EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2023
EMA/CHMP/68947/2023
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Invented name: Ronapreve

International non-proprietary name: casirivimab / imdevimab

Procedure No. EMEA/H/C/005814/II/0002

Marketing authorisation holder (MAH) Roche Registration GmbH

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| | |
|---|---|
| ACE2 | angiotensin-converting enzyme 2 |
| ADA | anti-drug antibody |
| ADE | antibody-dependent enhancement |
| ADR | adverse drug reaction |
| AE | adverse event |
| AESI | adverse event of special interest |
| AUC | area under the concentration-time plot |
| AUC28 | area under the concentration-time curve from time 0 to Day 28 |
| AUC | inf area under the concentration-time curve from time 0 extrapolated to infinity time |
| CDC | United States Centers for Disease Control and Prevention |
| CI | confidence interval |
| CL | individual predicted clearance |
| C28 | serum concentration on Day 28 following single dose |
| Cmax | maximum serum concentration |
| Cs, | target target drug concentration in serum required to achieve IC90 in respiratory tract fluids |
| CHMP | Committee for Medicinal Products for Human Use |
| COVID-19 | Coronavirus disease 2019 |
| CP | clinical pharmacology |
| CPAP | continuous positive airway pressure |
| CRP | c-reactive protein |
| CSR | clinical study report |
| CUP | compassionate use program |
| ECDC | European Centre for Disease Prevention and Control |
| eCRF | electronic case report form |
| ELF | epithelial lining fluid |
| EMA | European Medicines Agency |
| EOI | end of infusion |
| ESAF | early safety population |
| EUA | emergency use authorization |
| EU | European Union |
| FAS | full analysis set |
| FDA | US Food and Drug Administration |
| FDS | formulated drug substance |
| GM-CSF | granulocyte-macrophage colony-stimulating factor |
| IC90 | concentrations necessary for 90% inhibition |
| ICU | intensive care unit |
| IDMC | Independent Data Monitoring Committee |
| IQR | interquartile range |
| IRR | infusion-related reactions |
| ISR | Injection site reactions |
| ITT | intent-to-treat |
| IV | intravenous |
| MA | marketing authorization |
| mAb | monoclonal antibody |
| mFAS | modified full analysis set |
| NAb | neutralizing antibodies |
| NERVTAG | New and Emerging Respiratory Virus Threats Advisory Group |
| NF | nasopharyngeal fluid |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NP | nasopharyngeal |
| OR | odds ratio |
| PD | pharmacodynamic |
| PK | pharmacokinetic(s) |
| Pop-PK | population pharmacokinetic |
| PT | preferred term |
| PTE | potentially treatment-emergent |
| RBD | receptor binding domain |
| RMP | risk management plan |

| | |
|---|---|
| RNA | ribonucleic acid |
| RR | rate ratio |
| RRR | relative risk reduction |
| RT-PCR | reverse transcription polymerase chain reaction (test) |
| RT-qPCR | quantitative reverse transcription polymerase chain reaction (test) |
| S | spike protein of the SARS-CoV-2 virus |
| SAE | serious adverse event |
| SAF | safety analysis set |
| SARS-CoV | severe acute respiratory syndrome coronavirus |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SC | subcutaneous |
| SBP | summary of biopharmaceutics and analytical methods |
| SCE | summary of clinical efficacy |
| SCP | summary of clinical pharmacology |
| SCS | summary of clinical safety |
| SD | standard deviation |
| SmPC | summary of product characteristics |
| SSAR | suspected serious adverse reactions |
| suPAR | soluble urokinase plasminogen activator receptor |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| TWA | time weighted average |
| VAS | variant analysis set |
| VL | viral load |
| VOC | variants of concern |
| VOI | variants of Interests |
| VUS | variants under Surveillance |
| WHO | World Health Organization |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 28 January 2022 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |

Extension of indication to include treatment of COVID-19 in hospitalised patients in adults and adolescents aged 12 years and older weighing at least 40 kg for Ronapreve; as a consequence, sections 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 1.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0044/2022) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0044/2022 was not yet completed as some measures were deferred.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *MAH request for additional market protection*

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

## *Scientific advice*

The MAH did not seek Scientific Advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Jayne Crowe

| Timetable | Actual dates |
|---|---|
| Submission date | 28 Jan 2022 |
| Start of procedure: | 19 Feb 2022 |
| CHMP Co-Rapporteur Assessment Report | 14 April 2022 |
| CHMP Rapporteur Assessment Report | 14 April 2022 |
| PRAC Rapporteur Assessment Report | 14 April 2022 |
| PRAC members comments | 26 April 2022 |
| PRAC Outcome | 5 May 2022 |
| CHMP members comments | 6 May 2022 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 12 May 2022 |
| Request for supplementary information (RSI) | 19 May 2022 |
| CHMP Rapporteur Assessment Report | 19 Sep 2022 |
| PRAC members comments | 21 Sep 2022 |
| PRAC Outcome | 29 Sep 2022 |
| CHMP members comments | 03 Oct 2022 |
| Updated CHMP Rapporteur Assessment Report | 7 Oct 2022 |
| Request for supplementary information (RSI) | 13 Oct 2022 |
| CHMP Rapporteur Assessment Report | 24 Jan 2023 |
| PRAC Rapporteur Assessment Report | 27 Jan 2023 |
| PRAC members comments | 1 Feb 2023 |
| PRAC Outcome | 9 Feb 2023 |
| CHMP members comments | 14 Feb 2023 |
| Updated CHMP Rapporteur Assessment Report | 16 Feb 2023 |
| Request for supplementary information (RSI) | 23 Feb 2023 |
| PRAC Rapporteur Assessment Report | 3 April 2023 |
| CHMP Rapporteur Assessment Report | 5 April 2023 |
| Opinion | 26 April 2023 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

### *Disease or condition*

SARS-CoV-2 is a novel ribonucleic acid (RNA) betacoronavirus initially identified from patients experiencing atypical pneumonia in Wuhan City, China (Zhu, 2020).

Infection with SARS-CoV-2 may be asymptomatic or it may cause a wide spectrum of illness, ranging from a mild upper respiratory tract infection to severe acute respiratory distress syndrome and multiple organ failure (Wiersinga et al. 2020). Severe/critical COVID-19 is associated with high mortality and places extensive burdens on hospital resources including high dependency and intensive care units (ICU) to provide mechanical ventilation and other advanced forms of life support (Guan et al. 2020; Yang et al. 2020).

## *State the claimed the therapeutic indication*

Treatment of COVID-19 in hospitalised patients in adults and adolescents aged 12 years and older weighing at least 40 kg.

## *Epidemiology and risk factors, screening tools/prevention*

The 2019 novel coronavirus disease 2019 (COVID-19) outbreak has been categorized as a pandemic by the WHO since March 2020, which has resulted in approximately 767,750,853 cumulative cases globally with more than 2.2 million deaths reported across the EU region (https://covid19.who.int / last accessed June 2023). There have been approximately 276 million cases in Europe with 6.9 million cumulative deaths reported globally.

The majority of patients with SARS-CoV-2 infection exhibit relatively mild symptoms or are asymptomatic (Hu, 2020; Oran et al. 2020), especially considering the widespread vaccination efforts and high efficacy of currently available vaccines. However, vaccines are not 100% effective and there have been reports of breakthrough infections that result in hospitalization. Although it is expected that the majority of breakthrough infections are likely to be mild to moderate, those considered high risk or those coming to the end of their vaccine immunity remain susceptible to severe disease. Furthermore, those that choose not to be vaccinated remain at risk with higher levels of morbidity and mortality.

As of 20 April 2023, following ECDC data, in EU/EEA countries, approximately, 75.6% of the population has received at least 1 dose of vaccine against COVID-19 and 54.8% a first booster, leaving around 24.4 % population unvaccinated. https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab

## *Biologic features*

SARS-CoV-2 infection is initiated by binding of the viral transmembrane spike glycoprotein to angiotensin converting enzyme 2 (ACE2) on the surface of host cells. The receptor binding domain of the spike glycoprotein is, consequently, the main target for neutralising antibodies.

Studies among hospitalized patients have found that high SARS-CoV-2 viral load is associated with worse outcomes, including increased mortality rates (Magleby et al. 2020) (Westblade et al. 2020). Community-based studies in non-hospitalized patients show symptomatic patients have higher viral load across both adults and children compared to asymptomatic individuals (Chung et al. 2021). Natural history observations of COVID-19 in the placebo arm across all studies in the Ronapreve clinical development program demonstrate that the burden of disease following SARS-CoV-2 infection is associated with high viral load (initial MAA, Module 2.7.3). This association has been reported repeatedly throughout the pandemic, with numerous studies showing the strong association between high viral load and worse outcomes for infectivity, disease phenotype, morbidity and mortality (Magleby et al. 2020) (Néant et al. 2021) (Westblade et al. 2020).

## *Prevention*

Prevention measures include infection control consisting of widespread vaccination efforts, and non-therapeutic based approaches such as quarantining, social and physical distancing, and wearing

masks. At time of the submission, five vaccines had marketing authorization (MA) in the EU (Comirnay, Spikevax, Vaxzevria, Jcovden, Nuvaxovid) being 3 more approved along the procedure (Valneva, Vidprevtyn Beta and Bimervax).

## *Clinical presentation, diagnosis and stage/prognosis*

The majority of patients with SARS-CoV-2 infection exhibit relatively mild symptoms or are asymptomatic (Hu, 2020; Oran et al. 2020).

Approximately 15% of COVID-19 patients develop severe symptoms characterized by the same clinical signs of mild to moderate COVID-19 and with one of the following: respiratory rate (≥30 breaths/minute); severe respiratory distress; or hypoxia requiring hospitalization and oxygen support (WHO 2020a) (Cascella et al. 2021). In approximately 5% of infected patients, the severe form of interstitial alveolar damage may rapidly progress to critical manifestations of the disease characterized by respiratory failure associated with acute respiratory distress syndrome that necessitates mechanical ventilation and support in an ICU. Complications include sepsis, septic shock and/or multi-organ failure including acute kidney and cardiac injury, and even death (WHO 2020a).

## *Management*

Initially, treatment of COVID-19 was largely supportive in the outpatient or hospitalized setting and included the use of antipyretics, fluids, antibiotics if bacterial secondary or co-infection was suspected, and supplemental oxygen. Further treatments have been developed for the treatment of COVID-19 including both symptomatic and anti-viral therapies and the section below presents a non-exhaustive overview of these treatments.

Remdesivir (Veklury), an antiviral treatment, was granted conditional approval by EMA on 25 June 2020, for use in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen. The recommendation was mainly based on data from Study NIAID-ACTT-1, sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID), that showed that treatment with remdesivir resulted in clinically meaningful improvements across multiple outcome assessments (including shortening the time to recovery) compared with placebo in hospitalized patients with COVID-19 (Beigel et al. 2020).

On the 11 November 2021, the CHMP issued a positive scientific opinion recommending marketing authorization for regdanvimab, a monoclonal antibody treatment for adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

On the 16 December 2021, the CHMP issued a positive scientific opinion recommending approval of a Type II variation extending the use of Kineret (anakinra) to include treatment of COVID-19 in adult patients with pneumonia requiring supplemental oxygen (low or high flow oxygen) and who are at risk of developing severe respiratory failure, as determined by blood levels of a protein called soluble urokinase plasminogen activator receptor (suPAR) of at least 6 ng per ml.

On the 17 December 2021, the CHMP issued a positive scientific opinion recommending authorization for sotrovimab.

Another monoclonal antibody against COVID-19, Evusheld, reached positive scientific opinion in March 2022.

Molnupiravir became available with emergency use authorization (EUA) status in US (molnupiravir, 23 December 2021) and UK Conditional Approvals (molnupiravir 4 November 2021), for treatment of outpatients with COVID-19. This product was also subject to Article 5(3) assessments in the EU in November 2022 and it is under review for marketing authorization.

Another oral treatment, nirmatrelvir/ritonavir reached positive opinion in January 2022.

In the hospitalized setting, the treatment of severe COVID-19 has primarily targeted the management of hyper-inflammatory responses. The EMA endorsed use of dexamethasone (a corticosteroid) in COVID-19 patients on oxygen or on mechanical ventilation on 18 September 2020 (EMA 2020a). On 6 December 2021, EMA recommended extending the indication of tocilizumab, an IL-6 receptor antagonist, to include the treatment of adults with COVID-19 who are receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation (EMA 2021b).

Futhermore, RoActemra ( tocilizumab) was approved for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Given the continuum of risk of disease with SARS-CoV-2, multiple ongoing global waves of infection and the limited treatment options available for patients hospitalized with COVID-19, there remains a substantial unmet need for more effective therapies which neutralize SARS-CoV-2 viral replication and:

- prevent the progression of disease, or
- reduce the need for more invasive ventilator support therapy, or
- reduce the risk of death related to COVID-19.

Vaccination is the mainstay of prevention of COVID-19 and although vaccination reduces the relative risk of severe COVID-19, the absolute risk remains substantial in high-risk patients who have been exposed to the virus (Munro et al. 2021). There are patient populations for whom vaccination could not prevent, or is unlikely to be effective in preventing, COVID-19, i.e., those with primary or secondary immunodeficiencies (e.g. solid organ transplant recipients, those receiving B-cell depleting therapies etc.). As transmission rates increase, those who are fully vaccinated and immunodeficient remain at risk and can still develop severe COVID-19 with breakthrough infections requiring hospitalization (Munro et al. 2021, Lontok 2021). This is further compounded by the circulation of new variants which may not remain susceptible to vaccine immunity.

Finally, the long-term effectiveness of vaccines is currently under investigation and remains uncertain. Recently, booster strategies have been required to continue to protect individuals from COVID-19 and it is likely that subgroups of the population may continue to require booster doses to remain protected. It is highly likely that SARS-CoV- 2 will continue to evolve and transmit given the mechanism of action of all available vaccines which provide neutralizing but not sterilizing immunity. This remains a major concern for the fight against SARS-CoV-2. A long-term vaccination strategy will most likely be required, should SARS-CoV-2 continue to evolve and cause high levels of morbidity and mortality

### 2.1.2. About the product

Casirivimab and imdevimab (also referred to as Ronapreve, REGEN-COV, REGN-COV, REGN-COV2 and REGN-COV-2) are 2 human, high affinity, IgG1 mAbs that bind non-overlapping epitopes on the receptor binding domain (RBD) of the SARS-CoV-2 S protein and block interaction with ACE2 and consequently blocking viral entry into host cells. These mAbs are non-competing with one another, exhibit potent neutralization and can bind simultaneously to the S protein RBD.

When co-administered as combination therapy, casirivimab+imdevimab treatment neutralizes SARS-CoV-2 in cell culture, minimizes the likelihood of viral escape due to genetic mutations and prevents and treats infection in animal models (MAA, Module 2.4).

### 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

To evaluate the safety and efficacy of casirivimab+imdevimab broadly across the SARSCoV- 2 infection and COVID-19 spectrum, the clinical development program for casirivimab+imdevimab employed multiple trials comprised consisting of different participant populations, including adolescents and adults with or without risk factors for severe COVID-19, in the outpatient and hospitalized settings.

### 2.1.4. General comments on compliance with GCP

The applicant provided a statement to the effect that R10933-10987-COV-2066 conducted outside of the European Union complies with the ethical requirements of Directive 2011/20/EC as amended and NCT04381936 (RECOVERY) is conducted in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines and approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and given a favourable opinion by the Cambridge East Research Ethics Committee (ref: 20/EE/0101).

Clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

List of countries involved in each study:

| Study Number | EU Countries | Non-EU Countries |
|---|---|---|
| R10933-10987-COV-2066 | Romania | Brazil<br>Chile<br>Moldova<br>USA |
| NCT04381936 (RECOVERY) | N/A | United Kingdom |
| N/A=not applicable | | |

## *2.2. Non-clinical aspects*

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity/environmental risk assessment

Not applicable.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

- Tabular overview of clinical studies

The current application is supported by two clinical studies, an overview of the clinical studies that contribute data to this application is provided in the table below:

| Study Population | Study Design | Number of Randomized Participants | Dose, Route, and Regimen | Study Duration/ Study Status |
|---|---|---|---|---|
| RECOVERY | | | | |
| Hospitalized patients ≥12 years of age with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Pregnant or breastfeeding women were eligible for study inclusion. | Phase 3, adaptive, factorial, randomized, controlled, open-label, platform trial. | Casirivimab+imdevimab plus Usual Care<br>N=4839<br>1. Seronegative at baseline: n=1633<br>2. Seropositive at baseline: n=2636<br>3. Unknown serostatus at baseline: n=570<br>Usual Care alone: n=4946<br>4. Seronegative at baseline: n=1520<br>5. Seropositive at baseline: n=2636<br>Unknown serostatus at baseline: n=790 | Casirivimab+imdevimab plus Usual Care:<br>Casirivimab+imdevimab 8000 mg (4000 mg of each mAb), single dose IV infusion over 60 minutes.<br>Usual Care alone:<br>Usual standard of care. | 18 September 2020 to 22 May 2021[a]<br>Upon recommendation from the Trial's Steering Committee, recruitment into the casirivimab+imdevimab comparison was stopped on 22 May 2021. Based on the number of patients recruited and the overall number of events observed for the primary and secondary outcome measures, it was determined that the trial had sufficient power to detect plausible treatment effects. Casirivimab+imdevimab was subsequently removed from the protocol on 5 July 2021 (Amendment 16.0). |

| Study Population | Study Design | Number of Randomized Participants | Dose, Route, and Regimen | Study Duration/ Study Status |
|---|---|---|---|---|
| COV-2066 | | | | |
| Adult and adolescent patients ≥18 years of age, hospitalized for ≤72 hours at screening, who have a positive diagnostic test for SARS-CoV-2, on varying degrees of oxygen support at randomization. | Phase 1/2/3 adaptive, randomized, double-blinded, placebo-controlled master study. | Casirivimab+imdevimab 2400 mg IV: 757 patients<br>Casirivimab+imdevimab 8000 mg IV: 750 patients<br>Placebo: 745 patients | Phase 1, 2 and 3: In addition to background standard of care, patients in each cohort were randomized in a 1:1:1 allocation ratio to one of the following:<br>• casirivimab+imdevimab 2400 mg (1200 mg of each mAb) IV single dose<br>• casirivimab+imdevimab 8000 mg (4000 mg of each mAb) IV single dose<br>• Placebo IV single dose | 10 June 2020 to 9 April 2021[b]<br>Phase 1/2 safety and efficacy data were previously described in an abbreviated interim CSR (COV-2066 Abbreviated Interim CSR, 2021) finalized on 15 Jun 2021. The interim analysis was performed on patients who were randomized through 1 December 2020 in Phase 1 (Cohort 1 only) and Phase 2 (Cohorts 1, 2, and 3), using a data cut-off date of 9 December 2020 and a database lock date of 22 December 2020.<br><br>The final CSR (COV-2066 Final CSR, 2021) describes results from the final analyses of the study, including all phases and all cohorts based on a database lock date of 08 June 2021. This represents the final data for the main study. |

CSR = clinical study report; IV = intravenous; mAb = monoclonal antibody.

[a] For the casirivimab+imdevimab treatment evaluation. All randomized patients were to be followed-up until death, discharge from hospital, or 28 days after randomization (whichever occurred sooner). Additional information on longer term outcomes after 28-days post randomization could have been collected through review of medical records or linkage to medical databases where available, but this data was not available at the time of this submission.

[b] A subset of patients from Cohorts 1 and 1A at select study sites were enrolled in an ongoing long COVID sub-study, but this data was not available at the time of this submission.

## 2.3.2. Pharmacokinetics

In the context of this variation procedure, the following to-be-marketed dosage in adult and adolescent patients (12 years of age and older weighing at least 40 kg) who require supplemental oxygen is foreseen:

- 4000 mg of casirivimab and 4000 mg of imdevimab administered together as a single IV infusion for patients who are on low-flow or high-flow oxygen devices, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

**Study COV-2066**

The clinical pharmacology program for this submission is supported by data from COV-2066 only and by population PK (pop-PK) analyses from data pooled from several studies included in the Marketing Authorization Application. No PK data was collected from RECOVERY.

Summary of studies contributing to PK, IG and PD evaluation:

| Study Number (Phase) | Study Design | Population | No. of Patients Evaluable for PK and IG | No. of Patients Evaluable for PD | Dose, Route, and Regimen |
|---|---|---|---|---|---|
| COV-2066 (Phase 1/2/3) | Adaptive, randomized, double-blinded, placebo-controlled master study | Adult participants ≥18 years of age, symptomatic for COVID-19 and hospitalized for ≤72 hours with varying degrees of oxygen support at randomization | 2203 | 2203 | Casirivimab+imdevimab IV 2.4 g single dose or placebo<br>Casirivimab+imdevimab IV 8.0 g single dose or placebo |

ADA=anti-drug antibody; COVID-19= coronavirus disease 2019; IG=immunogenicity; IV=intravenous; PD=pharmacodynamics; PK=pharmacokinetics.

Study COV-2066 was an adaptive, Phase 1/2/3, randomized, double-blinded, placebo-controlled study in hospitalized adult patients with four cohorts in the study according to disease severity.

| Study Cohort | Description |
|---|---|
| Cohort 1A | With COVID-19 symptoms, but not requiring supplemental oxygen |
| Cohort 1 | $O_2$ saturation >93% on low flow oxygen via nasal cannula, simple face mask, or other similar device |
| Cohort 2[a,b] | On high-intensity oxygen therapy but not on mechanical ventilation |
| Cohort 3[a] | On mechanical ventilation(not including those on ECMO) |

COVID-19= coronavirus disease 2019; ECMO= extracorporeal membrane oxygenation.

[a] Enrollment in Cohort 2 and Cohort 3 was placed on hold on 30 October 2020 per independent Data Monitoring Committee (iDMC) recommendation.

[b] High-intensity oxygen therapy is defined as the use of non-rebreather mask with an oxygen flow rate of at least 10 L/min; use of a high flow device with at least 50% $FiO_2$, or use of non-invasive ventilation to treat hypoxemia.

Enrolment in Cohort 2 and 3 was placed on hold during Phase 2 recruitment. Patients were randomized in each cohort and each phase to receive a single IV dose of 2400 mg, 8000 mg or placebo in a 1:1:1 ratio (see table below). Immunogenicity, as measured by ADAs and Nabs, was accessible (all phases combined + placebo) in 1504 patients. PK samples were collected: Phase1 - at pre-dose and post-dose (within 60 minutes after the end of infusion) on study Day 1, at discharge before Day 29, on Days 3, 5, 7, 15, 29, 57, and 113 over the hospitalization/post-discharge period, and at End of Study on Day 29; Phase 2 and 3: at pre-dose and post-dose (within 60 minutes after the end of infusion) on Day 1, at discharge before Day 29, and on Days 15 and 29 over the hospitalization/post-discharge period.

**Overview of COV-2066 Study Design to Evaluate Pharmacokinetics, Pharmacodynamics, and Immunogenicity for Casirivimab+Imdevimab**

| Study | PK- and ADA-Related Endpoints | Study Design and Duration | Treatment: Route of Administration, Frequency and Dose, Number of patients analyzed for PK/ADA/Nab |
|---|---|---|---|
| R10933-10987-COV-2066 | 1. Concentrations of casirivimab and imdevimab in serum and corresponding PK parameters<br><br>2. Immunogenicity, as measured by ADAs and NAbs to casirivimab and imdevimab | PK collected at:<br>**Phase 1**, at pre-dose and post-dose (within 60 minutes after the end of infusion) on study Day 1, at discharge before Day 29, on Days 3, 5, 7, 15, 29, 57, and 113 over the hospitalization/post-discharge period, and at End of Study on Day 29.<br>ADA: at pre-dose, at discharge before Day 29, on Days 29, 57, 169<br>NP VL – at predose and postdose (within 60 minutes after the end of infusion) on study Day 1, at discharge before Day 29, on Days 3, 5, 7, 9, 11, 13, 15, 22, 29.<br><br>**Phase 2 and 3:** at pre-dose and post-dose (within 60 minutes after the end of infusion) on Day 1, at discharge before Day 29, and on Days 15 and 29 over the hospitalization/post-discharge period.<br><br>ADA: at pre-dose, at discharge before Day 29, on Days 29, 57, 169<br><br>NP VL – at pre-dose and post-dose (within 60 minutes after the end of infusion) on study Day 1, at discharge before Day 29, on Days 3, 5, 7, 9, 11, 13, 15, 22, 29. | Single IV dose:<br>Casirivimab 1200 mg<br>Imdevimab 1200 mg<br>Casirivimab 4000 mg<br>Imdevimab 4000 mg<br><br>**Phase 1 PK:**<br>• Cohort 1 (active treatment): PK – 17 (2400 mg[a]) + 20 (8000 mg[a]) patients<br><br>**Phase 2 PK:**<br>• Cohort 1A (active treatment): PK – 178 (2400 mg[a]) + 170 (8000 mg[a]) patients<br>• Cohort 1 (active treatment): PK – 187 (2400 mg[a]) + 183 (8000 mg[a]) patients<br>• Cohort 2 (active treatment): PK – 56 (2400 mg[a]) + 53 (8000 mg[a]) patients<br>• Cohort 3 (active treatment): PK – 12 (2400 mg[a]) + 11 (8000 mg[a]) patients<br><br>ADA (all phase combined + placebo) - 1504 patients<br><br>Nabs (Phase 2/3 + placebo) - 1478 patients |

ADA = anti-drug antibody; NAbs = neutralizing antibodies; NP VL = nasopharyngeal viral load; PK = pharmacokinetic.

[a] Casirivimab+Imdevimab combined IV dose

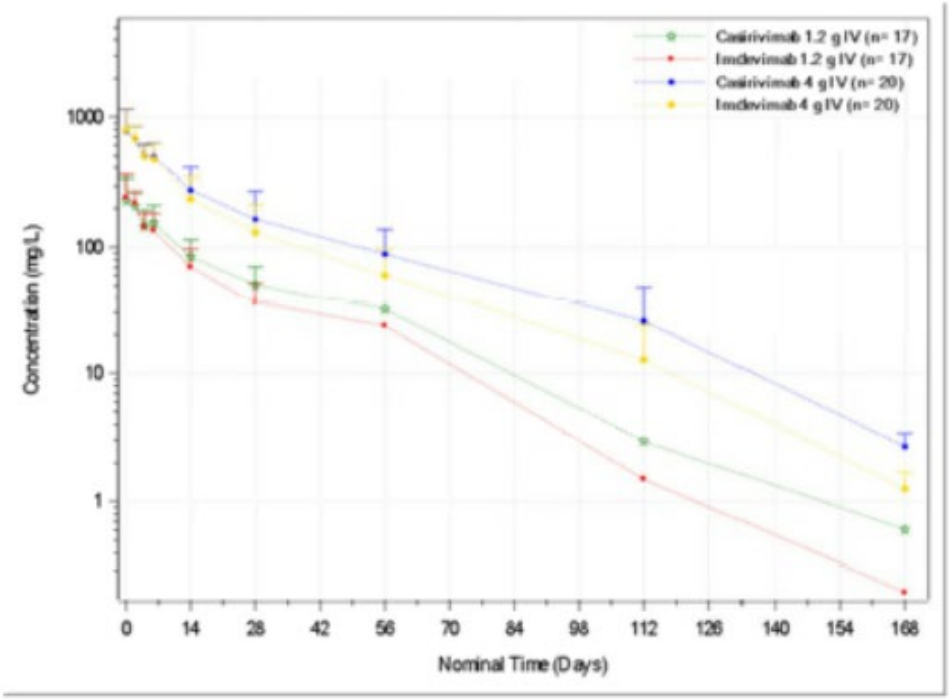
Source: Clinical Pharmacology (CP) Report R10933-10987-COV-2066-CP-01V1, Table 5, 6, 12, and 13.

***Phase 1***

Casirivimab and imdevimab concentration-time profiles in serum following 1.2 g and 4.0 g single IV doses of each antibody (2.4 g and 8.0 g combined doses, respectively) in Phase 1 showed a profile consistent with linear pharmacokinetics, defined by an initial distribution phase followed by a terminal mono-exponential elimination phase (see figure below). Peak serum concentrations for each antibody were generally achieved at around EOI. Due to small patient numbers and variability of concentrations

in the terminal phase, mono-exponential decline is not clearly discernible in the mean concentration-time profiles.

**Figure 1 Mean (+SD) Concentrations of Casirivimab and Imdevimab in Serum by Treatment Group and Nominal Time in Hospitalized Adult Patients with COVID-19 (Log-Scaled, Phase 1 Cohort 1, PKAS)**




| Treatment | EOI | D2 | D4 | D6 | D14 | D28 | D56 | D112 | D168 |
|---|---|---|---|---|---|---|---|---|---|
| Casirivimab 1.2 g IV | 15 | 10 | 7 | 10 | 10 | 9 | 2 | 2 | 2 |
| Imdevimab 1.2 g IV | 15 | 10 | 7 | 10 | 10 | 9 | 2 | 2 | 2 |
| Casirivimab 4 g IV | 20 | 11 | 10 | 11 | 10 | 9 | 4 | 4 | 3 |
| Imdevimab 4 g IV | 20 | 11 | 10 | 11 | 10 | 9 | 4 | 4 | 3 |

BLQ=below the limit of quantitation; D=day; EOI=end of infusion; IV=intravenous; LLOQ=lower limit of quantitation; n=number of patients; PKAS=pharmacokinetic analysis set; SD=standard deviation.

Notes: BLQs were set to LLOQ/2. Pre-infusion concentrations are not presented.

Number of participants per timepoint, per treatment group is tabulated.

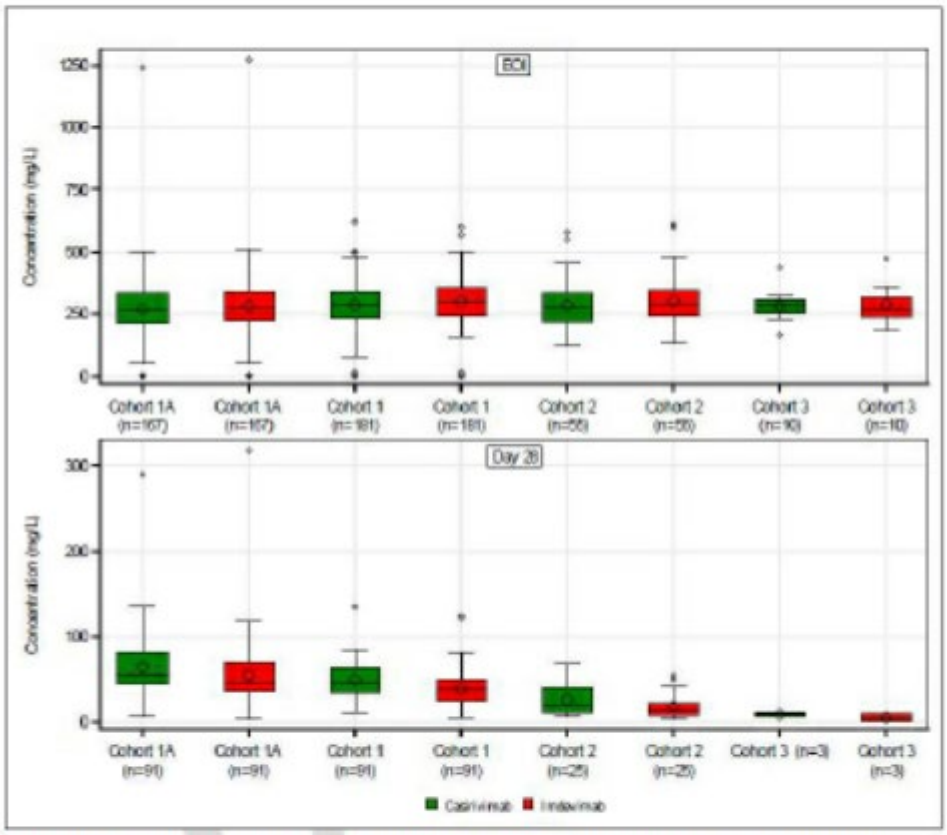
Source: R10933-10987-COV-2066, Appendix 16.1.15, Figure 1.

**Phase 2 and 3**

Casirivimab and imdevimab concentrations in serum following 1.2 g and 4.0 g single doses of each antibody were similar to each other at the EOI as well as on Day 28 in Phase 2 and in Phase 3 for each cohort of patients (see tables and figures below).

**Phase 2:**

**Figure 2 Box and Whisker Plot of Concentrations of Casirivimab and Imdevimab in Serum at EOI and Day 28 for 2.4 g IV Casirivimab+Imdevimab Dose (1.2 g per mAb) in Hospitalized Adult Patients with COVID-19 (Study R10933-10987-COV-2066, Phase 2, PKAS)**

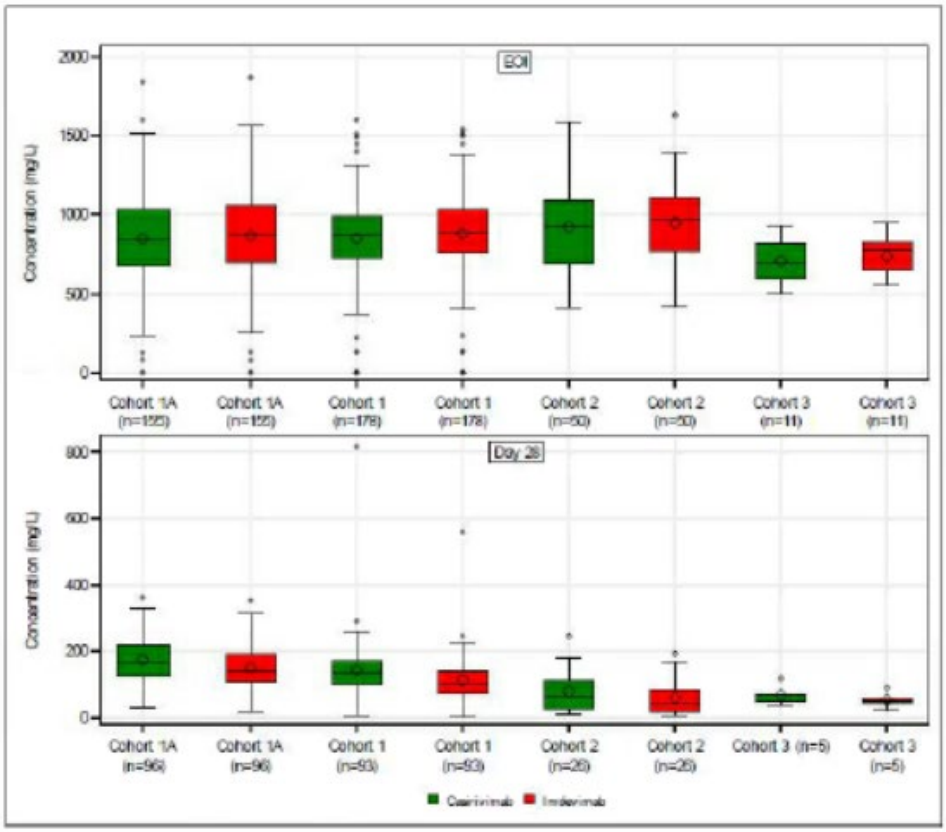



BLQ=below the limit of quantitation; EOI=end of infusion; IV=intravenous; n=number of patients; PKAS=pharmacokinetic analysis set; Q=quartile.

Notes: BLQs were set to 0.

Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence respectively; circles are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.

**Figure 3 Box and Whisker Plot of Concentrations of Casirivimab and Imdevimab in Serum at EOI and Day 28 for 8.0 g IV Casirivimab+Imdevimab Dose (4.0 g per mAb) in Hospitalized Adult Patients with COVID-19 (Study R10933-10987-COV-2066, Phase 2, PKAS)**




BLQ=below the limit of quantitation; EOI=end of infusion; IV=intravenous; n=number of patients; PKAS=pharmacokinetic analysis set; Q=quartile.

Notes: BLQs were set to 0.

Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence respectively; circles are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR=Q3 - Q1.

