Prophylactic efficacy of CD388, a novel Drug Fc -Conjugate (DFC), in an influenza A/H3N2 human challenge model

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Abstract

Background: Influenza remains a significant public health concern due to the limited efficacy of vaccines, especially in immunocompromised patients[1,2]. CD388 is a multivalent conjugate of a dimeric neuraminidase inhibitor stably linked to a proprietary human IgG1 Fc fragment engineered for extended half-life. In nonclinical *in vitro* and *in vivo* models, CD388 has demonstrated highly potent, universal antiviral activity against influenza A and B. Here we describe the prophylactic efficacy of CD388 against the influenza A/Perth/16/2009 (H3N2) strain in a human challenge model.

Methods: This is a proof-of-concept, single-center, randomized, double-blind, placebo-controlled, Phase 2a study of CD388 in healthy participants 18 to 55 years of age. The primary objective is to assess the prophylactic antiviral activity of CD388 against influenza using a single dose of CD388, administered subcutaneously (SC) 5 days before intranasal viral challenge. The primary efficacy outcome is the area under the viral load -time curve (VL-AUC) as determined by qRT-PCR in nasopharyngeal swabs.

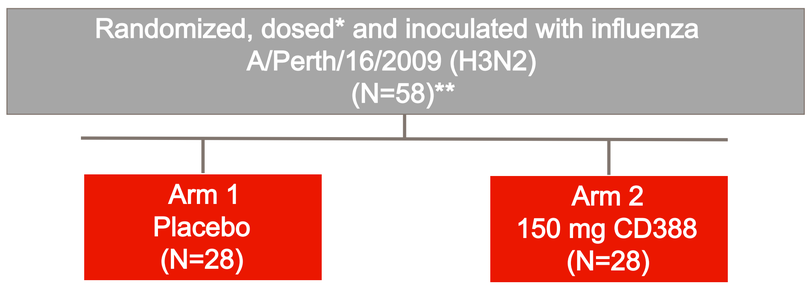
Results: Out of 58 volunteers that were randomized and challenged with influenza, 28 received 150 mg of CD388, and 28 received placebo. A reduction in the VL-AUC in nasal samples was observed in the CD388 arm vs the placebo arm (mean 10.70 log_{10} [copies/mL] x days vs mean 16.09 log_{10} [copies/mL] x days; p= 0.0390). Both peak intranasal viral load (VL) and rate of qRT-PCR confirmed influenza infection were significantly lower in CD388 vs placebo (p=0.0185; p=0.0248 respectively). Additionally, shorter duration of viral shedding, lower total clinical symptom scores and lower peak symptom score were observed in CD388 vs placebo, but these differences were not statistically significant. CD388 was well tolerated with limited number of treatment emergent adverse events (TEAEs), including one injection site reaction, that were mostly mild in severity and resolved spontaneously within the exposure timeframe. **Conclusions:** A single SC dose of CD388 administered 5 days prior to influenza challenge was well tolerated and demonstrated statistically significant antiviral effects. This data supports the potential of CD388 for seasonal prophylaxis of influenza.

Objectives

- To determine the prophylactic antiviral activity of CD388 against experimental influenza infection in a healthy adult population.
- To confirm the safety and tolerability of CD388 after a single SC injection.

