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Effects of Casirivimab and Imdevimab on Symptom Outcomes in Outpatients with COVID-19

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Background

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) continue to pose a threat to global health, with over 5.3 million deaths reported to date.[1]
- Patients with COVID-19 can develop mild to severe symptoms, and even sometimes respiratory failure.[2]
- Symptoms reduction is a crucial outcome to be considered when testing novel treatments for COVID-19.
- Casirivimab and imdevimab (CAS+IMD; REGEN-COV®) is a combination (1:1) of two noncompeting human immunoglobulin G1 monoclonal antibodies that bind and neutralize susceptible SARS-CoV-2 variants.[3] CAS+IMD is highly unlikely to be active against the Omicron variant.
- The aim of this study (conducted before the emergence of the Omicron variant) was to assess the impact of CAS+IMD dose/exposure on the trajectory and time to resolution of symptoms in outpatients with COVID-19.

Methods

- Analysis data came from an adaptive Phase 1–3, randomized, double-blind, placebo-controlled trial conducted prior to October 2020 (NCT04425629).[4]
- A single IV dose of CAS+IMD (total dose 1200, 2400, or 8000 mg) or placebo was administered in a 1:1 ratio.
- Symptoms data were collected using the Symptoms Evolution of COVID-19 (SE-C19), a patient-reported outcome instrument developed *de novo* to assess the symptomatic course of COVID-19.[5]
- Based on patients' responses to the SE-C19, a Rasch analysis was used to derive a latent score to infer their overall underlying symptom severity.
- The analysis population included adult (≥18 years) SARS-CoV-2 infected outpatients who received a single IV dose of either placebo or CAS+IMD, with at least one derived latent score available between Day 1 and Day 29 and no missing values for baseline severity of COVID-19 symptoms (n=4159).
- A direct response model was fitted to the latent score-time data to quantify the effects of dose/exposure, demographic, and clinical characteristics on latent symptom trajectory.
- Symptoms resolution time was defined as time from randomization to the first day during which the patient scored "no symptom" (score of 0) on 19 out of the 23 symptoms (excluding confusion, vomiting, rash, and sneezing) except cough, fatigue, and headache, which can be 'mild/moderate symptom' (score of 1) or 'no symptom' (score of 0). The analysis population further excluded patients with a baseline symptoms score ≤3 and those with no post baseline symptoms data recorded (n=2551).
- Several parametric models were tested as a structural model, assuming a known distribution, eg, exponential or Weibull, for time to symptoms resolution data. Risk variables (eg, binary treatment or categorical dose levels, exposure metrics, baseline demographic, clinical, and biological characteristics) were tested as covariates using parametric regression models.

Results

Subjects

- Demographic and baseline characteristics for the patients from the Phase 3 portion of the study are summarized in **Table 1**.
  - Median age was 48.5–51.0 years, 47.2–51.8% were male, 65.9–69.4% were seronegative for anti-SARS-CoV-2 antibodies at baseline, and 100% had ≥1 risk factor for hospitalization.
  - Demographic and baseline characteristics for patients in Phases 1 and 2 were similar to Phase 3.[4]

Table 1. Demographic and baseline medical characteristics for the Phase 3 portion (mFAS*)

Characteristic	Placebo§ (n=1341)	CAS+IMD 1200 mg (n=736)	CAS+IMD 2400 mg (n=1355)	CAS+IMD 8000 mg (n=625)
Median age (IQR), years	50.0 (37.0–58.0)	48.5 (37.0–57.5)	50.0 (39.0–60.0)	51.0 (40.0–59.0)
Male sex, n (%)	633 (47.2)	364 (49.5)	656 (48.4)	324 (51.8)
Hispanic or Latino ethnic group, n (%)†	471 (35.1)	312 (42.4)	464 (34.2)	177 (28.3)
Race, White, n (%)†	1136 (84.7)	595 (80.8)	1161 (85.7)	534 (85.4)
Mean BMI, (SD)‡	31.19±6.63	31.54±7.31	31.09±6.33	31.90±7.23
At least one risk factor for severe COVID-19, n (%)§	1341 (100)	736 (100)	1355 (100)	625 (100)
Median baseline viral load (range), log_{10} copies/mL	6.95 (2.6–10.2)	6.92 (2.6–10.5)	7.01 (2.6–10.0)	7.00 (2.6–9.8)
Baseline serum antibody status, n (%) Negative	930 (69.4)	500 (67.9)	940 (69.4)	412 (65.9)

*Included patients who were RT-qPCR-positive by central lab test and had ≥1 risk factor for severe COVID-19. †Race and ethnic group reported by patients. ‡BMI is the weight in kilograms divided by the square of the height in meters. §Risk factors for hospitalization: age ≥50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised (immunosuppression or receipt of immunosuppressants). §2400 mg concurrent.
BMI, body mass index; IQR, interquartile range; mFAS, modified full analysis set; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SD, standard deviation.

