Safety and Efficacy of CR6261 in an Influenza A H1N1 Healthy Human Challenge Model

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BACKGROUND

- A potential target for improved influenza vaccine and therapeutics is the relatively conserved stalk region of the influenza A hemagglutinin (HA) surface protein (1).
- Influenza challenge models have been validated (2,3) and used to study vaccines and therapeutics.

OBJECTIVES

- Primary: Determine if there was a reduction in area under the curve (AUC) using 1-step real-time qRT-PCR.
- Secondary: Compare clinical illness severity and evaluate safety and pharmacokinetics of CR6261.

METHODS

We conducted a randomized, double-blind, Phase II placebo-controlled trial of a monoclonal antibody that targets the HA stalk (CR6261) in a H1N1pdm09 healthy volunteer human challenge model. A single 50mg/kg dose of CR6261 was infused 24 hours after challenge.

ENROLLMENT

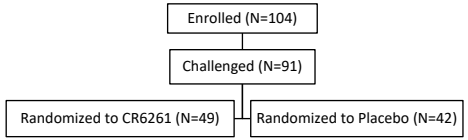

Figure 1. Study enrollment

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RESULTS

Table 1. Median AUC Log(RNA copies/mL) x days (IQR)*

	CR6261 (N=49)	Placebo (N=42)	p-value
Janssen Lab (N=69)	29.7 (251)	19.8 (178)	0.396
NIH Lab (N= 22)	66.5 (144)	32.4 (82)	0.615
Combined (N=91)	48.6 (202)	25.5 (155)	0.315†

* IQR =75th percentile – 25th percentile
† Stratified for lab via nonparametric covariate adjustment

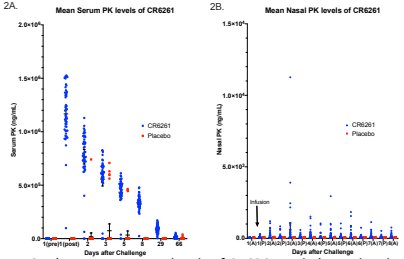

Figure 2. A) Mean serum PK levels of CR6261 and B) Nasal PK levels of CR6261 after influenza challenge. Lines represent means and 95% CI.

Table 2. Clinical Endpoints

Influenza severity	CR6261 (N=49)	Placebo (N=42)	p-value
MMID, N (%)	26 (53%)	29 (69%)	0.137
Confirmed influenza infection, N (%)	36 (73%)	37 (88%)	0.114
Any Symptoms, N (%)	37 (76%)	39 (93%)	0.045*
Number of Symptoms, median (95% CI)	3 (2-5)	4 (3-5)	0.244
Duration of Symptoms, median (95%CI)	5 (3-7)	6 (5-7)	0.141
Any Shedding, N (%)	33 (67%)	31 (74%)	0.646
Duration of Shedding, median (95%CI)	2 (1-4)	2.5 (1-5)	0.498
FLU-PRO scores, median (95%CI)	0.038 (0.013-0.084)	0.057 (0.041-0.084)	0.230

Abbreviations: MMID, Mild to moderate influenza disease (≥ 1 symptom and shedding)
* denotes statistical significance of p <0.05.

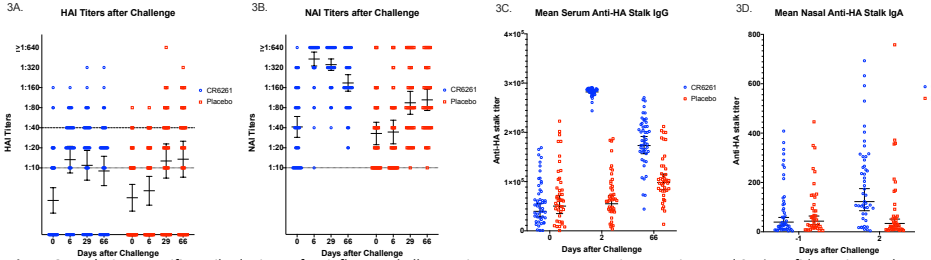

Figure 3. A-D) Virus-specific antibody titers after influenza challenge. Lines represent geometric mean titers and 95% confidence intervals.

Table 3. Logistic regression models of MMID and confirmed influenza infection

Outcome	Covariate	Odds Ratio* (CI)	p-value
MMID	Baseline HAI	0.77 (0.27, 2.20)	0.63
	Baseline NAI	0.66 (0.49, 0.89)	0.0070†
	Treatment (reference: placebo)	0.52 (0.20, 1.36)	0.18
Confirmed influenza infection	Baseline HAI	1.06 [0.32 , 3.52]	0.93
	Baseline NAI	0.82 [0.70 , 0.97]	0.017†
	Treatment (reference: placebo)	0.33 [0.10, 1.11]	0.07

* Odds ratio defined in terms of 50-unit increase in baseline titer
† Denotes statistical significant of p <0.05

Safety of CR6261

- Overall, CR6261 was well-tolerated.
- No SAE occurred related to any study intervention.
- 2 participants developed CR6261 infusion reactions and both infusions were stopped early. No infusion reactions were noted after a change in CR6261 lot.
- Other AEs were mild, not clinically significant, and resolved without intervention.

CONCLUSIONS

- CR6261 did not significantly reduce viral shedding (Table 1) or clinical disease (Table 2).
- CR6261 infusion was overall safe. The cause of hives in the 2 CR6261 participants was not identified though no further reactions occurred after a change in lot.
- Efficacy may be limited due to the low penetration of CR6261 at the mucosal level (Figure 2), while levels of naturally occurring anti-NA antibody appeared to be the best predictor of disease severity (Table 3).

REFERENCES

1. Ekiert DC, Bhabha G, Elsliger MA, et al. Antibody recognition of a highly conserved influenza virus epitope. Science 2009; 324(5924): 246-51.
2. Memoli MJ, Czajkowski L, Reed S, et al. Validation of the wild-type influenza A human challenge model H1N1pdMIST: an A(H1N1)pdm09 dose-finding investigational new drug study. Clin Infect Dis 2015; 60(5): 693-702.
3. Han A, Czajkowski LM, Donaldson A, et al. A Dose-finding Study of a Wild-type Influenza A(H3N2) Virus in a Healthy Volunteer Human Challenge Model. Clin Infect Dis 2019; 69(12): 2082-90.