**Summary of Concentrations of Casirivimab, Imdevimab and Casirivimab+Imdevimab Combined in Serum by Time, Treatment Group and Cohort in Hospitalized Adult Patients with COVID-19 (Study R10933-10987-COV-2066, Phase 2, PKAS)**

**Casirivimab+Imdevimab 2.4 g IV**

| | Concentration of | | | | | |
|---|---|---|---|---|---|---|
| | Casirivimab (mg/L) (N=448) | | Imdevimab (mg/L) (N=448) | | Casirivimab and Imdevimab (mg/L) (N=448) | |
| Nominal Sampling Time Post First Dose (Days) Timepoint | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) |
| Cohort 1A | | | | | | |
| 0 | | | | | | |
| Pre-dose | 178 | 11.5 (69.7) | 178 | 9.66 (57.6) | 178 | 21.2 (127) |
| End of Infusion | 167 | 272 (124) | 167 | 283 (127) | 167 | 554 (249) |
| 14 | 81 | 87.7 (32.0) | 81 | 78.0 (30.3) | 81 | 166 (61.7) |
| 28 | 91 | 64.8 (35.9) | 91 | 54.7 (37.6) | 91 | 119 (73.1) |
| Discharge before Day 29 | 97 | 180 (65.3) | 97 | 175 (67.0) | 97 | 356 (131) |
| Cohort 1 | | | | | | |
| 0 | | | | | | |
| Pre-dose | 187 | 2.16 (25.5) | 187 | 1.62 (18.3) | 187 | 3.78 (43.8) |
| End of Infusion | 181 | 288 (86.8) | 181 | 300 (87.3) | 181 | 588 (170) |
| 14 | 90 | 82.6 (34.0) | 90 | 72.4 (31.4) | 90 | 155 (64.6) |
| 28 | 91 | 50.0 (20.4) | 91 | 39.8 (18.9) | 91 | 89.8 (38.7) |
| Discharge before Day 29 | 120 | 158 (69.0) | 120 | 147 (67.3) | 120 | 306 (135) |
| Cohort 2 | | | | | | |
| 0 | | | | | | |
| Pre-dose | 56 | 0.0984 (0.736) | 56 | 0.0900 (0.673) | 56 | 0.188 (1.41) |
| End of Infusion | 55 | 286 (93.5) | 55 | 302 (94.0) | 55 | 588 (184) |
| 14 | 29 | 53.6 (22.2) | 29 | 46.0 (23.1) | 29 | 99.6 (44.9) |
| 28 | 25 | 26.4 (18.5) | 25 | 18.7 (14.7) | 25 | 45.1 (32.7) |
| Discharge before Day 29 | 17 | 97.8 (52.1) | 17 | 84.5 (51.3) | 17 | 182 (103) |
| Cohort 3 | | | | | | |
| 0 | | | | | | |
| Pre-dose | 12 | 0 (0) | 12 | 0 (0) | 12 | 0 (0) |
| End of Infusion | 10 | 284 (69.3) | 10 | 290 (81.7) | 10 | 574 (147) |
| 14 | 7 | 32.0 (22.6) | 7 | 25.2 (18.9) | 7 | 57.2 (41.2) |
| 28 | 3 | 9.06 (2.64) | 3 | 5.25 (4.12) | 3 | 14.3 (4.23) |
| Discharge before Day 29 | 1 | 67.3 (---) | 1 | 59.5 (---) | 1 | 127 (---) |

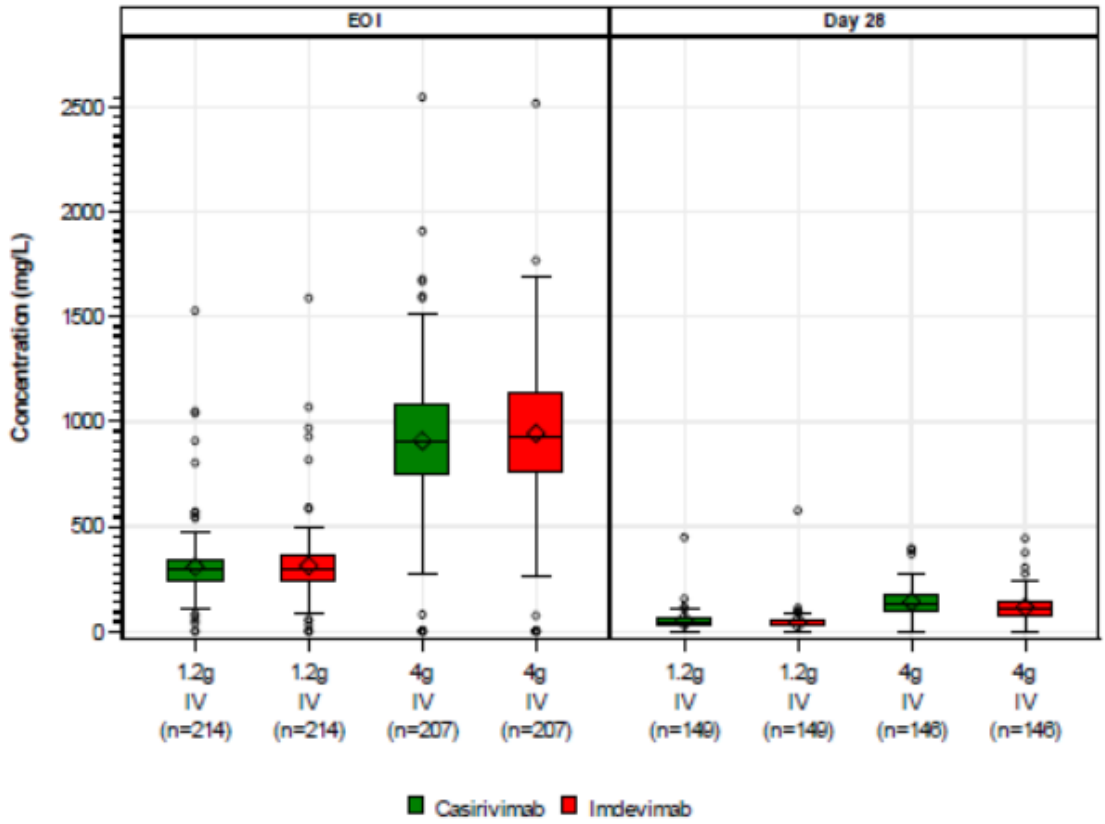
**Casirivimab+Imdevimab 8.0 g IV**

| | Concentration of | | | | | |
|---|---|---|---|---|---|---|
| | Casirivimab (mg/L) (N=431) | | Imdevimab (mg/L) (N=431) | | Casirivimab and Imdevimab (mg/L) (N=431) | |
| Nominal Sampling Time Post First Dose (Days) Timepoint | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) |
| Cohort 1A | | | | | | |
| 0 | | | | | | |
| Pre-dose | 170 | 11.8 (150) | 170 | 8.71 (109) | 170 | 20.5 (259) |
| End of Infusion | 155 | 847 (300) | 155 | 868 (298) | 155 | 1714 (591) |
| 14 | 86 | 278 (100) | 86 | 247 (89.7) | 86 | 524 (186) |
| 28 | 96 | 174 (65.1) | 96 | 150 (62.9) | 96 | 325 (127) |
| Discharge before Day 29 | 97 | 571 (236) | 97 | 565 (241) | 97 | 1136 (472) |
| Cohort 1 | | | | | | |
| 0 | | | | | | |
| Pre-dose | 183 | 0.689 (9.31) | 183 | 0.683 (9.24) | 183 | 1.37 (18.6) |
| End of Infusion | 178 | 848 (261) | 178 | 880 (268) | 178 | 1728 (522) |
| 14 | 88 | 231 (76.7) | 88 | 201 (68.2) | 88 | 431 (143) |
| 28 | 93 | 144 (89.8) | 93 | 113 (68.8) | 93 | 257 (158) |
| Discharge before Day 29 | 109 | 455 (192) | 109 | 425 (188) | 109 | 879 (378) |
| Cohort 2 | | | | | | |
| 0 | | | | | | |
| Pre-dose | 53 | 17.4 (121) | 53 | 18.2 (127) | 53 | 35.7 (248) |
| End of Infusion | 50 | 921 (262) | 50 | 946 (244) | 50 | 1867 (496) |
| 14 | 36 | 143 (69.5) | 36 | 124 (72.4) | 36 | 268 (141) |
| 28 | 26 | 79.4 (61.4) | 26 | 60.0 (53.9) | 26 | 139 (113) |
| Discharge before Day 29 | 13 | 252 (119) | 13 | 228 (114) | 13 | 480 (231) |
| Cohort 3 | | | | | | |
| 0 | | | | | | |
| Pre-dose | 11 | 0 (0) | 11 | 0 (0) | 11 | 0 (0) |
| End of Infusion | 11 | 708 (128) | 11 | 738 (124) | 11 | 1446 (234) |
| 14 | 5 | 138 (29.7) | 5 | 112 (22.5) | 5 | 250 (52.1) |
| 28 | 5 | 67.8 (31.1) | 5 | 52.4 (24.7) | 5 | 120 (55.4) |
| Discharge before Day 29 | 4 | 168 (81.0) | 4 | 140 (71.8) | 4 | 308 (150) |

BLQ = Below the limit of quantitation; IV = Intravenous; N = Number of patients in PKAS; n = Number of patients; PKAS = Pharmacokinetic analysis set; SD = Standard Deviation.
Note: BLQs were set to 0.

**Phase 3:**

**Figure 9: Box and Whisker Plot of Concentrations of Casirivimab and Imdevimab in Serum at EOI and Day 28 in Hospitalized Adult Patients with COVID-19 (Study R10933-10987-COV-2066, Phase 3 Cohort 1, PKAS)**




BLQ = Below the limit of quantitation; EOI = End of infusion; IV = Intravenous; n = Number of patients; PKAS = Pharmacokinetic analysis set; Q = Quartile.
Note: BLQs were set to 0.
Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence respectively; circles are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.

**Summary of Concentrations of Casirivimab, Imdevimab and Casirivimab+Imdevimab Combined in Serum by Time, Treatment Group in Hospitalized Adult Patients with COVID-19 (Study R10933-10987-COV-2066, Phase 3 Cohort 1, PKAS)**

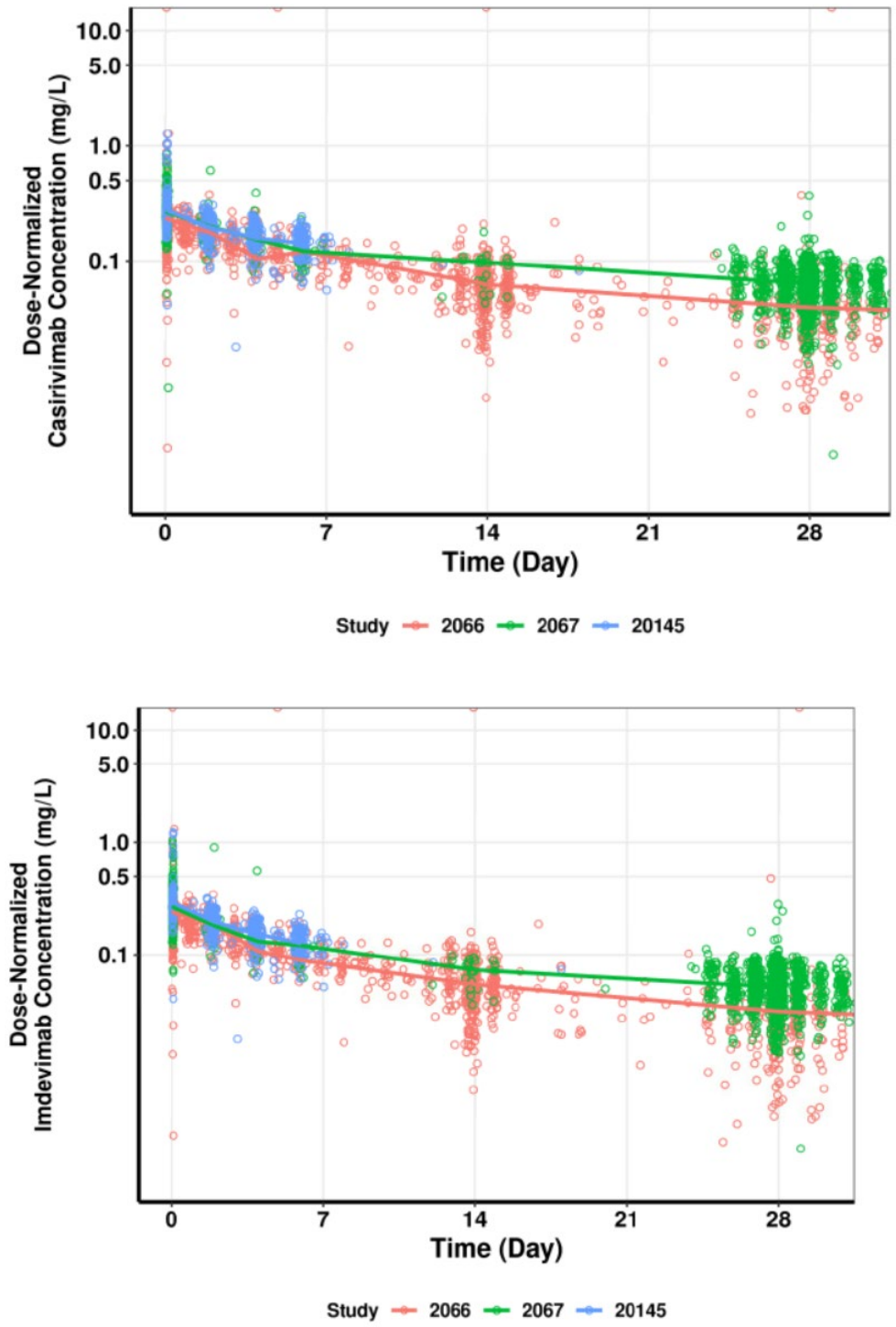
| Casirivimab+Imdevimab 2.4 g IV | | | | | | |
|---|---|---|---|---|---|---|
| | Concentration of | | | | | |
| Nominal Sampling Time Post First Dose (Days) | Casirivimab (mg/L) (N=231) | | Imdevimab (mg/L) (N=231) | | Casirivimab+Imdevimab (mg/L) (N=231) | |
| Timepoint | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) |
| 0 | | | | | | |
| Predose | 229 | 0 (0) | 229 | 0 (0) | 229 | 0 (0) |
| End of Infusion | 214 | 307 (153) | 214 | 312 (157) | 214 | 619 (307) |
| 14 | 121 | 76.1 (34.9) | 121 | 67.4 (28.6) | 121 | 144 (62.7) |
| 28 | 149 | 49.1 (40.4) | 149 | 40.8 (48.3) | 149 | 89.9 (88.1) |
| Discharge before Day 29 | 134 | 142 (61.2) | 134 | 136 (60.4) | 134 | 278 (121) |
| **Casirivimab+Imdevimab 8.0 g IV** | | | | | | |
| | Concentration of | | | | | |
| Nominal Sampling Time Post First Dose (Days) | Casirivimab (mg/L) (N=226) | | Imdevimab (mg/L) (N=226) | | Casirivimab+Imdevimab (mg/L) (N=226) | |
| Timepoint | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) |
| 0 | | | | | | |
| Predose | 221 | 12.0 (99.2) | 221 | 10.7 (88.5) | 221 | 22.7 (188) |
| End of Infusion | 207 | 908 (338) | 207 | 945 (351) | 207 | 1853 (683) |
| 14 | 124 | 228 (104) | 124 | 195 (91.8) | 124 | 423 (192) |
| 28 | 146 | 140 (66.1) | 146 | 114 (62.6) | 146 | 254 (127) |
| Discharge before Day 29 | 135 | 471 (257) | 135 | 444 (246) | 135 | 914 (499) |

BLQ = Below the limit of quantitation; IV = Intravenous; N = Number of patients in PKAS; n = Number of patients; PKAS = Pharmacokinetic analysis set; SD = Standard Deviation.
Note: BLQs were set to 0.

Additionally, casirivimab and imdevimab Ceoi and C28 in serum for Phase 3 Cohort 1 patients were comparable to Cohort 1 patients from Phase 1 and Phase 2.

The median observed concentrations for hospitalized patients in Study COV-2066 are lower than the median observed concentrations for outpatients with COVID-19 in Studies COV-2067 and COV-20145, suggesting that the CL of casirivimab and imdevimab in hospitalized patients is faster than in the outpatient setting.

**Figure 5: Observed Dose-Normalized Casirivimab and Imdevimab Concentration vs. Time Profiles Following Single IV Dose Administration of 2400 mg Casirivimab+Imdevimab (Semi-Log Scale)**




Note: Lines represent median observed dose-normalized concentrations at each study.

***NCA***

Non-compartmental analysis to estimate PK parameters such area under the concentration-time curve from time 0 to 28 days post dose (AUC0-28), maximum serum concentration (Cmax), and serum

concentration at 28 days post dose (C28) was performed only for data collected in the Phase 1 portion of this study, where dense sampling over the first 28 days was available.

**Summary of PK Parameters of Casirivimab, Imdevimab, and Casirivimab+Imdevimab Combined in Serum in Hospitalized Adult Participants with COVID-19 by Treatment (Phase 1 Cohort 1, PKAS)**

| | Casirivimab (N=16) | | | |
|---|---|---|---|---|
| PK Parameters | n | Mean (SD) | Median | Min : Max |
| 1200 mg IV | | | | |
| $AUC_{0\text{-}28}$ (day*mg/L) | 9 | 3026 (719) | 3184 | 1913 : 3897 |
| $AUC_{0\text{-}28}$/Dose ((day*mg/L)/mg) | 9 | 2.52 (0.599) | 2.65 | 1.59 : 3.25 |
| $C_{max}$ (mg/L) | 14 | 267 (60.3) | 258 | 165 : 375 |
| $C_{max}$/Dose (mg/L/mg) | 14 | 0.223 (0.0503) | 0.215 | 0.138 : 0.313 |
| $t_{max}$ (day) | 14 | — | 0.0590 | 0.0486 : 1.76 |
| $C_{eoi}$ (mg/L) | 15 | 231 (110) | 246 | 0 : 375 |
| $C_{eoi}$/Dose (mg/L/mg) | 15 | 0.193 (0.0920) | 0.205 | 0 : 0.313 |
| $C_{28}$ (mg/L) | 9 | 50.7 (19.5) | 40.2 | 26.8 : 77.2 |
| $C_{28}$/Dose (mg/L/mg) | 9 | 0.0423 (0.0163) | 0.0340 | 0.0220 : 0.0640 |
| | Imdevimab (N=16) | | | |
| PK Parameters | n | Mean (SD) | Median | Min : Max |
| 1200 mg IV | | | | |
| $AUC_{0\text{-}28}$ (day*mg/L) | 9 | 2582 (581) | 2666 | 1810 : 3637 |
| $AUC_{0\text{-}28}$/Dose ((day*mg/L)/mg) | 9 | 2.15 (0.484) | 2.22 | 1.51 : 3.03 |
| $C_{max}$ (mg/L) | 14 | 280 (64.4) | 264 | 172 : 384 |
| $C_{max}$/Dose (mg/L/mg) | 14 | 0.233 (0.0536) | 0.220 | 0.143 : 0.320 |
| $t_{max}$ (day) | 14 | — | 0.0590 | 0.0486 : 1.76 |
| $C_{eoi}$ (mg/L) | 15 | 243 (117) | 258 | 0 : 384 |
| $C_{eoi}$/Dose (mg/L/mg) | 15 | 0.203 (0.0971) | 0.215 | 0 : 0.320 |

Due to the limited PK sample collection in subsequent phases of the study, only concentrations of casirivimab and imdevimab in serum are summarized descriptively at the EOI and at Day 28 by treatment group, phase and/or cohort for Phase 2 and Phase 3.

**Population PK**

Previous pop-PK modelling was updated with data from hospitalized patients infected with SARS-CoV-2 (COV-2066) to characterize the PK and identify and quantify source of variability on the PK of both antibodies. The model was developed based on data from uninfected and infected individuals with SARS-CoV-2 and household contacts of individuals infected with SARS-CoV-2.

The primary objectives of the analysis were to:

- Characterize the concentration-time profiles of casirivimab and imdevimab in uninfected subjects, patients infected with SARS-CoV-2, and household contacts of individuals infected with SARS-CoV-2, and hospitalized patients infected with SARS-CoV-2.

- Evaluate candidate covariate effects on PK parameters, such as hospitalization status, disease severity, and inflammatory biomarkers.

- Estimate individual PK parameters and individual metrics of drug exposure.

The final updated model included data from four clinical studies: one Phase 1/2/3 study in outpatients infected with SARS-CoV-2 (COV-2067), one Phase 3 study in household contacts of patients infected with SARS-CoV-2 (COV-2069), one Phase 2 study in outpatients infected with SARS-CoV-2 (COV-20145), and data from the Phase 1/2/3 study in hospitalized patients infected with SARS-CoV-2 (COV-2066), with a total of approximately 5000 individuals including approximately 1300 hospitalized patients. Casirivimab+imdevimab was administered IV (300 mg [150 mg per mAb] to 8000 mg [4000 mg per mAb], single dose) or subcutaneously (600 mg [300 mg per mAb] to 1200 mg [600 mg per mAb], single dose).

The popPK modelling updates for casirivimab and imdevimab were performed using pooled data totalling 4981 unique subjects/patients with 10552 quantifiable casirivimab concentrations and 5009 unique subjects/patients with 11019 quantifiable imdevimab concentrations in serum.

**Table 15: Summary of Subjects and PK Samples Included in the Population PK Analysis of Casirivimab**

| Study | Treatment | Number of Samples | Number of Subjects | Number of Quantifiable Samples | Number of Post-dose BLQ Samples | Percent (%) of Post-dose BLQ Samples | Number of Post-dose Samples Excluded for Other Reasons | Percent (%) of Post-dose Samples Excluded for Other Reasons |
|---|---|---|---|---|---|---|---|---|
| 2066 | 1.2 g IV | 1758 | 670 | 1711 | 15 | 0.87 | 32 | 1.85 |
| | 4 g IV | 1765 | 624 | 1653 | 22 | 1.31 | 90 | 5.37 |
| 2067 | 0.6 g IV | 330 | 277 | 328 | 0 | 0.00 | 2 | 0.61 |
| | 1.2 g IV | 2204 | 1405 | 2156 | 29 | 1.33 | 19 | 0.87 |
| | 4 g IV | 1916 | 1162 | 1889 | 17 | 0.89 | 10 | 0.52 |
| 2069 | 0.6 g SC | 482 | 167 | 475 | 6 | 1.25 | 1 | 0.21 |
| 20145 | 0.15 g IV | 424 | 114 | 416 | 8 | 1.89 | 0 | 0.00 |
| | 0.3 g IV | 407 | 111 | 394 | 9 | 2.23 | 4 | 0.99 |
| | 0.3 g SC | 417 | 111 | 350 | 66 | 15.87 | 1 | 0.24 |
| | 0.6 g IV | 431 | 114 | 422 | 9 | 2.09 | 0 | 0.00 |
| | 0.6 g SC | 404 | 114 | 353 | 49 | 12.19 | 2 | 0.50 |
| | 1.2 g IV | 420 | 112 | 405 | 6 | 1.46 | 9 | 2.19 |
| Overall | Overall | 10958 | 4981 | 10552 | 236 | 2.19 | 170 | 1.58 |

BLQ = Below the limit of quantification; IV = Intravenous; SC = Subcutaneous

**Table 16: Summary of Subjects and PK Samples Included in the Population PK Analysis for Imdevimab**

| Study | Treatment | Number of Samples | Number of Subjects | Number of Quantifiable Samples | Number of Post-dose BLQ Samples | Percent (%) of Post-dose BLQ Samples | Number of Post-dose Samples Excluded for Other Reasons | Percent (%) of Post-dose Samples Excluded for Other Reasons |
|---|---|---|---|---|---|---|---|---|
| 2066 | 1.2 g IV | 1758 | 669 | 1710 | 16 | 0.93 | 32 | 1.85 |
| | 4 g IV | 1765 | 624 | 1653 | 22 | 1.31 | 90 | 5.37 |
| 2067 | 0.6 g IV | 343 | 290 | 341 | 0 | 0.00 | 2 | 0.59 |
| | 1.2 g IV | 2249 | 1433 | 2201 | 29 | 1.30 | 19 | 0.85 |
| | 2.4 g IV | 2 | 1 | 2 | 0 | 0.00 | 0 | 0.00 |
| | 4 g IV | 1914 | 1149 | 1887 | 18 | 0.94 | 9 | 0.47 |
| 2069 | 0.6 g SC | 484 | 166 | 471 | 12 | 2.48 | 1 | 0.21 |
| 20145 | 0.15 g IV | 424 | 114 | 416 | 8 | 1.89 | 0 | 0.00 |
| | 0.3 g IV | 407 | 111 | 394 | 9 | 2.23 | 4 | 0.99 |
| | 0.3 g SC | 418 | 112 | 359 | 58 | 13.91 | 1 | 0.24 |
| | 0.6 g IV | 430 | 114 | 422 | 8 | 1.86 | 0 | 0.00 |
| | 0.6 g SC | 404 | 114 | 374 | 28 | 6.97 | 2 | 0.50 |
| | 1.2 g IV | 421 | 112 | 406 | 6 | 1.46 | 9 | 2.18 |
| Overall | Overall | 11019 | 5009 | 10636 | 214 | 1.97 | 169 | 1.56 |

BLQ = Below the limit of quantification; IV = Intravenous; SC = Subcutaneous

**Casirivimab and Imdevimab Final Population Pharmacokinetic Model Parameter Estimates**

**Table 3: Casirivimab Final Population Pharmacokinetic Model Parameter Estimates and Bootstrapped Confidence Intervals**

| Parameter (Units) | Estimate | RSE (%) | CI (95%) | Bootstrap Median (2.5th, 97.5th Percentiles) |
|---|---|---|---|---|
| CL: Clearance (L/day) | 0.198 | 1.831 | (0.191, 0.206) | 0.198 (0.191, 0.206) |
| $V_c$: Central Volume of Distribution (L) | 3.910 | 1.283 | (3.81, 4.01) | 3.91 (3.82, 4.01) |
| Q: Intercompartmental Clearance (L/day) | 0.501 | 6.150 | (0.440, 0.561) | 0.500 (0.444, 0.562) |
| $V_p$: Peripheral Volume of Distribution (L) | 3.162 | 3.206 | (2.96, 3.36) | 3.16 (2.97, 3.36) |
| $K_a$: Absorption Rate Constant (1/Day) | 0.218 | 7.736 | (0.185, 0.251) | 0.219 (0.187, 0.258) |
| F1: Bioavailability | 0.725 | 2.615 | (0.688, 0.762) | 0.727 (0.689, 0.763) |
| Baseline Weight on CL | 0.762 | 3.960 | (0.703, 0.821) | 0.760 (0.698, 0.822) |
| Baseline Weight on Vc | 0.609 | 5.049 | (0.548, 0.669) | 0.606 (0.547, 0.666) |
| Albumin on CL | -0.786 | 7.470 | (-0.901, -0.670) | -0.787 (-0.904, -0.679) |
| Female on CL | -0.130 | 9.541 | (-0.155, -0.106) | -0.131 (-0.154, -0.103) |
| Black Race on CL | 0.061 | 40.720 | (0.0123, 0.110) | 0.0605 (0.0155, 0.117) |
| Mild Hepatic Impairment on CL | 0.051 | 31.800 | (0.0191, 0.0824) | 0.0513 (0.0180, 0.0854) |
| Albumin on $V_c$ | -0.140 | 40.770 | (-0.252, -0.0281) | -0.139 (-0.248, -0.0376) |
| Female on $V_c$ | -0.104 | 14.230 | (-0.133, -0.0752) | -0.104 (-0.133, -0.0729) |
| Viral load on CL | -0.006 | 51.120 | (-0.0121, 0.0000127) | -0.00618 (-0.0124, -0.000287) |
| Low Flow Oxygen on CL | 0.062 | 49.700 | (0.00159, 0.122) | 0.0634 (0.00605, 0.124) |
| High Flow Oxygen/Mechanical Ventilation on CL | 0.316 | 21.100 | (0.185, 0.447) | 0.315 (0.192, 0.449) |
| Hospitalization Status on CL | 0.215 | 15.930 | (0.148, 0.282) | 0.213 (0.147, 0.282) |
| Hospitalization Status on $V_c$ | 0.110 | 20.640 | (0.0657, 0.155) | 0.110 (0.0708, 0.161) |
| C-reactive protein on CL | 0.037 | 16.060 | (0.0256, 0.0492) | 0.0377 (0.0253, 0.0496) |
| IL-8 on CL | 0.093 | 19.300 | (0.0576, 0.128) | 0.0927 (0.0593, 0.127) |
| IIV in CL | 0.063 | 12.840 | (0.0471, 0.0788) | 0.0628 (0.0460, 0.0790) |
| IIV in $V_c$ | 0.138 | 16.600 | (0.0928, 0.182) | 0.138 (0.0976, 0.185) |
| Residual Variability | 0.080 | 11.850 | (0.0613, 0.0984) | 0.0782 (0.0641, 0.0984) |
| Objective Function Value | -9802.885 | | | |

CI = Confidence interval; IIV = Inter-individual variability; RSE = Relative standard error;
Note: Covariates are time-varying unless otherwise noted.

**Table 4: Imdevimab Final Population Pharmacokinetic Model Parameter Estimates and Bootstrapped Confidence Intervals**

| Parameter (Units) | Estimate | RSE (%) | 95% CI | Bootstrap Median (2.5th, 97.5th Percentiles) |
|---|---|---|---|---|
| CL: Clearance (L/day) | 0.243 | 1.640 | (0.236, 0.251) | 0.243 (0.235, 0.252) |
| $V_c$: Central Volume of Distribution (L) | 3.961 | 1.194 | (3.87, 4.05) | 3.96 (3.86, 4.05) |
| Q: Intercompartmental Clearance (L/day) | 0.455 | 6.056 | (0.401, 0.509) | 0.452 (0.405, 0.513) |
| $V_p$: Peripheral Volume of Distribution (L) | 3.222 | 3.446 | (3.00, 3.44) | 3.21 (3.00, 3.43) |
| $K_a$: Absorption Rate Constant (1/Day) | 0.198 | 6.892 | (0.171, 0.225) | 0.198 (0.174, 0.228) |
| F1: Bioavailability | 0.726 | 2.527 | (0.690, 0.762) | 0.726 (0.688, 0.766) |
| Baseline Weight on CL | 0.690 | 3.897 | (0.637, 0.742) | 0.688 (0.635, 0.743) |
| Baseline Weight on Vc | 0.592 | 5.221 | (0.531, 0.652) | 0.588 (0.529, 0.651) |
| Albumin on CL | -0.735 | 7.801 | (-0.848, -0.623) | -0.740 (-0.855, -0.639) |
| Female on CL | -0.127 | 8.859 | (-0.149, -0.105) | -0.127 (-0.149, -0.103) |
| Black Race on CL | 0.063 | 36.760 | (0.0175, 0.108) | 0.0626 (0.0214, 0.110) |
| Mild Hepatic Impairment on CL | 0.073 | 21.050 | (0.0431, 0.104) | 0.0740 (0.0429, 0.105) |
| Albumin on $V_c$ | -0.304 | 12.500 | (-0.378, -0.229) | -0.303 (-0.385, -0.232) |
| Female on $V_c$ | -0.104 | 14.230 | (-0.133, -0.0748) | -0.105 (-0.133, -0.0736) |
| Viral load on CL | -0.009 | 31.910 | (-0.0141, -0.00325) | -0.00868 (-0.0140, -0.00325) |
| Low Flow Oxygen on CL | 0.060 | 45.780 | (0.00622, 0.115) | 0.0608 (0.0106, 0.118) |
| High Flow Oxygen/Mechanical Ventilation on CL | 0.332 | 18.850 | (0.209, 0.455) | 0.329 (0.215, 0.451) |
| Hospitalization Status on CL | 0.136 | 20.830 | (0.0806, 0.192) | 0.138 (0.0836, 0.196) |
| C-reactive protein on CL | 0.034 | 15.270 | (0.0242, 0.0448) | 0.0343 (0.0235, 0.0451) |
| NLR on CL | 0.043 | 27.950 | (0.0194, 0.0665) | 0.0426 (0.0210, 0.0684) |
| IIV in CL | 0.049 | 12.350 | (0.0370, 0.0607) | 0.0483 (0.0362, 0.0601) |
| IIV in $V_c$ | 0.126 | 17.520 | (0.0829, 0.170) | 0.126 (0.0889, 0.171) |
| Residual Variability | 0.094 | 10.970 | (0.0741, 0.115) | 0.0930 (0.0752, 0.113) |
| Objective Function Value | -8831.488 | | | |

CI = Confidence interval; IIV = Inter-individual variability; RSE = Relative standard error
Note: Covariates are time-varying unless otherwise noted.

**Individual PK Parameters**

Predicted exposure metrics for a 2400 mg and 8000 mg IV casirivimab+imdevimab single dose are presented in the tables below for patients hospitalized for SARS-CoV-2 infection from Study 2066. Patients on high-intensity oxygen or mechanical ventilation had a more severe infection compared to patients requiring only low-flow oxygen; therefore, predicted metrics from the 8000 mg IV dose of casirivimab+imdevimab were calculated for these more severe patients.

**Table 5: Exposure Predictions for Casirivimab and Imdevimab Following Single REGEN-COV 2400 mg IV Dose (1200 mg per mAb) for Hospitalized Patients on Low Flow Oxygen**

| Exposure Metrics | Mean ± SD | Median (5th percentile, 95th percentile) |
|---|---|---|
| **Casirivimab** | | |
| $AUC_{d28}$ (day*mg/L) | 2934.2 ± 674.1 | 2870 (1936.6, 4153.7) |
| $AUC_{inf}$ (day*mg/L) | 5002.7 ± 1786.6 | 4697.6 (2681.5, 8360) |
| $C_{day28}$ (mg/L) | 55 ± 18.5 | 54.1 (26.7, 88.1) |
| $C_{max}$ (mg/L) | 313.6 ± 135 | 287.2 (147.2, 578.6) |
| **Imdevimab** | | |
| $AUC_{d28}$ (day*mg/L) | 2647.7 ± 589 | 2606.7 (1777.8, 3696.3) |
| $AUC_{inf}$ (day*mg/L) | 3854.5 ± 1233.5 | 3657.4 (2175.8, 6128) |
| $C_{day28}$ (mg/L) | 40.9 ± 15.2 | 39.7 (18.2, 67.4) |
| $C_{max}$ (mg/L) | 339.7 ± 141 | 312.7 (164.3, 613.6) |

$AUC_{day28}$ = Area under the concentration time curve for 28-day interval after dosing; $AUC_{inf}$ = Area under the concentration time curve from time 0 extrapolated to infinite time; $C_{max}$ = Maximum (peak) concentration for a 28-day interval following dosing; $C_{28}$ = Concentration on Day 28 after single dose; IV = Intravenous; SD = Standard deviation

**Table 6: Exposure Predictions for Casirivimab and Imdevimab Following Single REGEN-COV 8000 mg IV Dose (4000 mg per mAb) for Hospitalized Patients on High Flow Oxygen or Mechanical Ventilation**

| Exposure Metrics | Mean ± SD | Median (5th percentile, 95th percentile) |
|---|---|---|
| **Casirivimab** | | |
| $AUC_{d28}$ (day*mg/L) | 8809.7 ± 2097.5 | 8578.4 (5706.8, 12596.4) |
| $AUC_{inf}$ (day*mg/L) | 13450.2 ± 4803.4 | 12630.1 (7209.6, 22476.7) |
| $C_{day28}$ (mg/L) | 146.8 ± 56.9 | 141.6 (62.2, 249.3) |
| $C_{max}$ (mg/L) | 1045 ± 449.7 | 957 (490.7, 1927.3) |
| **Imdevimab** | | |
| $AUC_{d28}$ (day*mg/L) | 7713.7 ± 1801.5 | 7543.3 (5039.3, 10867.5) |
| $AUC_{inf}$ (day*mg/L) | 10229.2 ± 3273.5 | 9705.9 (5774.3, 16262.5) |
| $C_{day28}$ (mg/L) | 101.4 ± 43.8 | 95.5 (38.8, 180.9) |
| $C_{max}$ (mg/L) | 1131.6 ± 469.6 | 1041.6 (547.4, 2044.3) |

$AUC_{day28}$ = Area under the concentration time curve for 28-day interval after dosing; $AUC_{inf}$ = Area under the concentration time curve from time 0 extrapolated to infinite time; $C_{max}$ = Maximum (peak) concentration for a 28-day interval following dosing; $C_{28}$ = Concentration on Day 28 after single dose; IV = Intravenous; SD = Standard deviation

**Model development**

Patients hospitalized for COVID-19 were observed to have faster clearances of casirivimab+imdevimab compared to the clearances from the previous population of non-hospitalized patients. Therefore, the impact of hospitalization status and disease severity was evaluated in the model via post-hoc covariate analyses using the previously developed PopPK models for casirivimab and imdevimab as the reference models. Disease severity was defined by the level of baseline oxygen supplementation therapy required, where patients were defined as requiring no oxygen therapy, receiving low-flow oxygen via nasal cannula or other similar devices (low flow oxygen), or requiring high-intensity oxygen therapy or

mechanical ventilation (high flow oxygen). Furthermore, time-varying albumin was also evaluated to assess whether there was any additional improvement to the model fit over baseline albumin levels.

Each covariate-parameter combination was evaluated one at a time using a forward selection process, where the covariate-parameter relationship leading to the greatest reduction in objective function value (OFV) relative to the reference model was retained. This process was repeated until no additional covariates met the selection criteria (ie, ΔOFV >10.8 [p<0.001] for df =1 [hospitalization status]; ΔOFV >13.8 for df=2 [baseline level of oxygen therapy]). As a final step in the process, baseline albumin was replaced with time-varying albumin to evaluate whether the replacement of the baseline value with time-varying values would improve model fit as evaluated by ΔOFV >10.8 (p<0.001).

Patients hospitalized for SARS-CoV-2 infections were anticipated to have a higher inflammatory response compared to individuals in the outpatient setting based on observations from a study with sarilumab in hospitalized COVID-19 patients. Therefore, a full model was developed to explore the impact of inflammatory biomarkers which were not considered in the previous analysis.

A stepwise backward elimination procedure using the likelihood ratio test (LRT) was used to identify parsimonious PopPK models once the full models for casirivimab and imdevimab were built. Statistical tests of covariate parameter relationships were assessed with the LRT, based on the property that the difference of the NONMEM® objective function values (dOFV or ΔOFV) of two hierarchical models (-2 log-likelihood) is asymptotically χ2-distributed. The full model was subjected to a backward elimination procedure associated with p<0.001 (ΔOFV>10.8) when one covariate parameter was excluded. The covariate-parameter relationship which had the lowest change in OFV and did not meet the inclusion criteria (ie, ΔOFV <10.8 [p>0.001]) was eliminated and the stepwise backward elimination procedure was repeated until all covariate parameters met the inclusion criteria.

In this current analysis, the following covariates were evaluated:

• Hospitalization status – a categorical variable indicating whether patients were hospitalized for SARS-CoV-2 infection or were in the outpatient setting (ie, Study 2066 vs. Other [Studies 2067, 2069, and 20145])

• Disease severity – a categorical variable describing degree of SARS-CoV-2 disease severity based on baseline levels of oxygen supplementation required, defined as follows:

– No supplemental oxygen required

– Low Flow Oxygen – Patients receiving low-flow oxygen therapy

– High Flow Oxygen – Patients receiving high-intensity oxygen therapy or mechanical ventilation

• Inflammatory biomarkers – continuous variables quantifying biomarker levels present for each subject

– Availability of biomarkers per study is provided in the table below.

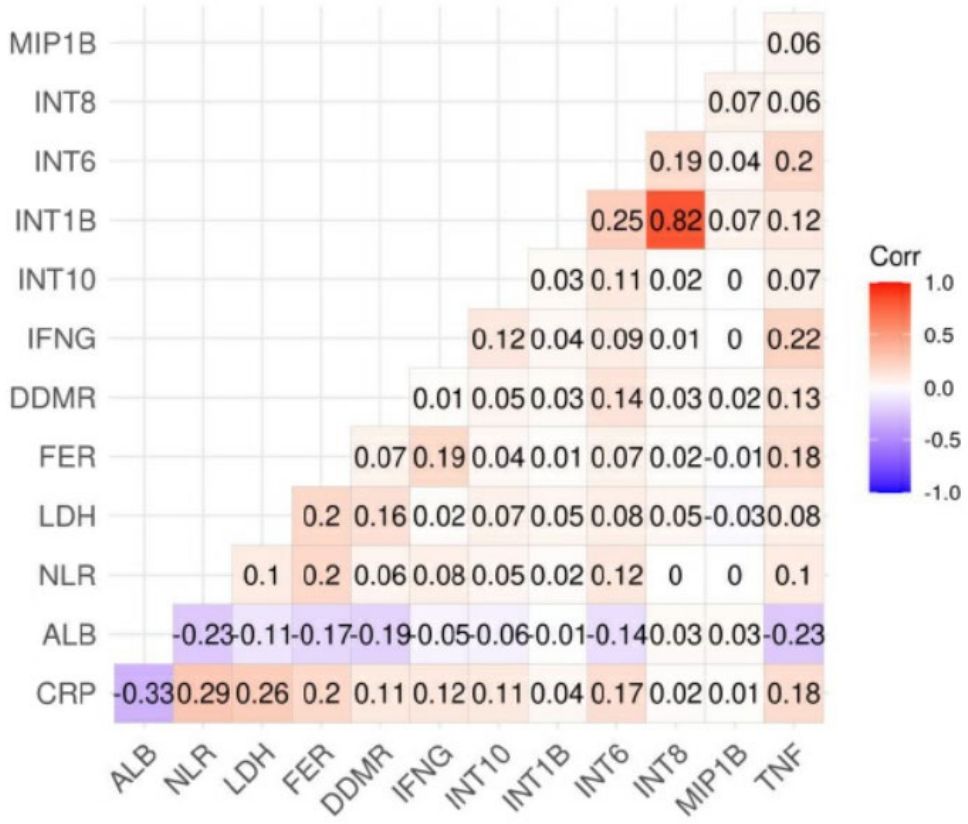
**Table 14: Availability of Inflammatory Biomarkers by Study**

| Study | Available Covariates |
|---|---|
| All Studies | LDH, NLR |
| 2066 + 2067 | C-reactive protein, ferritin |
| 2066-only | D-dimer, IL-1β, IL-6, IL-8, IL-10, TNF, IFNg, MIP-1B |

LDH = Lactate dehydrogenase; NLR = Neutrophil-lymphocyte ratio; IFNg = Interferon gamma; IL = Interleukin; MIP = Macrophage inflammatory protein; TNF = Tumor necrosis factor
Note: All biomarkers are time-varying unless otherwise noted.

The correlation plot provided in the figure below demonstrate that INT-1β and INT-8 are highly correlated (ρ > 0.8); therefore, INT-1β was removed from consideration from the full model.

**Figure 8: Correlation Plot of Inflammatory Biomarkers**




Casirivimab – full model

The covariate-parameter relationships which showed trends based on the screening procedure above and are included in the full model for casirivimab were C-reactive protein (CRP) on CL, ferritin on CL, lactate dehydrogenase (LDH) on CL, neutrophil-lymphocyte ratio (NLR) on CL, IL-8 on CL, TNF on CL, MIP-1β on CL, IL-6 on CL, IL-10 on CL, IFN-g on Vc, IL-6 on Vc, IL-8 on Vc, and TNF on Vc. After backward elimination (ΔOFV > 10.8 [p<0.001]), the covariate-parameter relationships included in the final model (Run 7000) for casirivimab were CRP on CL and IL-8 on CL.

Imdevimab – full model

The covariate-parameter relationships which showed trends based on the screening procedure above and are included in the full model for imdevimab were C-reactive protein (CRP) on CL, ferritin on CL, lactate dehydrogenase (LDH) on CL, neutrophil-lymphocyte ratio (NLR) on CL, IL-8 on CL, TNF on CL, MIP-1β on CL, IL-6 on CL, IL-10 on CL, IL-6 on Vc, IL-8 on Vc, and TNF on Vc. After backward elimination (ΔOFV > 10.8 [p<0.001]), the covariate-parameter relationships included in the final model (Run 7000) for imdevimab were CRP on CL and NLR on CL.

**Model evaluation and validation**

Diagnostic plots were generated including concordance (eg, PRED vs DV and IPRED vs DV), residual (eg, CWRES vs PRED, CWRES vs time, IWRES vs IPRED, and IWRES vs time), and overlay plots (eg, DV, PRED, and IPRED vs time). Plots of the individual random effect values versus covariate values were generated in order to identify trends indicating possible covariate effects to be accounted for in the full covariate model. In addition, boxplots of the η values versus dose and study were generated to evaluate dose invariance and adequacy of pooling studies for this analysis, respectively. Furthermore, a comparison of the OFV and parameter estimates for the starting models, the updated full models, and resulting final models was used to assess the degree of parsimony of the final models.