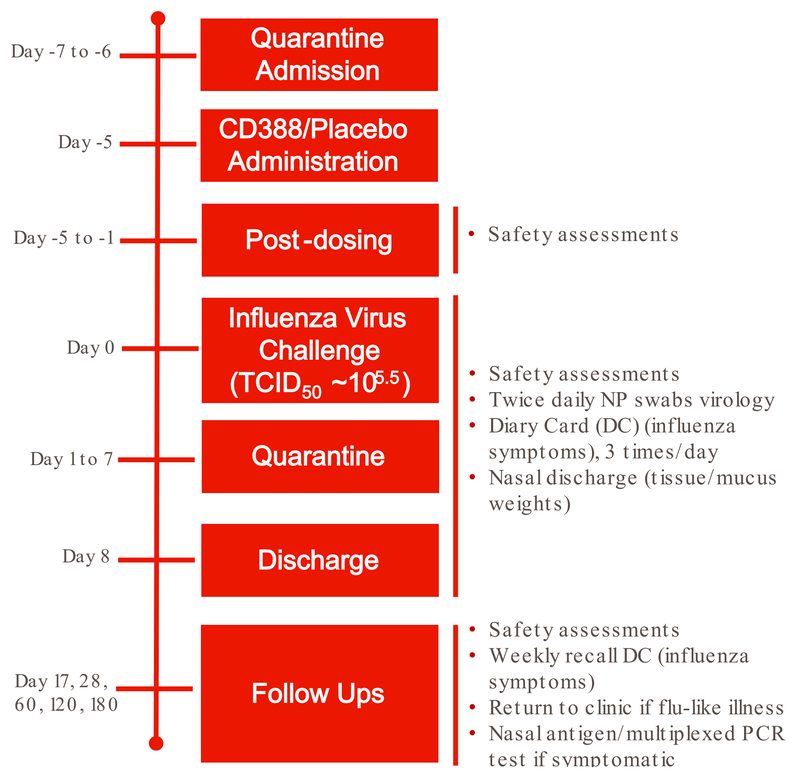
Methods

Figure 1. Study Design



*One participant in the Placebo arm withdrew consent before viral challenge and was not included in the per-protocol (PP) set.**Two participants were randomized to receive 50 mg CD388 and challenged with virus. Due to lower-than-expected recruitment, enrollment of this arm was stopped (Arm 3, not shown). All results shown are for Arms 1 and 2.

Figure 2. Schematics of the human challenge study



Results

Prophylactic Efficacy: Viral Load (VL)

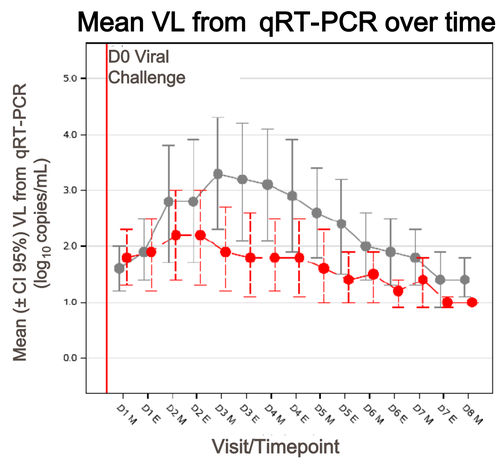


Figure 3. Mean VL (top) and VL-AUC (bottom) determined by qRT-PCR in nasopharyngeal swabs. On the top, mean (± 95% CI) VL measurements are depicted over time (grey: PLACEBO; red: CD388 150 mg). On the bottom, individual VL-AUC calculations (grey: PLACEBO; red: CD388 150 mg), along with the mean (star symbol) and the median (green line) are shown. Analyses were done in the per-protocol (PP) analysis set (all participants randomized, having received treatment [placebo/CD388], inoculated with the virus, who had valid results for at least 80% of the planned qRT-PCR in nasal samples from Day 1 to Day 8). Wilcoxon p-value=0.0390 (one sided) is shown. N= 28/treatment arm.

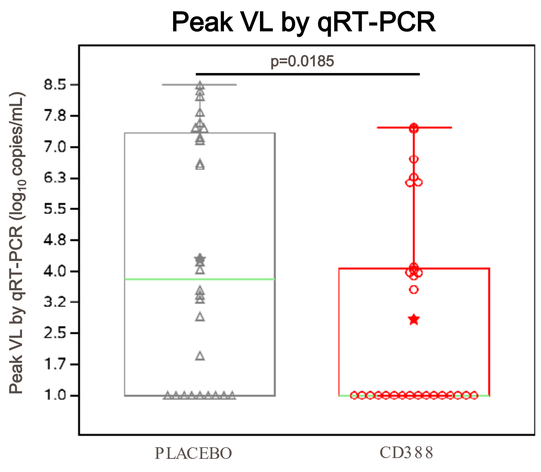


Figure 4. Peak VL determined by qRT-PCR in nasopharyngeal swabs. Shown are individual peak VL measurements (grey: PLACEBO; red: CD388 150 mg), along with the mean (star symbol) and the median (green line). Analysis was done in the PP analysis set (all participants randomized, having received treatment [placebo/CD388], inoculated with the virus, who had valid results for at least 80% of the planned qRT-PCR in nasal samples from Day 1 to Day 8). Wilcoxon p-value=0.0185 (one sided) is shown. N= 28/treatment arm.

