Casirivimab and Imdevimab (CAS+IMD) Antibody Combination for the Treatment of Immunocompromised Hospitalized Patients with COVID-19

#1079

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Background

- Despite widespread vaccination, immunocompromised (IC) persons are at high risk of developing severe COVID-19 if infected by SARS-CoV-2.[1]
- Casirivimab and imdevimab (CAS+IMD) is a monoclonal antibody combination that binds non-overlapping epitopes of the SARS-CoV-2 spike protein receptor-binding domain, neutralizing susceptible SARS-CoV-2 variants.
  - CAS+IMD was previously authorized in the USA for the treatment of patients with mild-to-moderate COVID-19 infection as well as for post-exposure prophylaxis in certain settings.[2]
  - While CAS+IMD retains neutralization potency against historical variants, including the Delta variant, it has diminished neutralization potency against Omicron-lineage variants[3] and is not currently authorized in any US region.[4]
- The efficacy and safety of CAS+IMD in hospitalized patients infected with susceptible variants of SARS-CoV-2 was demonstrated in an open-label platform trial in the UK (RECOVERY),[5] as well as a Phase 1/2/3, double-blind, placebo-controlled trial (COV-2066).[6]
- To understand whether CAS+IMD may be similarly effective in IC patients, we examined the natural history of COVID-19 and the efficacy and safety of CAS+IMD in IC patients with B-cell deficiency or dysfunction, who were hospitalized with COVID-19, in the COV-2066 study.[6]
  - This study was conducted prior to the widespread circulation of Omicron-lineage variants, and so the results are reflective of CAS+IMD treatment in patients infected with susceptible variants of SARS-CoV-2.

Methods

Trial design

- This was a post-hoc analysis of study COV-2066, a Phase 1/2/3 double-blind placebo-controlled trial (clinical trials.gov, NCT04426695) conducted between June 10, 2020, and April 9, 2021.[6]
- Patients were eligible for enrolment in study COV-2066 if they were ≥18 years, hospitalized with SARS-CoV-2 (confirmed by antigen or molecular testing) within 72 hours, and had symptom onset ≤10 days from randomization.
  - Subgroup analyses in IC patients, defined here as those with B-cell deficiencies and dysfunction as determined by examination of medical history and concomitant medications (**Table 1**), are the focus of the results reported here.
- Patients were randomized 1:1:1 to a single dose of 2.4 g CAS+IMD, 8.0 g CAS+IMD, or placebo.

Analyses

- Data were pooled from Phase 1/2/3 patients on low-flow supplemental oxygen (cohort 1), Phase 2 patients on no supplemental oxygen (cohort 1A), Phase 2 patients on high-intensity supplemental oxygen (cohort 2), and Phase 2 patients on mechanical ventilation (cohort 3); CAS+IMD dose groups (2.4 g and 8.0 g) were combined for analysis.
- All patients were assessed prior to dosing for baseline SARS-CoV-2 viral load, serostatus and neutralizing antibody status.
  - Serostatus was evaluated using a composite of three individual assays: anti-spike [S1] IgA (EUROIMMUN), anti-spike [S1] IgG (EUROIMMUN), and anti-nucleocapsid IgG (Abbott). Seropositive was defined as having a positive serology test result in at least one assay; seronegative was defined as being negative in all available results. Patients were categorized as other if they had borderline or undetermined serostatus.
  - Neutralizing antibodies were assessed using modifications of the IMMUNO-COV assay.[7]
- Efficacy analyses assessed change in viral load and the composite clinical endpoint of death or mechanical ventilation, which were the primary virologic and clinical endpoints for the main COV-2066 study.
  - Analyses in the overall population utilized the modified full analysis set (mFAS), which excluded patients who had a negative SARS-CoV-2 quantitative reverse transcriptase polymerase chain reaction test result at baseline; analyses in the IC population utilized the subset of patients as defined in **Table 1** from the mFAS.
  - Virologic results were plotted using raw data, and modelled data for the summary table.
  - Viral load over time was analyzed using linear regression; time-weighted average daily change in viral load from baseline was analyzed using an analysis of covariance model.
  - The composite clinical endpoint was analyzed using Kaplan–Meier estimates.
- Safety analyses assessed TEAEs, AESIs, and deaths in IC patients versus the overall population.
  - Safety was assessed in all randomized patients who received any amount of study drug (safety analysis set; SAF); analyses in the IC population utilized the subset of patients from the SAF as defined in **Table 1**.