Bootstrapping, which mitigates concerns about a potential asymmetrical distribution of parameters or non-asymptotic assumptions, was performed on the respective final models for casirivimab and imdevimab.

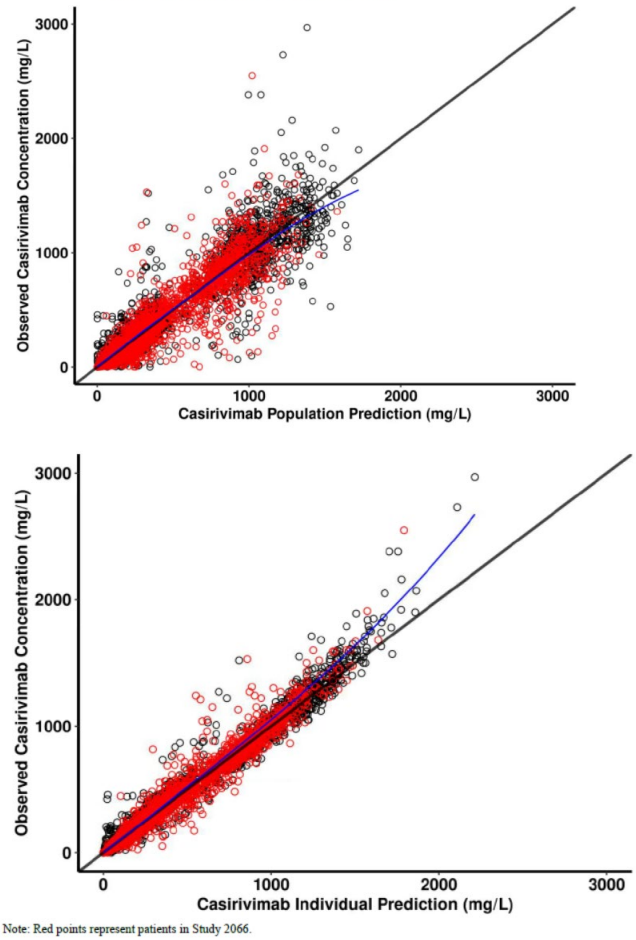
An internal visual predictive check (VPC) was performed on the respective final models for casirivimab and imdevimab. The parameter estimates were fixed to the values estimated in the final model runs and used to generate 500 datasets which replicated the design, subject population, dose regimens, sample sizes, and covariate distributions from the pooled observed dataset.

The 95% confidence intervals (CI) of the simulated median, 2.5th , and 97.5th percentiles of the simulated casirivimab and imdevimab concentrations were calculated and plotted as a function of time overlaid on the observed casirivimab and imdevimab concentrations to provide a visual assessment of the predictive performance of the PK model.

Diagnostic plots of concordance provided in the figure below suggest good agreement between the observed data and the model predictions, and casirivimab and imdevimab concentrations in Study 2066 highlighted in the plots span the range of observed concentrations from Studies 2067, 2069, and 20145:

Casirivimab

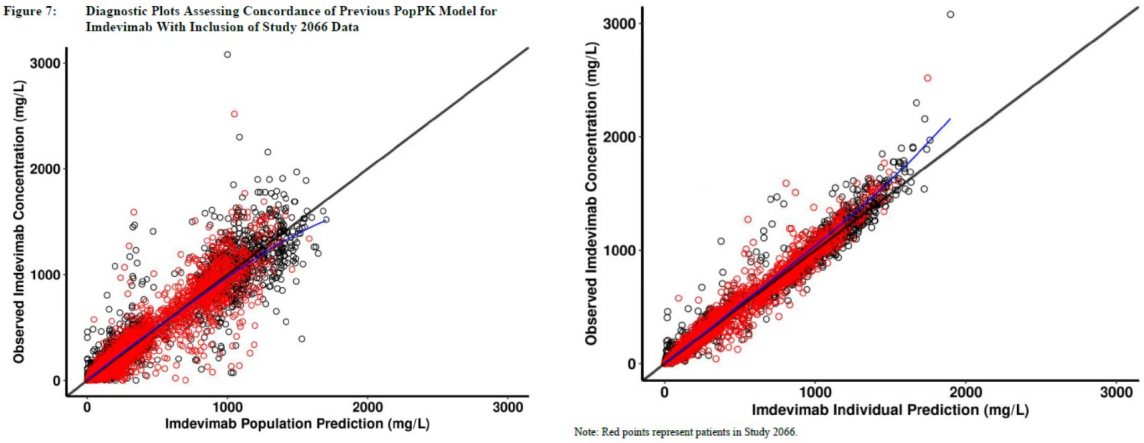
Figure 6: Diagnostic Plots Assessing Concordance of Previous PopPK Model for Casirivimab With Inclusion of Study 2066 Data




Note: Red points represent patients in Study 2066.

Imdevimab

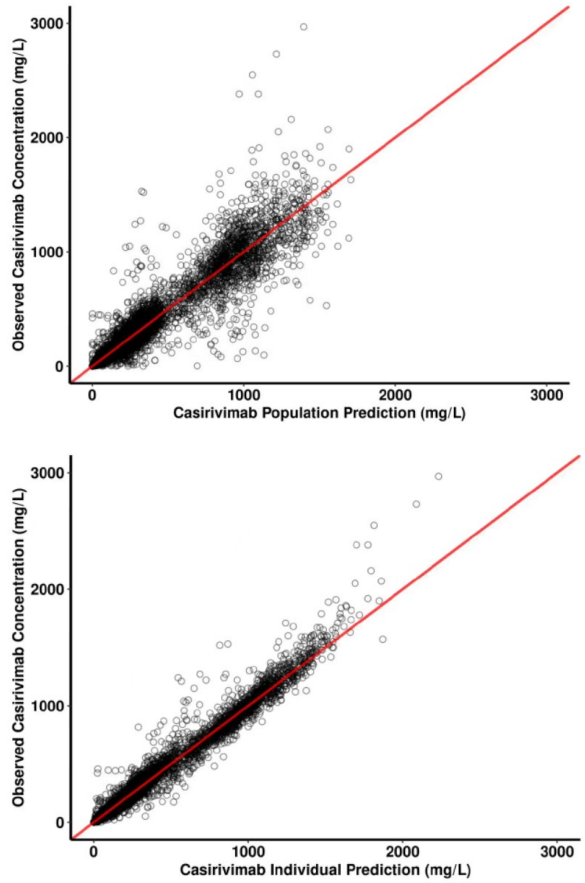
Figure 7: Diagnostic Plots Assessing Concordance of Previous PopPK Model for Imdevimab With Inclusion of Study 2066 Data

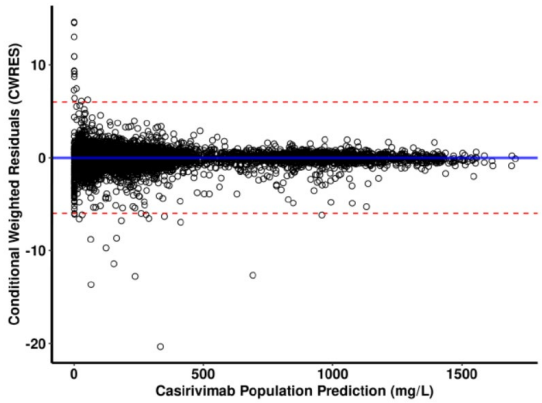


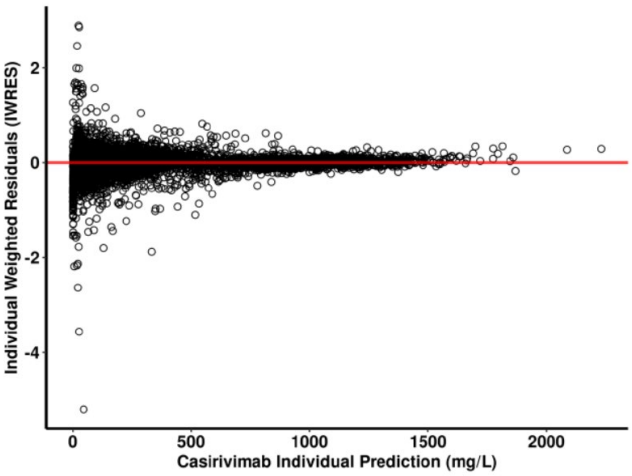

Note: Red points represent patients in Study 2066.

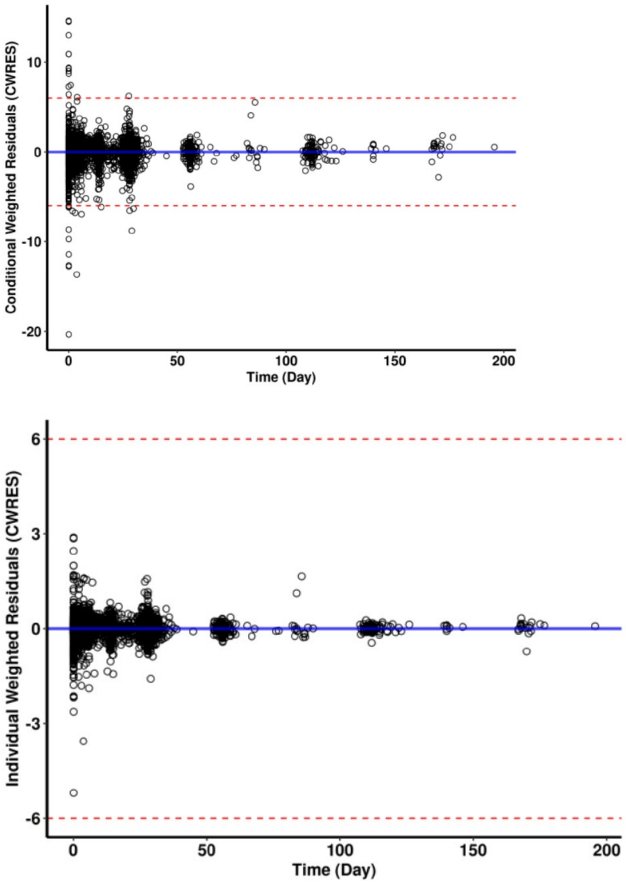
## Casirivimab – final model

Figure 9: Diagnostic Plots for Casirivimab Final Model



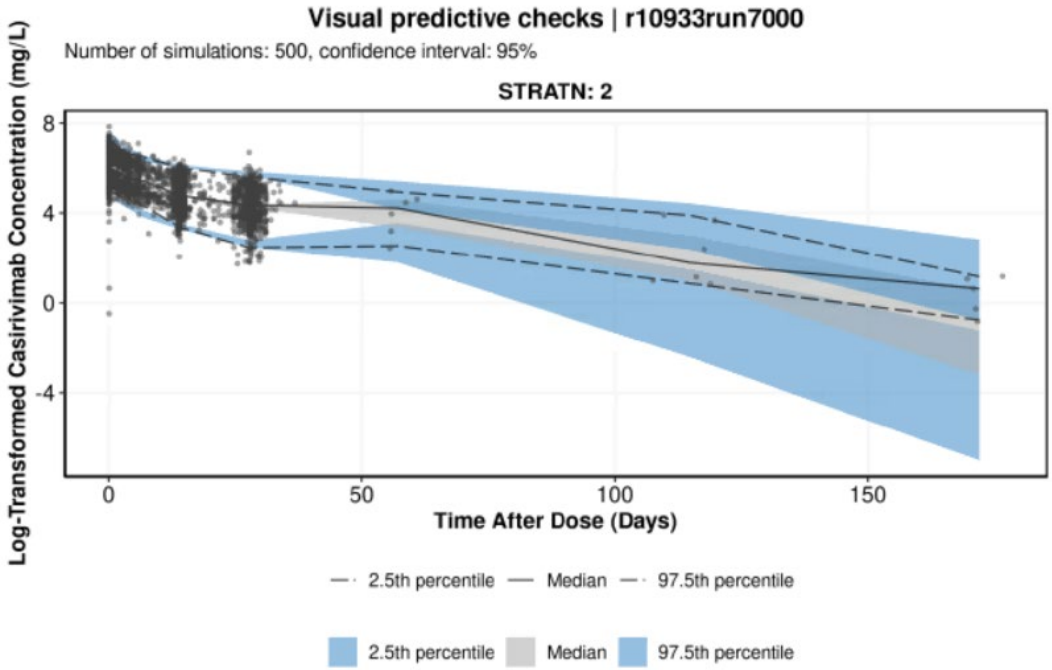

Conditional Weighted Residuals (CWRES)
10
0
-10
-20
0
500
1000
1500
Casirivimab Population Prediction (mg/L)


Individual Weighted Residuals (IWRES)
2
0
-2
-4
0
500
1000
1500
2000
Casirivimab Individual Prediction (mg/L)

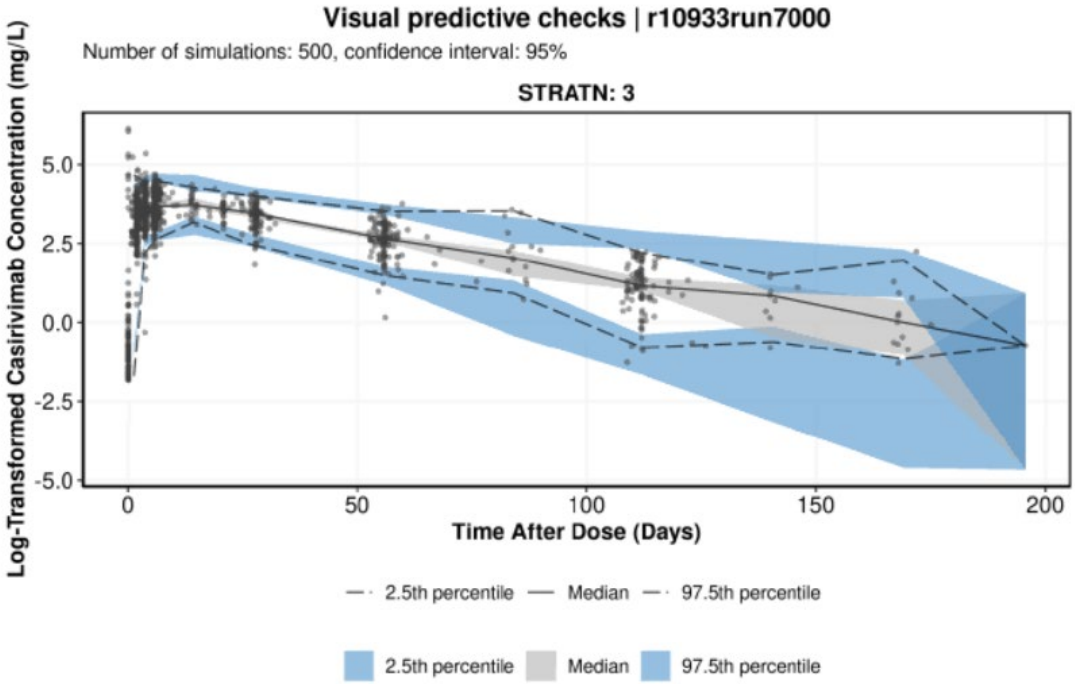



VPC Casirivimab (hospitalized-IV)

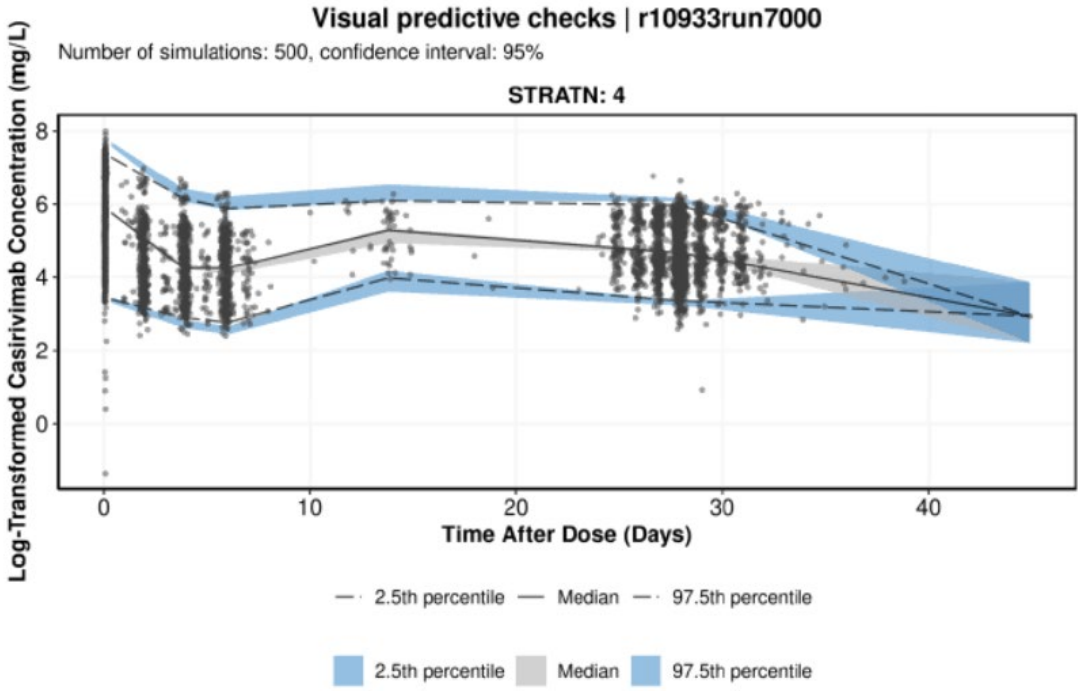
**Figure 13: Visual Predictive Check Plots for Casirivimab Final Model**




VPC Casirivimab (non-hospitalized-SC)



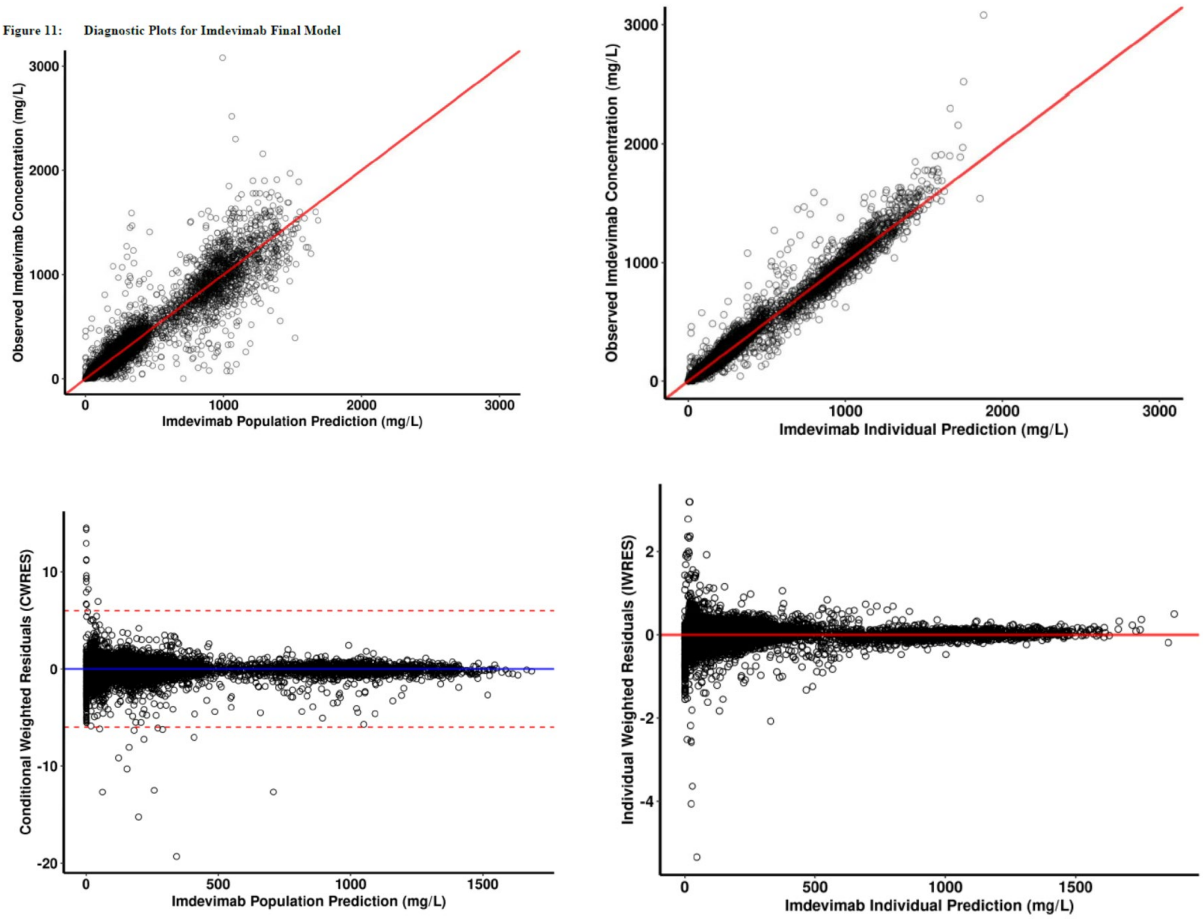

VPC Casirivimab (non-hospitalized-IV)

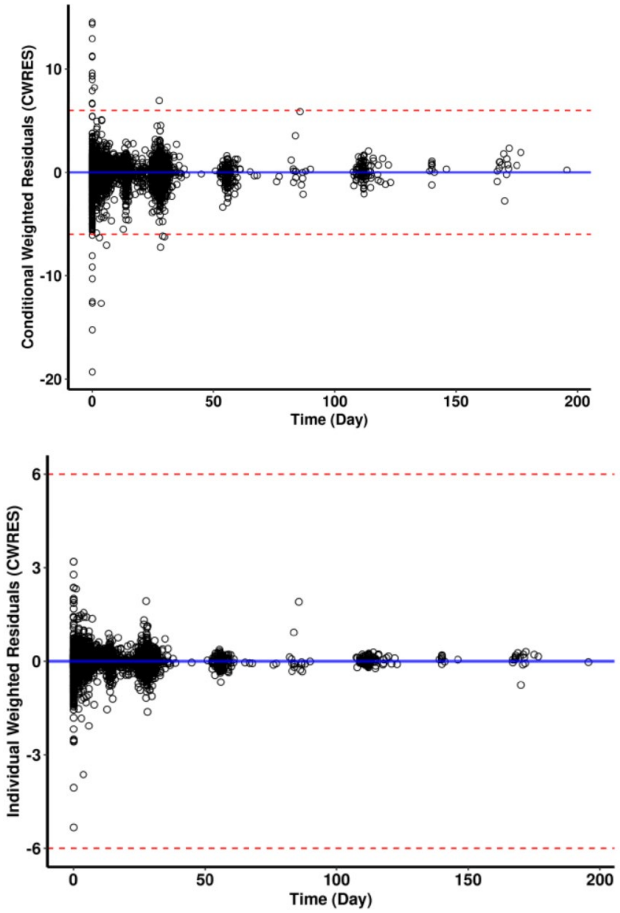



Note: STRATN:2 represents hospitalized patients receiving IV administration; STRATN:3 represents non-hospitalized patients receiving SC administration; and STRATN:4 represents non-hospitalized patients receiving IV administration. Lines represent observed data, and shaded regions represent simulated data.

Imdevimab – final model

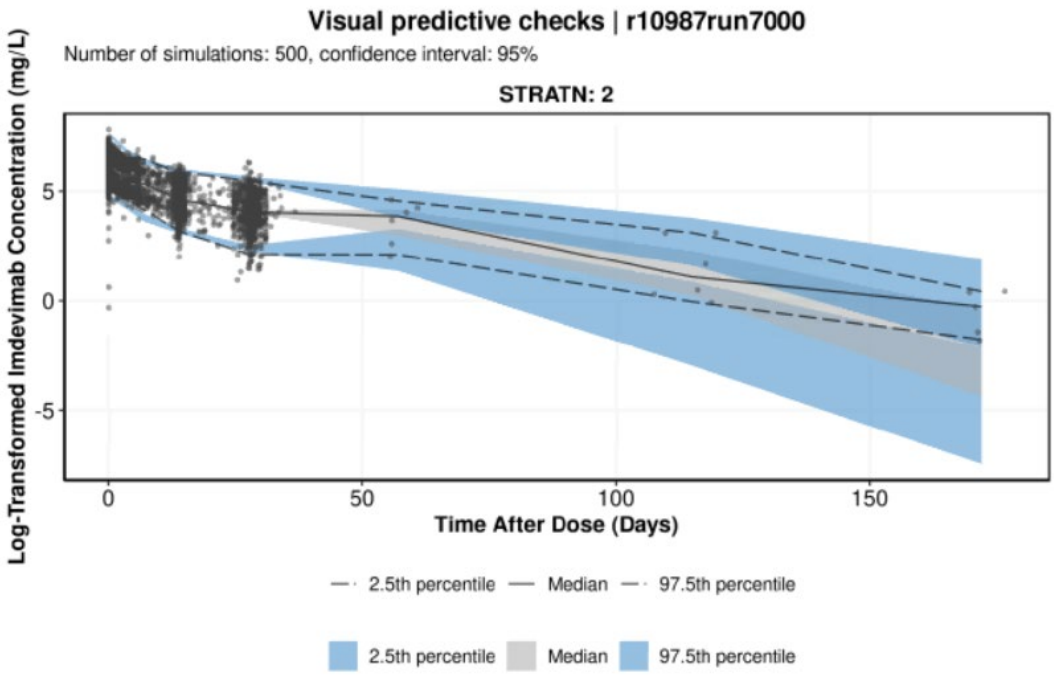
Figure 11: Diagnostic Plots for Imdevimab Final Model



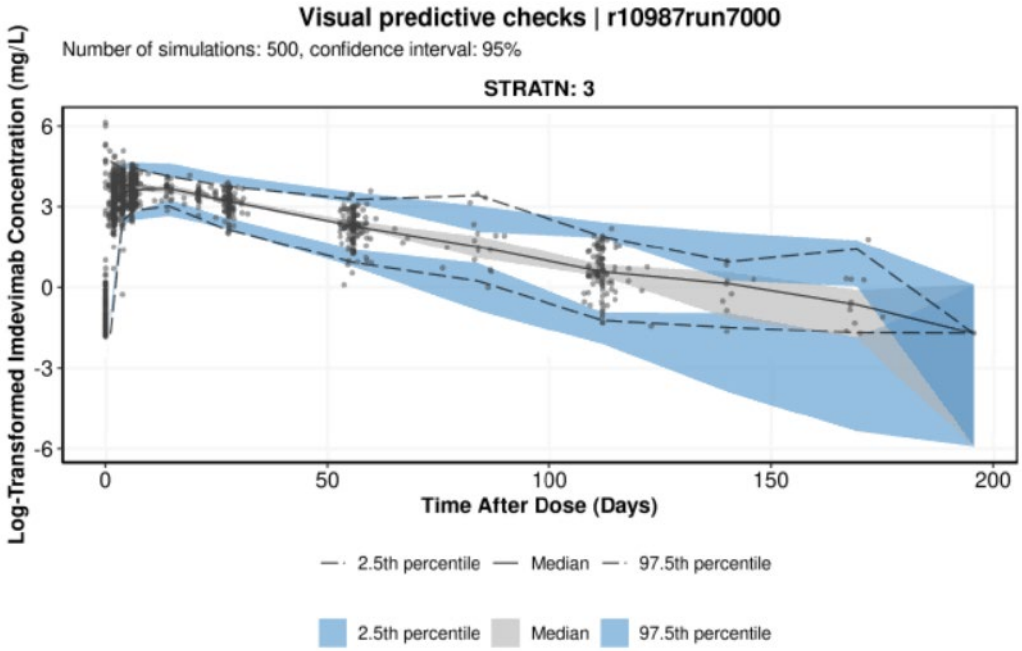



VPC Imdevimab (hospitalized-IV)

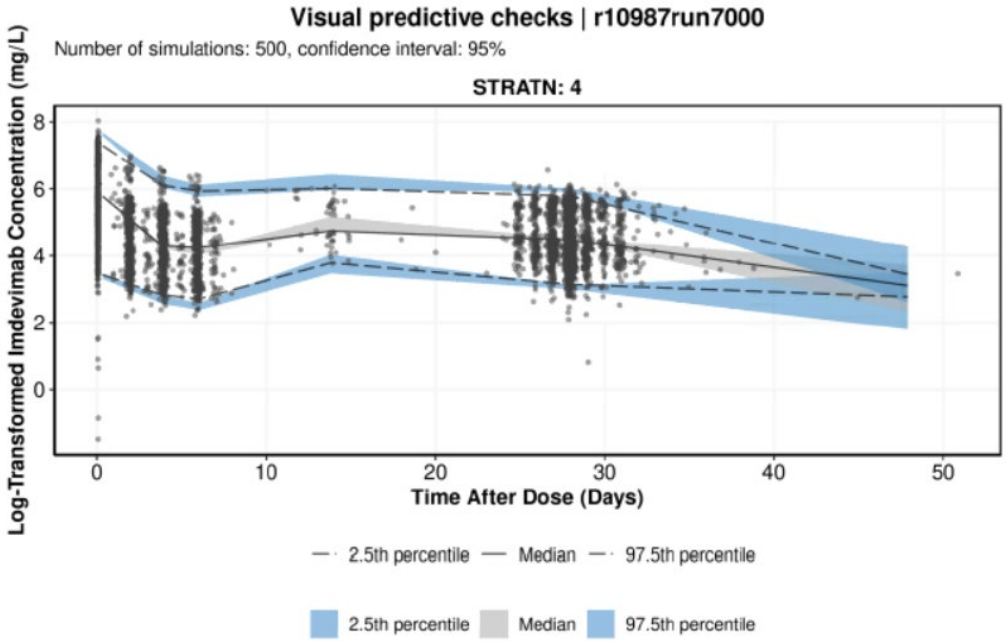
**Figure 14: Visual Predictive Check Plots for Imdevimab Final Model**




VPC Imdevimab (non-hospitalized-SC)




VPC Imdevimab (non-hospitalized-IV)




Note: STRATN:2 represents hospitalized patients receiving IV administration; STRATN:3 represents non-hospitalized patients receiving SC administration; and STRATN:4 represents non-hospitalized patients receiving IV administration. Lines represent observed data, and shaded regions represent simulated data.

## *Absorption*

For the treatment of hospitalized patients, the IV route of administration results in 100% bioavailability of casirivimab+imdevimab. Following IV administration of casirivimab and imdevimab, peak serum concentrations for each antibody is generally achieved at end of infusion.

## *Distribution*

Based on population PK analysis, the total volume of distribution in hospitalized patients is estimated to be 7.072 L and 7.183 L for casirivimab and imdevimab, respectively, consistent with previously reported values estimated from a dataset of non-hospitalized patients.

## *Elimination*

As monoclonal antibodies, casirivimab and imdevimab are not expected to be eliminated by the kidney due to their large molecular weight, or metabolized in the liver, but are catabolised to small peptides and individual amino acids. Casirivimab and imdevimab showed comparable clearance and elimination half-life values in hospitalized patients (see table below). Results from pop-PK analysis suggests an increase in casirivimab and imdevimab clearance in hospitalized patients as compared with non-hospitalized patients with increased degree of disease severity. The estimated mean CL for casirivimab and imdevimab in hospitalized participants requiring high flow oxygen (0.563 L/day and 0.668 L/day, respectively) was higher compared to hospitalized participants not requiring oxygen supplementation or on low flow oxygen (0.358 L/day and 0.417 L/day, respectively). The terminal half-life also decreased as the degree of disease severity increased. Besides, weight – as expected from previous PK analyses – was indicated to be one of the most influential covariates on clearance.

**Table 5 Summary Statistics of Population PK Predicted Half-Life and Clearance for Casirivimab and Imdevimab by Patient Status**

| | | Casirivimab | | Imdevimab | |
|---|---|---|---|---|---|
| PK Parameter | Patient Status | Mean | $5^{th}$,$95^{th}$ percentile | Mean | $5^{th}$,$95^{th}$ percentile |
| Half-life (day) | Outpatient | 28.8 | 19.4, 38.6 | 24.2 | 17.2, 31.6 |
| | Hospitalized overall | 18.4 | 11.0, 26.1 | 16.0 | 10.3, 22.2 |
| | Hospitalized on no oxygen or low flow oxygen | 19.0 | 12.0, 26.6 | 16.4 | 11.2, 22.4 |
| | Hospitalized on high flow oxygen or mechanical ventilation | 12.7 | 9.18, 16.9 | 11.4 | 8.47, 14.6 |
| CL (L/day) | Outpatient | 0.192 | 0.118, 0.304 | 0.235 | 0.150, 0.358 |
| | Hospitalized overall | 0.362 | 0.180, 0.677 | 0.384 | 0.223, 0.761 |
| | Hospitalized on no oxygen or low flow oxygen | 0.358 | 0.201, 0.585 | 0.417 | 0.244, 0.670 |
| | Hospitalized on high flow oxygen or mechanical ventilation | 0.563 | 0.320, 0.847 | 0.668 | 0.387, 1.00 |

CL= clearance; PK = pharmacokinetic.
Source: Pop-PK report R10933-PK-21187-SR-01V1, Table 41, 42, 43, 44 and Table 47, 48, 49, 50.

## *Dose proportionality and time dependencies*

Casirivimab and imdevimab showed similar, linear, and dose-proportional PK following single IV doses of 2400 mg and 8000 mg casirivimab+imdevimab. Concentration of casirivimab and imdevimab in serum on Day 28 (C28) decreased with increasing COVID-19 disease severity (as approximated by study Cohort 3) while concentrations at the end of infusion (EOI) or dose normalized concentration at EOI remained similar between cohorts, indicating that casirivimab and imdevimab clearance increases as disease severity increases.

Only single dose PK data was collected, thus no information on multiple dosing and steady state reached is assessable. Following a single IV dose administration of casirivimab and imdevimab, the increase in concentration at the end of infusion between the 1200 mg and 4000 mg doses of each antibody appeared to be proportional to the increase in dose in hospitalized patients.

A summary of PK parameters after a single IV dose, calculated using a pop-PK model for each antibody is provided in the table below.

**Table 4 Population PK Exposure Predictions for Casirivimab and Imdevimab After a Single Casirivimab+Imdevimab IV Dose of 2400 mg and 8000 mg for Hospitalized Patients**

| PK Parameter | Casirivimab | Imdevimab |
|---|---|---|
| | **1200 mg[a]** | **1200 mg[a]** |
| $AUC_{28}$ (mg*day/L) | 2934.2 (674.1) | 2647.7 (589) |
| $AUC_{inf}$ (mg*day/L) | 5002.7 (1786.6) | 3854.5 (1233.5) |
| $C_{max}$ (mg/L) | 313.6 (135) | 339.7 (141) |
| $C_{28}$ (mg/L) | 55 (18.5) | 40.9 (15.2) |
| | **4000 mg[b]** | **4000 mg[b]** |
| $AUC_{28}$ (mg*day/L) | 8809.7 (2097.5) | 7713.7 (1801.5) |
| $AUC_{inf}$ (mg*day/L) | 13450.2 (4803.4) | 10229.2 (3273.5) |
| $C_{max}$ (mg/L) | 1045 (449.7) | 1131.6 (469.6) |
| $C_{28}$ (mg/L) | 146.8 (56.9) | 101.4 (43.8) |

[a] Estimated from patients on no oxygen or low flow oxygen

[b] Estimated from patients on high flow oxygen or on mechanical ventilation

$AUC_{28}$ = area under the concentration-time curve from time 0 to Day 28; $AUC_{inf}$ = area under the concentration-time curve from time 0 extrapolated to infinity time; $C_{max}$ = maximum serum concentration; $C_{28}$ = serum concentration on Day 28 following single dose; PK = pharmacokinetic.

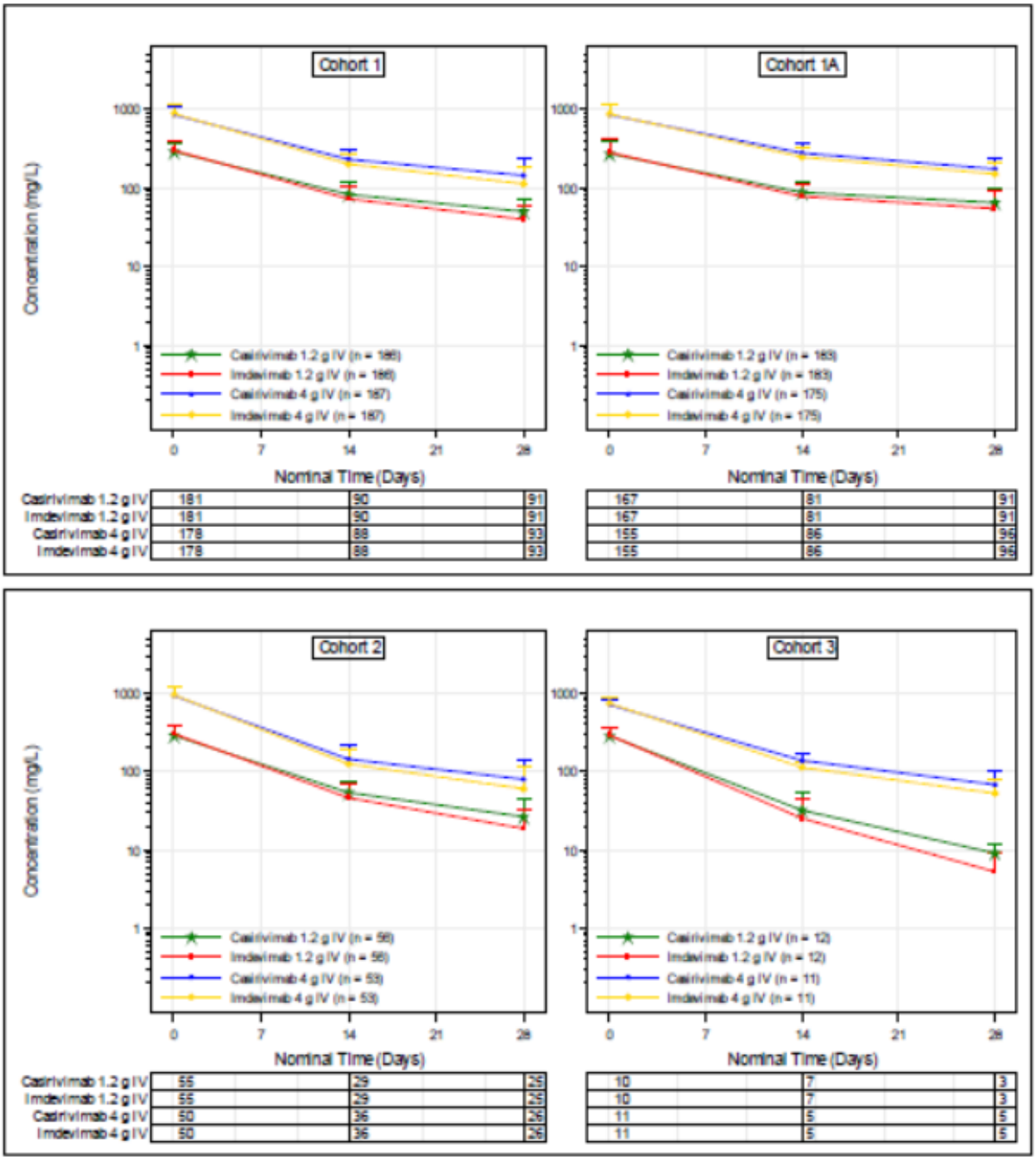
Values are presented as arithmetic mean (±SD) for all parameters.

Source: Pop-PK report R10933-PK-21187-SR-01V1, Table 5 and Table 6.

Phase 1: The increase in serum concentration of each antibody was proportional to the increase in dose from 2.4 g to 8.0 g. Casirivimab and imdevimab exposures in serum increased proportionally with increases in dose from 2.4 g to 8.0 g as evidenced by similar dose-normalized Cmax and AUC0-28. At each dose level, mean concentrations of casirivimab and imdevimab were similar over the month following dosing. However, imdevimab concentrations in serum were lower than casirivimab at later time points, suggesting concentrations of imdevimab decline more rapidly than casirivimab.

Phase 2: The 8.0 g combined dose resulted in greater casirivimab and imdevimab concentrations as compared to the 2.4 g combined dose in all cohorts, with the increase in concentrations appearing dose proportional (see figure below).