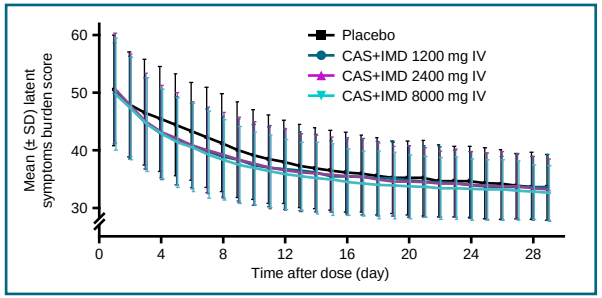
Exploratory data analysis

- CAS+IMD altered the trajectory of symptoms as indicated by the latent score over time (**Figure 1**). However, within the tested dose range (1200 to 8000 mg), there was no noticeable dose-dependency.

Direct response modeling on latent score

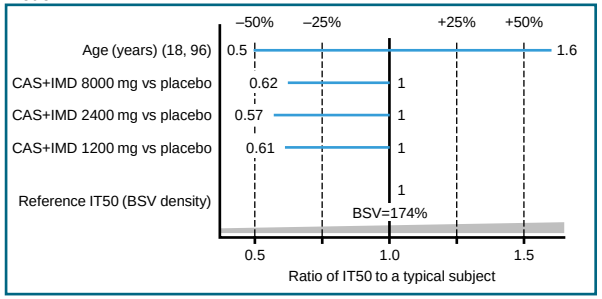
- Results from the direct response model suggested each dose, as compared to placebo, reduced IT50 (the time taken to achieve half of the maximal response of reducing symptom) by approximately 40% in a dose-independent manner.
- Age was also another statistically significant covariate on IT50, implying older patients have a longer symptoms resolution time (**Figure 2**).

Figure 1. Mean (±SD) latent symptoms burden score over time for different doses of CAS+IMD



IV, intravenous; SD, standard deviation.

Figure 2. Effect of dose of CAS+IMD and age on IT50 based on the final model



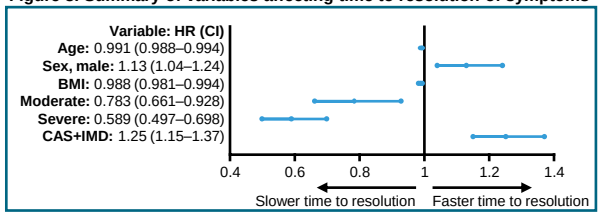
Note: X axis is the ratio of IT50 to a typical subject in analysis dataset: an asymptomatic female on placebo, whose baseline BMI is 30.6 kg/m^2, albumin 43 g/L, age 49 years, and viral load 6.9 log_{10} copies/mL. Continuous covariate range represents the extreme values from analysis dataset. To model the trajectory of latent score, an immediate response model with nominal time as driver was used:
Score (t)=S0×(1- (Imax×t)/(IT50+t)), where Score (t) is latent score at nominal time t. S0 is baseline latent score, Imax is the maximal magnitude of reduction in latent score, and IT50 the time taken to achieve half of the maximal response.
BSV, between-subject variability; IT50, time taken to achieve half of the maximal response.

- Sensitivity analyses were conducted by excluding data from the placebo arm. None of the tested doses or predicted exposures were significant covariates on any of the model parameters.

Time to resolution of symptoms analysis

- Results from the parametric regression analysis confirmed treatment with IV CAS+IMD (HR=1.25) shortens symptoms resolution time in a dose- and exposure-independent manner (**Figure 3**).
- Furthermore, males (HR=1.13) had a shorter symptoms resolution time, whereas older age (HR=0.991), higher body mass index (BMI; HR=0.988), and more severe baseline symptoms (HR=0.783 for moderate and HR=0.589 for severe) significantly contribute to longer symptoms resolution time (**Figure 3**).

Figure 3. Summary of variables affecting time to resolution of symptoms



BMI, body mass index; CI, confidence interval; HR, hazard ratio.

Conclusions

- Treatment with CAS+IMD (1200 to 8000 mg) resolved symptoms faster than placebo in outpatients in a dose- and exposure-independent manner, as indicated by a direct response model using derived latent score and further confirmed by a parametric survival analysis using time to symptoms resolution.
- Symptom severity, age, BMI, and sex were all major risk factors affecting symptoms resolution time.

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Disclosures

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