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Viral Kinetics in COVID-19 Outpatients Treated with Casirivimab+Imdevimab Combination

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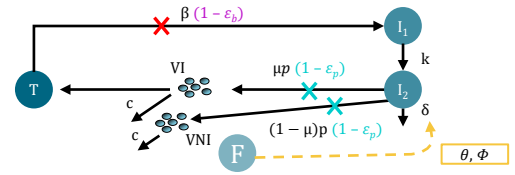
Background

- Results from a Phase 3 study of casirivimab+imdevimab (CAS+IMD, REGEN-COV®) in SARS-CoV-2–infected outpatients enrolled between September 2020 and January 2021 have shown a reduction in hospitalization/death by 70% when administered within 72 hours of a positive test in the course of the infection (NCT04425629; enrollment was prior to the circulation of omicron, against which CAS+IMD is not expected to be active).
- Our aim was to estimate antiviral efficacy of CAS+IMD *in vivo* and to estimate its effect on the time to viral clearance.

Methods

- Analysis data came from two clinical studies conducted prior to October 2020 (NCT04425629 and NCT04666441; enrollment was prior to the circulation of omicron variant, against which CAS+IMD is not expected to be active), where individuals received a single dose of placebo (N=1426) or CAS+IMD (N=3074), by intravenous or subcutaneous routes, with drug doses ranging from 300 mg to 8000 mg.
- The study population comprised SARS-CoV-2–infected outpatients with no (n=3107) or ≥1 risk factor (n=1393) for severe COVID-19. The median patient age was 42 years, with a similar proportion of male and female patients. The median time of symptom onset and treatment initiation was 3 days.
- All patients had viral load assessed by nasopharyngeal swab. The median number of viral load assessments per patient was 5 (range 1–8) within up to 14 days of follow-up time. The median viral load at baseline was 6.79 $\log_{10}$ copies/mL.
- A viral kinetic model with an antigen-dependent stimulation of immune response was used to estimate the time of infection and reconstruct viral kinetic profiles.
- Based on previous results, antiviral drug effect was incorporated in an exposure-independent manner, and different putative mechanism of actions were tested. The best model assumed an effect of drug in blocking *de novo* infection and reducing the viral production from infected cells (**Figure 1**).

Figure 1. Viral kinetic model with antigen-dependent stimulation of immune response

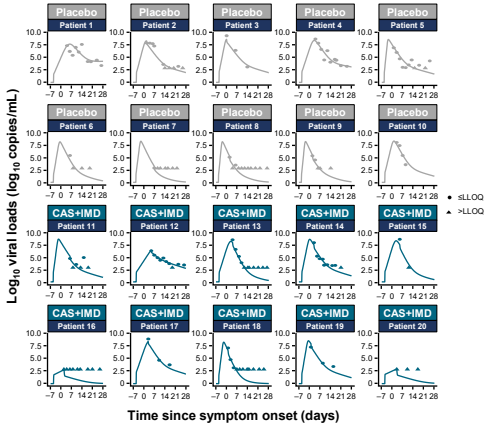


$$\frac{dT}{dt} = -\beta \cdot (1-\varepsilon_b) \cdot V_i \cdot T$$
$$\frac{dI_1}{dt} = \beta \cdot (1-\varepsilon_b) \cdot V_i \cdot T - k \cdot I_1$$
$$\frac{dI_2}{dt} = k \cdot I_1 - \delta \cdot I_{2_} \Phi \cdot \frac{F}{F+\theta} \cdot I_2$$
$$\frac{dV_i}{dt} = \mu \cdot p \cdot (1-\varepsilon_p) \cdot I_2 - c \cdot V_i$$
$$\frac{dV_{ni}}{dt} = (1-\mu) \cdot p \cdot (1-\varepsilon_p) \cdot I_{2_} c \cdot V_{ni}$$
$$\frac{dF}{dt} = I_2 - df \cdot F$$

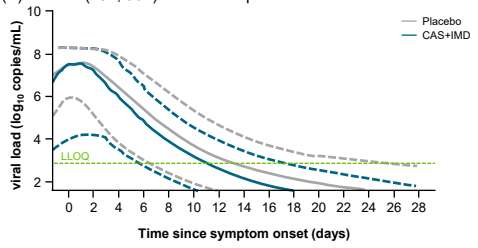
Three types of cell populations: uninfected susceptible target cells (T), infected cells in an eclipse phase (I_1), and productively infected cells (I_2). Target cells are infected at a constant rate of infection β (milliliters per virus copies per day). Once infected, cells enter an eclipse phase and become productively infected at a constant rate k (per day). Productively infected cells are eliminated at a constant rate δ (per day) and produce viral particles at a constant rate p (per day). A fraction μ of the viral particles are from infectious virus (V_i), and the remaining viral particles ($1-\mu$) are from noninfectious virus (V_{ni}). Viral load, as measured by RNA copies, is the sum of infectious and noninfectious viral particles, both cleared at the same rate c. Drug blocks de novo infection (ε_b) and reduces viral production from infected cells (ε_p) in an exposure-independent manner. Immune response (F) increases the rate of elimination of I_2, with a nonlinear and saturable effect defined by $\Phi \cdot \frac{F}{F+\theta}$, where ϕ represents the maximal immune response and θ is the level of F required to achieve 50% of this maximal response.

Figure 2. Model predictions

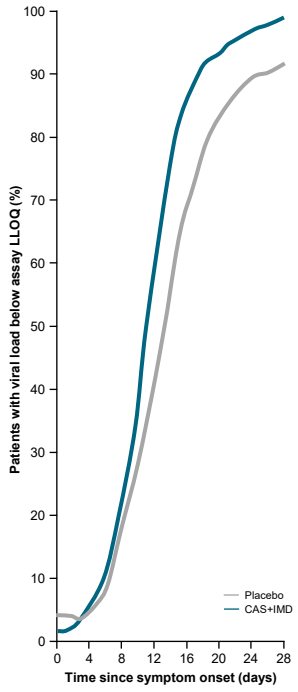
(A) Representative individual viral kinetic profiles



(B) Median (10^{th}, 90^{th}) viral kinetic profiles



(C) Time to viral clearance



LLOQ, lower limit of quantification.

Results

- The viral kinetic model with an antigen-dependent stimulation of immune response described the observed viral load-time profiles reasonably well (**Figure 2A**).
- Model results show that CAS+IMD main mechanisms of action *in vivo* is blocking *de novo* infection with an estimated median efficacy of 99.7%, and subsequent reduction of viral production by infected cells with an estimated median efficacy of 75.5% for all dose regimens evaluated herein.
- CAS+IMD reduced the median time to viral clearance (ie, time to reach below assay quantification limit) by 1.4 days (median 10.6 vs 12.0 days).
- CAS+IMD reduced the proportion of individuals with prolonged viral shedding, with 90% of patients clearing virus within 17.4 days compared to 26.0 days in patients receiving placebo (**Figures 2B and 2C**).

Conclusions

- In clinical studies conducted prior to October 2020, CAS+IMD had a high antiviral activity, reducing the rate of *de novo* cell infection by 99.7% and reducing viral production from infected cells by 75.6%.
- This viral kinetic model will be used to better understand the effects of viral dynamics on disease progression and evaluate the impact of different treatment strategies (timing of initiation, dose) on disease outcomes.

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Disclosures
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