**Figure 32: Mean (+SD) Concentrations of Casirivimab and Imdevimab in Serum by Cohort, Treatment Group, and Nominal Time in Hospitalized Adult Patients with COVID-19 (Study R10933-10987-COV-2066, Log-Scaled, Phase 2, PKAS)**




## *Special populations*

The pop-PK models for casirivimab and imdevimab were updated to include data from hospitalized patients enrolled in COV-2066. Additional covariates in this updated model were disease severity, c-reactive protein (CRP), and IL-8 on CL, and hospitalization status on clearance (CL) and Vc for

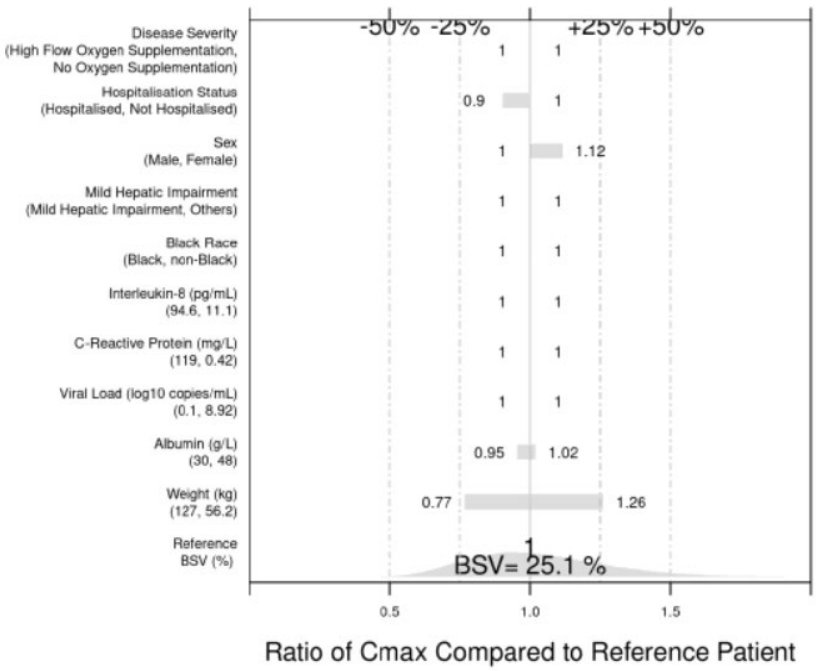
casirivimab; and hospitalization status, disease severity, CRP, and neutrophil-tolymphocyte ratio on CL for imdevimab.

Forest plots demonstrating covariates effects on casirivimab or imdevimab concentration on Day 28 (Cday28) after administration of a single 8000 mg IV casirivimab+imdevimab dose (4000 mg per mAb) are presented in the figures below for casirivimab and imdevimab, respectively. Analogous plots for a single 2400 mg IV dose (1200 mg per mAb) are presented, respectively, that appear comparable.

For casirivimab, the reference subject is defined with the following characteristics: Non-Black, male, hepatic function other than mild hepatic impairment, not hospitalized, not receiving oxygen therapy, weight of 82.2 kg, albumin level of 42 g/L, viral load of 6.29 log10 copies/mL, CRP level of 4.29 mg/L, and IL-8 levels of 28.1 pg/mL. Mild hepatic impairment, Black race, and viral load provided casirivimab exposure ratios of ~1 compared to the reference. Females had approximately 10-13% higher casirivimab exposures compared to males. Both CRP and IL-8 were predicted to have about 3-10% impact on exposures at the 5th and 95th percentiles of CRP and IL-8 in the study population compared to the approximate median value.

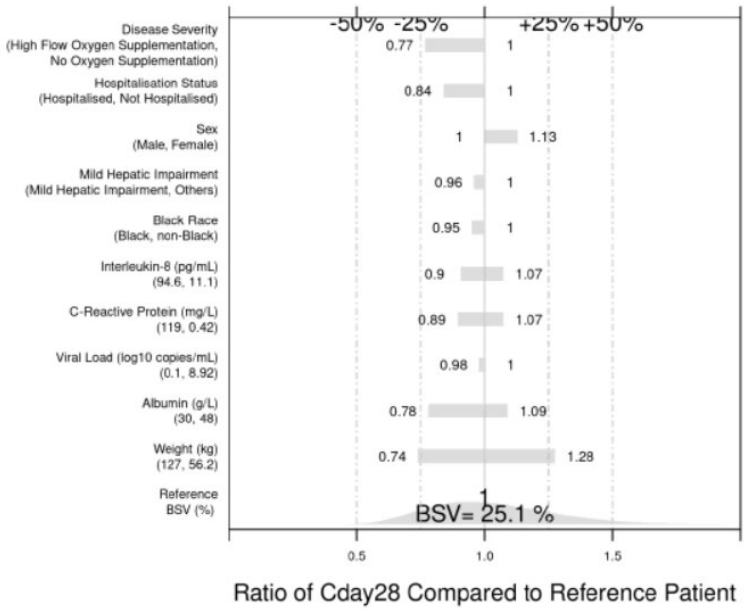
The primary covariates impacting casirivimab PK (> 16% impact on exposures) were disease severity, hospitalization status, albumin, and body weight. Cday28 was predicted to be 23% lower in patients requiring high-intensity oxygen flow or mechanical ventilation compared to reference, 16% lower in hospitalized patients compared to outpatients, 22% lower in patients with lower albumin levels (5th percentile: 30 g/L) compared to the reference level of 42 g/L, and 26% lower in patients with higher body weight (95th percentile: 127 kg) compared to the reference weight of 82.2 kg.

**Figure 16: Impact of Statistically Significant Covariates on Casirivimab $C_{max}$ Following Single Dose of REGEN-COV 8000 mg IV (4000 mg per mAb)**



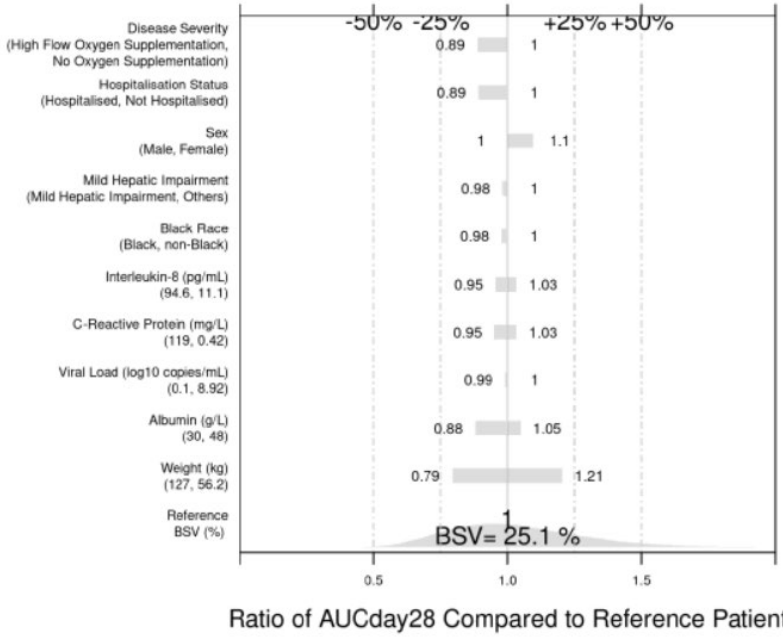

BSV = Between-subject variability; $C_{max}$ = Maximum concentration for a for 28-day interval after single dose administration
Note: Covariate effects are depicted as gray bars representing the ratio of typical predicted $C_{max}$ at that covariate value to the reference condition. The log-normal distribution of inter-individual variability in $C_{max}$ is depicted centered on the reference subject. For continuous covariates, the selected ranges represent the 5$^{th}$ and 95$^{th}$ percentiles of the values in the analysis population.

**Figure 1: Impact of Statistically Significant Covariates on Casirivimab $C_{day28}$ Following Single Dose of REGEN-COV 8000 mg IV (4000 mg per mAb)**




BSV = Between-subject variability; $C_{day28}$ = Concentration on day 28 after single dose administration
Note: Covariate effects are depicted as gray bars representing the ratio of typical predicted $C_{day28}$ at that covariate value to the reference condition. The log-normal distribution of inter-individual variability in $C_{day28}$ is depicted centered on the reference subject. For continuous covariates, the selected ranges represent the 5$^{th}$ and 95$^{th}$ percentiles of the values in the analysis population. Reference individual is non-Black, male, no mild hepatic impairment, not hospitalized, not receiving oxygen therapy, weight of 82.2 kg, albumin level of 42 g/L, viral load of 6.29 log10 copies/mL, CRP level of 4.29 mg/L, and IL-8 levels of 28.1 pg/mL.

**Figure 15: Impact of Statistically Significant Covariates on Casirivimab AUCday28 Following Single Dose of REGEN-COV 8000 mg IV (4000 mg per mAb)**



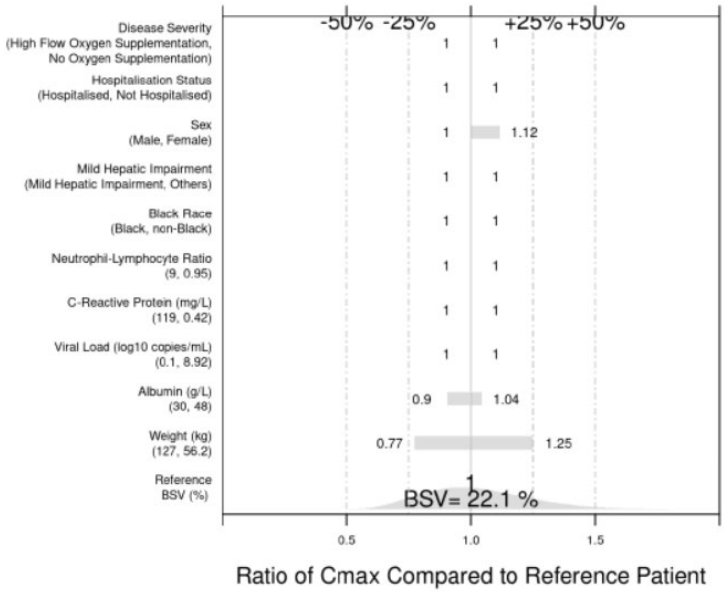

$AUC_{day28}$ = Area under the concentration time curve for 28-day interval after single dose administration; BSV = Between-subject variability

Note: Covariate effects are depicted as gray bars representing the ratio of typical predicted AUC at that covariate value to the reference condition. The log-normal distribution of inter-individual variability in AUC is depicted centered on the reference subject. For continuous covariates, the selected ranges represent the 5th and 95th percentiles of the values in the analysis population.

For imdevimab, the reference subject is defined with the following characteristics: Non-Black, male, hepatic function other than mild hepatic impairment, not hospitalized, not receiving oxygen therapy, weight of 82.2 kg, albumin level of 42 g/L, viral load of 6.29 log10 copies/mL, CRP level of 4.29 mg/L, and NLR of 2.07. Mild hepatic impairment, Black race, viral load, and NLR provided imdevimab exposure ratios of ~1 compared to the reference. Females had approximately 10-14% higher imdevimab exposures compared to males. CRP was predicted to have about 4-11% impact on exposures at the 5th and 95th percentiles of CRP in the study population compared to the approximate median value.

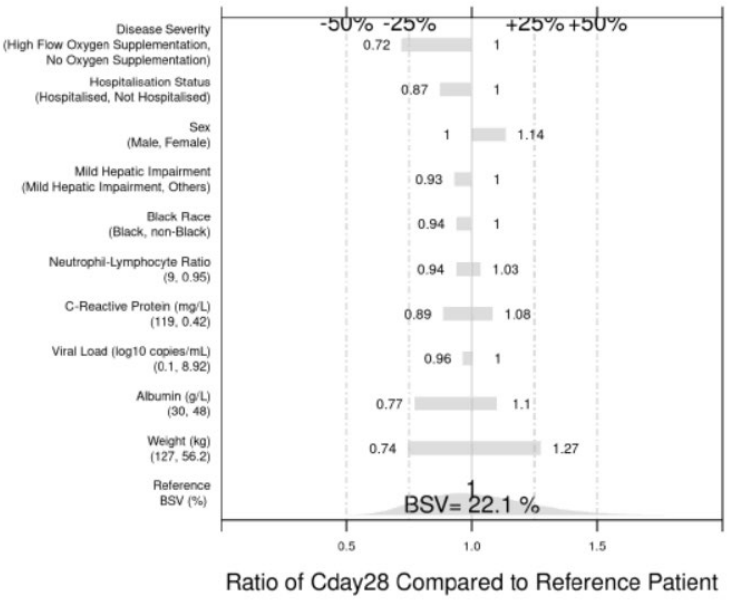
The primary covariates impacting imdevimab PK (> 23% impact on exposures) were disease severity, albumin, and body weight. Cday28 was predicted to be 28% lower in patients requiring high-intensity oxygen flow or mechanical ventilation compared to reference, 23% lower in patients with lower albumin levels (5th percentile: 30 g/L) compared to the reference level of 42 g/L, and 26% lower in patients with higher body weight (95th percentile: 127 kg) compared to the reference weight of 82.2 kg.

**Figure 19: Impact of Statistically Significant Covariates on Imdevimab $C_{max}$ Following Single Dose of REGEN-COV 8000 mg IV (4000 mg per mAb)**



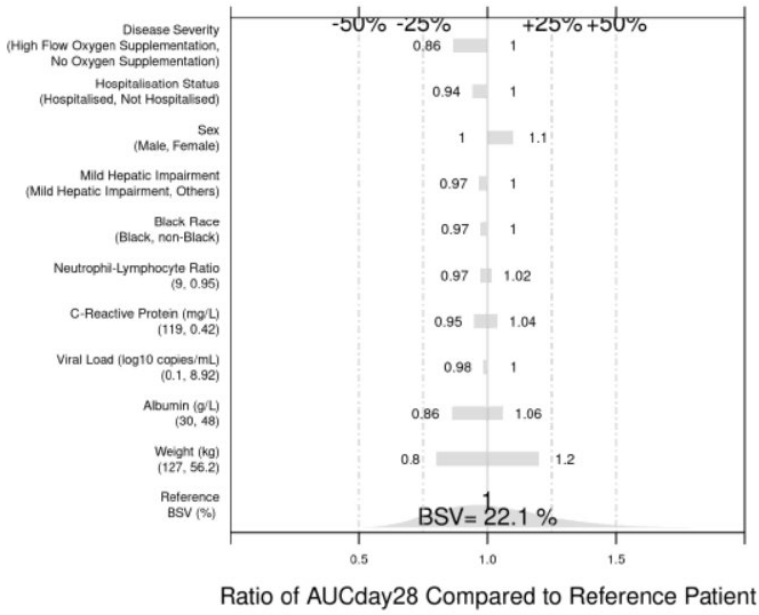

BSV = Between-subject variability; $C_{max}$ = Maximum concentration for a for 28-day interval after single dose administration
Note: Covariate effects are depicted as gray bars representing the ratio of typical predicted $C_{max}$ at that covariate value to the reference condition. The log-normal distribution of inter-individual variability in $C_{max}$ is depicted centered on the reference subject. For continuous covariates, the selected ranges represent the 5th and 95th percentiles of the values in the analysis population.

**Figure 2: Impact of Statistically Significant Covariates on Imdevimab $C_{day28}$ Following Single Dose of REGEN-COV 8000 mg IV (4000 mg per mAb)**




BSV = Between-subject variability; $C_{day28}$ = Concentration on day 28 after single dose administration
Note: Covariate effects are depicted as gray bars representing the ratio of typical predicted $C_{day28}$ at that covariate value to the reference condition. The log-normal distribution of inter-individual variability in $C_{day28}$ is depicted centered on the reference subject. For continuous covariates, the selected ranges represent the 5th and 95th percentiles of the values in the analysis population. Reference individual is non-Black, male, no mild hepatic impairment, not hospitalized, not receiving oxygen therapy, weight of 82.2 kg, albumin level of 42 g/L, viral load of 6.29 log10 copies/mL, CRP level of 4.29 mg/L, and IL-8 levels of 28.1 pg/mL.

**Figure 18: Impact of Statistically Significant Covariates on Imdevimab $AUC_{day28}$ Following Single Dose of REGEN-COV 8000 mg IV (4000 mg per mAb)**

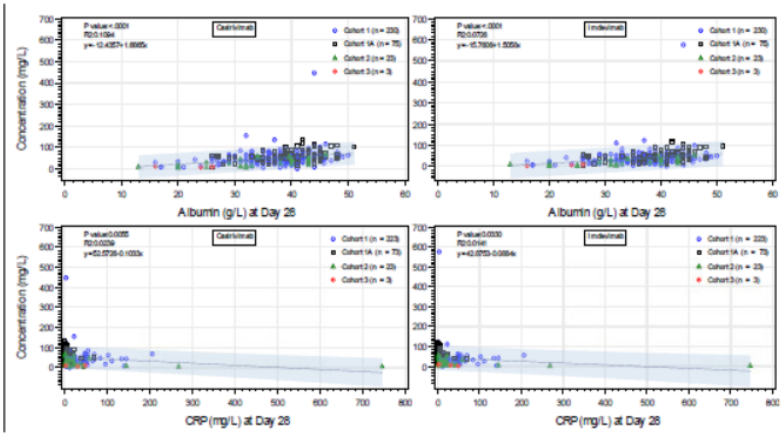



$AUC_{day28}$ = Area under the concentration time curve for 28-day interval after single dose administration; BSV = Between-subject variability
Note: Covariate effects are depicted as gray bars representing the ratio of typical predicted AUC at that covariate value to the reference condition. The log-normal distribution of inter-individual variability in AUC is depicted centered on the reference subject. For continuous covariates, the selected ranges represent the 5$^{th}$ and 95$^{th}$ percentiles of the values in the analysis population.

**Disease severity**

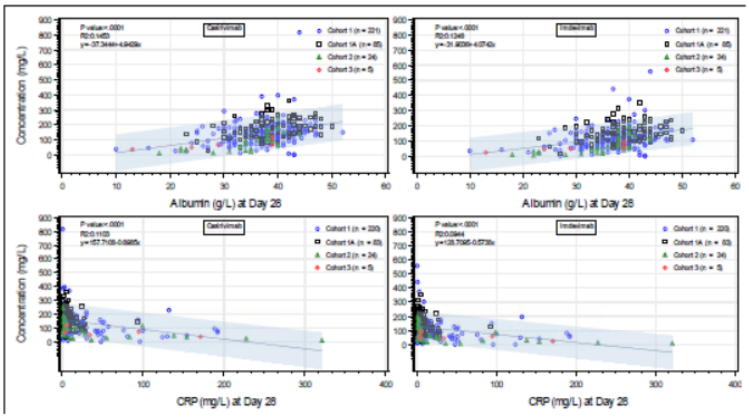
Phase 2: Casirivimab and imdevimab C28 in serum decreased with increasing COVID-19 disease severity, as assessed by Cohort in Phase 2, while Ceoi or dose normalized Ceoi remained similar between Cohorts, indicating that casirivimab and imdevimab clearance increases as disease severity increases (Figure 2 and Figure 3, Table 6). The increased clearance of casirivimab and imdevimab, particularly in patients requiring high intensity oxygen or ventilatory support, may be related to physiological changes secondary to an increased inflammatory state in these patients.
The relationship between casirivimab and imdevimab C28 and serum albumin concentration (baseline and Day 28), as well as the relationship between casirivimab and imdevimab C28 and serum CRP concentration (baseline and Day 28) were evaluated. Weak positive associations between casirivimab and imdevimab C28 and Day 28 concentration of serum albumin, and weak inverse associations between casirivimab and imdevimab C28 and Day 28 concentration of CRP were observed for both the 2400 mg and 8000 mg doses (see figures below).

**Figure 18: Scatter Plot with Regression Line of Casirivimab and Imdevimab $C_{28}$ Versus Albumin Level and hsCRP Level at Day 28 for 2.4 g IV Casirivimab+Imdevimab Dose (1.2 g per mAb) in Hospitalized Patients with COVID-19 (Study R10933-10987-COV-2066, Phase 1, 2, and 3, PKAS)**




CRP = C-reactive protein; hsCRP = High-sensitivity C-reactive protein; IV = Intravenous; mAb = Monoclonal antibody; n = Number of patients with available concentration at Day 28 and albumin or CRP data at Day 28; PKAS = Pharmacokinetic analysis set.
Note: The blue line represents the regression line and the shaded region is the 90% confidence interval.

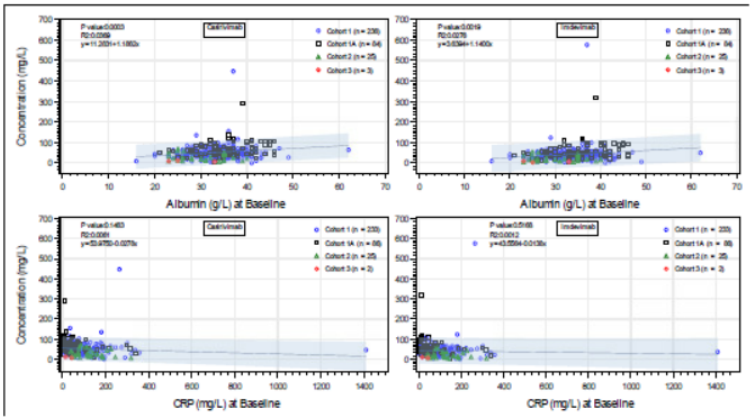
**Figure 19: Scatter Plot with Regression Line of Casirivimab and Imdevimab $C_{28}$ Versus Albumin Level and hsCRP Level at Day 28 for 8.0 g IV Casirivimab+Imdevimab Dose (4.0 g per mAb) in Hospitalized Patients with COVID-19 (Study R10933-10987-COV-2066, Phase 1, 2, and 3, PKAS)**




CRP = C-reactive protein; hsCRP = High-sensitivity C-reactive protein; IV = Intravenous; mAb = Monoclonal antibody; n = Number of patients with available concentration at Day 28 and albumin or CRP data at Day 28; PKAS = Pharmacokinetic analysis set.
Note: The blue line represents the regression line and the shaded region is the 90% confidence interval.

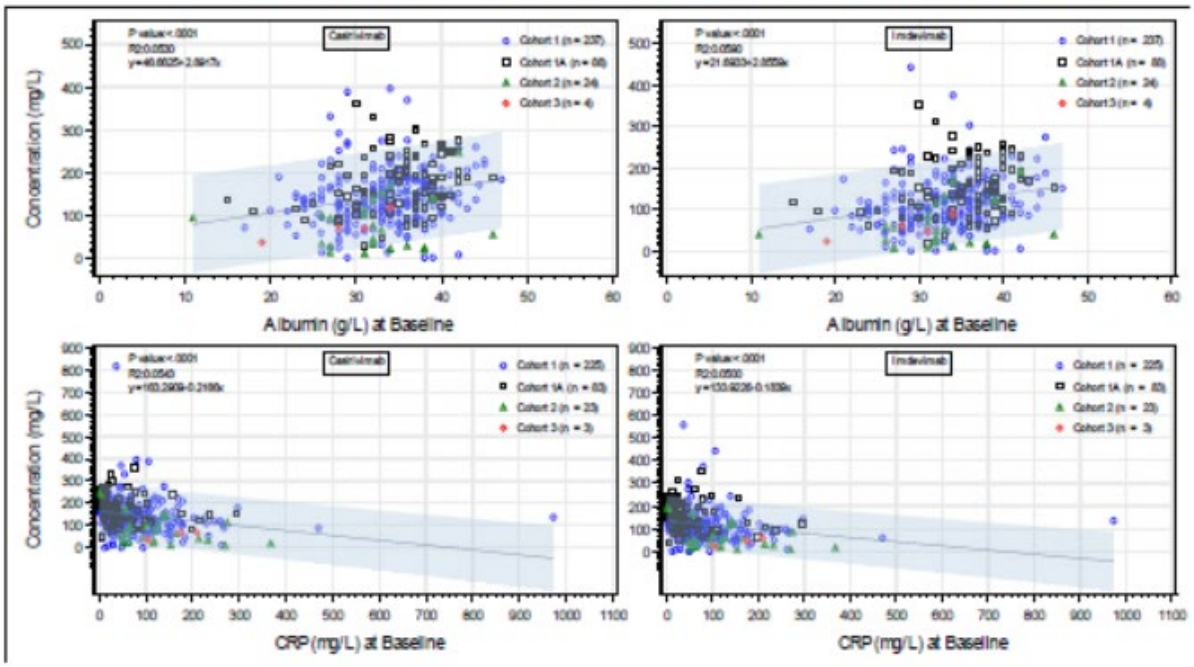
Weak positive associations between casirivimab and imdevimab C28 and baseline concentration of albumin in serum, and week inverse associations between casirivimab and imdevimab C28 and baseline concentration of CRP in serum were also observed at baseline (see the 2 figures below)

**Figure 38: Scatter Plot with Regression Line of Casirivimab and Imdevimab $C_{28}$ Versus Baseline Albumin Level and Baseline hsCRP Level for 2.4 g IV Casirivimab+Imdevimab Dose (1.2 g per mAb) in Hospitalized Patients with COVID-19 (Study R10933-10987-COV-2066, Phase 1, 2, and 3, PKAS)**




$C_{28}$ = Concentration at Day 28; CRP = C-reactive protein; hsCRP = High-sensitivity C-reactive protein; IV = Intravenous; mAb = Monoclonal antibody; n = Number of patients with available concentration at Day 28 and albumin or CRP data at Day 28; PKAS = Pharmacokinetic analysis set.
Note: The blue line represents the regression line and the shaded region is the 90% confidence interval.

**Figure 39: Scatter Plot with Regression Line of Casirivimab and Imdevimab $C_{28}$ Versus Baseline Albumin Level and Baseline hsCRP Level for 8.0 g IV Casirivimab+Imdevimab Dose (4.0 g per mAb) in Hospitalized Patients with COVID-19 (Study R10933-10987-COV-2066, Phase 1, 2, and 3, PKAS)**




$C_{28}$ = Concentration at Day 28; CRP = C-reactive protein; hsCRP = High-sensitivity C-reactive protein; IV = Intravenous; mAb = Monoclonal antibody; n = Number of patients with available concentration at Day 28 and albumin or CRP data at Day 28; PKAS = Pharmacokinetic analysis set.
Note: The blue line represents the regression line and the shaded region is the 90% confidence interval.

Stochastic simulations to predict exposure metrics for patients receiving a single dose of 2400 mg IV casirivimab+imdevimab (1200 mg per mAb for hospitalized patients receiving low-flow oxygen therapy) or 8000 mg IV of casirivimab+imdevimab (4000 mg per mAb for hospitalized patients receiving high-flow oxygen therapy) are presented below.

**Table 37: Exposure Predictions for Casirivimab Following Single 2400mg (1200 mg per mAb) IV Dose for by Hospitalized Adult Patients on Low Flow Oxygen**

| Exposure Metrics | Mean ± SD | Median (5th percentile, 95th percentile) |
|---|---|---|
| $AUC_{d28}$ (day*mg/L) | 2934.2 ± 674.1 | 2870 (1936.6, 4153.7) |
| $AUC_{inf}$ (day*mg/L) | 5002.7 ± 1786.6 | 4697.6 (2681.5, 8360) |
| $C_{day28}$ (mg/L) | 55 ± 18.5 | 54.1 (26.7, 88.1) |
| $C_{max}$ (mg/L) | 313.6 ± 135 | 287.2 (147.2, 578.6) |

$AUC_{day28}$ = Area under the concentration time curve for 28-day interval after dosing; $AUC_{inf}$ = Area under the concentration time curve from time 0 extrapolated to infinite time; IV = Intravenous; $C_{max}$ = Maximum (peak) concentration for a 28-day interval following dosing; $C_{28}$ = Concentration on Day 28 after single dose; SD = Standard deviation

**Table 38: Exposure Predictions for Casirivimab Following Single 8000mg (4000 mg per mAb) IV Dose for by Hospitalized Adult Patients on High Flow Oxygen**

| Exposure Metrics | Mean ± SD | Median (5th percentile, 95th percentile) |
|---|---|---|
| $AUC_{d28}$ (day*mg/L) | 8809.7 ± 2097.5 | 8578.4 (5706.8, 12596.4) |
| $AUC_{inf}$ (day*mg/L) | 13450.2 ± 4803.4 | 12630.1 (7209.6, 22476.7) |
| $C_{day28}$ (mg/L) | 146.8 ± 56.9 | 141.6 (62.2, 249.3) |
| $C_{max}$ (mg/L) | 1045 ± 449.7 | 957 (490.7, 1927.3) |

$AUC_{day28}$ = Area under the concentration time curve for 28-day interval after dosing; $AUC_{inf}$ = Area under the concentration time curve from time 0 extrapolated to infinite time; $C_{max}$ = Maximum (peak) concentration for a 28-day interval following dosing; $C_{28}$ = Concentration on Day 28 after single dose; IV = Intravenous; SD = Standard deviation

**Table 40: Exposure Predictions for Imdevimab Following Single 8000mg (4000 mg per mAb) IV Dose for by Hospitalized Adult Patients on High Flow Oxygen**

| Exposure Metrics | Mean ± SD | Median (5th percentile, 95th percentile) |
|---|---|---|
| $AUC_{d28}$ (day*mg/L) | 7713.7 ± 1801.5 | 7543.3 (5039.3, 10867.5) |
| $AUC_{inf}$ (day*mg/L) | 10229.2 ± 3273.5 | 9705.9 (5774.3, 16262.5) |
| $C_{day28}$ (mg/L) | 101.4 ± 43.8 | 95.5 (38.8, 180.9) |
| $C_{max}$ (mg/L) | 1131.6 ± 469.6 | 1041.6 (547.4, 2044.3) |

$AUC_{day28}$ = Area under the concentration time curve for 28-day interval after dosing; $AUC_{inf}$ = Area under the concentration time curve from time 0 extrapolated to infinite time; $C_{max}$ = Maximum (peak) concentration for a 28-day interval following dosing; $C_{28}$ = Concentration on Day 28 after single dose; IV = Intravenous; SD = Standard deviation

**Table 39: Exposure Predictions for Imdevimab Following Single 2400mg (1200 mg per mAb) IV Dose for by Hospitalized Adult Patients on Low Flow Oxygen**

| Exposure Metrics | Mean ± SD | Median (5th percentile, 95th percentile) |
|---|---|---|
| $AUC_{d28}$ (day*mg/L) | 2647.7 ± 589 | 2606.7 (1777.8, 3696.3) |
| $AUC_{inf}$ (day*mg/L) | 3854.5 ± 1233.5 | 3657.4 (2175.8, 6128) |
| $C_{day28}$ (mg/L) | 40.9 ± 15.2 | 39.7 (18.2, 67.4) |
| $C_{max}$ (mg/L) | 339.7 ± 141 | 312.7 (164.3, 613.6) |

$AUC_{day28}$ = Area under the concentration time curve for 28-day interval after dosing; $AUC_{inf}$ = Area under the concentration time curve from time 0 extrapolated to infinite time; $C_{max}$ = Maximum (peak) concentration for a 28-day interval following dosing; $C_{28}$ = Concentration on Day 28 after single dose; IV = Intravenous; SD = Standard deviation

Two additional simulations were performed where patients in Study 2066 received casirivimab+imdevimab as a single dose of 2400 mg IV (1200 mg per mAb) and 8000 mg IV (4000 mg per mAb) to examine Cday28 values across cohorts:

## APPENDIX W. PREDICTED CASIRIVIMAB CONCENTRATION AT DAY 28 FOR PATIENTS IN STUDY 2066

| Casirivimab Dose | Cohort | Median | 5th, 95th Percentile |
|---|---|---|---|
| 1200 mg IV | Cohort 1A (No Supplemental Oxygen) | 44.3 | (21.4, 76.8) |
| | Cohort 1 (Low-Flow Oxygen) | 38.4 | (17.5, 65.1) |
| | Cohort 2 (High-Flow Oxygen) | 21.3 | (10.5, 41.8) |
| | Cohort 3 (Mechanical Ventilation) | 17.0 | (6.86, 37.6) |
| 4000 mg IV | Cohort 1A (No Supplemental Oxygen) | 148.0 | (71.5, 256) |
| | Cohort 1 (Low-Flow Oxygen) | 128.0 | (58.3, 217) |
| | Cohort 2 (High-Flow Oxygen) | 70.9 | (34.9, 139) |
| | Cohort 3 (Mechanical Ventilation) | 56.7 | (22.9, 125) |

## APPENDIX CC. PREDICTED IMDEVIMAB CONCENTRATION AT DAY 28 FOR PATIENTS IN STUDY 2066

| Imdevimab Dose | Cohort | Median | 5th, 95th Percentile |
|---|---|---|---|
| 1200 mg IV | Cohort 1A (No Supplemental Oxygen) | 36.0 | (16.9, 64) |
| | Cohort 1 (Low-Flow Oxygen) | 30.0 | (13.3, 51) |
| | Cohort 2 (High-Flow Oxygen) | 15.4 | (6.58, 30.4) |
| | Cohort 3 (Mechanical Ventilation) | 11.5 | (4.69, 27.5) |
| 4000 mg IV | Cohort 1A (No Supplemental Oxygen) | 120.0 | (56.5, 213) |
| | Cohort 1 (Low-Flow Oxygen) | 100.0 | (44.3, 170) |
| | Cohort 2 (High-Flow Oxygen) | 51.4 | (21.9, 101) |
| | Cohort 3 (Mechanical Ventilation) | 38.4 | (15.6, 91.5) |

Exposure metrics for casirivimab and imdevimab were calculated using the individual full concentration-time profiles predicted following either a single dose of 2400 mg IV or 8000 mg IV of casirivimab+imdevimab and are provided in the tables below, respectively.

**Table 45: Post-Hoc Exposure Predictions by Covariate Categories for Casirivimab Following Single Dose of REGEN-COV 2400 mg IV (1200 mg per mAb)**

| Covariate | Category | | $C_{max}$ (mg/L) | $C_{day28}$ (mg/L) | $AUC_{d28}$ (day*mg/L) | $AUC_{inf}$ (day*mg/L) |
|---|---|---|---|---|---|---|
| C-reactive Protein | < 4.29 mg/L | N | 2581.0 | 2581.0 | 2581.0 | 2581.0 |
| | | Mean | 365.5 | 63.4 | 3332.2 | 5712.0 |
| | | Med | 332.7 | 63.1 | 3316.8 | 5592.5 |
| | | SD | 417.2 | 14.3 | 559.8 | 1358.9 |
| | >= 4.29 mg/L | N | 2429.0 | 2429.0 | 2429.0 | 2429.0 |
| | | Mean | 303.3 | 41.5 | 2619.0 | 3851.1 |
| | | Med | 296.7 | 40.4 | 2601.0 | 3672.4 |
| | | SD | 71.7 | 17.6 | 653.6 | 1417.1 |
| Hospitalization Status | Hospitalized | N | 1294.0 | 1294.0 | 1294.0 | 1294.0 |
| | | Mean | 289.7 | 31.0 | 2269.0 | 3038.9 |
| | | Med | 284.9 | 30.3 | 2254.1 | 2951.2 |
| | | SD | 71.6 | 13.3 | 545.7 | 1007.6 |
| | Outpatient | N | 3716.0 | 3716.0 | 3716.0 | 3716.0 |
| | | Mean | 351.3 | 60.4 | 3236.2 | 5426.4 |
| | | Med | 325.7 | 60.0 | 3214.9 | 5306.8 |
| | | SD | 350.4 | 14.9 | 568.2 | 1391.1 |
| Interleukin-8 | < 28.1 pg/mL | N | 499.0 | 499.0 | 499.0 | 499.0 |
| | | Mean | 286.6 | 33.4 | 2344.2 | 3202.1 |
| | | Med | 281.1 | 31.9 | 2295.7 | 3045.5 |
| | | SD | 69.7 | 13.3 | 529.4 | 1032.0 |
| | >= 28.1 pg/mL | N | 795.0 | 795.0 | 795.0 | 795.0 |
| | | Mean | 291.6 | 29.4 | 2221.8 | 2936.5 |
| | | Med | 286.8 | 28.9 | 2226.3 | 2877.5 |
| | | SD | 72.7 | 13.0 | 550.8 | 978.8 |
| Supplemental Oxygen Therapy | High Flow Oxygen/Mechanical Ventilation | N | 125.0 | 125.0 | 125.0 | 125.0 |
| | | Mean | 276.4 | 15.6 | 1683.3 | 1965.3 |
| | | Med | 273.0 | 13.9 | 1615.8 | 1845.4 |
| | | SD | 66.7 | 8.0 | 425.1 | 621.6 |
| | Low Flow Oxygen | N | 1509.0 | 1509.0 | 1509.0 | 1509.0 |
| | | Mean | 360.7 | 45.7 | 2767.8 | 4269.2 |
| | | Med | 307.3 | 43.7 | 2697.6 | 4016.6 |
| | | SD | 543.9 | 20.7 | 770.9 | 1728.1 |
| | No Oxygen Therapy | N | 3376.0 | 3376.0 | 3376.0 | 3376.0 |
| | | Mean | 326.2 | 57.3 | 3132.3 | 5156.7 |
| | | Med | 319.1 | 57.3 | 3128.5 | 5047.6 |
| | | SD | 73.0 | 16.5 | 598.1 | 1497.0 |

$AUC_{day28}$ = Area under the concentration time curve for 28-day interval after dosing; $AUC_{inf}$ = Area under the concentration time curve from time 0 extrapolated to infinite time; $C_{max}$ = Maximum (peak) concentration for a 28-day interval following dosing; $C_{28}$ = Concentration on Day 28 after single dose; IV = Intravenous; SD = Standard deviation

**Table 46: Post-Hoc Exposure Predictions by Covariate Categories for Casirivimab Following Single Dose of REGEN-COV 8000 mg IV (4000 mg per mAb)**

| Covariate | Category | | $C_{max}$ (mg/L) | $C_{day28}$ (mg/L) | $AUC_{d28}$ (day*mg/L) | $AUC_{inf}$ (day*mg/L) |
|---|---|---|---|---|---|---|
| C-reactive Protein | < 4.29 mg/L | N | 2581.0 | 2581.0 | 2581.0 | 2581.0 |
| | | Mean | 1218.4 | 211.5 | 11107.3 | 19040.1 |
| | | Med | 1109.0 | 210.3 | 11055.9 | 18641.8 |
| | | SD | 1390.6 | 47.8 | 1866.0 | 4529.6 |
| | >= 4.29 mg/L | N | 2429.0 | 2429.0 | 2429.0 | 2429.0 |
| | | Mean | 1011.0 | 138.2 | 8729.9 | 12837.0 |
| | | Med | 988.9 | 134.8 | 8670.0 | 12241.3 |
| | | SD | 239.0 | 58.7 | 2178.6 | 4723.6 |
| Hospitalization Status | Hospitalized | N | 1294.0 | 1294.0 | 1294.0 | 1294.0 |
| | | Mean | 965.7 | 103.2 | 7563.3 | 10129.8 |
| | | Med | 949.6 | 100.9 | 7513.6 | 9837.5 |
| | | SD | 238.5 | 44.2 | 1819.0 | 3358.6 |
| | Outpatient | N | 3716.0 | 3716.0 | 3716.0 | 3716.0 |
| | | Mean | 1170.8 | 201.3 | 10787.4 | 18088.1 |
| | | Med | 1085.7 | 200.0 | 10716.2 | 17689.3 |
| | | SD | 1168.0 | 49.8 | 1893.9 | 4637.1 |
| Interleukin-8 | < 28.1 pg/mL | N | 499.0 | 499.0 | 499.0 | 499.0 |
| | | Mean | 955.3 | 111.2 | 7814.1 | 10673.7 |
| | | Med | 937.1 | 106.4 | 7652.4 | 10151.6 |
| | | SD | 232.3 | 44.3 | 1764.8 | 3440.1 |
| | >= 28.1 pg/mL | N | 795.0 | 795.0 | 795.0 | 795.0 |
| | | Mean | 972.2 | 98.1 | 7405.9 | 9788.5 |
| | | Med | 956.1 | 96.4 | 7421.1 | 9591.6 |
| | | SD | 242.3 | 43.5 | 1835.9 | 3262.5 |
| Supplemental Oxygen Therapy | High Flow Oxygen/Mechanical Ventilation | N | 125.0 | 125.0 | 125.0 | 125.0 |
| | | Mean | 921.3 | 52.1 | 5611.1 | 6551.1 |
| | | Med | 909.9 | 46.2 | 5385.9 | 6151.5 |
| | | SD | 222.4 | 26.7 | 1417.1 | 2072.1 |
| | Low Flow Oxygen | N | 1509.0 | 1509.0 | 1509.0 | 1509.0 |
| | | Mean | 1202.3 | 152.2 | 9226.1 | 14230.8 |
| | | Med | 1024.5 | 145.7 | 8992.1 | 13388.7 |
| | | SD | 1813.1 | 69.0 | 2569.8 | 5760.3 |
| | No Oxygen Therapy | N | 3376.0 | 3376.0 | 3376.0 | 3376.0 |
| | | Mean | 1087.4 | 191.2 | 10441.2 | 17189.1 |
| | | Med | 1063.6 | 190.9 | 10428.2 | 16825.4 |
| | | SD | 243.2 | 54.8 | 1993.6 | 4989.9 |

