# CD388, a Drug Fc-Conjugate, shows long half-life in early clinical studies

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## Abstract

**Background:** CD388 is a multivalent conjugate of a dimeric neuraminidase inhibitor, with an engineered (mutated) hIgG1 Fc domain for extended half-life. The drug is being developed in collaboration with Cidara Therapeutics for the seasonal prevention of both influenza A and B.
Currently, available options for influenza protection include drugs with short half-lives or vaccines that offer variable protection and depend on a properly functioning immune system. CD388 offers convenience due to its extended half-life, allowing for long-lasting prophylactic concentrations. It also works independently from the immune system, which makes it particularly beneficial for patients who may have a lower response to vaccines.
**Methods:** A Phase 1 single ascending dose (SAD) study is being conducted in healthy volunteers evaluating safety, tolerability and pharmacokinetics of 4 dose levels of subcutaneous (SC) and intramuscular (IM) CD388. Preliminary results from the SAD were analysed through non-linear mixed effects modelling.
**Results:** A total of 66 healthy volunteers dosed on placebo (N=3 per cohort) or CD388 (N=8 per cohort, at 50 mg, 150 mg, or 450 mg SC and IM) were included in an interim analysis.
CD388 concentrations were sampled in plasma and quantified using a hybrid LCMS method with a polyclonal antibody to CD388, with low cross-reactivity to human Fc alone. The observed PK was adequately described by a linear one-compartment disposition model with first-order absorption. Half-life was 6-8 weeks.
All participants were predicted to reach 90% of $C_{max}$ at day 5 post-administration. Model predicted plasma concentrations for a single dose of 150 mg given or 300 mg on Day 1 show slow concentration peak to trough decline of approximately 1 Log over flu season (6 months), whereas giving a 2nd 150 mg dose mid flu season leads to accumulation and reduced peak to trough ratio.
**Conclusions:** CD388 showed an extended half-life of 6 to 8 weeks, which could provide seasonal prevention with one or two doses per season.

## Objectives

- To identify the typical half-life of CD388 through non-linear mixed effects modeling
- To predict the CD388 absorption profile, informing the time of viral challenge in a Human Challenge Study (HCS)
- To predict the CD388 150mg concentration at 6-months post-dose, and the dose yielding these concentrations at day 5 post-administration- informing the projected concentrations at the time of the viral challenge in the HCS and the potential for achieving prophylactic concentrations at the end of an influenza season
- To predict the 6-month post-dose concentration in a future patient population for doses of 300mg or 150mg+150mg.

## Available data

**Table 1. Overview of available data**

| Dose | Route | N of Participants | #PK samples | #PK samples <LLOQ* | Last available sample (day) |
|---|---|---|---|---|---|
| 50 mg | SC | 8 | 144 | 4 | 120 |
| 150 mg | SC | 8 | 137 | 1 | 120 |
| 450 mg | SC | 8 | 112 | 0 | 30 |

*: Lower limit of quantification (LLOQ) of 0.1 µg/mL

## Model development

A base model was developed as an open linear 1-compartment disposition model with first-order absorption. The model was parameterized in terms of apparent clearance and volume of distribution, as well as absorption rate constant. Inter-individual variability was described using an exponential error model, and it accounted for the correlation between apparent clearance and central volume. Residual error was characterized using a combined proportional + additive error.

The final model was evaluated using goodness-of-fit plots, visual predictive checks (VPC per dose group) and prediction-corrected VPC using 2000 replicates.

## Model development (cont.)

**Table 2. Parameter Estimates in Final Population Pharmacokinetic Model**

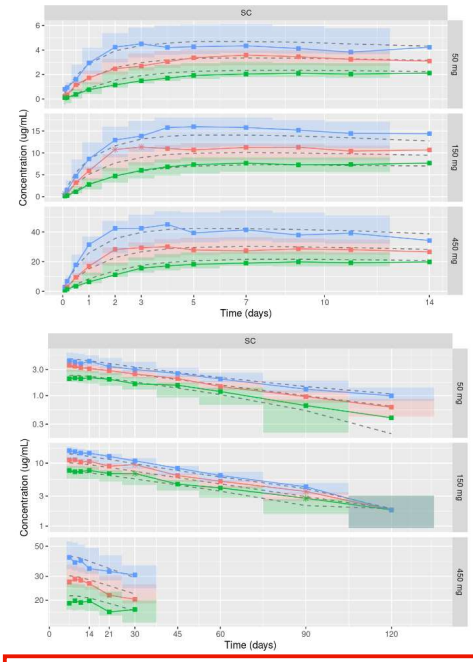
| Parameters | Population Estimate | RSE (%) | Shrinkage (%) |
|---|---|---|---|
| $K_a$ (/h) | 0.02493 | 10.53 | N.A. |
| CL/F (L/h) | 0.00826 | 4.74 | N.A. |
| equivalent $T_{1/2}$ (days) * | 45.91 | | |
| $V_c$/F (L) | 13.13 | 5.66 | N.A. |
| IIV of $K_a$ (CV%) | 54 | 11.81 | 1.3 |
| IIV of CL (CV%) | 19.4 | 14.69 | 9.8 |
| IIV of $V_c$ (CV%) | 27.6 | 14.05 | 0.51 |
| Correlation between IIV of CL and $V_c$ | 0.6218 | 20.32 | N.A. |
| Proportional residual error (CV%) | 7.96 | 12.79 | 7.9 |
| Additive residual error (µg/mL) | 0.3109 | 20.22 | |

RSE: relative standard error; CL: clearance; $V_c$: central volume of distribution; IIV: inter-individual variability, estimates in CV% calculated as exp(variance-1)$^{1/2}$ and RSE calculated as (std error/variance)/2.