Table 1. Criteria for determining IC conditions for enrolled patients

Primary B-cell immunodeficiencies	Secondary B-cell immunodeficiencies	Drug-induced immunodeficiencies	
X-linked agammaglobulinemia	Multiple myeloma	Rituximab	Methotrexate
X-linked immunodeficiency with hyper IgM	Plasma cell leukemia	Ofatumumab	Mycophenolate mofetil
Selective IgA deficiency	Acute lymphocytic leukemia	Ocrelizumab	Azathioprine
Selective IgM deficiency	Non-Hodgkin's lymphoma[a]	Obinutuzumab	Systemic radiation (excluding localized)
IgG subclass deficiency	Hodgkin's lymphoma	Inotuzumab ozogamicin	Chemotherapy
Transient hypogammaglobulinemia of infancy	Human immunodeficiency virus/ acquired immunodeficiency syndrome	Blinatumomab	Tacrolimus
Common variable immunodeficiency	Chronic lymphocytic leukemia not on treatment	Alemtuzumab	Sirolimus
Kappa/lambda light-chain deficiency	Rheumatoid arthritis on methotrexate	Tocilizumab	Everolimus
Severe combined immunodeficiency		Sarilumab	Cyclosporinne
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome		Siltuximab	Lenalidomide
		Belimumab	

[a]Includes follicular lymphoma, Burkitt's lymphoma, diffuse B-cell lymphoma, mantle cell lymphoma, anaplastic large-cell lymphoma, lymphoblastic lymphoma, lymphoplasmacytic lymphoma, marginal zone B-cell lymphoma/mucosa-associated lymphoid tissue lymphoma, small-cell lymphocytic lymphoma, and non-Hodgkin lymphoma unspecified/other. Ig, immunoglobulin.

Results

Baseline characteristics

- A total of 99/1940 (5.1%) of treated patients were identified as having IC conditions of B-cell deficiency or dysfunction (**Table 2**).
- At baseline, IC patients were more likely to be seronegative for SARS-CoV-2 antibodies (68.7% vs 41.2%) and had higher median viral loads (7.21 $\log_{10}$ copies/mL vs 6.32 $\log_{10}$ copies/mL) as compared to the overall population, respectively.
- For seropositive IC patients, baseline antibodies were less likely to be neutralizing positive compared to the overall population (56.0% vs 75.9% respectively).
- IC patients were more likely to be on no supplemental oxygen as compared to the overall population (55.6% vs 27.3%, respectively).