$AUC_{day28}$ = Area under the concentration time curve for 28-day interval after dosing; $AUC_{inf}$ = Area under the concentration time curve from time 0 extrapolated to infinite time; $C_{max}$ = Maximum (peak) concentration for a 28-day interval following dosing; $C_{28}$ = Concentration on Day 28 after single dose; IV = Intravenous; SD = Standard deviation

**Table 51: Post-Hoc Exposure Predictions by Covariate Categories for Imdevimab Following Single Dose of REGEN-COV 2400 mg IV (1200 mg per mAb)**

| Covariate | Category | | $C_{max}$ (mg/L) | $C_{day28}$ (mg/L) | $AUC_{d28}$ (day*mg/L) | $AUC_{inf}$ (day*mg/L) |
|---|---|---|---|---|---|---|
| C-reactive Protein | < 4.29 mg/L | N | 2581.0 | 2581.0 | 2581.0 | 2581.0 |
| | | Mean | 365.5 | 63.4 | 3332.2 | 5712.0 |
| | | Med | 332.7 | 63.1 | 3316.8 | 5592.5 |
| | | SD | 417.2 | 14.3 | 559.8 | 1358.9 |
| | >= 4.29 mg/L | N | 2429.0 | 2429.0 | 2429.0 | 2429.0 |
| | | Mean | 303.3 | 41.5 | 2619.0 | 3851.1 |
| | | Med | 296.7 | 40.4 | 2601.0 | 3672.4 |
| | | SD | 71.7 | 17.6 | 653.6 | 1417.1 |
| Hospitalization Status | Hospitalized | N | 1294.0 | 1294.0 | 1294.0 | 1294.0 |
| | | Mean | 289.7 | 31.0 | 2269.0 | 3038.9 |
| | | Med | 284.9 | 30.3 | 2254.1 | 2951.2 |
| | | SD | 71.6 | 13.3 | 545.7 | 1007.6 |
| | Outpatient | N | 3716.0 | 3716.0 | 3716.0 | 3716.0 |
| | | Mean | 351.3 | 60.4 | 3236.2 | 5426.4 |
| | | Med | 325.7 | 60.0 | 3214.9 | 5306.8 |
| | | SD | 350.4 | 14.9 | 568.2 | 1391.1 |
| Neutrophil-Lymphocyte Ratio | < 2.07 | N | 2367.0 | 2367.0 | 2367.0 | 2367.0 |
| | | Mean | 353.7 | 61.3 | 3259.9 | 5513.9 |
| | | Med | 327.5 | 61.0 | 3248.2 | 5381.4 |
| | | SD | 342.9 | 15.2 | 577.2 | 1426.3 |
| | >= 2.07 | N | 2643.0 | 2643.0 | 2643.0 | 2643.0 |
| | | Mean | 318.9 | 45.2 | 2741.5 | 4179.2 |
| | | Med | 306.0 | 44.2 | 2736.4 | 4001.7 |
| | | SD | 265.7 | 19.6 | 717.1 | 1620.2 |
| Supplemental Oxygen Therapy | High Flow Oxygen/Mechanical Ventilation | N | 125.0 | 125.0 | 125.0 | 125.0 |
| | | Mean | 276.4 | 15.6 | 1683.3 | 1965.3 |
| | | Med | 273.0 | 13.9 | 1615.8 | 1845.4 |
| | | SD | 66.7 | 8.0 | 425.1 | 621.6 |
| | Low Flow Oxygen | N | 1509.0 | 1509.0 | 1509.0 | 1509.0 |
| | | Mean | 360.7 | 45.7 | 2767.8 | 4269.2 |
| | | Med | 307.3 | 43.7 | 2697.6 | 4016.6 |
| | | SD | 543.9 | 20.7 | 770.9 | 1728.1 |
| | No Oxygen Therapy | N | 3376.0 | 3376.0 | 3376.0 | 3376.0 |
| | | Mean | 326.2 | 57.3 | 3132.3 | 5156.7 |
| | | Med | 319.1 | 57.3 | 3128.5 | 5047.6 |
| | | SD | 73.0 | 16.5 | 598.1 | 1497.0 |

$AUC_{day28}$ = Area under the concentration time curve for 28-day interval after dosing; $AUC_{inf}$ = Area under the concentration time curve from time 0 extrapolated to infinite time; $C_{max}$ = Maximum (peak) concentration for a 28-day interval following dosing; $C_{28}$ = Concentration on Day 28 after single dose; IV = Intravenous; SD = Standard deviation

**Table 52: Post-Hoc Exposure Predictions by Covariate Categories for Imdevimab Following Single Dose of REGEN-COV 8000 mg IV (4000 mg per mAb)**

| Covariate | Category | | $C_{max}$ (mg/L) | $C_{day28}$ (mg/L) | $AUC_{d28}$ (day*mg/L) | $AUC_{inf}$ (day*mg/L) |
|---|---|---|---|---|---|---|
| C-reactive Protein | < 4.29 mg/L | N | 2581.0 | 2581.0 | 2581.0 | 2581.0 |
| | | Mean | 1218.4 | 211.5 | 11107.3 | 19040.1 |
| | | Med | 1109.0 | 210.3 | 11055.9 | 18641.8 |
| | | SD | 1390.6 | 47.8 | 1866.0 | 4529.6 |
| | >= 4.29 mg/L | N | 2429.0 | 2429.0 | 2429.0 | 2429.0 |
| | | Mean | 1011.0 | 138.2 | 8729.9 | 12837.0 |
| | | Med | 988.9 | 134.8 | 8670.0 | 12241.3 |
| | | SD | 239.0 | 58.7 | 2178.6 | 4723.6 |
| Hospitalization Status | Hospitalized | N | 1294.0 | 1294.0 | 1294.0 | 1294.0 |
| | | Mean | 965.7 | 103.2 | 7563.3 | 10129.8 |
| | | Med | 949.6 | 100.9 | 7513.6 | 9837.5 |
| | | SD | 238.5 | 44.2 | 1819.0 | 3358.6 |
| | Outpatient | N | 3716.0 | 3716.0 | 3716.0 | 3716.0 |
| | | Mean | 1170.8 | 201.3 | 10787.4 | 18088.1 |
| | | Med | 1085.7 | 200.0 | 10716.2 | 17689.3 |
| | | SD | 1168.0 | 49.8 | 1893.9 | 4637.1 |
| Neutrophil-Lymphocyte Ratio | < 2.07 | N | 2367.0 | 2367.0 | 2367.0 | 2367.0 |
| | | Mean | 1179.1 | 204.3 | 10866.3 | 18379.5 |
| | | Med | 1091.6 | 203.3 | 10827.3 | 17937.9 |
| | | SD | 1143.1 | 50.8 | 1923.9 | 4754.5 |
| | >= 2.07 | N | 2643.0 | 2643.0 | 2643.0 | 2643.0 |
| | | Mean | 1063.0 | 150.5 | 9138.2 | 13930.8 |
| | | Med | 1020.1 | 147.4 | 9121.2 | 13339.0 |
| | | SD | 885.8 | 65.2 | 2390.2 | 5400.7 |
| Supplemental Oxygen Therapy | High Flow Oxygen/Mechanical Ventilation | N | 125.0 | 125.0 | 125.0 | 125.0 |
| | | Mean | 921.3 | 52.1 | 5611.1 | 6551.1 |
| | | Med | 909.9 | 46.2 | 5385.9 | 6151.5 |
| | | SD | 222.4 | 26.7 | 1417.1 | 2072.1 |
| | Low Flow Oxygen | N | 1509.0 | 1509.0 | 1509.0 | 1509.0 |
| | | Mean | 1202.3 | 152.2 | 9226.1 | 14230.8 |
| | | Med | 1024.5 | 145.7 | 8992.1 | 13388.7 |
| | | SD | 1813.1 | 69.0 | 2569.8 | 5760.3 |
| | No Oxygen Therapy | N | 3376.0 | 3376.0 | 3376.0 | 3376.0 |
| | | Mean | 1087.4 | 191.2 | 10441.2 | 17189.1 |
| | | Med | 1063.6 | 190.9 | 10428.2 | 16825.4 |
| | | SD | 243.2 | 54.8 | 1993.6 | 4989.9 |

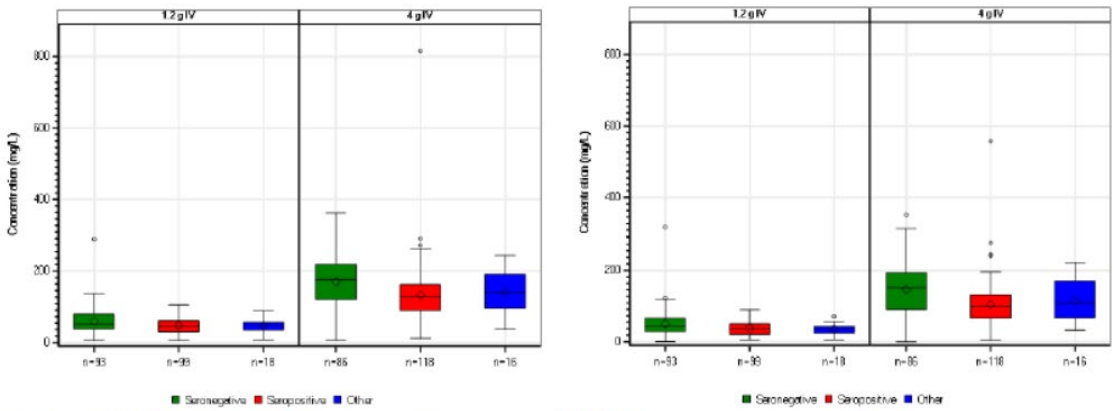
$AUC_{day28}$ = Area under the concentration time curve for 28-day interval after dosing; $AUC_{inf}$ = Area under the concentration time curve from time 0 extrapolated to infinite time; $C_{max}$ = Maximum (peak) concentration for a 28-day interval following dosing; $C_{28}$ = Concentration on Day 28 after single dose; IV = Intravenous; SD = Standard deviation

***Serostatus***

Concentrations of casirivimab and imdevimab in serum were not affected by baseline serostatus (positive or negative) or by baseline viral load (Phase 2: two first figures below; Phase 3: 3rd and 4th figures below), indicating that baseline viral load and serostatus did not alter the pharmacokinetics of either casirivimab or imdevimab.

**Figure 28: Concentrations of (A) Casirivimab and (B) Imdevimab in Serum at Day 28 by Treatment Group and Baseline Serostatus (All Cohorts [Phase 2]; PKAS)**

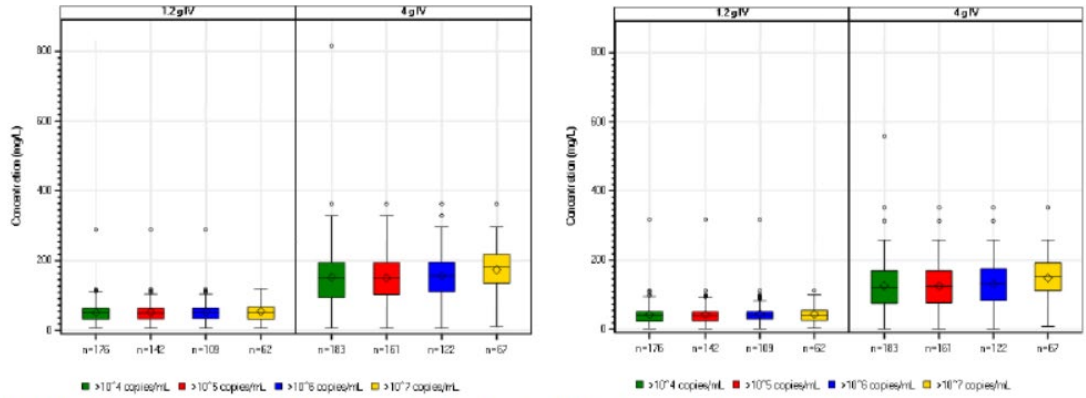
**(A) Casirivimab** **(B) Imdevimab**




BLQ = Below the limit of quantitation; IV = Intravenous; n = Number of patients; PKAS = Pharmacokinetic analysis set; Q = Quartile.
Notes: BLQs were set to 0.
Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence respectively; circles are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.
Source: Appendix 16.1.15 Figures 5 and 6

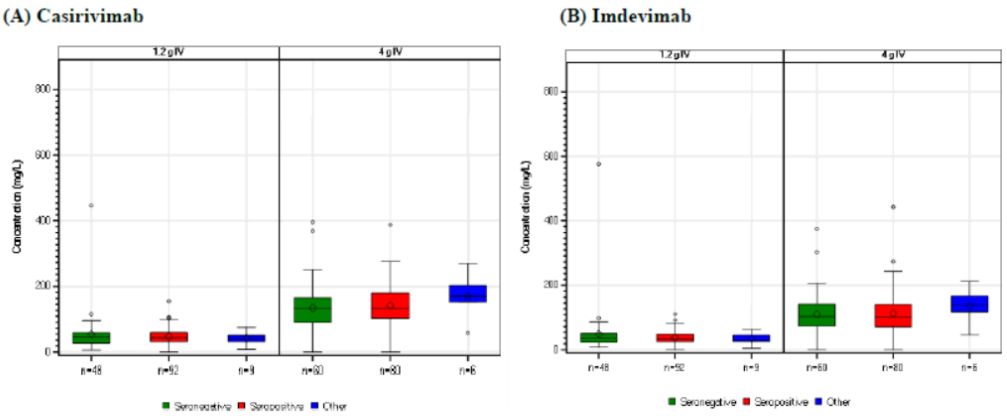
**Figure 29: Concentrations of (A) Casirivimab and (B) Imdevimab in Serum at Day 28 by Treatment Group and Baseline Viral Load Category (All Cohorts [Phase 2]; PKAS)**

**(A) Casirivimab** **(B) Imdevimab**



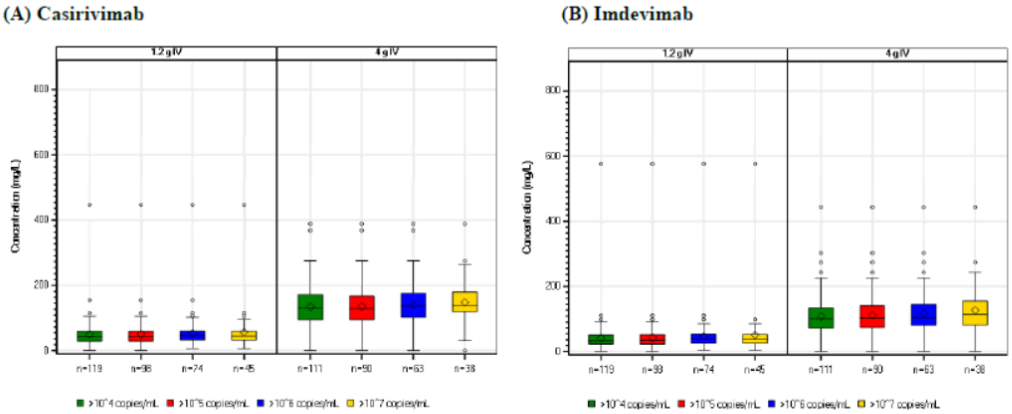

BLQ = Below the limit of quantitation; IV = Intravenous; n = Number of patients; PKAS = Pharmacokinetic analysis set; Q = Quartile.
Notes: BLQs were set to 0.
Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence respectively; circles are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.
Source: Appendix 16.1.15 Figures 7 and 8

**Figure 30: Concentrations of (A) Casirivimab and (B) Imdevimab in Serum at Day 28 by Treatment Group and Baseline Serostatus (Cohort 1 [Phase 3]; PKAS)**




BLQ = Below the limit of quantitation; IV = Intravenous; n = Number of patients; PKAS = Pharmacokinetic analysis set; Q = Quartile.
Notes: BLQs were set to 0.
Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence respectively; circles are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.
Source: Appendix 16.1.15 Figures 10 and 11

**Figure 31: Concentrations of (A) Casirivimab and (B) Imdevimab in Serum at Day 28 by Treatment Group and Baseline Viral Load Category (Cohort 1 [Phase 3]; PKAS)**




BLQ = Below the limit of quantitation; IV = Intravenous; n = Number of patients; PKAS = Pharmacokinetic analysis set; Q = Quartile.
Notes: BLQs were set to 0.
Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence respectively; circles are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.
Source: Appendix 16.1.15 Figures 12 and 13

### *Pharmacokinetic interaction studies*

N/A

### *Pharmacokinetics using human biomaterials*

N/A

## 2.3.3. Pharmacodynamics

### *Mechanism of action*

Casirivimab and imdevimab are potent neutralizing antibodies that block the interaction between the transmembrane S protein (spike protein of the SARS-CoV-2 virus) and its canonical host receptor angiotensin-converting enzyme 2 (ACE2). The combination of casirivimab+imdevimab retained neutralization potency against the full sequences or key residues of the spike protein of the B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.6172 (Delta), AY.1/2 (commonly referred to as Delta+),

B.1.617.1 (Kappa), C.37 (Lambda), and B.1.619 (Mu) variants. Likewise, casirivimab+imdevimab neutralized the L452R and E484K mutations, which have been flagged by the CDC as substitutions of therapeutic concern. Compared with reference virus, the B.1.1.529/BA.1 (Omicron) variant is approximately a thousand-fold less susceptible to casirivimab+imdevimab. Therefore, casirivimab+imdevimab is expected to retain activity against all currently known SARS-CoV-2 VUS except for Omicron.

## *Primary and secondary pharmacology*

Immunogenicity

This is the first time that clinical pharmacology results including NAb analyses are submitted in this product registration. There was no impact of immunogenicity on concentrations of casirivimab or imdevimab in serum, as indicated below.

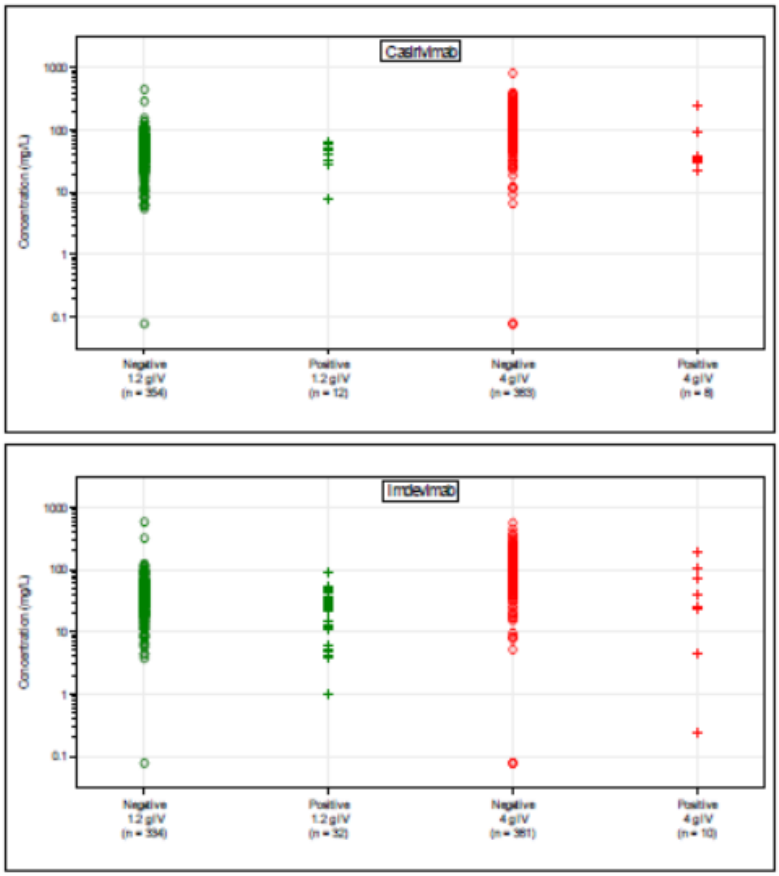
The incidence of ADA and neutralizing antibodies in hospitalized patients receiving casirivimab and imdevimab as a single IV dose was low and similar for all treatment groups, i.e. 2400 mg, 8000 mg and placebo: The majority of hospitalized patients were negative for ADA at all times (96.0% for casirivimab; 91.4% for imdevimab), indicating minimal immunogenicity following administration of single IV doses of 2400 mg or 8000 mg of casirivimab+imdevimab.
The incidence of treatment-emergent immunogenicity for patients who received active treatment (2400 mg and 8000 mg combined) was 2.1% (21/1001) and 4.4% (44/1001) for casirivimab and imdevimab, respectively. Patients who received placebo had an immunogenicity rate of 1.4% (7/503) and 3.0% (15/503) for casirivimab and imdevimab, respectively. In the combined treatment-emergent and treatment-boosted group from patients who received active treatment, most (greater than 95%) of the few ADA responses detected were low, with no high titer response observed.

**Table 11: Summary of Casirivimab and Imdevimab ADA Status and ADA Category by Treatment Group in Hospitalized Adult Patients with COVID-19 (Study R10933-10987-COV-2066, AAS)**

| Analyte<br>ADA Status and Category | Placebo<br>n (%) | Casirivimab +Imdevimab 2.4 g IV<br>n (%) | Casirivimab +Imdevimab 8.0 g IV<br>n (%) | All Active Doses<br>n (%) | Overall<br>n (%) |
|---|---|---|---|---|---|
| Casirivimab | | | | | |
| ADA Analysis Set | 503 (100%) | 504 (100%) | 497 (100%) | 1001 (100%) | 1504 (100%) |
| Negative | 489 (97.2%) | 471 (93.5%) | 484 (97.4%) | 955 (95.4%) | 1444 (96.0%) |
| Pre-existing Immunoreactivity | 7 (1.4%) | 20 (4.0%) | 5 (1.0%) | 25 (2.5%) | 32 (2.1%) |
| Treatment-Boosted Response | 0 | 0 | 0 | 0 | 0 |
| Treatment-Emergent Response | 7 (1.4%) | 13 (2.6%) | 8 (1.6%) | 21 (2.1%) | 28 (1.9%) |
| Imdevimab | | | | | |
| ADA Analysis Set | 503 (100%) | 504 (100%) | 497 (100%) | 1001 (100%) | 1504 (100%) |
| Negative | 467 (92.8%) | 444 (88.1%) | 463 (93.2%) | 907 (90.6%) | 1374 (91.4%) |
| Pre-existing Immunoreactivity | 20 (4.0%) | 26 (5.2%) | 22 (4.4%) | 48 (4.8%) | 68 (4.5%) |
| Treatment-Boosted Response | 1 (0.2%) | 1 (0.2%) | 1 (0.2%) | 2 (0.2%) | 3 (0.2%) |
| Treatment-Emergent Response | 15 (3.0%) | 33 (6.5%) | 11 (2.2%) | 44 (4.4%) | 59 (3.9%) |

AAS = Anti-drug antibody analysis set; ADA = Anti-drug antibody; IV = Intravenous; n = Number of patients contributing to each category.

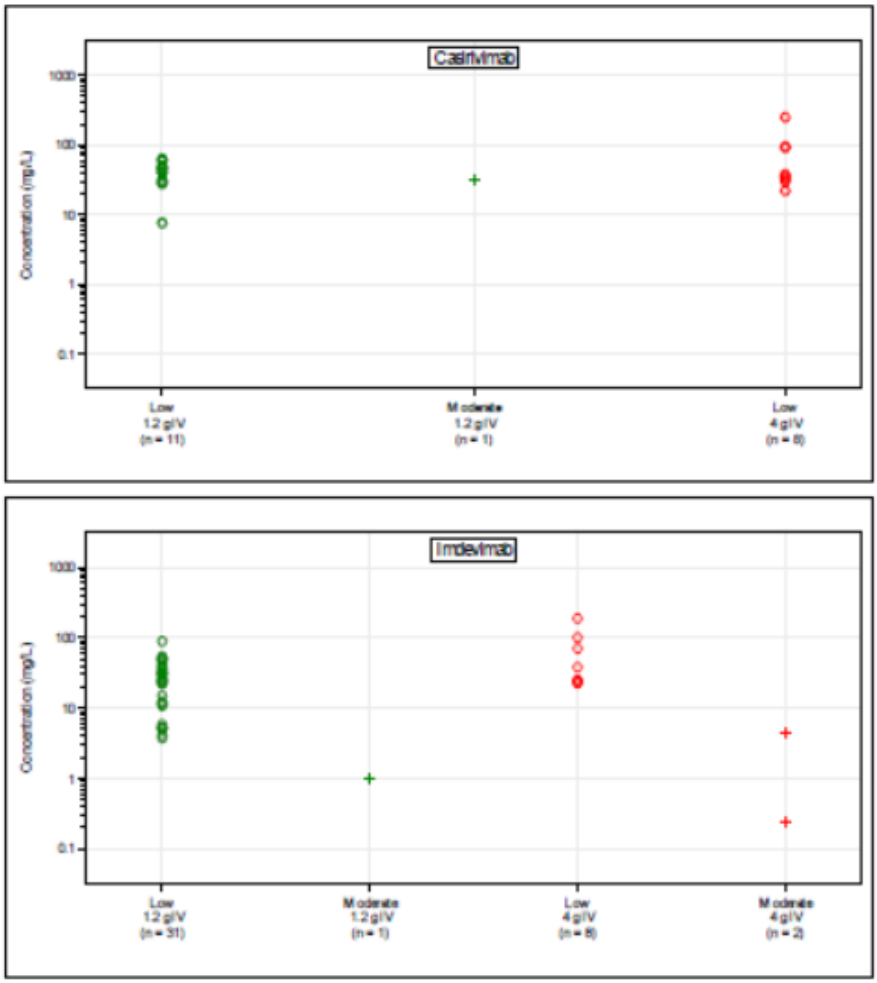
**Figure 21: Dot Plot of Casirivimab and Imdevimab $C_{28}$ in Serum by Treatment Group and ADA Status in Hospitalized Adult Patients with COVID-19 (Study R10933-10987-COV-2066, PKAS and AAS)**




BLQ = Below the limit of quantitation; AAS = ADA analysis set; ADA = Anti-drug antibody; IV = Intravenous; n = Number of patients; PKAS = Pharmacokinetic analysis set.
Note: BLQs were set to LLOQ/2.

In patients with treatment-emergent or treatment-boosted ADA, casirivimab and imdevimab C28 in serum appeared similar for patients with low and moderate maximum titer, although too few patients had moderate titer to draw definitive conclusions (see figure below).

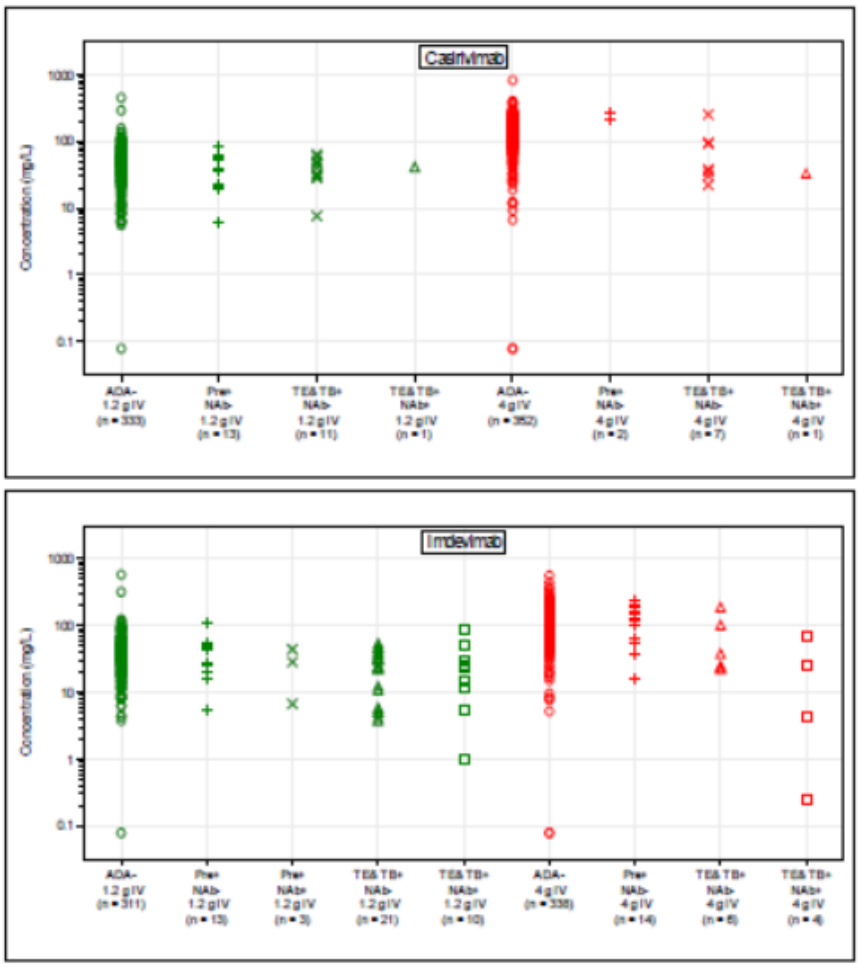
**Figure 22: Dot Plot of Casirivimab and Imdevimab $C_{28}$ in Serum by Treatment Group and Maximum Titer Category in Treatment-emergent and Treatment-boosted Hospitalized Adult Patients with COVID-19 (Study R10933-10987-COV-2066, PKAS and AAS)**




BLQ = Below the limit of quantitation; AAS = ADA analysis set; ADA = Anti-drug antibody; IV = Intravenous; PKAS = Pharmacokinetic analysis set
Note: BLQs were set to LLOQ/2.

For patients who had pre-existing, treatment-emergent, or treatment-boosted ADA with or without NAb, casirivimab and imdevimab C28 in serum were similar and within the range of values in patients who were ADA negative (see figure below).

**Figure 23: Dot Plot of Casirivimab and Imdevimab $C_{2s}$ in Serum by Treatment Group, ADA Status and NAb Status in Hospitalized Adult Patients with COVID-19 (Study R10933-10987-COV-2066, PKAS and AAS)**




BLQ = Below the limit of quantitation; AAS = ADA analysis set; ADA = Anti-drug antibody; ADA- = ADA negative; IV = Intravenous; n = Number of patients; NAb- = Negative in NAb assay; NAb+ = Positive in NAb assay; PKAS = Pharmacokinetic analysis set; Pre+ = Pre-existing immunoreactivity; TB = Treatment-boosted; TE = Treatment emergent.
Note: BLQs were set to LLOQ/2.

**PD Biomarker**

The PD effect of casirivimab+imdevimab was assessed by measuring SARS-CoV-2 viral load reduction, which is considered a direct effect driven by the mechanism of action of casirivimab+imdevimab in blocking the interaction of the S protein of the virus with human ACE2 receptor. As blocking viral entry would result in decreased infection of host cells and corresponding reduction in viral shedding in affected tissues, virologic efficacy was assessed by collecting NP swab samples from participants to determine the relative quantification of viral load. The SARS-CoV-2 viral loads (log10 copies/mL) in NP swabs were quantified by quantitative reverse transcription polymerase chain reaction (RT-qPCR) assay with an LLOQ of 714 copies/mL (2.85 log10 copies/mL).

**SARS-CoV-2 Viral Load Reduction in Clinical Studies**

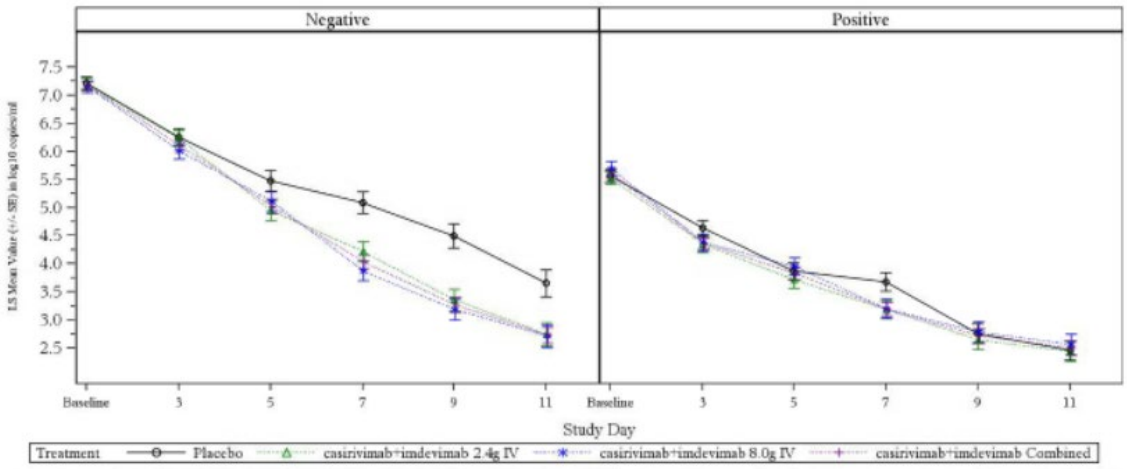
Nasopharyngeal viral load

The concentration-response relationship between viral load reduction and casirivimab+imdevimab combined concentration in serum was assessed in the concentration-response-seronegative participants across Phases 1, 2, and 3 of COV-2066. As a PD marker, nasopharyngeal viral load (NP VL) data were collected at predose and postdose (within 60 minutes after the end of infusion) on study Day 1, at discharge before Day 29, on Days 3, 5, 7, 9, 11, 13, 15, 22, 29 (Phase 1, 2 and 3).

**Primary Virologic Efficacy Endpoint:**
Time-Weighted Average (TWA) Daily Change from Baseline in Viral Load from Day 1 to Day 7.

The TWA daily change from baseline in SARS-CoV-2 viral load in NP as assessed from Days 1 to 7 was a primary virologic efficacy variable. The analysis was performed in those who were seronegative at baseline (seronegative mFAS) to minimize any confounding effects that the endogenous immune response would have on measuring the magnitude of anti-viral effect with casirivimab+imdevimab treatment. In seronegative patients, casirivimab+imdevimab treatment (combined doses) reduced the TWA daily viral load through Day 7, compared to placebo, by -0.28 log10 copies/mL [95% CI -0.51, -0.05], p=0.0172). This met the first primary efficacy endpoint pre-specified in the statistical hierarchy.

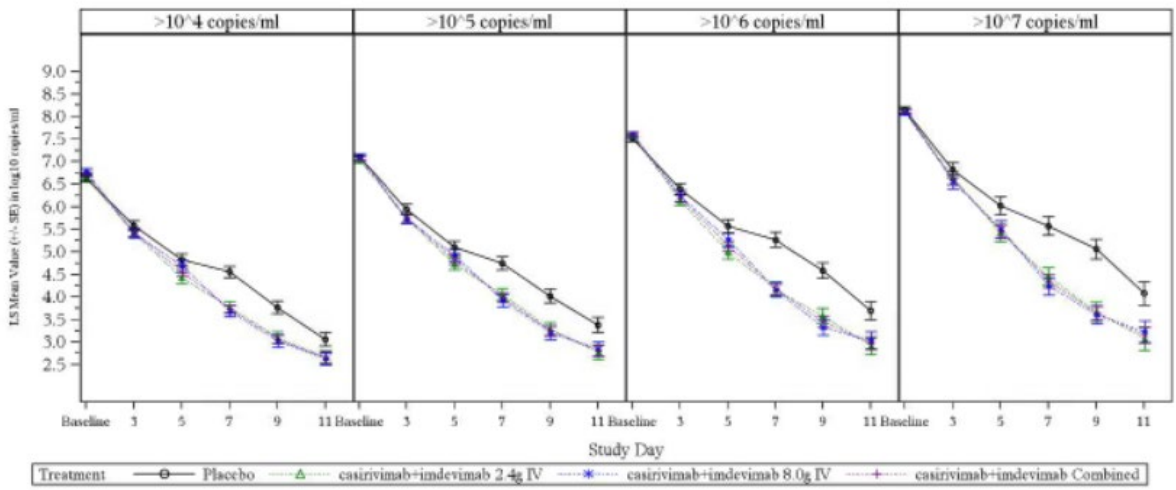
**Figure 4 Least Squares Mean of Viral Load by Baseline Serostatus (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A; mFAS)**




Benefit was also observed in the overall mFAS (difference vs. placebo of -0.26 log10 [95 % CI -0.41, -0.02 copies/mL]), but antiviral activity was most striking in seronegative participants who had not yet mounted their own endogenous immune response at baseline as opposed to seropositive patients.

Additionally, a greater treatment effect was observed in participants with high baseline viral load >106 copies/mL (difference vs. placebo of -0.32 log10 copies/mL, [95% CI -0.51, -0.13 copies/mL]) compared to those with a baseline viral load ≤106 copies/mL (difference vs placebo of -0.17 log10 copies/mL [95% CI -0.39, 0.05 copies/mL]);

**Figure 5 Least Squares Mean of Viral Load by Baseline Viral Load (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A; mFAS)**



Consistent results were observed for both individual doses (2400 mg IV and 8000 mg IV) compared to placebo in seronegative participants, indicating the absence of a dose response effect (2400 mg: least squares [LS] mean -0.25 log10 copies/mL [95% CI -0.51, 0.02]; 8000 mg: LS mean -0.31 log10 copies/mL [95% CI -0.57, -0.05]) (Figure 4).

The time-weighted average (TWA) daily change from baseline in viral load from day 1 to day 7 is presented in the table below.

**Table 28: Time-Weighted Average Daily Change from Baseline in Viral Load from Day 1 to Day 7: Comparison of Casirivimab+Imdevimab Versus Placebo (Pooled Cohort 1 [Phase 3] and Cohort 1A)**

| | | Casirivimab+Imdevimab IV | | |
|---|---|---|---|---|
| | Placebo | 2400 mg | 8000 mg | Combined |
| *Overall mFAS*[a] | | | | |
| **Baseline viral load ($log_{10}$ copies/mL)** | | | | |
| n | 393 | 406 | 398 | 804 |
| Mean (SD) | 6.32 (1.733) | 6.34 (1.735) | 6.44 (1.704) | 6.39 (1.719) |
| Median | 6.31 | 6.37 | 6.50 | 6.45 |
| Q1 : Q3 | 4.99 : 7.59 | 5.06 : 7.62 | 5.27 : 7.79 | 5.15 : 7.72 |
| Min : Max | 2.6 : 10.0 | 2.6 : 10.5 | 2.6 : 10.2 | 2.6 : 10.5 |
| **Time-weighted average change from baseline from Day 1 to Day 7 ($log_{10}$ copies/mL)** | | | | |
| n | 337 | 354 | 344 | 698 |
| Mean (SD) | -0.98 (1.181) | -1.26 (1.156) | -1.21 (1.145) | -1.24 (1.150) |
| Median | -0.84 | -1.18 | -1.15 | -1.16 |
| Q1 : Q3 | -1.66 : -0.24 | -1.95 : -0.48 | -1.83 : -0.46 | -1.87 : -0.46 |
| Min : Max | -5.5 : 3.3 | -6.4 : 1.9 | -5.6 : 1.6 | -6.4 : 1.9 |
| LS Mean (SE)[1] | -0.99 (0.07) | -1.28 (0.07) | -1.23 (0.07) | -1.25 (0.05) |
| 95% CI[1] | (-1.12, -0.86) | (-1.41, -1.15) | (-1.36, -1.10) | (-1.35, -1.15) |
| **Difference vs. Placebo by Day 7 ($log_{10}$ copies/mL)** | | | | |
| LS Mean (SE)[1] | | -0.29 (0.08) | -0.24 (0.09) | -0.26 (0.07) |
| 95% CI[1] | | (-0.45, -0.12) | (-0.40, -0.07) | (-0.41, -0.12) |
| p-value[1] | | 0.0007 | 0.0056 | 0.0004 |
| *Seronegative mFAS* | | | | |
| **Baseline viral load ($log_{10}$ copies/mL)** | | | | |
| n | 160 | 172 | 188 | 360 |
| Mean (SD) | 7.21 (1.461) | 7.19 (1.520) | 7.15 (1.434) | 7.17 (1.474) |
| Median | 7.27 | 7.39 | 7.26 | 7.33 |
| Q1 : Q3 | 6.29 : 8.40 | 6.18 : 8.47 | 6.13 : 7.99 | 6.16 : 8.18 |
| Min : Max | 2.6 : 10.0 | 2.9 : 10.5 | 2.6 : 10.2 | 2.6 : 10.5 |

with treatment group, the type of background standard-of-care (antiviral therapies and non-antiviral therapies) as fixed effects

**Secondary Virologic Efficacy Endpoint**: Time-Weighted Average (TWA) Change from Baseline Viral Load in NP Samples from Day 1 to Day 11.