* $\theta_{T_{1/2}} = \log(2) * \frac{\theta_{V_c}}{\theta_{CL}}$

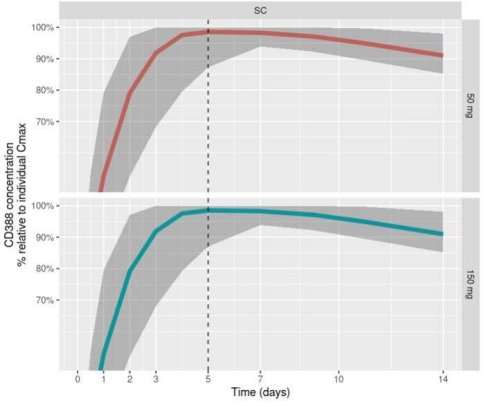
## Simulation of absorption profile

**Figure 1. Visual Predictive Check (VPC) of the final CD388 popPK model in study CD388.SQ.1.01. Upper plot shows absorption during first 14 days post-dose, lower plot shows full profile without first 7 days (log-scale). Red shows median, blue and green show 80% prediction interval, areas show 90% confidence interval.**




**Typical half-life was estimated at 6 – 8 weeks**

**Figure 2. Predicted median (line), 10th percentile and 90th percentile (grey area) of CD388 drug concentrations relative to individual $C_{max}$. Day 5 is shown as dotted vertical line.**




**At day 5 post-administration, 90% of the population is predicted to reach 90% of $C_{max}$. This confirms day 5 post-administration is an appropriate time for viral challenge in a Human Challenge Study.**

## Simulation of day-5-equivalent dose

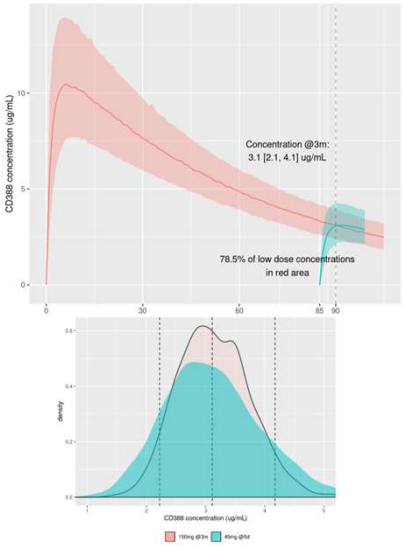



**Figure 3. Population simulation of 150mg over 6 months post-dose.**

**A dose of 45mg is predicted to yield day 5 concentrations equivalent to concentrations achieved at 3 months after a 150mg dose**

## Predicted concentrations over an influenza season

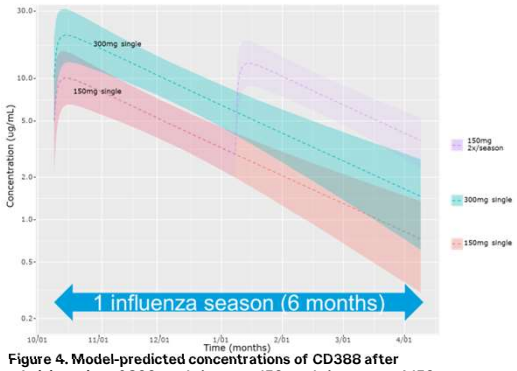



**Figure 4. Model-predicted concentrations of CD388 after administration of 300 mg 1x/season, 150 mg 1x/season and 150 mg 2x/season doses.**

**A dose of 300mg provided a 10-fold peak-to-trough ratio over 6 months influenza season.**
**A regimen of 150mg every 3 months is predicted to yield lower peak-to-trough variation and higher final trough concentrations.**

## Conclusions

- ❑ A single dose of 300 mg CD388 was predicted to show slow concentration peak to trough decline of approximately 10 fold over a potential influenza season.
- ❑ An initial 150mg dose amended with a 2nd 150 mg dose mid-influenza season leads to accumulation and reduced peak to trough variation.
- ❑ The extended half-life of CD388 could provide seasonal prevention with one or two doses per season.
- ❑ At the projected doses, CD388 concentrations would be at adequate levels on Day 5 post-administration in order to perform a proof–of-concept viral Human Challenge Study.

## References

1. CDC Seasonal Flu Vaccine Effectiveness. https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm
2. Hughes et al. Clinical Infectious Diseases. 2021 Dec 6;73(11):e4353-e4360. doi: 10.1093/cid/ciaa1927.