Table 2. Demographics and baseline characteristics

	Overall population			IC population		
	Placebo (n=633)	CAS+IMD combined doses (n=1307)	Total (n=1940)	Placebo (n=35)	CAS+IMD combined doses (n=64)	Total (n=99)
Age, years						
Mean (SD)	62.1 (16.2)	61.5 (15.6)	61.7 (15.8)	64.8 (11.8)	61.1 (14.1)	62.4 (13.4)
≥65, n (%)	296 (46.8)	563 (43.1)	859 (44.3)	20 (57.1)	27 (42.2)	47 (47.5)
Male sex, n (%)	341 (53.9)	718 (54.9)	1059 (54.6)	22 (62.9)	40 (62.5)	62 (62.6)
Hispanic/Latino ethnicity, n (%)	183 (28.9)	381 (29.2)	564 (29.1)	8 (22.9)	12 (18.8)	20 (20.2)
Black/African American race (%)	82 (13.0)	169 (12.9)	251 (12.9)	3 (8.6)	12 (18.8)	15 (15.2)
BMI ≥30 kg/m², n (%)	346 (54.7)	656 (50.2)	1002 (51.6)	19 (54.3)	22 (34.4)	41 (41.4)
Viral load, $\log_{10}$ copies/mL, median (Q1:Q3)[a]	6.28 (4.93:7.55)	6.36 (5.10:7.56)	6.32 (5.05:7.55)	6.89 (6.09:7.85)	7.36 (6.19:8.45)	7.21 (6.11:7.85)
CRP, mg/L, median (Q1:Q3)	63.30 (27.00:120.22)	59.98 (27.15:114.00)	61.60 (27.00:115.60)	45.60 (30.10:93.00)	52.31 (22.00:112.00)	52.21 (24.36:103.25)
Serostatus, n (%)						
Seronegative	246 (38.9)	553 (42.3)	799 (41.2)	19 (54.3)	49 (76.6)	68 (68.7)
Seropositive	342 (54.0)	652 (49.9)	994 (51.2)	15 (42.9)	10 (15.6)	25 (25.3)
Presence of neutralizing antibodies in seropositive patients, n/N (%)	255/342 (74.6)	499/652 (76.5)	754/994 (75.9)	7/15 (46.7)	7/10 (70.0)	14/25 (56.0)
Patient cohorts, n (%)						
Low-flow supplemental oxygen (cohort 1)[b]	407 (64.3)	822 (62.9)	1229 (63.4)	17 (48.6)	25 (39.1)	42 (42.4)
No supplemental oxygen (cohort 1A)	170 (26.9)	360 (27.5)	530 (27.3)	17 (48.6)	38 (59.4)	55 (55.6)
High-intensity supplemental oxygen (cohort 2)[c]	46 (7.3)	102 (7.8)	148 (7.6)	1 (2.9)	1 (1.6)	2 (2.0)
Mechanical ventilation (cohort 3)	10 (1.6)	23 (1.8)	33 (1.7)	0	0	0

[a]Evaluated at the central laboratory; [b]Maintains O_2 saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or other similar device; [c]High-intensity oxygen therapy without mechanical ventilation, where high intensity is defined as receiving supplemental oxygen delivered by one of the following devices: 1) non-rebreather mask (with an SpO_2 ≤96% while receiving an oxygen flow rate of at least 10 L/min); 2) high-flow device (e.g., AIRVO™ or Optiflow™) with at least 50% FiO_2; 3) non-invasive ventilator, including continuous positive airway pressure. BMI, body mass index; CAS+IMD, casirivimab and imdevimab; CRP, C-reactive protein; SD, standard deviation.

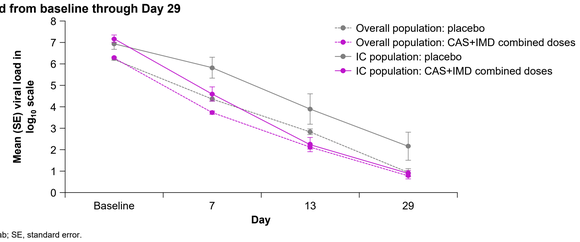
Viral load

- IC patients receiving placebo had slower viral load declines compared with patients receiving placebo in the overall population (**Figure 1**).
  - The slope of the line from baseline to Day 7 for the placebo group was -0.32 in the overall population, and -0.16 in the IC population; as expected, these differences in the slopes were not apparent by Day 29.
- Treatment with CAS+IMD (combined dose group) in IC patients led to a reduction in viral load from baseline that was numerically greater than that observed in the overall population (**Figure 1**):
  - Least-squares mean time-weighted average change in viral load difference versus placebo at Day 7 and at Day 29 was -0.69 (95% confidence interval [CI]: -1.25, -0.41) and -1.53 (95% CI: -2.40, -0.66) for IC patients compared to -0.31 (95% CI: -0.42, -0.20) and -0.47 (95% CI: -0.63, -0.31) for the overall population, respectively.