The TWA daily change from baseline in SARS-CoV-2 viral load in NP as assessed from Day 1 to Day 11 was assessed as a secondary virological efficacy variable. Casirivimab+imdevimab treatment (combined and individual doses) reduced the TWA daily viral load through Day 11, compared to placebo in the Seronegative mFAS ($p<0.0001$), the High Viral Load (nominal $p=0.0010$), and the Overall mFAS ($p<0.0001$)

Table 14.2.2.1.5em Time-Weighted Average Change from Baseline in Viral Load from Day 1 at Each Visit in Nasopharyngeal (NP) Samples by Baseline Viral Load (<=10^6 vs >10^6 copies/mL)
Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A
Modified Full Analysis Set (mFAS)

Baseline Viral Load: >10^6 copies/mL

| | Placebo (N=229) | R10933+R10987 2.4 g IV (N=231) | R10933+R10987 8.0 g IV (N=236) | R10933+R10987 Combined (N=467) |
|---|---|---|---|---|
| Time-weighted average change from baseline from Day 1 to Day 11 (log10 copies/mL) | | | | |
| n | 202 | 205 | 208 | 413 |
| Mean (SD) | -1.58 (1.263) | -2.21 (1.312) | -2.10 (1.405) | -2.15 (1.359) |
| Median | -1.54 | -2.12 | -1.97 | -1.99 |
| Q1 : Q3 | -2.40 : -0.59 | -3.10 : -1.30 | -2.90 : -1.23 | -2.95 : -1.25 |
| Min : Max | -5.5 : 1.5 | -6.9 : 0.5 | -6.1 : 1.0 | -6.9 : 1.0 |
| LS Mean (SE) [1] | -1.58 (0.10) | -2.21 (0.10) | -2.11 (0.10) | -2.16 (0.08) |
| 95% CI [1] | (-1.78, -1.39) | (-2.41, -2.01) | (-2.31, -1.91) | (-2.31, -2.01) |
| Difference vs. Placebo by Day 11 (log10 copies/mL) | | | | |
| LS Mean (SE) [1] | | -0.62 (0.13) | -0.53 (0.13) | -0.57 (0.11) |
| 95% CI [1] | | (-0.88, -0.37) | (-0.78, -0.27) | (-0.79, -0.36) |
| p-value [1] | | <.0001 | <.0001 | <.0001 |

Notes: n = Number of subjects within a specified category. SD = Standard deviation, Min = Minimum, and Max = Maximum. LS Mean = Least squares mean, SE = Standard error of the LS Mean, CI = Confidence interval.
Baseline is defined as the last non-missing value measured prior to dosing.
[1] LS Mean, 95% CI, and p-value for change from baseline on log scale for each treatment group is based on the ANCOVA model with treatment group, the type of background standard-of-care (antiviral therapies and non-antiviral therapies) and baseline Serostatus as fixed effects and baseline viral load and treatment*baseline as covariate. Negative changes imply improvement in viral load

TWA daily change from baseline also remained nominally significant through Day 29 in these populations.

Table 14.2.2.1.5em Time-Weighted Average Change from Baseline in Viral Load from Day 1 at Each Visit in Nasopharyngeal (NP) Samples by Baseline Viral Load (<=10^6 vs >10^6 copies/mL)
Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A
Modified Full Analysis Set (mFAS)

Baseline Viral Load: >10^6 copies/mL

| | Placebo (N=229) | R10933+R10987 2.4 g IV (N=231) | R10933+R10987 8.0 g IV (N=236) | R10933+R10987 Combined (N=467) |
|---|---|---|---|---|
| Time-weighted average change from baseline from Day 1 to Day 29 (log10 copies/mL) | | | | |
| n | 214 | 214 | 216 | 430 |
| Mean (SD) | -3.02 (1.831) | -3.77 (1.824) | -3.69 (2.006) | -3.73 (1.916) |
| Median | -3.06 | -3.81 | -4.01 | -3.94 |
| Q1 : Q3 | -4.45 : -1.78 | -5.22 : -2.52 | -5.16 : -2.08 | -5.20 : -2.45 |
| Min : Max | -7.7 : 1.0 | -7.5 : 0.3 | -7.8 : 1.0 | -7.8 : 1.0 |
| LS Mean (SE) [1] | -2.99 (0.14) | -3.73 (0.14) | -3.66 (0.14) | -3.69 (0.11) |
| 95% CI [1] | (-3.27, -2.72) | (-4.00, -3.45) | (-3.94, -3.38) | (-3.90, -3.48) |
| Difference vs. Placebo by Day 29 (log10 copies/mL) | | | | |
| LS Mean (SE) [1] | | -0.73 (0.18) | -0.66 (0.18) | -0.70 (0.15) |
| 95% CI [1] | | (-1.08, -0.38) | (-1.01, -0.31) | (-1.00, -0.39) |
| p-value [1] | | <.0001 | 0.0002 | <.0001 |

Notes: n = Number of subjects within a specified category. SD = Standard deviation, Min = Minimum, and Max = Maximum. LS Mean = Least squares mean, SE = Standard error of the LS Mean, CI = Confidence interval.
Baseline is defined as the last non-missing value measured prior to dosing.
[1] LS Mean, 95% CI, and p-value for change from baseline on log scale for each treatment group is based on the ANCOVA model with treatment group, the type of background standard-of-care (antiviral therapies and non-antiviral therapies) and baseline Serostatus as fixed effects and baseline viral load and treatment*baseline as covariate. Negative changes imply improvement in viral load

The TWA change from baseline in viral load (as assessed from Days 1 to 7, 1 to 11, and 1 to 28) exhibited no concentration-related differences over the exposure range investigated, indicating that concentrations in serum for both the 2400 mg and 8000 mg IV doses were sufficient to achieve maximum effect on viral load for hospitalized participants.
This finding was observed despite the increased CL in hospitalized participants compared to non-hospitalized participants, as well as the increased CL of casirivimab and imdevimab particularly in patients requiring high flow oxygen or respiratory support.

Notably, the number of participants on high flow oxygen (Cohort 2) or requiring mechanical ventilation (Cohort 3) included in this analysis were very small. Therefore, the results from these analyses are mainly driven by participants not requiring oxygen or on low flow oxygen, which supports the use of 2400 mg IV for these patients.

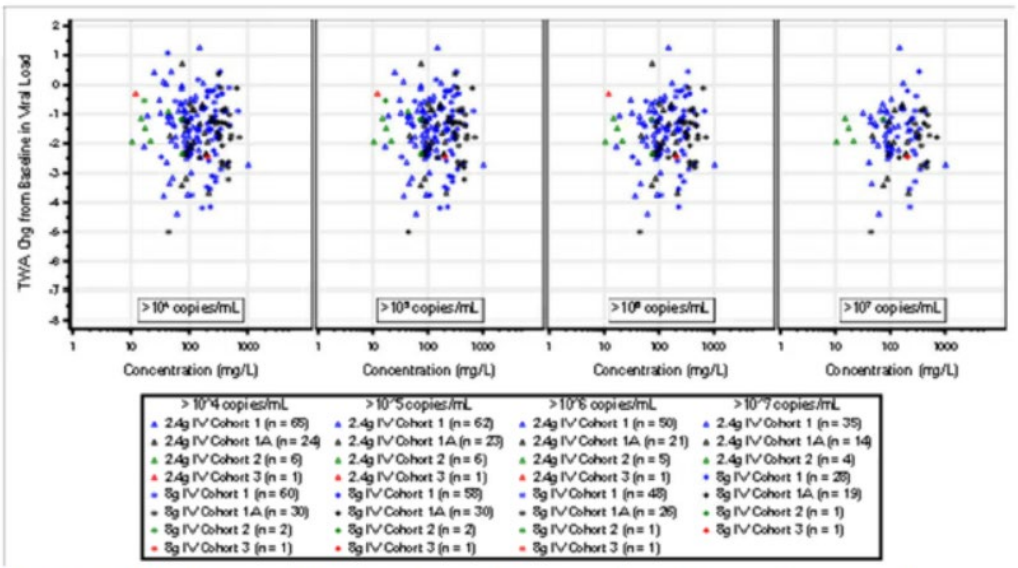
## 2.3.4. PK/PD modelling

**Concentration-Response Analysis of Viral Load (compare 5.3.3)**

The concentration-response relationship between viral load reduction and C28 of casirivimab+imdevimab combined in serum was assessed in the concentration-response-seronegative participants across Phases 1, 2, and 3 of COV-2066 (CR-seronegative mFAS). Because casirivimab and imdevimab both compete with the host immune response, the CR relationship was conducted in individuals that had not yet mounted an immune response and were seronegative at baseline.

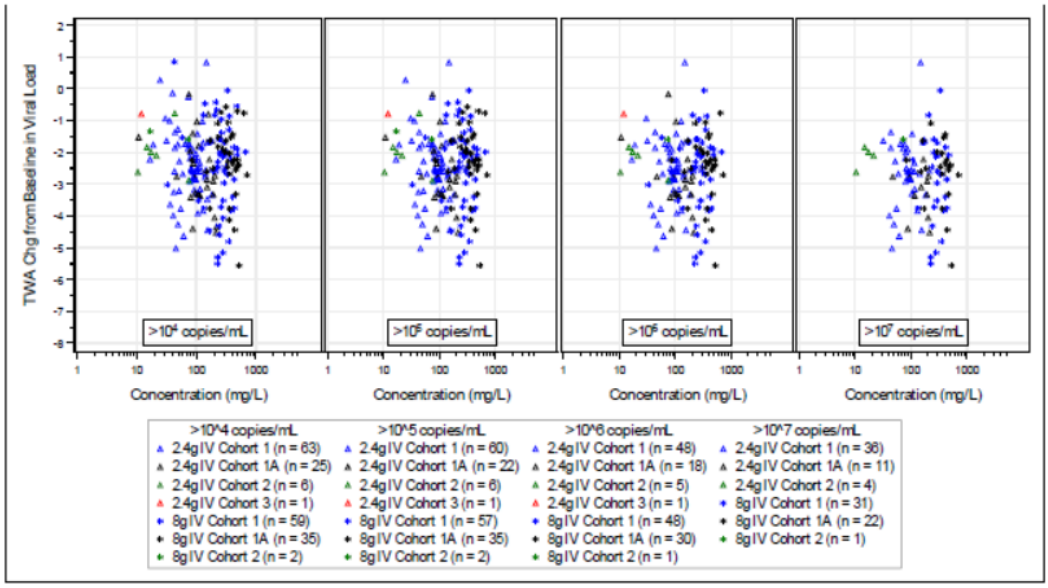
The TWA change from baseline in viral load (as assessed from Days 1 to 7, 1 to 11, and 1 to 28) exhibited no concentration-related differences over the exposure range investigated, indicating that concentrations in serum for both the 2400 mg and 8000 mg IV doses were sufficient to achieve maximum effect on viral load for hospitalized participants. Scatter plots of TWA change from baseline in viral load versus log-scaled C28 of casirivimab+imdevimab combined in serum by baseline viral load category are presented in Figure 6 (from Day 1 through Day 7) and Figure 52 (from Day 1 through Day 11) Figure 53 (from Day 1 through Day 28).

**Figure 6 Scatter Plot of Time-weighted Average Change from Baseline in Viral Load ($Log_{10}$ Copies/mL) from Day 1 Through Day 7 vs. Concentration at Day 28 (Log-Scaled) of Combined Casirivimab+Imdevimab in Serum by Baseline Viral Load Category in Hospitalized Adult Patients with COVID-19 (Phase 1, 2 and 3, CR-Seronegative mFAS)**



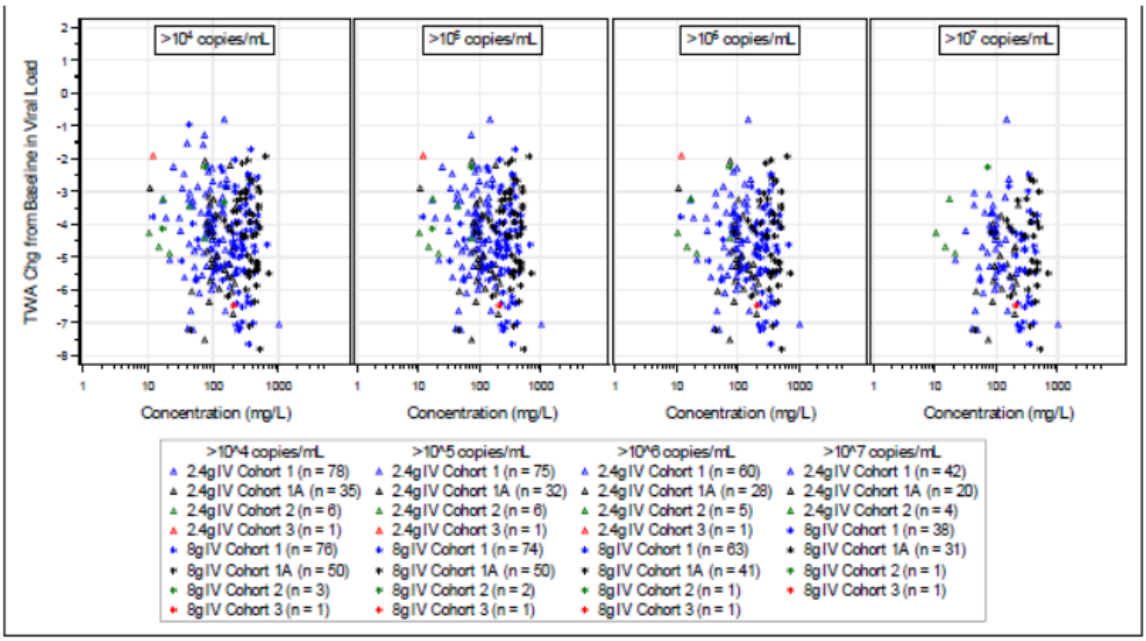

BLQ=Below the limit of quantitation; Chg=change; CR seronegative mFAS=modified seronegative concentration response analysis set; n=number of patients; TWA=time weighted average.
Note: BLQs were set to LLOQ/2.
Source: R10933-10987-COV-2066 CSR, Figure 27.

**Figure 52: Scatter Plot of Time-Weighted Average Change from Baseline in Viral Load (log10 copies/mL) from Day 1 through Day 11 vs Concentration at Day 28 (Log-Scaled) of Combined Casirivimab and Imdevimab in Serum by Baseline Viral Load Category in Hospitalized Adult Patients with COVID-19 (Study R10933-10987-COV-2066, Phase 2, CR-seronegative mFAS)**




BLQ = Below the limit of quantitation; Chg = change; CR-seronegative mFAS = Modified seronegative concentration response analysis set; n = Number of patients; TWA = Time weighted average.
Note: BLQs were set to LLOQ/2.

**Figure 53: Scatter Plot of Time-Weighted Average Change from Baseline in Viral Load (log10 copies/mL) from Day 1 through Day 28 vs Concentration at Day 28 (Log-Scaled) of Combined Casirivimab and Imdevimab in Serum by Baseline Viral Load Category in Hospitalized Adult Patients with COVID-19 (Study R10933-10987-COV-2066, Phase 2, CR-seronegative mFAS)**




BLQ = Below the limit of quantitation; Chg = change; CR-seronegative mFAS = Modified seronegative concentration response analysis set; n = Number of patients; TWA = Time weighted average.
Note: BLQs were set to LLOQ/2.

**Dose justification:**

Whereas Ronapreve 1200 mg intravenous (IV) or subcutaneous (SC) was approved for treatment of COVID-19 in out-patients, higher doses, 2400 mg and 8000 mg IV, are proposed for the treatment of more severe COVID-19 disease in hospitalized patients, recommend depending on disease severity.

**Concentrations of Casirivimab and Imdevimab in serum required to neutralize SARS-CoV-2 Reference Viruses and VOI/VOC**

Serum concentrations of casirivimab + imdevimab combined, casirivimab and imdevimab required to achieve 90% neutralization concentrations (IC90) in respiratory tract fluids (Cs,target) on Day 28 were estimated for hospitalized patients with SARS-CoV-2 for the proposed doses. The results are shown for casirivimab+imdevimab combined in table below. Notably, due to poor or lack of neutralization, IC50 and IC90 values were not calculated for the Omicron variant. Therefore, the following assumptions were derived for all currently circulating SARSCoV-2 variants with the exception of the Omicron variant.

For hospitalized patients the serum concentrations of casivirimab+imdevimab combined on Day 28 (C28) were in excess of serum concentrations required to achieve Cs,target for SARS-CoV-2 variants for both dose groups and all cohorts (table below). For the 2400 mg IV dose group, the median C28 of casirivimab+imdevimab combined from hospitalized patients not on oxygen or on low flow oxygen were at least 9-fold above Cs,target for all known circulating SARS-CoV-2 VUS prior to Omicron, further reaffirming that the 2400 mg IV dose in these patients should provide maximal antiviral effect against all known circulating SARS-CoV-2 VUS (with the exception of Omicron) over a 28-day period.

For patients on high flow oxygen or mechanical ventilation who received 2400 mg IV, the C28 of casirivimab+imdevimab combined was only 4.9-fold and 3.8-fold, respectively, above Cs,target for E484K variant, suggesting that 2400 mg might be a subtherapeutic dose for those patients. While the 8000 mg IV dose, provided a C28 of casirivimab+imdevimab combined that were at least 12.6-fold above Cs,target for all known circulating SARS-CoV- 2 VUS prior to Omicron. This suggested that 8000 mg IV will maintain maximal antiviral effect over this 28-day period in hospitalized patients on high flow oxygen or mechanical ventilation (table below).

**Table 6 Simulated Median Concentrations of Casirivimab+Imdevimab Combined in Serum 28 Days After Dosing ($C_{28}$) Relative to Concentrations in Serum Required to Achieve In Vitro Neutralization ($IC_{90}$) in Respiratory Tract Fluids for SARS-CoV-2 Variants**

| SARS-CoV-2 variants | | | Cohort 1A No $O_2$ Supplementation | | | | Cohort 1 Low-flow $O_2$ | | | | Cohort 2 High-flow $O_2$ | | | | Cohort 3 Mechanical Ventilation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2400 mg IV | | 8000 mg IV | | 2400 mg IV | | 8000 mg IV | | 2400 mg IV | | 8000 mg IV | | 2400 mg IV | | 8000 mg IV | |
| Pango Lineage | WHO label | $C_{s,target}$[1] | $C_{28}$[2] | $C_{28}/C_{s,target}$[3] | $C_{28}$[2] | $C_{28}/C_{s,target}$[3] | $C_{28}$[2] | $C_{28}/C_{s,target}$[3] | $C_{28}$[2] | $C_{28}/C_{s,target}$[3] | $C_{28}$[2] | $C_{28}/C_{s,target}$[3] | $C_{28}$[2] | $C_{28}/C_{s,target}$[3] | $C_{28}$[2] | $C_{28}/C_{s,target}$[3] | $C_{28}$[2] | $C_{28}/C_{s,target}$[3] |
| WT, PSV | ref | 3.76 | 80.3 (38.9, 140) | 21.39 | 268 (130, 466) | 71.29 | 68.0 (31.3, 116) | 18.10 | 227 (104, 386) | 60.33 | 37.0 (17.4, 72.6) | 9.85 | 123 (57.9, 242) | 32.84 | 28.5 (12.7, 65.1) | 7.59 | 95.1 (42.5, 217) | 25.30 |
| D614Ge | ref | 1.64 | 80.3 (38.9, 140) | 49.11 | 268 (130, 466) | 163.70 | 68.0 (31.3, 116) | 41.56 | 227 (104, 386) | 138.53 | 37.0 (17.4, 72.6) | 22.62 | 123 (57.9, 242) | 75.42 | 28.5 (12.7, 65.1) | 17.43 | 95.1 (42.5, 217) | 58.10 |
| B.1.351 | Beta | 1.57 | 80.3 (38.9, 140) | 51.23 | 268 (130, 466) | 170.76 | 68.0 (31.3, 116) | 43.35 | 227 (104, 386) | 144.50 | 37.0 (17.4, 72.6) | 23.60 | 123 (57.9, 242) | 78.66 | 28.5 (12.7, 65.1) | 18.18 | 95.1 (42.5, 217) | 60.61 |
| B.1.1.7 | Alpha | 2.05 | 80.3 (38.9, 140) | 39.18 | 268 (130, 466) | 130.60 | 68.0 (31.3, 116) | 33.16 | 227 (104, 386) | 110.52 | 37.0 (17.4, 72.6) | 18.05 | 123 (57.9, 242) | 60.16 | 28.5 (12.7, 65.1) | 13.91 | 95.1 (42.5, 217) | 46.35 |
| P.1 | Gamma | 2.37 | 80.3 (38.9, 140) | 33.85 | 268 (130, 466) | 112.84 | 68.0 (31.3, 116) | 28.65 | 227 (104, 386) | 95.49 | 37.0 (17.4, 72.6) | 15.60 | 123 (57.9, 242) | 51.98 | 28.5 (12.7, 65.1) | 12.01 | 95.1 (42.5, 217) | 40.05 |
| B.1.617.2 | Delta | 1.71 | 80.3 (38.9, 140) | 46.96 | 268 (130, 466) | 156.54 | 68.0 (31.3, 116) | 39.74 | 227 (104, 386) | 132.47 | 37.0 (17.4, 72.6) | 21.63 | 123 (57.9, 242) | 72.11 | 28.5 (12.7, 65.1) | 16.67 | 95.1 (42.5, 217) | 55.56 |
| B.1.617.1 | Kappa | 4.03 | 80.3 (38.9, 140) | 19.96 | 268 (130, 466) | 66.52 | 68.0 (31.3, 116) | 16.89 | 227 (104, 386) | 56.29 | 37.0 (17.4, 72.6) | 9.19 | 123 (57.9, 242) | 30.64 | 28.5 (12.7, 65.1) | 7.08 | 95.1 (42.5, 217) | 23.61 |
| C.37 | Lambda | 2.69 | 80.3 (38.9, 140) | 29.85 | 268 (130, 466) | 99.49 | 68.0 (31.3, 116) | 25.26 | 227 (104, 386) | 84.19 | 37.0 (17.4, 72.6) | 13.75 | 123 (57.9, 242) | 45.83 | 28.5 (12.7, 65.1) | 10.59 | 95.1 (42.5, 217) | 35.31 |
| B.1.621 | Mu | 2.45 | 80.3 (38.9, | 32.75 | 268 (130, 466) | 109.18 | 68.0 (31.3, | 27.72 | 227 (104, | 92.39 | 37.0 (17.4, | 15.09 | 123 (57.9, | 50.30 | 28.5 (12.7, | 11.62 | 95.1 (42.5, | 38.75 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 140) | | | | 116) | | 386) | | 72.6) | | 242) | | 65.1) | | 217) | |
| L452R | | 2.71 | 80.3 (38.9, 140) | 29.61 | 268 (130, 466) | 98.71 | 68.0 (31.3, 116) | 25.06 | 227 (104, 386) | 83.53 | 37.0 (17.4, 72.6) | 13.64 | 123 (57.9, 242) | 45.47 | 28.5 (12.7, 65.1) | 10.51 | 95.1 (42.5, 217) | 35.03 |
| E484K | | 7.54 | 80.3 (38.9, 140) | 10.65 | 268 (130, 466) | 35.50 | 68.0 (31.3, 116) | 9.01 | 227 (104, 386) | 30.04 | 37.0 (17.4, 72.6) | 4.91 | 123 (57.9, 242) | 16.35 | 28.5 (12.7, 65.1) | 3.78 | 95.1 (42.5, 217) | 12.60 |

$C_{28}$ = serum concentration on Day 28 following single dose; $C_{s,target}$ = target drug concentration in serum required to achieve $IC_{90}$ in respiratory tract fluids.

[1] Concentration in serum (mg/mL) required to achieve $IC_{90}$ in target respiratory tract fluid ($C_{s,target}$) = $IC_{90}$/Pc, where Pc = 0.01; $IC_{90}$ of each variant is reported in the Nonclinical Study Report: R10933-PH-20091-SR-01V5. Target respiratory tract fluids are nasopharyngeal fluid (NF) and lung epithelial lining fluid (ELF); serum-to-NF and serum-to-lung ELF partition coefficient (Pc) is conservatively estimated as 0.01 (Wollacott et al. 2016).

[2] Population PK predicted median (5th, 95th percentile) concentration of casirivimab+imdevimab combined in serum at 28 days after dose ($C_{28}$).

[3] Ratio of casirivimab+imdevimab combined $C_{28}$ / $C_{s,target}$

In vitro $IC_{90}$ (M) values from in vitro studies assessing pVSV-SARS-CoV-2-S pseudoparticles expressing SARS-CoV-2 S protein of wild type virus or viral variants into Vero or Vero E6 cells.

$IC_{90}$ (mg/L) = [($IC_{90}$ (M)*0.5*145,230 kDa*1000) + ($IC_{90}$ (M)*0.5*144,140 kDa*1000)] for casirivimab+imdevimab, assuming equimolar amount present in the cocktail.

Source: 2.7.2 SCP, Table 8.

## 2.3.5. Discussion on clinical pharmacology

In the context of this variation procedure, the following to-be-marketed dosage in adult and adolescent patients (12 years of age and older weighing at least 40 kg) who require supplemental oxygen is foreseen:

- 4000 mg of casirivimab and 4000 mg of imdevimab administered together as a single IV infusion for patients who are on low-flow and high-flow oxygen devices, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

The clinical pharmacology program for this submission is supported by PK and PD data (viral load) from COV-2066 only and by population PK (pop-PK) analyses from data pooled from several studies included in the Marketing Authorization Application. No PK data was collected from RECOVERY.

Study COV-2066 was an adaptive, Phase 1/2/3, randomized, double-blinded, placebo-controlled study in hospitalized adult patients with four cohorts in the study according to disease severity. Of note, sample size decreased with disease severity, and was limited in cohorts 2 (N=53) and 3 (N=11).

Overall, the updated PopPK models for casirivimab and imdevimab with inclusion of data from hospitalized patients retained the same structure as the previously developed PopPK model with some additional statistically significant covariate effects reflecting the disease state and severity.

The popPK modelling updates for casirivimab and imdevimab were performed based on comprehensive pooled data of in total 4981 unique subjects/patients with 10552 quantifiable casirivimab concentrations and 5009 unique subjects/patients with 11019 quantifiable imdevimab concentrations in serum following a dose range from 150 mg to 4000 mg per mab.

For casirivimab PK, the strongest covariates impacting PK were disease severity, hospitalization status, albumin, and body weight, with an impact of > 16% on exposures, in particular for Cday28. For imdevimab PK, the primary covariates influencing PK were disease severity, albumin, and body weight, with an impact of > 22% compared to reference. Hospitalization status was predicted to impact imdevimab exposure of 13% on Cday28 compared to reference.

Baseline viral load, ADA and serostatus did not alter the pharmacokinetics of either casirivimab or imdevimab to a clinically relevant level.

Visual predictive check (VPC) results demonstrated that the final models for both monoclonal antibodies (mAbs) provide overall a reliable description of PK data collected from COV-2066 for at least 50 days post dose. A certain degree of shrinkage is indicated.

Based on population PK analysis, the total volume of distribution in hospitalized patients is estimated to be 7.072 L and 7.183 L for casirivimab and imdevimab, respectively, consistent with previously reported values estimated from a dataset of non-hospitalized patients. Bioavailability is 100% following a single dose IV.

The estimated elimination half-life for casirivimab and imdevimab in hospitalized patients was approximately 18 and 16 days compared to approximately 30 and 25 days for non-hospitalized patients, respectively, as an indication of increased clearance that may be attributed to an increased protein catabolism. The estimated mean CL for casirivimab and imdevimab in hospitalized participants requiring high flow oxygen (0.563 L/day and 0.668 L/day, respectively) was higher compared to hospitalized participants not requiring oxygen supplementation or on low flow oxygen (0.358 L/day and 0.417 L/day, respectively).

Casirivimab and imdevimab showed similar, linear, and dose-proportional PK following single IV doses of 2400 mg and 8000 mg casirivimab+imdevimab, with decreasing concentrations of casirivimab and imdevimab in serum on Day 28 (C28) with increasing COVID-19 disease severity (as approximated by study Cohort 3). Concentrations at the end of infusion (EOI) or dose normalized concentration at EOI remained similar between cohorts, indicating that casirivimab and imdevimab clearance increases as disease severity increases.

Only single dose PK data was collected, thus no information on multiple dosing and steady state reached is assessable. Following a single IV dose administration of casirivimab and imdevimab, the increase in concentration at the end of infusion between the 1200 mg and 4000 mg doses of each antibody appeared to be proportional to the increase in dose in hospitalized patients.

PK data was only collected from adult subjects in COV-2066, while doses proposed are also recommended for adolescents aged at least 12 years of age and weighing at least 40 kg. Weight ranged from 38.5 kg to 218 kg in COV-2066 and resulted in an increase in C28 of 27% and 21% for patients at 56.2 kg (5th percentile) compared to the reference patient (82.2 kg) for both antibodies. As weight was indicated as one of the most predictive covariates in addition to disease severity, dose recommendation should be subjected to scrutiny with regard to weight.

The PD effect of casirivimab+imdevimab was assessed by measuring SARS-CoV-2 viral load reduction. Virologic efficacy was assessed by collecting NP swab samples from participants to determine the relative quantification of viral load. The SARS-CoV-2 viral loads (log10 copies/mL) in nasopharyngeal swabs were quantified by quantitative reverse transcription polymerase chain reaction (RT-qPCR) assay with an LLOQ of 714 copies/mL (2.85 log10 copies/mL).

The primary virologic efficacy endpoint was defined as time-weighted average (TWA) daily change from baseline in SARS-CoV-2 viral load from Day1 to Day7 and was met in seronegative patients at baseline. In seronegative patients, casirivimab+imdevimab treatment reduced the TWA daily viral load through Day 7, compared to placebo, by -0.28 log10 copies/mL [95% CI -0.51, -0.05], p=0.0172). Consistent results were observed for both tested doses (2400 mg IV and 8000 mg IV) compared to placebo in seronegative participants, indicating the absence of a dose response effect (2400 mg: least squares [LS] mean -0.25 log10 copies/mL [95% CI -0.51, 0.02]; 8000 mg: LS mean -0.31 log10 copies/mL [95% CI -0.57, -0.05]). Similar results have been observed considering the secondary virologic efficacy endpoint – TWA change from baseline viral load in NP samples from Day1 to Day11. Casirivimab+imdevimab treatment reduced the TWA daily viral load through Day 11, compared to placebo in the Seronegative mFAS ($p<0.0001$), the High Viral Load (nominal $p=0.0010$), and the Overall mFAS ($p<0.0001$) population.

Overall, as indicated in all clinical studies providing clinical pharmacology data throughout the clinical development, no dose-dependent and no exposure-dependent differences – as between time-weighted average (TWA) change from baseline in viral load (as assessed from Days 1 to 7, 1 to 11, and 1 to 28) and C28 of casirivimab+imdevimab combined in serum - were observed for the exposure range investigated in the seronegative modified full analysis set (mFAS) population across all phases of the study. These results indicate that concentrations following 2400 mg and 8000 mg IV are expected to provide maximum effect on viral load. Of note, PD biomarker viral load is not deemed predictive in terms of clinical efficacy and for definite dose selection. Viral load is expected to be highest with start of symptoms and is expected to decline within about one week. Thus, a more than three times higher dose in case of hospitalization and severe disease is not fully plausible from the PD point of view.

Further, such a high dose might in particular not be fully justified especially for adolescent patients at low weight and given the clinical outcome (see section clinical efficacy).

As sample size of patients on high flow oxygen (Cohort 2) or respiratory support (Cohort 3) included in this analysis were very small, the results from these analyses are mainly driven by patients not on oxygen or on low flow oxygen.

With regard to dose justification, fold changes in C28 to Cs target have been proposed for patients on high flow oxygen or mechanical ventilation who received 2400 mg IV or 8000 mg IV. The expected C28 of casirivimab+imdevimab combined following 2400 mg IV was only 4.9-fold and 3.8-fold, respectively, above Cs, target for E484K variant. The MAH suggested that 2400 mg might be a subtherapeutic dose for those patients while the 8000 mg IV dose would provided a C28 of casirivimab+imdevimab combined that is at least 12.6-fold above Cs,target for all known circulating SARS-CoV- 2 VUS prior to Omicron. Weight has not been considered in any dosing considerations by the MAH. The assumption of serum-to NF and serum-to lung ELF partition coefficient of 0.01 is agreed as reflecting a conservative estimate.

Given that C28 might not be the optimal PK metrics for comparison in a treatment setting, and viral load as a PD is not predictive with respect to dose-response and the clinical outcome, the MAH was asked to further justify the 8000 mg IV dose, especially for adult and adolescent patients at low weight. The MAH was also asked to calculate the expected exposure following 8000 mg IV and 2400 mg IV assuming hospitalization (and different degrees of severity cohorts) for 10-kilogram body weight bins (40-50kg, 50-60 kg, 60-70kg,…, 150-160 kg), respectively. Ratios of C28/Cs,target of casirivimab+imdevimab combined and C14/Cs,target should be calculated for each bin, assuming an in vitro inhibition of 90% (IC90) for all strains prior to Omicron. In response to this point, an evaluation of the concentrations of casirivimab+imdevimab combined in serum required to achieve in vitro neutralization potency IC90 in lung epithelial lining fluid (ELF) at Days 14 and 28 following 8000 mg IV, 2400 mg IV and 1200 mg IV doses for patients on no supplemental oxygen, low-flow oxygen, and high-flow oxygen was provided by 10 kg body weight bins (range 40-160 kg) as requested. The target adjusted-IC90 values (ta-IC90) for pre-Omicron variants was calculated using serum-to-lung ELF penetration values of 1% (as previously used) which is considered a conservative measure and supported.

**Table 1 Target-Adjusted IC90 Values for Strains Prior to Omicron**

| Strain | IC90 (mg/L) | Respiratory Penetration | Target-Adjusted IC90 (mg/L) |
|---|---|---|---|
| alpha | 0.021 | 0.01 | 2.1 |
| beta | 0.016 | 0.01 | 1.6 |
| gamma | 0.024 | 0.01 | 2.4 |
| delta | 0.017 | 0.01 | 1.7 |
| kappa | 0.040 | 0.01 | 4.0 |
| lambda | 0.027 | 0.01 | 2.7 |
| mu | 0.025 | 0.01 | 2.5 |

Simulation results following SD treatment with 1200 mg, 2400 mg and 8000 mg indicate that:

- For all dose levels (1200 mg to 8000 mg), all hospitalized patients with a body weight ranging from 40 kg to 160 kg have a concentration of casirivimab+imdevimab combined in serum that exceeds the ta-IC90 for 14 days after dosing, irrespective of disease severity.

- For the 1200 mg IV dose, outlier patients with body weights ≥ 80 kg have concentrations of casirivimab+imdevimab combined in serum at or below the ta-IC90 values at 28 days post dosing regardless of oxygen group.

- For the 2400 mg IV dosing at 28 days, outlier patients in the high-flow oxygen group with body weights ≥ 80 kg have concentrations of casirivimab+imdevimab combined in serum at or below the ta-IC90 values.

- For the 8000 mg IV dose, all hospitalized patients regardless of oxygen group and body weight have a concentration of casirivimab+imdevimab combined in serum that exceed the ta-IC90 for 28 days after dosing.

Simulation results of the PK simulation indicate that the 8000 mg IV dose for patients on high-flow oxygen are expected to provide maximal antiviral effect against all known pre-Omicron circulating variants over a 28-day period in individual patients (40 kg to 160 kg).

Considering all the data submitted, the 8000 mg IV dose for treatment is considered a recommendable dose for the treatment of patients receiving oxygen.

"Hospitalization" as indicator per se is not considered to meaningfully impact the PK, thus, should not be used for defining the posology statement in Section 4.2 of the SmPC as primarily indicated by the MAH. However, as indicated above supplemental oxygen use seems to have a significant impact on pharmacokinetic parameters associated with the efficacy of casirivimab+imdevimab and therefore 4000 mg IV is the optimal dose for patients receiving supplemental oxygen (including low flow and high flow oxygen devices, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO))

For patients who are not receiving oxygen the recommended posology is 600 mg of casirivimab and 600 mg of imdevimab as it was authorised previously based on the data from COV-2067: A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19 (Study COV-2067)

Therefore, the CHMP recommended to update 4.2 of the SmPC as recorded below:

> *The dosage in patients who do not require supplemental oxygen is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection (see Tables 1 and 3). See sections 4.4 and 5.1. For these patients only, casirivimab with imdevimab should be given within 7 days of the onset of symptoms of COVID-19.*
>
> *The dosage in patients who require supplemental oxygen (including low flow and high flow oxygen devices, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)) is 4000 mg of casirivimab and 4 000 mg of imdevimab administered as a single intravenous infusion (see Table 2 of Ronapreve SmPC 120 mg/mL + 120 mg/mL). See section 5.*

The proposal is accepted by the company and the SmPC updated accordingly.

## 2.3.6. Conclusions on clinical pharmacology

PK and PD data (viral load) from COV-2066 supported the adequate description of casirivimab and imdevimab PK by pop PK over a comprehensive over 10-fold dose range up to 4000 mg of each monoclonal antibody.

Data from RECOVERY (pivotal study) and COV-2066 (supportive) have been collected informing the clinical pharmacology in the hospitalization setting, following the total dose of 8000 mg IV (RECOVERY) and in addition 2400 mg IV (COV-2066).

Dose selection and dose justification based on PD marker viral load is hampered by the lack of dose and exposure-response relationships with respect to virologic efficacy and no definite link to the clinical outcome. Thus, results from RECOVERY following 8000 mg IV only are considered pivotal for considering posology conclusion.

Based on the totality of data from pivotal and supportive studies informing the pharmacology and given that the need for oxygen supply in contrast to the hospitalization status is indicated to have an impact on PK, in was concluded that the 8000 mg IV (4000 mg of casirivimab and 4000 mg of imdevimab administered together as a single IV infusion) dose for treatment is considered a recommendable dose for the treatment of patients receiving oxygen (low-flow and high-flow).

For patients who do not require oxygen supply the previously authorized dose of 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection is recommended, in line with the out-patient setting.

## 2.4. *Clinical efficacy*

**Table 1 Summary of Studies Contributing to Efficacy Evaluation**

| Study No (Phase) | Population | Study Design | Number of Participants | Dose, Route, and Regimen | Study Duration |
|---|---|---|---|---|---|
| RECOVERY (Phase 3) | Hospitalized children ≥12 years of age and adults with clinically suspected or laboratory-confirmed SARS-CoV-2 infection | Factorial, individually randomized, controlled, open-label, platform trial | Casirivimab+imdevimab plus Usual Care:<br>4839 participants<br>-Seronegative at baseline: 1633 participants<br>-Seropositive at baseline: 2636 participants<br>-Unknown serostatus at baseline: 570 participants<br>Usual Care arm:<br>4946 participants<br>-Seronegative at baseline: 1520 participants<br>-Seropositive at baseline: 2636 participants<br>-Unknown serostatus at baseline: 790 participants | Casirivimab+imdevimab plus Usual Care:<br>Single dose casirivimab+imdevimab 8000 mg IV (casirivimab 4000 mg and imdevimab 4000 mg)<br>Usual Care arm:<br>Usual standard of care | 18 September 2020 to 22 May 2021[b] |
| COV-2066[a] (Phase 1/2/3) | Adult participants ≥18 years of age, symptomatic for COVID-19 and hospitalized for ≤72 hours with varying degrees of oxygen support at randomization | Adaptive, randomized, double-blinded, placebo-controlled master study | Casirivimab+imdevimab 2400 mg IV: 757 participants<br>Casirivimab+imdevimab 8000 mg IV: 750 participants<br>Placebo: 745 participants | Casirivimab+imdevimab 2400 mg IV<br>Casirivimab+imdevimab 8000 mg IV<br>Placebo | 10 June 2020 to 9 April 2021[c] |

IV = intravenous, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] For the purpose of the SCE, pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A are presented, i.e., primary efficacy analysis population.