Prophylactic Efficacy: Incidence of Infection

Table 1. Incidence of qRT-PCR-confirmed influenza infection

	Placebo (N=28) n (%)	CD388 (150 mg) (N=28) n (%)	Placebo vs CD388 One-sided Fisher's exact p- value
RT-PCR-confirmed influenza infection*	14 (50)	6 (21)	0.0248
RT-PCR-confirmed symptomatic influenza infection**	9 (32)	4 (14)	0.1023
RT-PCR-confirmed moderate to severe symptomatic influenza infection***	7 (25)	3 (11)	0.1477

*RT-PCR-confirmed influenza infection: 2 quantifiable (≥ lower limit of quantification [LLOQ]) qRT-PCR measurements (reported on 2 or more independent samples over 2 days), from Day 1 (pm) up to Day 8 (am).
**RT-PCR-confirmed symptomatic influenza infection: RT-PCR-confirmed influenza infection (2 quantifiable [≥LLOQ] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 1 (pm) up to Day 8 (am), AND symptoms ≥2 at a single time point.
***RT-PCR-confirmed moderate to severe symptomatic influenza infection: RT-PCR confirmed influenza infection (2 quantifiable [≥LLOQ] qRT-PCR measurements [reported on 2 or more independent samples over 2 days]), from Day 1 (pm) up to Day 8 (am), AND any symptoms of grade ≥2 at a single time point.

Prophylactic Efficacy: Additional Endpoints

❖ **Influenza symptoms**
Incidence of symptomatic infection was low (32% placebo vs 14% CD388) and, although lower area under the total symptom score-time curve (TSS-AUC) and peak TSS were observed in CD388 vs placebo (mean TSS-AUC 2.22 ± 4.86 vs 7.66 ± 14.13; mean peak TSS 1.79± 3.12 vs 3.54 ± 5.34), these reductions were not statistically significant.

❖ **Viral load assessed by viral culture**
A statistically significant reduction in peak VL was observed in the CD388 arm compared to the placebo arm (Wilcoxon p-value=0.0236; one-sided). No statistically significant difference was observed in VL-AUC.

❖ **Viral shedding**
While the time to confirmed negative qRT-PCR was shorter in the CD388 -(median 79.4 hours, 95% CI, 24.4-143.1) vs the placebo arm (median 134.1 hours, 95% CI, 61-non-computable), these differences were not statistically significant.

❖ **Viral resistance**
Next generation sequencing of NA and HA genes in all qRT-PCR-positive samples did not identify any known resistance mutations in any of the CD388-treated participants.

Safety

Table 2. Summary of Adverse Events (Safety Analysis Set)

Description	Placebo (N=29) n (%) [e]*	CD388 150 mg (N=28) n (%) [e]*
Any unsolicited TEAE	19 (65.5) [25]	21 (75.0) [34]
Any unsolicited TEAE leading to study discontinuation	0 (0) [0]	0 (0) [0]
Any unsolicited TEAE considered as related to study treatment	0 (0) [0]	0 (0) [0]
Any serious adverse event (SAE)	0 (0) [0]	0 (0) [0]
Death	0 (0) [0]	0 (0) [0]
Any solicited AE	0 (0) [0]	1 (3.6) [1]

*e= number of events

Safety Summary

- ❖ Overall CD388 was safe and well-tolerated with no SAEs, no deaths and no TEAEs leading to study discontinuation.
- ❖ In total 59 TEAEs were reported in 40 (70%) participants, most of which were mild in severity, except for 4 TEAEs in the 150 mg CD388 arm and 2 TEAEs in the placebo arm of moderate severity.
- ❖ All TEAEs were considered as not related to treatment (CD388 or placebo) and as not related or unlikely to be related to the challenge virus.
- ❖ TEAEs by PT reported by more than 1 participant in the 150 mg CD388 arm were upper respiratory tract (URT) infection (19 events in 15 [53.6%] participants), headache (4 events in 4 [14.3%] participants) and AST elevated (3 events in 3 [10.7%] participants).
- ❖ TEAEs by PT reported by more than 1 participant in the placebo arm were URT infection (14 events in 12 [41.4%] participants) and headache (2 events in 2 [6.9%] participants).
- ❖ A single case of community-acquired influenza, that occurred in a participant that received placebo, was reported.
- ❖ One solicited AE (injection site pain), mild in severity, was reported in the 150 mg CD388 arm.

Conclusions

- ❑ A single SC dose of 150 mg CD388 5 days prior to viral challenge was well-tolerated and significantly reduced nasal viral load compared with placebo.
- ❑ A single SC dose of 150 mg CD388 showed a statistically significant lower incidence of qRT-PCR confirmed influenza infection compared to placebo. A reduction was also observed in the incidence of qRT-PCR-confirmed symptomatic influenza infection, and the incidence of qRT-PCR-confirmed moderate to severe symptomatic influenza infection, although these reductions were not statistically significant.

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.

Acknowledgements

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