A Randomized, Adaptive Phase I Study to Determine the Phase II dose of VIR-7832 (AGILE CST5)

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BACKGROUND

Despite widespread COVID-19 vaccination, anti-virals remain important for COVID-19 treatment.

Early treatment is crucial to avoid progression and severe disease, with **monoclonal antibodies** (mAb) offering possible advantages in single dosing and duration of effect. **VIR-7832** is a novel mAb derived from the same parental antibody as sotrovimab with the addition of an Fc domain XX2 modification to enhance effector function and modulate immune response.

Here we report data from the **First-in-Human trial of VIR-7832 in mild-moderate COVID-19 patients** (AGILE CST5, NCT04746183).

METHODS

Participants with PCR-confirmed mild-moderate COVID-19 infection, within 7 days of onset, were randomised (3:1, double-blind) to single dose VIR-7832 or placebo.

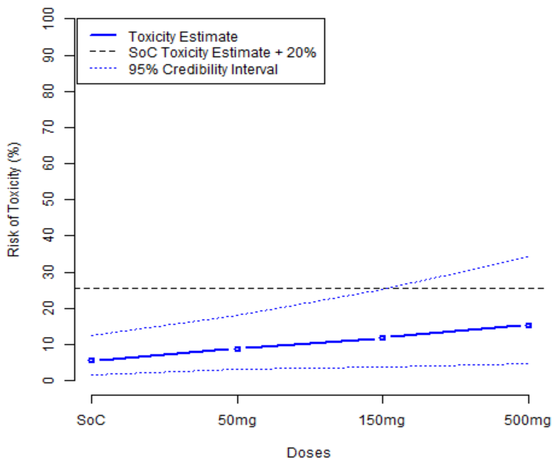
Three cohorts of 8 participants were recruited, with **dose escalation** in between (Cohort 1-50mg, Cohort 2-150mg, Cohort 3-500mg) supported by a **Bayesian dose-toxicity model**.

Participants were followed to day 253 post-dose, with assessments performed for safety (laboratory samples, electrocardiograms, vital signs), VIR-7832 pharmacokinetics (PK), patient reported outcomes (FLU-PRO PLUS) and viral swabs.

The **primary endpoint was safety & tolerability** to day 8 (AEs, SAEs and dose-limiting toxicities (DLT, defined as CTCAE >/= grade 3)) with secondary endpoint of VIR-7832 PK and exploratory endpoint of SARS-CoV-2 viral dynamics (PCR and viral load swab at days 1, 3, 5, 8, 11, 15, 22, 29).

VIR-7832, a novel monoclonal antibody for SARS-CoV-2 treatment, was well-tolerated at single doses up to 500mg, with predictable and durable pharmacokinetics in patients with mild-moderate COVID-19 infection

Figure 1 Dose-Toxicity Plot to Day 8



Dose level	Estimated DLT rate (95% credible interval)	Estimated additional toxicity above control	Target dose probability (15-25% additional toxicity)	Probability of additional toxicity≥30% over control arm
Standard care	5.6% (1.8 to 12.5)	N/A	N/A	N/A
Cohort 1 (50mg)	8.8% (3.0 to 18.2)	3.2%	0.0%	0.0%
Cohort 2 (150mg)	11.9% (3.9 to 25.1)	6.3%	3.9%	0.0%
Cohort 3 (500mg)	15.4% (4.6 to 34.3)	9.8%	14.5%	1.6%

Figure 2 Mean SARS-CoV-2 Viral Load

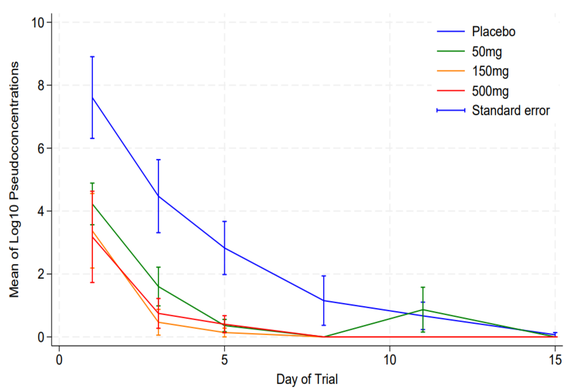


Table 1 Study Demographics	Group	50mg	150mg	500mg	Placebo	All
	N	6	6	6	6	24
Age (years)	Median	24.0	23.5	25.5	22.5	**23.5**
	IQR	23.0-28.0	23.0-24.0	19.0-27.0	21.0-33.0	**21.5-27.5**
	Range	21.0-39.0	21.0-37.0	19.0-29.0	20.0-52.0	**19.0-52.0**
Gender	Female N	1	2	2	3	**8**
	Female %	16.7	33.3	33.3	50	**33.3**
BMI (kg/m^2)	Median	19.7	21.5	24.0	24.4	**22.9**
	IQR	18.8-26.2	19.5-31.0	22.6-25.9	22.4-28.0	**19.7-27.1**
	Range	17.9-31.1	17.8-32.9	19.4-28.9	20.0-29.0	**17.8-32.9**
Time from symptom onset (days)	Median	5.5	3.5	4.5	4.0	**5.0**
	IQR	5.0-7.0	2.0-5.0	3.0-6.0	3.0-6.0	**3.0-6.0**
	Range	5.0-7.0	2.0-7.0	2.0-6.0	2.0-6.0	**2.0-7.0**
Previous SARS-CoV-2 Vaccination	N	0	0	6	2	**8**
	%	0.0	0.0	100.0	33.3	**33.3**

RESULTS

24 individuals (8 female) were recruited. Demographics are provided in **Table 1**. For the primary endpoint (**Figure 1**), to day 8, 1 participant receiving 150mg VIR-7832 reported a DLT (syncope); beyond day 8, 2 DLTs were reported in the placebo group (diarrhoea, neutropenia).

One SAE (dyspnoea, considered unrelated) was reported in a participant receiving 50mg VIR-7832. Skin rashes were reported by 2 participants receiving 150mg VIR-7832 (lichenoid reaction & maculopapular rash).

Time to negative SARS-CoV-2 PCR, defined by last participant negative in each cohort, was 15 days for those receiving 50mg VIR-7832, 8 days for 150mg VIR-7832, 8 days for 500mg VIR-7832 and 22 days for placebo. Abbreviated mean viral load data are presented in **Figure 2**. PK data demonstrated dose-proportional increases in VIR-7832 maximum concentrations and exposure, with median half-life between 41-49 days.

CONCLUSIONS

This is the first report of the safety, tolerability, pharmacokinetics and viral outcomes for VIR-7832, a novel mAb for treating SARS-CoV-2. These data suggest that VIR-7832 is safe and well tolerated at single doses up to 500mg which is supported by the Bayesian dose-toxicity model (**Figure 1**). SARS-CoV-2 PCR and mean viral load data are presented for each cohort; however, these data are limited by the small number of participants included in this study. PK data demonstrate predictable and durable VIR-7832 exposure following single doses.

In summary, these data support further clinical development of VIR-7832, at a single dose of 500mg, as a treatment for COVID-19 infection.

ADDITIONAL KEY INFORMATION

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