[b] This duration reflects the casirivimab+imdevimab evaluation of the 28-day primary endpoint.

[c] This duration reflects the enrollment period for the efficacy evaluation. The study is continuing for the long COVID evaluation.

RECOVERY and COV-2066 provide information on the role of casirivimab+imdevimab for the treatment of hospitalized patients with COVID-19, while RECOVERY is considered as pivotal study, COV-2066 is supportive.

### 2.4.1. Dose response study

No dose response studies were provided.

### 2.4.2. Main studies

### RECOVERY

In March 2020, when the original RECOVERY trial protocol was released by the University of Oxford (at the same time that the WHO declared COVID-19 to be a global pandemic), there were no approved treatments for COVID-19. The UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) and WHO expert group advised that several possible treatments should be evaluated, including existing drugs repurposed for COVID-19 as well as emerging investigational treatments that require evaluation. As such, the protocol was designed to provide reliable assessments of the effects of multiple different treatments (including re-purposed and novel drugs) on major outcomes in COVID-19 and allowed for treatment arms to be added or removed according to the emerging evidence. A factorial randomization was utilized to compare the selected treatments with usual care.

To facilitate collaboration, even in hospitals that suddenly become overloaded, patient enrolment (via the internet) and all other trial procedures are greatly streamlined. Informed consent is simple and data entry is minimal.

## *Methods*

RECOVERY is an investigator-initiated, individually randomized, controlled, open-label platform trial in which several treatments were compared with usual care in patients hospitalized with COVID-19. The multicenter study was conducted in the UK, Indonesia, and Nepal, with 127 hospitals in the UK taking part in the evaluation of casirivimab+imdevimab.

## Study participants

The key inclusion criteria included:

- Hospitalization
- Clinically suspected or PCR laboratory-confirmed SARS-CoV-2 infection associated disease
- No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

The key exclusion criteria included:

- Intravenous immunoglobulin treatment during the current hospital admission
- Children weighing <40 kg or aged <12 years

## Treatments

**REGN-COV**

Single 8000 mg dose (casirivimab 4000 mg and imdevimab 4000 mg)

**Treatments on top of SOC**

Patients could receive between 0 and 4 treatments on top of usual standard of care

- azithromycin versus usual care (Part A; 7 April 2020 – 27 November 2020)
- colchicine versus usual care (Part A; 19 November 2020 – 5 March 2021)
- dimethyl fumarate versus usual care (Part A; 15 February 2021 – ongoing)
- aspirin versus usual care (Part C; 1 November 2020 – 21 March 2021)
- baricitinib versus usual care (Part D; 26 January 2021 – ongoing)

Until 24 January 2021, the trial also allowed a subsequent randomisation for patients with progressive COVID-19 (evidence of hypoxia and a hyper-inflammatory state) to tocilizumab versus usual care.

## Outcomes/endpoints

**Table 7 RECOVERY Hierarchical Testing Order**

| Hierarchy Number | Type of Outcome | Outcome | Analysis Population | Significance Level, α (2-sided) |
|---|---|---|---|---|
| 1 | Primary | Mortality (all-cause), 28 days after randomization | Seronegative at randomization | 0.05 |
| 2 | Primary | Mortality (all-cause), 28 days after randomization | All participants randomized | 0.05 |
| 3* | Secondary | Time to discharge alive from hospital, within 28 days after randomization | Seronegative at randomization | 0.025 |
| 4 | Secondary | Time to discharge alive from hospital, within 28 days after randomization | All participants randomized | 0.025 |
| 3* | Secondary | Use of invasive mechanical ventilation (including ECMO) or death | Seronegative and not on invasive mechanical ventilation at randomization | 0.025 |
| 4 | Secondary | Use of invasive mechanical ventilation (including ECMO) or death | All participants randomized and not on invasive mechanical ventilation at randomization | 0.025 |

ECMO = extracorporeal membrane oxygenation.

* These were performed simultaneously. Testing only proceeded to the respective overall population if the null hypothesis was rejected in the seronegative group at the specified level of statistical significance.

The results of the study are published in the peer reviewed manuscript (which includes further study design details) and associated appendix (RECOVERY Collaborative Group, 2021, and RECOVERY Manuscript Supplementary Material, 2021).

## Sample size

According to the study protocol, realistic, appropriate sample sizes could not be estimated at the start of the trial. According to the supplementary statistical methods, on 27 April 2021, the Trial Steering Committee, whose members were unaware of the results of the trial comparisons, determined that, with over 9700 patients recruited to the REGEN-COV comparison and average daily recruitment of 4 patients, further recruitment was unlikely to increase the reliability of the results materially so should discontinue. At that point, the Trial Steering Committee estimated that once follow-up of all patients was complete there would be at least 90% power at two-sided P=0.01 to detect a proportional reduction in 28-day mortality of 20% in the seronegative patients and of 15% in the overall study population.

## Randomisation

A single participant could be randomised at most to 1 arm from each of part A, B, C, D and E of the factorial randomisations (depending on location), and thus receive between 0 and 4 treatments on top of usual standard of care.

Alongside the casirivimab+imdevimab evaluation, as stated above, participants could be simultaneously randomized to the following treatment groups in the Main Randomization:

- azithromycin versus no additional treatment (Part A; 7 April 2020 – 27 November 2020)
- colchicine versus no additional treatment (Part A; 19 November 2020 – 5 March 2021)
- dimethyl fumarate versus no additional treatment (Part A; 15 February 2021 – ongoing)
- aspirin versus no additional treatment (Part C; 1 November 2020 – 21 March 2021)
- baricitinib versus no additional treatment (Part D; 26 January 2021 – ongoing)

Further, participants could be randomized to receiving tocilizumab or no additional treatment on top of those treatments above, in a second randomization.

- tocilizumab versus no additional treatment (second randomization; 14 April 2020 – 24 January 2021)

Part A (from 19 March 2020)

Eligible participants could be randomised to one of the following arms:

| Treatment arm | Arm opened | Arm closed |
|---|---|---|
| No additional treatment | 19 March 2020 | Ongoing |
| Dexamethasone | 19 March 2020 | 8 June 2020 |
| Lopinavir-ritonavir | 19 March 2020 | 29 June 2020 |
| Hydroxychloroquine | 23 March 2020 | 5 June 2020 |
| Azithromycin | 7 April 2020 | 27 November 2020 |
| Colchicine | 27 November 2020 | 5 March 2021 |
| Dimethyl fumarate | 15 February 2021 | Ongoing |

Part B (from 14 May 2020)

Eligible participants could be randomised to one of the following arms:

| Treatment arm | Arm opened | Arm closed |
|---|---|---|
| No additional treatment | 14 May 2020 | 21 May 2021 |
| Convalescent plasma | 14 May 2020 | 15 January 2021 |
| REGEN-COV* | 18 September 2020 | 21 May 2021 |

* monoclonal neutralising antibody cocktail

Part C (from 1 November 2020)

Eligible participants could be randomised to one of the following arms:

| Treatment arm | Arm opened | Arm closed |
|---|---|---|
| No additional treatment | 1 November 2020 | 21 March 2021 |
| Aspirin | 1 November 2020 | 21 March 2021 |

Part D (from 1 November 2020)

Eligible participants could be randomised to one of the following arms:

| Treatment arm | Arm opened | Arm closed |
|---|---|---|
| No additional treatment | 2 February 2021 | Ongoing |
| Baricitinib | 2 February 2021 | Ongoing |

Part E (from 25 May 2021)

Eligible participants could be randomised to one of the following arms:

| Treatment arm | Arm opened | Arm closed |
|---|---|---|
| No additional treatment | 25 May 2021 | Ongoing |
| High-dose dexamethasone | 25 May 2021 | Ongoing |

*Second randomisation for adults (from 14 April 2020)*

From 14 April 2020, a participant could be randomised to one of the following arms and thus receive 0 or 1 treatment on top of those allocated in the initial randomisation and usual standard of care:

| Treatment arm | Arm opened | Arm closed |
|---|---|---|
| No additional treatment | 14 April 2020 | 24 January 2021 |
| Tocilizumab | 14 April 2020 | 24 January 2021 |

## Blinding (masking)

RECOVERY was an open-label study and no placebo comparator was administered in an effort to minimize trial procedures; therefore, participants, investigators, and local study staff were not blinded to the allocated treatment. The Trial Steering Committee, investigators, and all other individuals involved in the trial were masked to outcome data during the trial, however, the independent Data Monitoring Committee (iDMC) was not.

## Statistical methods

*Analysis set*

Comparisons were planned to be made between all patients randomized to the different treatment arms, irrespective of whether they received their allocated treatment ("intention-to-treat" analyses). The primary analysis for regn-cov-2 was planned to be conducted in seronegative patients only.

Pairwise comparisons within each randomisation were planned to be made between each treatment arm and the no additional treatment arm (reference group) in that particular randomisation (main randomisation part A, B, C or D, and second randomisation). However, since not all treatments might have been available or suitable for all patients, those in the no additional treatment arm were planned to be included in a given comparison only if, at the point of their randomisation, they could alternatively have been randomised to the active treatment of interest.

*Primary outcome variable and analysis model*

For the primary outcome of 28-day mortality, the log-rank observed minus expected statistic and its variance were planned to be used to test the null hypothesis of equal survival curves (ie, the log-rank test) and to calculate the one-step estimate of the average mortality rate ratio. Kaplan-Meier survival curves were planned to be constructed to display cumulative mortality over the 28-day period.

The main analyses described above were planned to be unadjusted for baseline characteristics.

*Missing values and censoring*

For the primary outcome (death within 28 days of randomisation), discharge alive before 28 days was planned to assume safety from the event (unless there is additional data confirming otherwise).

*Significance level and Multiplicity*

Evaluation of the primary trial (main randomisation) and secondary randomisation was planned to be conducted independently, and no adjustments have been made for these. Formal adjustments were not planned for multiple treatment comparisons, the testing of secondary and subsidiary outcomes, or subgroup analyses.

The primary outcome was planned to first be assessed among participants who are known to be seronegative at randomisation. If the null hypothesis is rejected in the seronegative group at 2-tailed p=0.05, then the primary outcome was planned to be assessed among the whole population (i.e. seronegative, seropositive, and those with unknown status combined). Otherwise, no further hypothesis testing was planned to be performed.

A similar approach was planned to be taken for each of the two pre-specified secondary outcomes (discharge alive within 28 days and, among patients not on invasive mechanical ventilation at baseline, the use of invasive mechanical ventilation or death) if both primary hypotheses are rejected. Hypothesis testing was planned to first be conducted among the participants who are known to be seronegative at randomisation and, if the null hypothesis is rejected at 2-tailed p=0.025, then it was planned to be assessed among the whole population (see Table).

**Table: Hierarchical Testing Order**

| Hierarchy Number | Type of Outcome | Outcome | Analysis Population | Significance level, α (2-sided) |
|---|---|---|---|---|
| 1. | Primary | Mortality (all-cause), 28 days after randomisation | Seronegative at randomisation | 0.05 |
| 2. | Primary | Mortality (all-cause), 28 days after randomisation | All participants randomised | 0.05 |
| 3.* | Secondary | Time to discharge alive from hospital, within 28 days after randomisation | Seronegative at randomisation | 0.025 |
| 4. | Secondary | Time to discharge alive from hospital, within 28 days after randomisation | All participants randomised | 0.025 |
| 3.* | Secondary | Use of invasive mechanical ventilation (including ECMO) or death | Seronegative and not on invasive mechanical ventilation at randomisation | 0.025 |
| 4. | Secondary | Use of invasive mechanical ventilation (including ECMO) or death | All participants randomised not on invasive mechanical ventilation at randomisation | 0.025 |

* These will be performed simultaneously. Testing will only proceed to the respective overall population if the null hypothesis is rejected in the seronegative group at the specified level of statistical significance.

*Interim analysis*

The independent Data Monitoring Committee was planned to review unblinded analyses of the study data and any other information considered relevant at intervals of around 2 to 4 weeks. The committee was charged with determining if, in their view, the randomised comparisons in the study provide evidence on mortality that is strong enough (with a range of uncertainty around the results that was narrow enough) to affect national and global treatment strategies. In such a circumstance, the Committee was planned to inform the Steering Committee who would make the results available to the public and amend the trial arms accordingly. Unless that happened, the Steering Committee, investigators, and all others involved in the trial were planned to remain blinded to the interim results until 28 days after the last patient had been randomised to a particular intervention arm.

The Data Monitoring Committee determined that to consider recommending stopping a treatment early for benefit would require at least a 3 to 3·5 standard error reduction in mortality. The Committee concluded that examinations of the data at every 10% (or even 5%) of the total data would lead to only a marginal increase in the overall type I error rate.

Subgroup analysis

Tests for heterogeneity (or tests for trend for 3 or more ordered groups) were planned to be conducted to assess whether there is any good evidence that the effects in particular subgroups differ materially from the overall effect seen in all patients combined. Results were planned to be presented on forest plots as event rate ratios, or risk ratios, with confidence intervals. The following subgroups were planned to be examined based on information at randomization:

- Age (<70; 70-79; 80+ years)
- Sex (Male; Female)

- Ethnicity (White; Black, Asian or Minority Ethnic)
- Region (UK, non-UK)
- Time since illness onset (≤7 days; >7 days)
- Requirement for respiratory support
    - For main randomisation: None; Oxygen only; Non-invasive ventilation; Invasive mechanical ventilation (including ECMO)
    - For second randomisation: No ventilator support (including no or low-flow oxygen); Non-invasive ventilation (including CPAP, other non-invasive ventilation, or high-flow nasal oxygen), Invasive mechanical ventilation (including ECMO)
- Use of systemic corticosteroid (including dexamethasone)
- For part B only: Recipient anti-SARS-CoV-2 antibody concentration at randomization (<8 $x10^6$ units; ≥8 $x10^6$ units). (This will be the key subgroup for the REGN-COV2 comparison.)
- *Important changes to the analysis plan*
- Initially the primary analysis was planned to be conducted in all randomized patients, but this was amended in SAP version 3.0 to be restricted to seronegatives only, with all randomized patients second in hierarchy. According to the applicant, the decision was made without knowledge of the study data.

*Important changes to the analysis plan*

Initially the primary analysis was planned to be conducted in all randomized patients, but this was amended in SAP version 3.0 to be restricted to seronegatives only, with all randomized patients second in hierarchy. According to the applicant, the decision was made without knowledge of the study data.

**Access to unblinded interim data**

Only the members of the Data Monitoring Committee (and the statisticians responsible for preparing their analyses) had access to the unblinded interim analyses during recruitment. Unblinded data were then shared as follows:

| Date | Activity |
|---|---|
| 21 May 2021 | Publication of Statistical Analysis Plan |
| 22 May 2021 | Close of recruitment (last patient randomised on 21 May 2021) |
| 27 May 2021 | Chief Investigators unblinded (on the advice of the DMC chairman) |
| 14 June 2021 | Unblinded results provided to Regeneron |
| 15 June 2021 | Trial Steering Committee unblinded |
| 16 June 2021 | Preliminary results made public |

## *Results*

## Participant flow

Between 18 September 2020 and 22 May 2021, 11,464 of 24,343 participants (47%) enrolled into the RECOVERY trial were eligible to be randomly allocated to receive casirivimab+imdevimab.

From the 11,464 participants who were eligible for randomization to casirivimab+imdevimab, 9785 were randomized between casirivimab+imdevimab (4839 participants) and the usual care group (4946 participants). Of these, 28 withdrew consent in the casirivimab+imdevimab group and 18 in the usual care group.

A higher number of participants proceeded to second randomization in the usual care group (535 participants) compared to the casirivimab+imdevimab group (374 participants). In total, 4839 participants were included in the 28-day ITT analysis in the casirivimab+imdevimab group and 4946 participants in the usual care group.

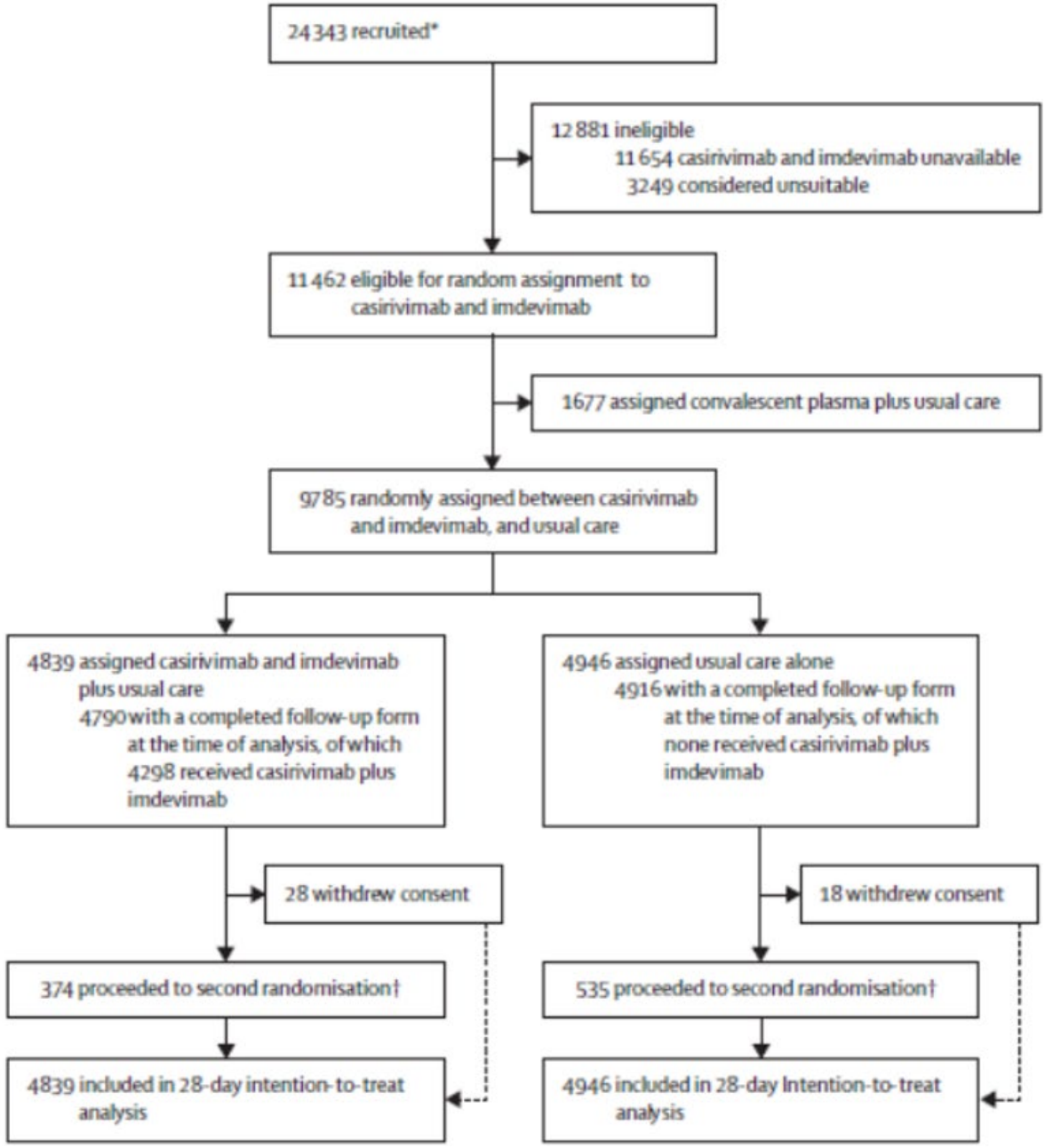



***Figure 1:*** **Trial profile**
Casirivimab and imdevimab unavailable and casirivimab and imdevimab unsuitable groups are not mutually exclusive. *Number recruited overall during the period that adult participants could be recruited into the casirivimab and imdevimab comparison. †Includes patients allocated to tocilizumab. Until Jan 24, 2021, tocilizumab was allocated via the second randomisation to 185 (4%) of 4839 patients allocated casirivimab and imdevimab and to 271 (5%) of 4946 patients allocated to usual care.

## Recruitment

The study was conducted in the UK, Indonesia, and Nepal, with 127 hospitals in the UK taking part in the evaluation of casirivimab+imdevimab.

Between 18 September 2020 and 22 May 2021 the REGEN-COV arm was open. All participants in the REGN-COV arm were enrolled at sites in the UK.

## Conduct of the study

**Table. Protocol changes to treatment comparisons**

| Protocol version | Date | Randomisation | Treatment arms |
|---|---|---|---|
| 1.0 | 13-Mar-2020 | Main (part A) | No additional treatment<br>Lopinavir-ritonavir[a]<br>Low-dose corticosteroid[b]<br>Nebulised Interferon-ß-1a (never activated) |
| 2.0 | 23-Mar-2020 | Main (part A) | No additional treatment<br>Lopinavir-ritonavir[a] |
| | | | Low-dose corticosteroid[b]<br>Hydroxychloroquine |
| 3.0 | 07-Apr-2020 | Main (part A) | No additional treatment<br>Lopinavir-ritonavir[a]<br>Low-dose corticosteroid[b]<br>Hydroxychloroquine[c]<br>Azithromycin[d] |
| 4.0 | 14-Apr-2020 | Main (part A) | No additional treatment<br>Lopinavir-ritonavir[a]<br>Low-dose corticosteroid[b]<br>Hydroxychloroquine[c]<br>Azithromycin[d] |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |
| 5.0 | 24-Apr-2020 | - | (no change – extension to children <18 years old) |
| 6.0 | 14-May-2020 | Main (part A) | No additional treatment<br>Lopinavir-ritonavir[a]<br>Low-dose corticosteroid[b]<br>Hydroxychloroquine[c]<br>Azithromycin[d] |
| | | Main (part B factorial) | No additional treatment<br>Convalescent plasma |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |
| 7.0 | 18-Jun-2020 | Main (part A) | No additional treatment<br>Lopinavir-ritonavir[a]<br>Low-dose corticosteroid[b]<br>Azithromycin[d] |
| | | Main (part B factorial) | No additional treatment<br>Convalescent plasma |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |
| 8.0 | 03-Jul-2020 | Main (part A) | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Azithromycin[d] |
| | | Main (part B factorial) | No additional treatment<br>Convalescent plasma |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |

| Protocol version | Date | Randomisation | Treatment arms |
|---|---|---|---|
| 9.1 | 18-Sep-2020 | Main (part A) | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Azithromycin[d] |
| | | Main (part B factorial) | No additional treatment<br>Convalescent plasma<br>REGEN-COV |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |
| 10.1 | 01-Nov-2020 | Main (part A) | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Azithromycin[d] |
| | | Main (part B factorial) | No additional treatment<br>Convalescent plasma<br>REGEN-COV |
| | | Main (part C factorial) | No additional treatment<br>Aspirin |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |
| 11.1 | 27-Nov-2020 | Main (part A) | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Colchicine |
| | | Main (part B factorial) | No additional treatment<br>Convalescent plasma<br>REGEN-COV |
| | | Main (part C factorial) | No additional treatment<br>Aspirin |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |
| 12.1 | 16-Dec-2020 | Main (part A)[h] | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Colchicine |
| | | Main (part B factorial)[h] | No additional treatment<br>Convalescent plasma<br>REGEN-COV |
| | | Main (part C factorial)[h] | No additional treatment<br>Aspirin |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f] |

| Protocol version | Date | Randomisation | Treatment arms |
|---|---|---|---|
| 13.0 | 26-Jan-2021 | Main (part A)[h] | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Colchicine |
| | | Main (part B factorial)[h] | No additional treatment<br>REGEN-COV |
| | | Main (part C factorial)[h] | No additional treatment<br>Aspirin |
| | | Main (part D factorial) | No additional treatment<br>Baricitinib |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f]<br>Anakinra |
| 14.0 | 15-Feb-2021 | Main (part A)[h] | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Colchicine<br>Dimethyl fumarate |
| | | Main (part B factorial)[h] | No additional treatment<br>REGEN-COV |
| | | Main (part C factorial)[h] | No additional treatment<br>Aspirin |
| | | Main (part D factorial) | No additional treatment<br>Baricitinib |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f]<br>Anakinra |
| 15.0 | 12-Apr-2021 | Main (part A)[h] | No additional treatment<br>Low-dose corticosteroid[b]<br>Intravenous immunoglobulin[g]<br>High-dose corticosteroid[g]<br>Dimethyl fumarate |
| | | Main (part B factorial)[h] | No additional treatment<br>REGEN-COV |
| | | Main (part D factorial) | No additional treatment<br>Baricitinib<br>Infliximab[j] |
| | | Main (part E factorial)[j] | High-dose dexamethasone[j] |
| | | Second[e,f] | No additional treatment<br>Tocilizumab[f]<br>Anakinra |

[a] enrolment ceased 29 June 2020 when the Data Monitoring Committee advised that the Chief Investigators should review the unblinded data.
[b] enrolment of adults ceased 8 June 2020 as more than 2,000 patients had been recruited to the active arm
[c] enrolment ceased 5 June 2020 when the Data Monitoring Committee advised that the Chief Investigators should review the unblinded data.
[d] enrolment of adults ceased 27 November 2020 as more than 2,500 patients had been recruited to the active arm
[e] for patients with (a) oxygen saturation <92% on air or requiring oxygen or children with significant systemic disease with persistent pyrexia; and (b) C-reactive protein ≥75 md/L)
[f] enrolment of adults ceased 24 January 2021 as more than 2,000 patients had been recruited to the active arm.
[g] for children only
[h] from protocol version 12.1, children could enter the second randomisation regardless of whether they were included in the main randomisation
[i] for patients with (a) oxygen saturation <92% on air or requiring oxygen
[j] for patients outside UK

## Baseline data

**Table 1: Baseline characteristics (seronegative and all participants) by treatment allocation**

| | Seronegative patients | | All patients | |
|---|---|---|---|---|
| | REGEN-COV (n=1633) | Usual Care (n=1520) | REGEN-COV (n=4839) | Usual Care (n=4946) |
| Age, years | 63.2 (15.5) | 64.0 (15.2) | 61.9 (14.8) | 61.9 (14.4) |
| <70* | 1054 (65) | 943 (62) | 3389 (70) | 3454 (70) |
| 70 to 79 | 348 (21) | 344 (23) | 936 (19) | 962 (19) |
| ≥80 | 231 (14) | 233 (15) | 514 (11) | 530 (11) |
| Sex | | | | |
| Men | 995 (61) | 879 (58) | 3033 (63) | 3095 (63) |
| Women† | 638 (39) | 641 (42) | 1806 (37) | 1851 (37) |
| Ethnicity | | | | |
| White | 1324 (81) | 1250 (82) | 3768 (78) | 3810 (77) |
| Black, Asian, and minority ethnic | 147 (9) | 136 (9) | 588 (12) | 696 (14) |
| Unknown | 162 (10) | 134 (9) | 483 (10) | 440 (9) |
| Number of days since symptom onset | 7 (4-10) | 7 (5-9) | 9 (6-12) | 9 (6-12) |
| Number of days since admission to hospital | 1 (1-2) | 1 (1-3) | 2 (1-3) | 2 (1-3) |
| Respiratory support received | | | | |
| No oxygen received | 182 (11) | 148 (10) | 332 (7) | 309 (6) |
| Simple oxygen | 1085 (66) | 995 (65) | 2980 (62) | 3016 (61) |
| Non-invasive ventilation | 332 (20) | 341 (22) | 1244 (26) | 1317 (27) |
| Invasive mechanical ventilation | 34 (2) | 36 (2) | 283 (6) | 304 (6) |
| Previous diseases | | | | |
| Diabetes | 403 (25) | 407 (27) | 1240 (26) | 1337 (27) |
| Heart disease | 407 (25) | 398 (26) | 1038 (21) | 1061 (21) |
| Chronic lung disease | 455 (28) | 456 (30) | 1085 (22) | 1159 (23) |
| Tuberculosis | 7 (<1) | 5 (<1) | 18 (<1) | 16 (<1) |
| HIV | 7 (<1) | 4 (<1) | 24 (<1) | 22 (<1) |
| Severe liver disease‡ | 28 (2) | 17 (1) | 69 (1) | 70 (1) |
| Severe kidney impairment§ | 114 (7) | 114 (8) | 266 (5) | 242 (5) |
| Any of the above | 935 (57) | 913 (60) | 2557 (53) | 2662 (54) |
| SARS-CoV-2 PCR test result | | | | |
| Positive | 1580 (97) | 1470 (97) | 4690 (97) | 4791 (97) |
| Negative | 17 (1) | 16 (1) | 38 (1) | 53 (1) |
| Unknown | 36 (2) | 34 (2) | 121 (3) | 102 (2) |
| Patient SARS-CoV-2 antibody test result | | | | |
| Positive | 0 | 0 | 2636 (54) | 2636 (53) |
| Negative | 1633 (100) | 1520 (100) | 1633 (34) | 1520 (31) |
| Missing | 0 | 0 | 570 (12) | 790 (16) |
| Corticosteroids received | | | | |
| Yes | 1481 (91) | 1399 (92) | 4530 (94) | 4639 (94) |
| No | 152 (9) | 118 (8) | 308 (6) | 299 (6) |
| Not recorded | 0 | 3 (<1) | 1 (<1) | 8 (<1) |
| Other randomised treatments | | | | |
| Azithromycin | 38 (2) | 43 (3) | 124 (3) | 124 (3) |
| Colchicine | 364 (22) | 350 (23) | 1085 (22) | 1139 (23) |
| Aspirin | 405 (25) | 372 (24) | 1339 (28) | 1389 (28) |

Data are mean (SD), n (%), or median (IQR). *Includes 11 children (<18 years). † Includes 25 pregnant women. ‡ Defined as requiring ongoing specialist care. § Defined as estimated glomerular filtration rate <30 mL/min per 1·73 m²

The participants' demographic characteristics including age, sex, and race/ethnicity were balanced between the treatment groups for the seronegative group and among all randomized participants.

Among all randomized participants at baseline, 54% were seropositive, 34% were seronegative, and 14% had an unknown serostatus.

**Seronegative patients**

Among participants that were seronegative at baseline, the mean age was 63.2 years (standard deviation [SD] 15.5) in the casirivimab+imdevimab group and 64.0 years (SD 15.2) in the usual care alone group. The majority were male (61% and 58%) and White (81% and 82%).

The baseline disease characteristics of the seronegative participants were mostly similar to those reported for all randomized participants. Differences observed in seronegative participants when compared to all randomized participants, albeit numerically small, included a shorter time from symptom onset (median 7 days) and a higher proportion of participants receiving no oxygen (~11%) and simple oxygen (~66%). Similar proportions of participants were randomized to azithromycin, aspirin and colchichine as per all the randomized group.

**All randomised patients**

Among all randomized participants, the mean age was 61.9 years (SD 14.6) in the casirivimab + imdevimab and usual care alone group. The majority of participants were male (63%) and White (~78%).

Both treatment groups had a median of 9 days from symptom onset and a median of 2 days since admission to hospital. Most participants received simple oxygen support (62% casirivimab+imdevimab vs. 61% usual care alone) followed by non-invasive ventilation (26% vs. 27%).

The frequency of comorbidities in the casirivimab+imdevimab and usual care groups was similar (53% vs. 54%), and the most common comorbidities were diabetes, chronic lung disease, and heart disease, the proportions of which were similar between the treatment groups.

Of the other treatments participants could be randomized to as part of the main randomization A, B, C and D, very few participants received azithromycin (3% for both groups), 28% received aspirin in both groups and 22% of those randomized to casirivimab+imdevimab vs. 23% to the usual care group received colchichine.

## Numbers analysed

The primary outcome was 28-day mortality assessed first among patients without detectable antibodies to SARS-CoV-2 at randomisation (seronegative) and then in the overall population.

9785 patients were randomly allocated to receive usual care plus REGEN-COV or usual care alone, including 3153 (32%) seronegative patients, 5272 (54%) seropositive patients and 1360 (14%) patients with unknown baseline antibody status.

## Outcomes and estimation

### Table 11 Overall Efficacy Outcomes among Seronegative Participants

| | REGEN-COV (n=1633) | Usual Care (n=1520) | RR (95% CI) |
|---|---|---|---|
| **Primary outcome** | | | |
| Mortality at 28 days | 396 (24%) | 451 (30%) | 0.80 (0.70-0.91) |
| **Secondary outcomes** | | | |
| Median duration of hospitalisation, days | 13 (7 to >28) | 17 (7 to >28) | - |
| Discharged from hospital within 28 days | 1046 (64%) | 878 (58%) | 1.19 (1.08-1.30) |
| Invasive mechanical ventilation or death* | 487/1599 (30%) | 542/1484 (37%) | 0.83 (0.75-0.92) |
| Invasive mechanical ventilation | 189/1599 (12%) | 200/1484 (13%) | 0.88 (0.73-1.06) |
| Death | 383/1599 (24%) | 434/1484 (29%) | 0.82 (0.73-0.92) |
| **Subsidiary outcomes** | | | |
| Use of ventilation † | 355/1267 (28%) | 370/1143 (32%) | 0.87 (0.77-0.98) |
| Non-invasive ventilation | 341/1267 (27%) | 360/1143 (31%) | 0.85 (0.75-0.97) |
| Invasive mechanical ventilation | 89/1267 (7%) | 119/1143 (10%) | 0.67 (0.52-0.88) |
| Successful cessation of invasive mechanical ventilation ‡ | 9/34 (26%) | 12/36 (33%) | 0.86 (0.36-2.03) |
| Renal replacement therapy § | 68/1616 (4%) | 64/1498 (4%) | 0.98 (0.71-1.38) |

Data are n (%), median (IQR) or n/N (%). RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes.
* Analyses exclude those on invasive mechanical ventilation at randomisation.
† Analyses exclude those on invasive or non-invasive ventilation at randomisation.
‡ Analyses exclude those not receiving invasive mechanical ventilation at randomisation.
§ Analyses exclude those on renal replacement therapy at randomisation.

Source: RECOVERY Collaborative Group, 2021 (Table 2).

### Table 12 Overall Efficacy Outcomes among All Randomized Participants

| | REGEN-COV (n=4839) | Usual Care (n=4946) | RR (95% CI) |
|---|---|---|---|
| **Primary outcome** | | | |
| Mortality at 28 days | 944 (20%) | 1026 (21%) | 0.94 (0.86-1.03) |
| **Secondary outcomes** | | | |
| Median duration of hospitalisation, days | 10 (6 to >28) | 10 (5 to >28) | - |
| Discharged from hospital within 28 days | 3375 (70%) | 3413 (69%) | 1.01 (0.97-1.07) |
| Invasive mechanical ventilation or death* | 1089/4556 (24%) | 1151/4642 (25%) | 0.96 (0.90-1.04) |
| Invasive mechanical ventilation | 479/4556 (11%) | 487/4642 (10%) | 1.00 (0.89-1.13) |
| Death | 836/4556 (18%) | 902/4642 (19%) | 0.94 (0.87-1.03) |
| **Subsidiary outcomes** | | | |
| Use of ventilation † | 751/3312 (23%) | 793/3325 (24%) | 0.95 (0.87-1.04) |
| Non-invasive ventilation | 726/3312 (22%) | 765/3325 (23%) | 0.95 (0.87-1.04) |
| Invasive mechanical ventilation | 181/3312 (5%) | 211/3325 (6%) | 0.86 (0.71-1.04) |
| Successful cessation of invasive mechanical ventilation ‡ | 103/283 (36%) | 116/304 (38%) | 0.97 (0.74-1.26) |
| Renal replacement therapy § | 203/4783 (4%) | 201/4887 (4%) | 1.03 (0.85-1.25) |

Data are n (%), median (IQR) or n/N (%). RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes.
* Analyses exclude those on invasive mechanical ventilation at randomisation.
† Analyses exclude those on invasive or non-invasive ventilation at randomisation.
‡ Analyses exclude those not receiving invasive mechanical ventilation at randomisation.
§ Analyses exclude those on renal replacement therapy at randomisation.

## Primary Efficacy Endpoint

**28-day All-cause Mortality**

Among participants who were seronegative at baseline, there was a statistically significant relative reduction of 20% in 28-day all-cause mortality among participants in the casirivimab+imdevimab group compared to participants receiving usual care alone, 24% (396/1633 participants) died in the casirivimab+imdevimab group vs. 30% (451/1520 participants) in the usual care group (rate ratio: 0.80; 95% CI: 0.70–0·91; p=0.001).

Among all randomized participants (including those who were seronegative, seropositive and serostatus unknown), there was no significant difference in 28-day all-cause mortality between the two groups: 20% (944/4839 participants) of participants in the casirivimab+imdevimab group died versus 21% (1026/4946 participants) of participants in the usual care alone group (rate ratio 0.94; 95% CI: 0.86 to 1.03; p=0.17)

28-day mortality was also assessed in participants who were seropositive at baseline. There was little difference in the 28-day all-cause mortality between the two groups: 16% (411/2636) of participants in the seropositive casirivimab+imdevimab group died versus 15% (383/2636) of participants in the usual care alone group (rate ratio 1.09; 95% CI: 0.95 to 1.26) (Figure 2, Figure 3). The proportional effect of casirivimab+imdevimab on mortality differed significantly between participants who were seronegative and seropositive at baseline (test for heterogeneity, p=0.001).