Death or mechanical ventilation

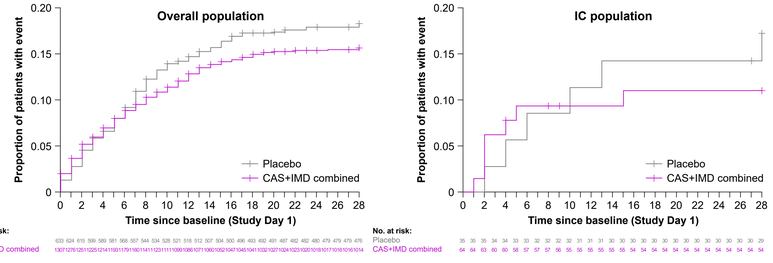
- Cumulative incidence of death or mechanical ventilation in both the IC and overall populations is shown in **Figure 2**.
- Although there were relatively few events in the IC population, trends in clinical outcome of death or mechanical ventilation at Day 29 for IC patients (CAS+IMD 7/64 [11.0%] vs placebo 6/35 [17.2%]) were consistent with those in the overall population (CAS+IMD 200/1307 [15.7%] vs placebo 113/633 [18.3%]).

Figure 1. Mean viral load from baseline through Day 29



CAS+IMD, casirivimab and imdevimab; SE, standard error.

Figure 2. Cumulative incidence of death or mechanical ventilation



Safety

- IC patients treated with CAS+IMD (combined dose) exhibited similar rates of the following events compared to patients treated with CAS+IMD in the overall population, respectively (**Table 3**):
  - Treatment emergent adverse events: 21/69 (30.4%) versus 392/1473 (26.6%); and lower than placebo
  - Adverse events of special interest, defined as grade ≥2 hypersensitivity or infusion-related reactions: 1/69 (1.4%) versus 37/1473 (2.5%)
  - Deaths: 6/69 (8.7%) versus 179/1473 (12.2%); and comparatively lower than placebo
- Both IC patients and overall study patients exhibited fewer treatment emergent adverse events when treated with CAS+IMD versus placebo.

Table 3. Overview of treatment-emergent adverse events

	Overall population		IC population	
n, (%)	Placebo (n=730)	CAS+IMD combined doses (n=1473)	Placebo (n=37)	CAS+IMD combined doses (n=69)
Patients with any TEAE	209 (28.6)	392 (26.6)	17 (45.9)	21 (30.4)
Patients with any TE SAE	203 (27.8)	358 (24.3)	17 (45.9)	20 (29.0)
Patients with any TE AESI[a]	8 (1.1)	37 (2.5)	0	1 (1.4)
Patients with any TE AESI of infusion-related reactions (grade ≥2) through Day 4	6 (0.8)	26 (1.8)	0	1 (1.4)
Patients with any TE AESI of hypersensitivity reactions (grade ≥2) through Day 4	0	8 (0.5)	0	0
Patients with any TE AESI of hypersensitivity reactions (grade ≥2) through Day 29	2 (0.3)	12 (0.8)	0	0
Patients with any TEAE leading to death	107 (14.7)	179 (12.2)	5 (13.5)	6 (8.7)

[a]Defined as grade ≥2 hypersensitivity or infusion-related reactions. AESI, adverse event of special interest; CAS+IMD, casirivimab and imdevimab; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Conclusion

- IC patients hospitalized with COVID-19 were more likely to exhibit high viral loads at baseline, to be SARS-CoV-2 seronegative, and their endogenous antibodies were less likely to neutralize SARS-CoV-2 compared to the overall study population.
- In this study, a single dose of CAS+IMD significantly reduced viral load (for variants circulating at the time, predominantly Alpha) in IC patients and resulted in lower incidences of death or mechanical ventilation.
- The safety profile between the IC and overall study population was comparable, and no new safety findings were observed in the IC population.

References

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Abbreviations

AESI, adverse event of special interest; CAS+IMD, casirivimab and imdevimab; CI, confidence interval; CRP, C-reactive protein; IC, immunocompromised; IV, intravenous; LS, least-squares; mFAS, modified full analysis set; NP, nasopharyngeal; SAE, serious adverse event; SAF, safety analysis set; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; TE SAE, treatment-emergent serious adverse event; TWA, time-weighted average.

Disclosures

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