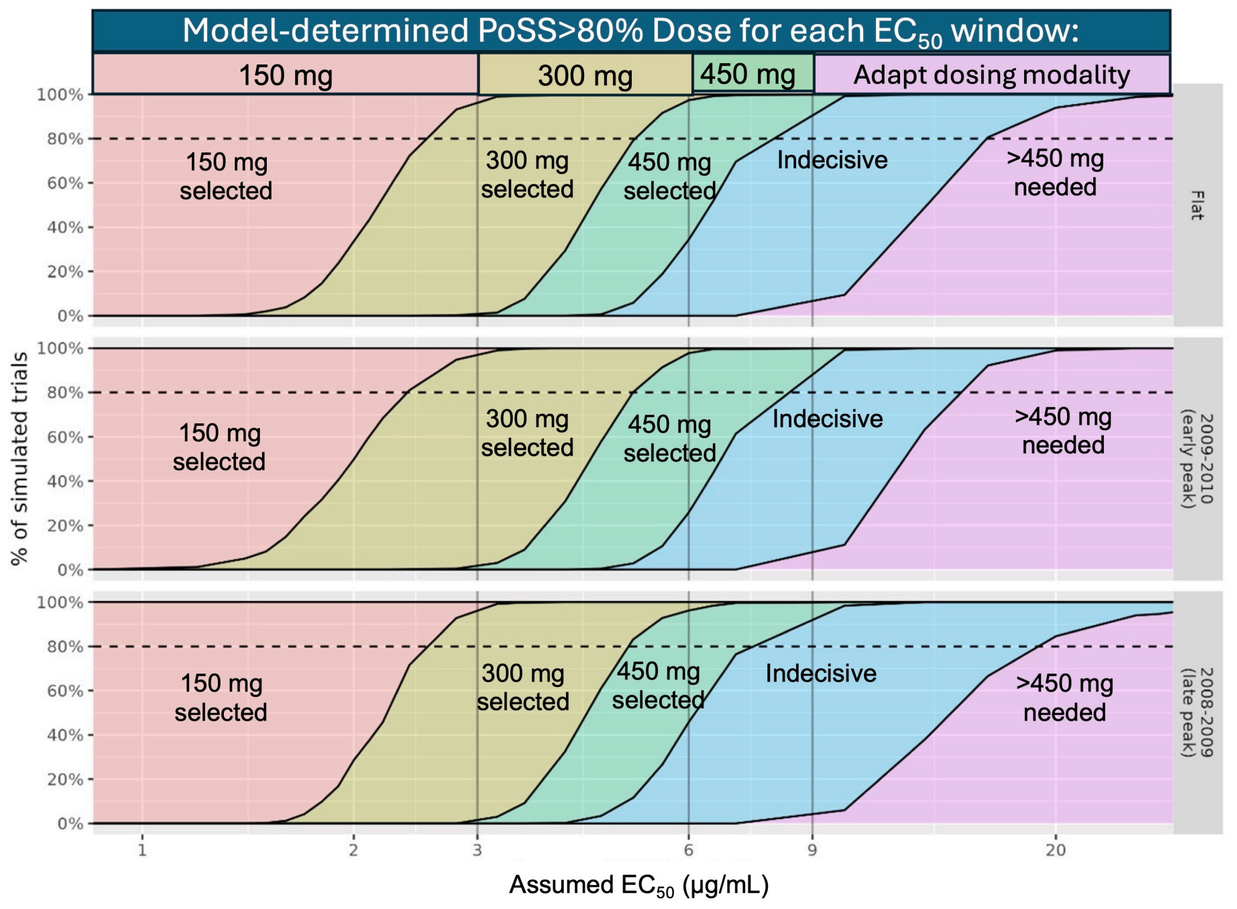
Figure 3. Probability of decision for assumed EC_{50} values from 1 to 25 µg/mL, for differently shaped influenza seasons, when applying proportion tests for dose selection.



<u>All dose groups used in model:</u>

Not sensitive to shape of influenza season

Figure 4. Probability of decision for assumed EC_{50} values from 1 to 25 µg/mL, for differently shaped influenza seasons, using an integrated model approach estimating EC_{50} for dose selection.



CONCLUSION

While a classic proportions test is sensitive to the influenza season for a long-acting drug, a model-based analysis is not, as it integrates multiple factors and increases decision power.

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ACKNOWLEDGEMENTS

This study was funded by Cidara Therapeutics, Inc. Production support provided by T. Chung (Scribant Medical) and funded by Cidara Therapeutics, Inc.

Presented at ICAR 2025 | March 17-21, 2025 | Las Vegas, NV