**Figure 2: Effect of allocation to REGEN−COV on 28−day mortality in: a) seronegative vs seropositive participants; and b) all participants**

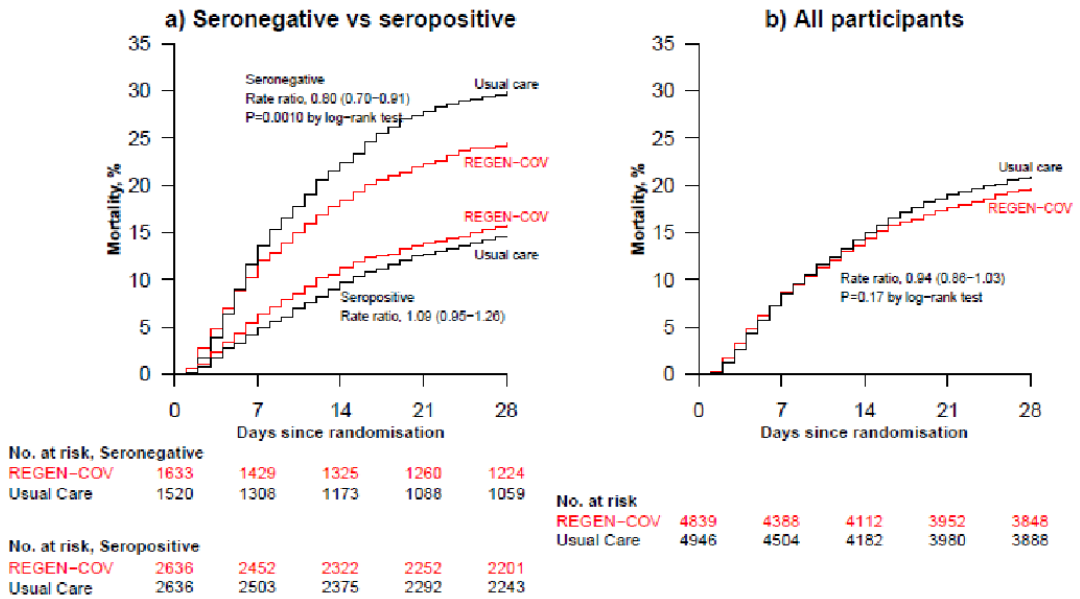
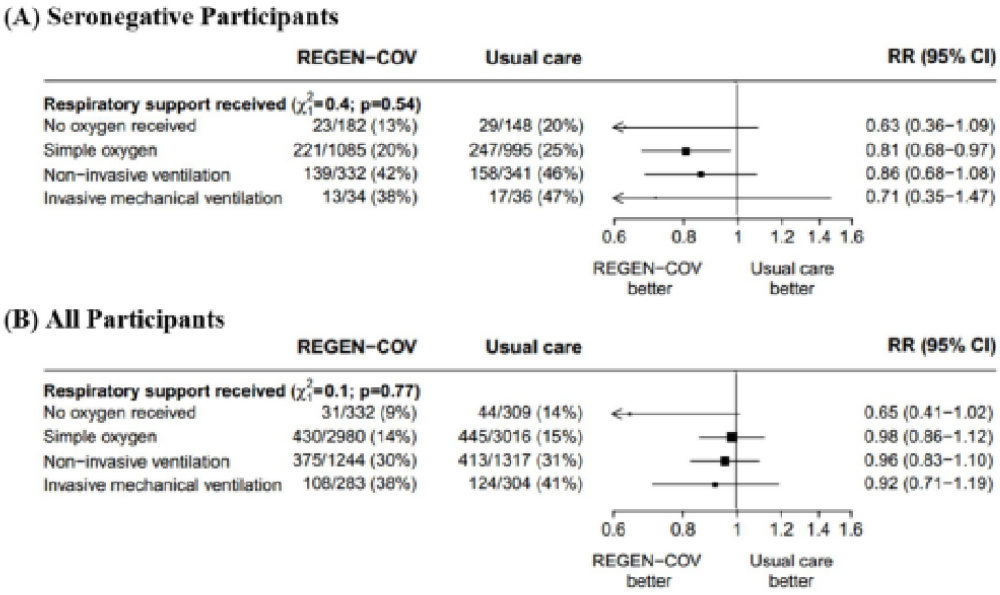
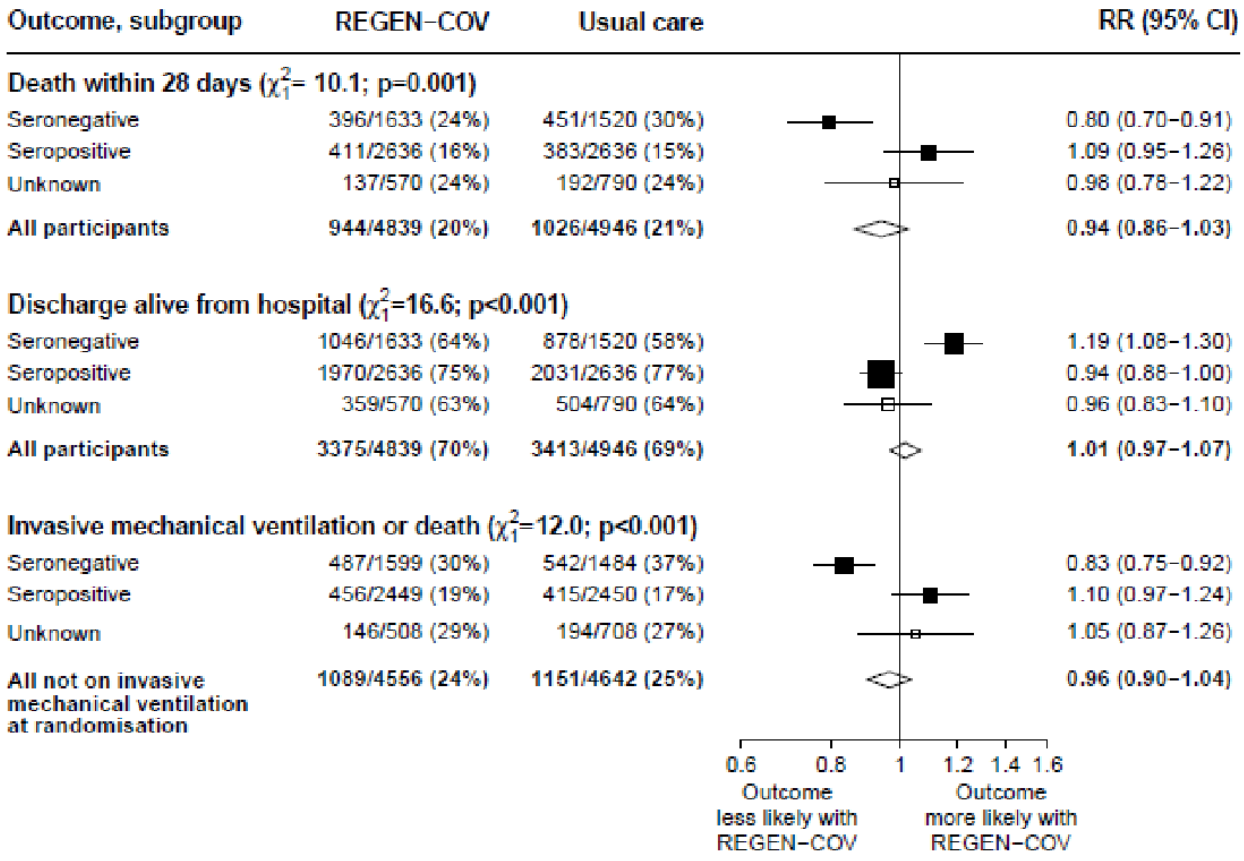


**Figure 6 Effect of Allocation on 28-Day Mortality by Baseline Respiratory Status**




Source: RECOVERY Supplementary Material, Webfigure 1, Webfigure 3.

**Figure 3: Primary and secondary outcomes, overall and by baseline antibody status**



Subgroup–specific rate ratio estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% CIs. The tests for heterogeneity compare the log RRs in the seronegative versus seropositive subgroups (ie, ignoring those with unknown antibody status).

**Secondary Efficacy Endpoints**

**Discharge alive from hospital**

Among seronegative participants, discharge alive within 28 days was more common among participants in the casirivimab+imdevimab group compared with the usual care group (64% vs. 58%; risk ratio: 1.19, 95% CI: 1.08 to 1.30; median 13 days, interquartile range [IQR] 7 to >28 vs. 17 days [IQR 7 to >28]) (Table 11, Figure 3).

Among all randomized participants, there was no meaningful difference observed in the casirivimab+imdevimab group compared with the usual care group in discharge alive within 28 days (70% vs. 69%; rate ratio 1.01, 95% CI: 0.97 to 1.07; median 10 days [IQR 6 to >28] vs. 10 days [IQR 5 to >28]) (Table 12, Figure 3).

**Use of invasive mechanical ventilation or death among patients not on invasive mechanical ventilation at randomization**

Among seronegative participants not on invasive mechanical ventilation at baseline, participants in the casirivimab+imdevimab group had a lower risk of progressing to the composite secondary outcome of invasive mechanical ventilation or death (30% vs. 37%, risk ratio 0.83, 95% CI: 0.75 to 0.92) (Table 11, Figure 3). However, there was little difference observed among all randomized participants (24% vs. 25%, risk ratio 0.96, 95% CI: 0.90 to 1.04) (Table 12, Figure 3).

For each secondary efficacy endpoint described above, there was clear evidence that the proportional effects differed between seropositive and seronegative participants (p value for heterogeneity <0.001 for both endpoints) (Figure 3).

**Subsidiary Clinical Outcomes**

**Use of invasive or non-invasive ventilation among patients not on any ventilation at randomization**

Seronegative participants receiving casirivimab+imdevimab were less likely to progress to the use of ventilation among those who were not receiving ventilation at baseline versus participant in the usual care group (28% vs. 32%; risk ratio 0.87, 95% CI: 0.77 to 0.98) (Table 11, Figure 3). This was not observed in the overall study population (23% vs. 24%; risk ratio 0.95, 95% CI: 0.87 to 1.04) (Table 12, Figure 3).

When evaluating the use of non-invasive ventilation and use of invasive mechanical ventilation separately, seronegative participants who received casirivimab+imdevimab were less likely to progress using either form of ventilatory support (use of noninvasive ventilation: 27% vs. 31%, risk ratio 0.85, 95% CI 0.75 to 0.97; use of invasive mechanical ventilation: 7% vs. 10%, risk ratio 0.67, 95% CI 0.52 to 0.88) (Table 11). However, this was not observed in the overall study population (use of non-invasive ventilation: 22% vs. 23%, risk ratio 0.95, 95% CI: 0.87 to 1.04; use of invasive mechanical ventilation: 5% vs. 6%, risk ratio 0.86, 95% CI: 0.71 to 1.04) (Table 12).

**Use of renal dialysis or hemofiltration**

Among seronegative participants not receiving renal replacement therapy at randomization, there was no meaningful difference in the use of renal replacement therapy among participants in the casirivimab+imdevimab group versus the usual care group (4% in both groups, risk ratio 0.98, 95% CI: 0.71 to 1.38) (Table 11). No difference between the groups was seen in the overall population (4% in both groups, risk ratio 1.03, 95% CI: 0.85 to 1.25) (Table 12).

## Ancillary analyses

As the participants with clinically suspected SARS-CoV-2 infection could enrol without PCR laboratory-confirmation as well as those with a positive test, an analysis was undertaken on those with a positive SARS-COV-2 PCR test at baseline. In seronegative participants with a positive SARS-CoV-2 PCR test, a similar mortality rate ratio to the main analysis was observed (rate ratio 0.80; 95% CI: 0.70-0.91) in the casirivimab+imdevimab group. Using a Cox model adjusted for all pre-specified subgroups, allocation to casirivimab+imdevimab was associated with a mortality rate ratio of 0.85 (95% CI: 0.74 to 0.98) in seronegative participants (table below).

**Table 13 Sensitivity Analyses on the Effect of Casirivimab+imdevimab on 28-day All-cause Mortality in Seronegative Participants and All Participant Combined**

| | RR (95% CI) | |
|---|---|---|
| | Seronegative patients | All participants |
| Main analysis (ie, as shown in Figure 2) | 0.80 (0.70-0.91) | 0.94 (0.86-1.03) |
| Analysis limited to those with positive SARS-COV PCR test result | 0.80 (0.70-0.92) | 0.95 (0.87-1.04) |
| Analysis adjusted for all pre-specified subgroup analyses* | 0.85 (0.74-0.98) | 0.97 (0.89-1.06) |

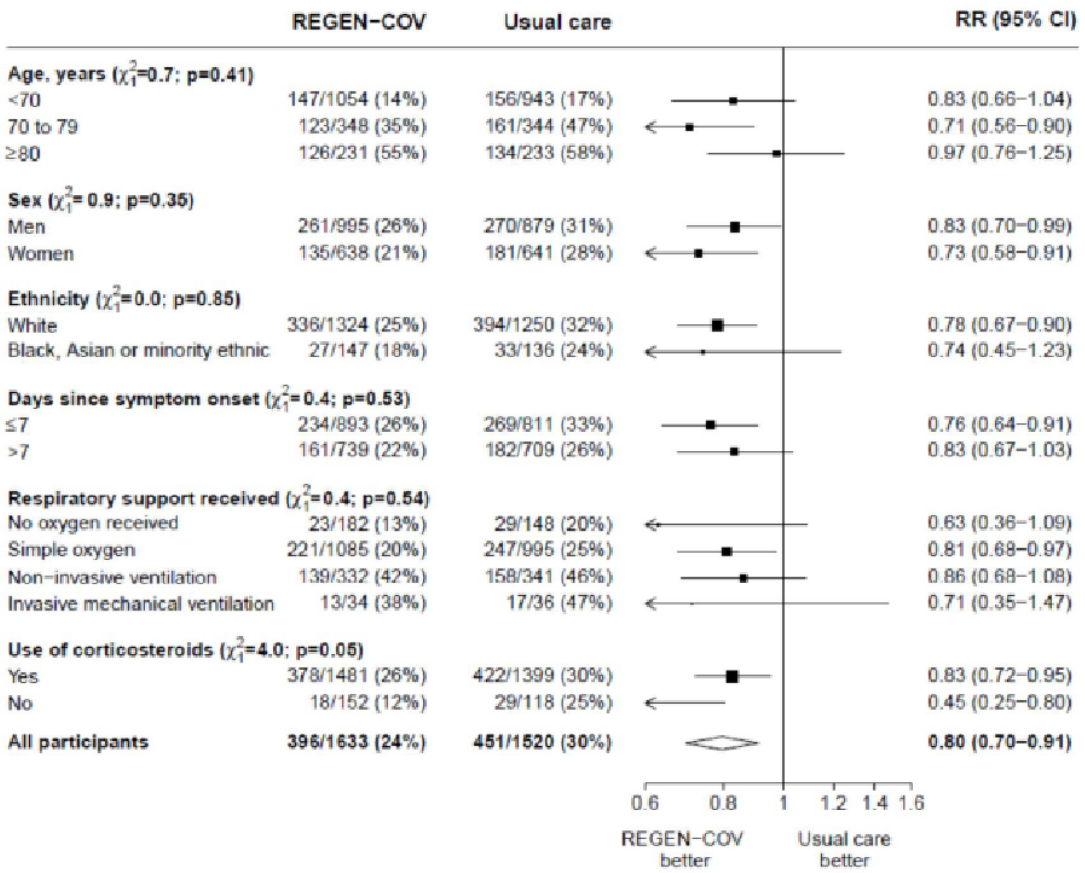
* For the average (conditional) estimate across all participants, the RR was approximated by the hazard ratio in a Cox model adjusted for age (<70, ≥70 to <80, ≥80 years), sex (male vs female), ethnicity (white, BAME, unknown), days since symptom onset (≤7 vs >7 days), respiratory support received (no oxygen received, simple oxygen, non-invasive ventilation, invasive mechanical ventilation), use of corticosteroids (yes vs no) and baseline antibody status (seronegative, seropositive, unknown). In this model the few with missing data for days since onset (n=9) and use of corticosteroids (n=9) were assigned to the largest of the non-missing categories. For the conditional RR estimate among seronegative patients, the model was further adjusted for interaction terms between treatment assignment and baseline antibody status, allowing the RR and its CI to be estimated separately for each subgroup.

Source: RECOVERY Manuscript Supplementary Material, 2021 (Webtable 5).

### *Subgroup analysis*

Among seronegative participants, the reduction in 28-day all-cause mortality in the casirivimab+imdevimab group was consistent across all other pre-specified subgroups (age, sex, ethnicity, days since symptom onset, respiratory support received and use of corticosteroids) (Figure 5).

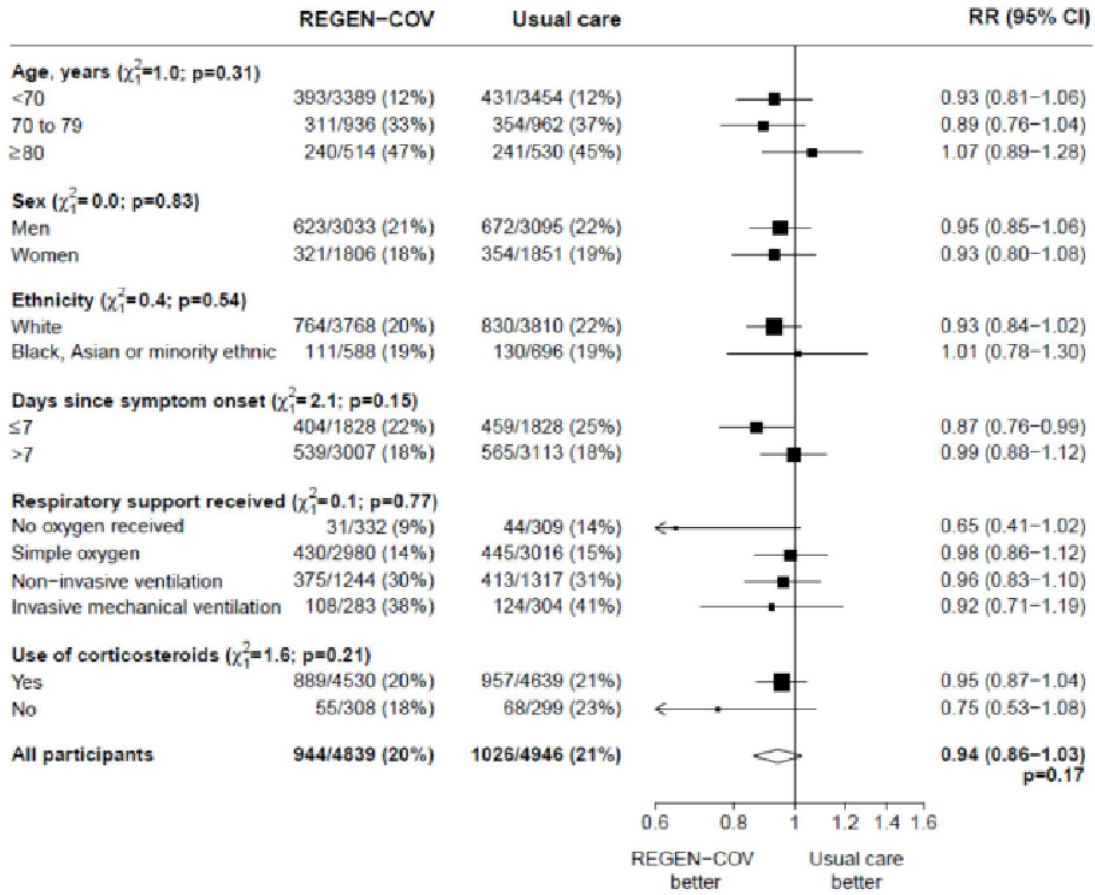
**Figure 5 Effect of Casirivimab+imdevimab on 28-day All-cause Mortality in Seronegative Participants by Pre-specified Baseline Characteristics**




Source: RECOVERY Manuscript Supplementary Material, 2021 (Webfigure 1).

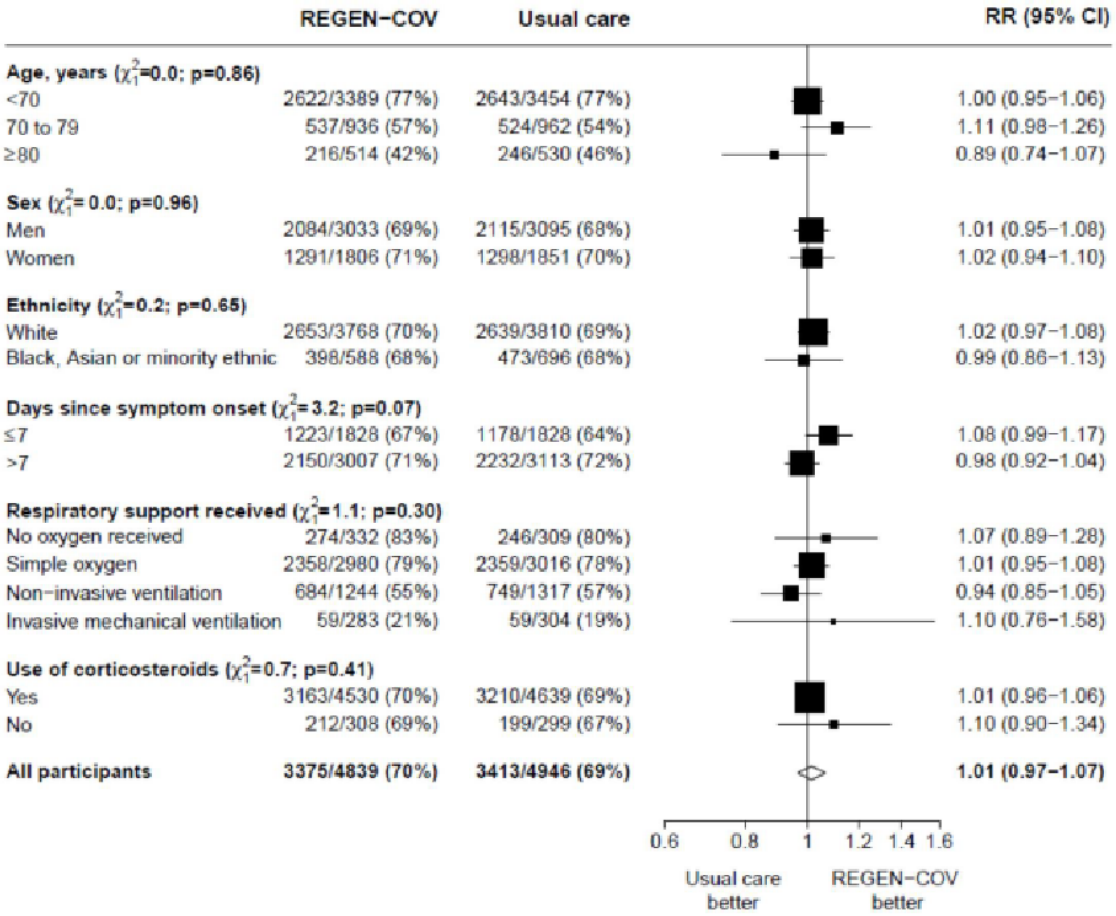
Most of the pre-specified subgroup analysis results among all randomized participants did not exclude 1 for the rate ratio comparisons between casirivimab+imdevimab and the usual care group alone for 28-day all-cause mortality (Figure 6), discharge alive from hospital (Figure 7), and progression to invasive mechanical ventilation or death (Figure 8). The subgroup analyses were broadly consistent with the result observed for the endpoints described in all participants (Figure 3).

**Figure 6 Effect of Casirivimab+imdevimab on 28-day All-cause Mortality in All Participants by Pre-specified Baseline Characteristics**



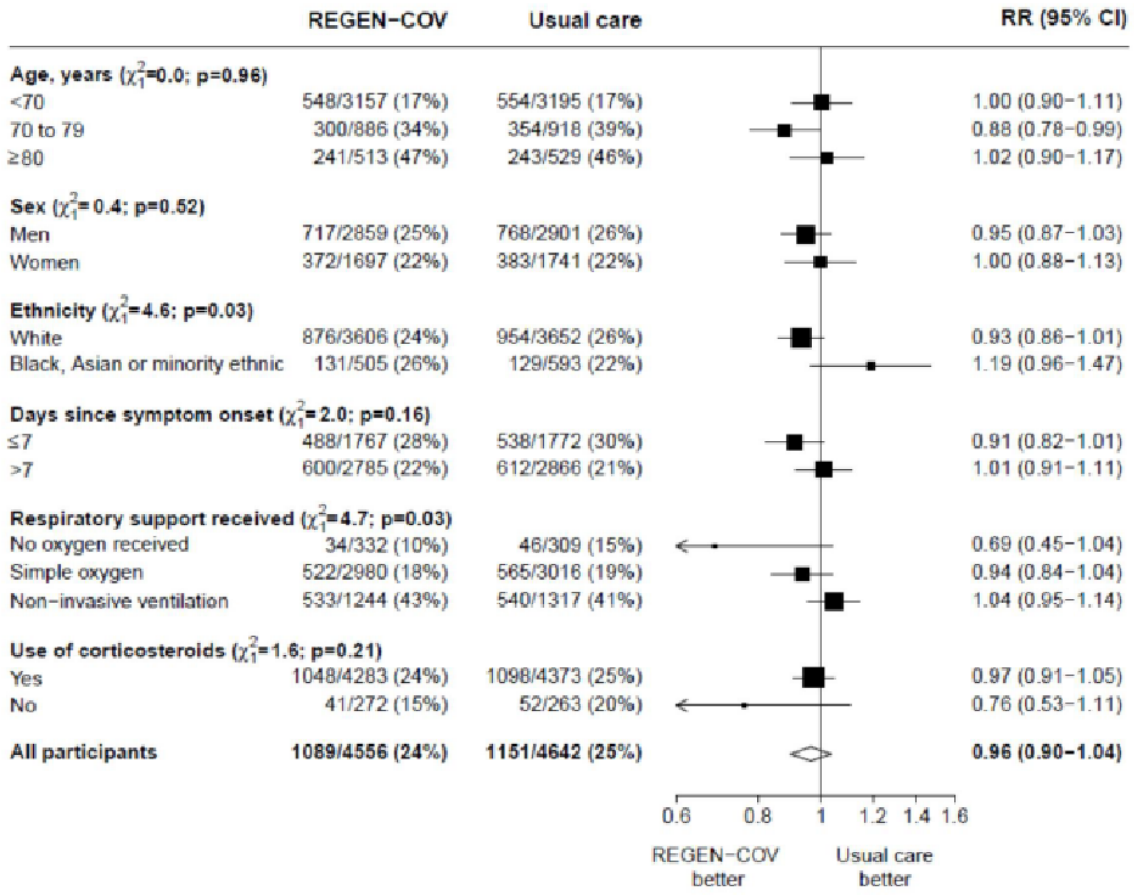

Source: RECOVERY Manuscript Supplementary Material, 2021 (Webfigure 2).

**Figure 7 Effect of Casirivimab+imdevimab on Discharge Alive from Hospital in All Participants by Pre-specified Baseline Characteristics**




Source: RECOVERY Manuscript Supplementary Material, 2021 (Webfigure 4).

**Figure 8 Effect of Casirivimab+imdevimab on Progression to Invasive Mechanical Ventilation or Death in All Participants by Pre-specified Baseline Characteristics**




Source: RECOVERY Manuscript Supplementary Material, 2021 (Webfigure 5).

## *Summary of main studies*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial RECOVERY

| **Title: Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial** | |
|---|---|
| Study identifier | RECOVERY<br>EudraCT: 2020-001113-21<br>ISRCTN50189673 |
| Design | Phase 3, factorial, investigator initiated, individually randomized, controlled, open-label, platform trial conducted at multiple hospitals. |

| | | | |
|---|---|---|---|
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 28 days<br>not applicable<br>not applicable |
| Hypothesis | Superiority: For each of the primary, secondary and subsidiary outcomes, the null hypothesis will be that there is no true difference in effect between the usual care arm and usual care plus casirivimab+imdevimab arm. | | |
| Treatments groups | Casirivimab+imdevimab | | Casirivimab+imdevimab 8000 mg IV single dose plus the usual care for COVID-19 at the participating hospitals.<br>4839 participants randomized |
| | Usual care | | Usual care for COVID-19 at the participating hospitals.<br>4946 participants randomized |
| Endpoints and definitions | Primary endpoint | Mortality | 28-day all-cause mortality<br>Endpoint assessed in (A) randomized participants who were seronegative at baseline and (B) in all randomized participants |
| | Secondary | Discharge | Discharged from hospital within 28 days<br>Endpoint assessed in (A) randomized participants who were seronegative at baseline and (B) in all randomized participants |
| | Secondary | Mechanical ventilation or death | Composite outcome of invasive mechanical ventilation or death among patients not on invasive mechanical ventilation at randomization assessed at 28 days after randomization<br>Endpoint assessed in (A) randomized participants who were seronegative at baseline and (B) in all randomized participants |
| | Subsidiary | Invasive or non-invasive ventilation | Use of invasive or non-invasive ventilation among patients not on any ventilation at randomization assessed at 28 days after randomization<br>Endpoint assessed in (A) randomized participants who were seronegative at baseline and (B) in all randomized participants |
| | Subsidiary | Cessation of mechanical ventilation | Successful cessation of invasive mechanical ventilation among patients not receiving mechanical ventilation at randomization assessed at 28 days after randomization<br>Endpoint assessed in (A) randomized participants who were seronegative at baseline and (B) in all randomized participants |
| | Subsidiary | Use of renal replacement therapy | Use of renal dialysis or hemofiltration among patients not receiving renal dialysis or hemofiltration at randomization, assessed at 28 days after randomization<br>Endpoint assessed in (A) randomized participants who were seronegative at baseline and (B) in all randomized participants |

| | | | |
|---|---|---|---|
| Database lock | 22 May 2021 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |
| Analysis population and time point description | (A) Randomized participants who were seronegative at baseline (Intent to treat)<br>Time point: 28 days after randomization | | |
| Descriptive statistics and estimate variability | Treatment group | Casirivimab+ imdevimab | Usual care |
| | Number of subjects | 1633 | 1520 |
| | Mortality<br>Number (%) | 396 (24%) | 451 (30%) |
| | Discharge<br>Number (%) | 1046 (64%) | 878 (58%) |
| | Mechanical ventilation or death<br>Number (%) | 487/1599 (30%) | 542/1484 (37%) |
| | Invasive or non-invasive ventilation<br>Number (%) | 355/1267 (28%) | 370/1143 (32%) |
| | Cessation of mechanical ventilation<br>Number (%) | 9/34 (26%) | 12/36 (33%) |
| | Use of renal replacement therapy<br>Number (%) | 68/1616 (4%) | 64/1498 (4%) |
| Analysis population and time point description | (B) All randomized participants (Intent to treat)<br>Time point: 28 days after randomization | | |
| Descriptive statistics and estimate variability | Treatment group | Casirivimab+ imdevimab | Usual care |
| | Number of subjects | 4839 | 4946 |
| | Mortality<br>Number (%) | 944 (20%) | 1026 (21%) |
| | Discharge<br>Number (%) | 3375 (70%) | 3413 (69%) |

| | | | |
|---|---|---|---|
| | Mechanical ventilation or death<br>Number (%) | 1089/4556 (24%) | 1151/4642 (25%) |
| | Invasive or non-invasive ventilation<br>Number (%) | 751/3312 (23%) | 793/3325 (24%) |
| | Cessation of mechanical ventilation<br>Number (%) | 103/283 (36%) | 116/304 (38%) |
| | Use of renal replacement therapy<br>Number (%) | 203/4783 (4%) | 201/4887 (4%) |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Mortality in seronegative participants | Comparison groups | Casirivimab+imdevimab vs. Usual care |
| | | Rate ratio | 0.80 |
| | | 95% confidence interval | 0.70-0.91 |
| | | P-value by log-rank test | P=0.001 |
| | Discharge in seronegative participants | Comparison groups | Casirivimab+imdevimab vs. Usual care |
| | | Rate ratio | 1.19 |
| | | 95% confidence interval | 1.08-1.30 |
| | | P-value | Not reported |
| | Mechanical ventilation or death in seronegative participants | Comparison groups | Casirivimab+imdevimab vs. Usual care |
| | | Risk ratio | 0.83 |
| | | 95% confidence interval | 0.75-0.92 |
| | | P-value | Not reported |
| | Invasive or non-invasive ventilation | Comparison groups | Casirivimab+imdevimab vs. Usual care |

| | | | |
|---|---|---|---|
| | in seronegative participants | Risk ratio | 0.87 |
| | | 95% confidence interval | 0.77-0.98 |
| | | P-value | Not reported |
| | Cessation of invasive mechanical ventilation in seronegative participants | Comparison groups | Casirivimab+imdevimab vs. Usual care |
| | | Risk ratio | 0.86 |
| | | 95% confidence interval | 0.36-2.03 |
| | | P-value | Not reported |
| | Use of renal replacement therapy in seronegative participants | Comparison groups | Casirivimab+imdevimab vs. Usual care |
| | | Risk ratio | 0.98 |
| | | 95% confidence interval | 0.71-1.38 |
| | | P-value | Not reported |
| Effect estimate per comparison | Mortality in all randomized participants | Comparison groups | Casirivimab+imdevimab vs. Usual care |
| | | Rate ratio | 0.94 |
| | | 95% confidence interval | 0.86-1.03 |
| | | P-value by log-rank test | P=0.17 |
| | Discharge in all randomized participants | Comparison groups | Casirivimab+imdevimab vs. Usual care |
| | | Rate ratio | 1.01 |
| | | 95% confidence interval | 0.97-1.07 |
| | | P-value | Not reported |
| | Mechanical ventilation or death in all randomized participants | Comparison groups | Casirivimab+imdevimab vs. Usual care |
| | | Risk ratio | 0.96 |
| | | 95% confidence interval | 0.90-1.04 |
| | | P-value | Not reported |
| | Invasive or non-invasive ventilation in all randomized participants | Comparison groups | Casirivimab+imdevimab vs. Usual care |
| | | Risk ratio | 0.95 |
| | | 95% confidence interval | 0.87-1.04 |
| | | P-value | Not reported |
| | Cessation of invasive mechanical ventilation in all participants | Comparison groups | Casirivimab+imdevimab vs. Usual care |
| | | Risk ratio | 0.97 |
| | | 95% confidence interval | 0.74-1.26 |
| | | P-value | Not reported |
| | Use of renal replacement therapy in all participants | Comparison groups | Casirivimab+imdevimab vs. Usual care |
| | | Risk ratio | 1.03 |
| | | 95% confidence interval | 0.85-1.25 |

| | | | |
|---|---|---|---|
| | | P-value | Not reported |
| Notes | RECOVERY met its pre-specified primary endpoint for 28-day all-cause mortality. Among participants who were seronegative at baseline, there was a statistically significant relative reduction of 20% in 28-day all-cause mortality among participants in the casirivimab+imdevimab group compared to participants receiving usual care alone, 24% (396/1633 participants) died in the casirivimab+imdevimab group vs. 30% (451/1520 participants) in the usual care group (rate ratio: 0.80; 95% CI: 0.70–0·91; p=0.001).<br>Among all randomized participants (including those who were seronegative, seropositive and serostatus unknown), there was no significant difference in 28-day all-cause mortality between the two groups: 20% (944/4839 participants) of participants in the casirivimab+imdevimab group died versus 21% (1026/4946 participants) of participants in the usual care alone group (rate ratio 0.94; 95% CI: 0.86 to 1.03; p=0.17).<br>Although not part of the testing hierarchy, 28-day mortality was also assessed in participants who were seropositive at baseline. There was little difference in the 28-day all-cause mortality between the two groups: 16% (411/2636) of participants in the seropositive casirivimab+imdevimab group died versus 15% (383/2636) of participants in the usual care alone group (rate ratio 1.09; 95% CI: 0.95 to 1.26). | | |

Analysis performed across trials (pooled analyses and meta-analysis)

The demonstration of the clinical and virologic efficacy of casirivimab+imdevimab for the treatment of hospitalized participants with COVID-19 consists of data from two studies: the pivotal RECOVERY trial and the supportive COV-2066 study. An integrated analysis of efficacy was not performed across these studies due to the following reasons:

- The Sponsor of each trial (University of Oxford for RECOVERY and Regeneron for COV-2066) did not collect data in a similar way that would allow for integration between the two studies.
- The disease characteristics of the participants in the efficacy analysis populations, as evidenced by the respiratory support received, were different between the studies. The population in RECOVERY included participants across the full disease spectrum of hospitalized patients with COVID-19 (no supplemental oxygen, simple oxygen, non-invasive ventilation, and invasive mechanical ventilation [including ECMO]), whereas the population in COV-2066 included those on no supplemental oxygen or on low-flow supplemental oxygen.
- The efficacy endpoints within the studies were sufficiently different. In RECOVERY the primary endpoint was mortality at Day 28, with secondary endpoints including discharge from hospital and progression to mechanical ventilation or death as part of the testing hierarchy. In COV-2066 there was a primary virological endpoint (reduction in viral load from Day 1 to Day 7) and a primary clinical endpoint (progression to mechanical ventilation or death) that was tested across different analysis populations in the testing hierarchy.
- RECOVERY was adequately powered to demonstrate clinical efficacy, whereas COV-2066 was prematurely discontinued.

## *Comparison across trials*

**Key inclusion and exclusion criteria**

RECOVERY was inclusive of participants regardless of their time from symptom onset to randomization or time from hospital admission to randomization. In an effort to enrol participants as soon as possible into the severe COVID-19 disease course, COV-2066 required participants to be < 10 days of COVID-19 symptom onset and hospitalized for < 72 hours.

RECOVERY was designed to enrol participants across the full range of COVID-19 disease severity in the hospitalized population, regardless of the type of respiratory support required. Ultimately and due to

changes in the study conduct, COV-2066 primarily enrolled participants towards the lower end of disease severity that required no supplemental oxygen or low-flow supplemental oxygen.

**Demographics**

Overall, the between treatment group baseline characteristics were balanced in both RECOVERY and COV-2066. Among all randomized participants who received casirivimab+imdevimab, over half were male (63% and 54.4%), most were White (78% and 63.4%), and the median age was 61.9 years and 61.3 years in RECOVERY and COV-2066 respectively.

**Table 25 Comparison of Baseline Characteristics in RECOVERY and COV-2066 in the overall trial population**

| | RECOVERY | | COV-2066 (pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A) | |
|---|---|---|---|---|
| | Casirivimab+ imdevimab 8000 mg (n=4839) | Usual care alone (n=4946) | Casirivimab+ imdevimab combined doses (n=804) | Placebo (n=393) |
| Age, mean (SD) | 61.9 (14.6) | 61.9 (14.4) | 61.3 (15.87) | 62.7 (16.38) |
| Sex, n (%) | | | | |
| Male | 3033 (63%) | 3095 (63%) | 437 (54.4%) | 210 (53.4%) |
| Female | 1806 (37%) | 1851 (37%) | 367 (45.6%) | 183 (46.6%) |
| Ethnicity/Race, n (%) | | | | |
| White | 3768 (78%) | 3810 (77%) | 510 (63.4%) | 239 (60.8%) |
| Black, Asian and minority ethnic | 588 (12%) | 696 (14%) | - | - |
| Black or African American | - | - | 99 (12.3%) | 46 (11.7%) |
| Asian | - | - | 31 (3.9%) | 16 (4.1%) |
| American Indian or Alaska Native | - | - | 22 (2.7%) | 9 (2.3%) |
| Native Hawaiian or Other Pacific Islander | - | - | 3 (0.4%) | 0 |
| Not reported | - | - | 89 (11.1%) | 57 (14.5%) |
| Unknown | 483 (10%) | 440 (9%) | 50 (6.2%) | 26 (6.6%) |

Source: RECOVERY Collaborative Group, 2021 (Table 1); t_121_1em_demo_pool.

**Baseline Disease Characteristics**

In the overall trial population, the proportion of enrolled participants with a negative SARS-COV-2 antibody test (i.e., seronegative) was lower in RECOVERY (34% vs. 31% in the casirivimab+imdevimab vs. usual care alone groups) compared to the COV-2066 study (44.8% vs. 40.7% in the combined doses vs. placebo). Furthermore, a greater proportion had a positive (i.e., seropositive) and unknown SARS-COV-2 antibody test result in RECOVERY compared to COV-2066.

Most participants in RECOVERY received simple oxygen support (62% vs. 61% in the casirivimab+imdevimab vs. usual care alone groups) followed by non-invasive ventilation (26% vs. 27% in the casirivimab+imdevimab vs. usual care alone groups). A smaller proportion of participants received invasive mechanical ventilation (6% in both the casirivimab+imevimab and usual care alone groups) or no supplemental oxygen (7% vs. 6% in the casirivimab+imdevimab vs. usual care alone groups). In COV-2066, 56.1% of the participants in the efficacy population received low-flow supplemental oxygen and 43.9% received no oxygen.

The median time from symptom onset to baseline was longer in RECOVERY compared to COV-2066 (9 days [IQR 6-12] vs. 5 days [IQR 4-8]) (table below). This was expected as RECOVERY was inclusive of participants regardless of their time from symptom onset.

**Table 26 Comparison of Baseline Disease Characteristics in RECOVERY and COV-2066 in the Overall Trial Population**

| | RECOVERY | | COV-2066 (pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A) | |
|---|---|---|---|---|
| | **Casirivimab+ imdevimab 8000 mg (n=4839)** | **Usual care alone (n=4946)** | **Casirivimab+ imdevimab combined doses (n=804)** | **Placebo (n=393)** |
| Type of respiratory support received | | | | |
| No oxygen | 332 (7%) | 309 (6%) | 358 (44.5%) | 167 (42.5%) |
| Simple oxygen | 2980 (62%) | 3016 (61%) | - | - |
| Non-invasive ventilation | 1244 (26%) | 1317 (27%) | - | - |
| Invasive mechanical ventilation | 283 (6%) | 304 (6%) | - | - |
| Non-invasive ventilation or high-flow oxygen devices | - | - | 0 | 1 (0.2%) |
| Supplemental oxygen (Not requiring high-flow oxygen devices) | - | - | 446 (55.5%) | 225 (57.3%) |
| Serostatus, n (%) | | | | |
| Seronegative | 1633 (34%) | 1520 (31%) | 360 (44.8%) | 160 (40.7%) |
| Seropositive | 2636 (54%) | 2636 (53%) | 369 (45.9%) | 201 (51.1%) |
| Seropositive-negative/borderline for neutralizing antibodies | - | - | 110/560 (19.6%)[a] | 68/304 (22.4%)[a] |
| Unknown/Other | 570 (12%) | 790 (16%) | 75 (9.3%) | 32 (8.1%) |
| Days since symptom onset, median (IQR) | 9 (6-12) | 9 (6-12) | 5 (4-8) | 6 (4-8) |
| Time from hospital admission, median (IQR) | 2 (1-3) | 2 (1-3) | 1 (1-2) | 1 (1-2) |
| Corticosteroids received at baseline, n (%) | 4530 (94%) | 4639 (94%) | 601 (74.8%) | 294 (74.8%) |

[a] Includes participants pooled across Phase 1/2/3 for Cohort 1 and Phase 2 for Cohort 1A.

Source: RECOVERY Collaborative Group, 2021 (Table 1), RECOVERY Manuscript Supplementary Material, 2021 (Webtables 2 and 3); t_121_1em_demo_pool, t_122_1em_blpneu_pool, t_124_1em_blhosp_pool, t_312_2em_cm_pool, t_p_dm_oth.

**Outcome**

Key clinical efficacy results supporting the treatment of hospitalised patients with COVID-19 are summarised below in a comparative manner for both studies. The efficacy outcomes in this section is for the 8000 mg IV dose in RECOVERY and the combined (2400 mg and 8000 mg) IV dose group for COV-2066.

**Mortality**

## Table 13 Efficacy Analysis for All-Cause Mortality

| All-cause mortality | Event rate: casirivimab+imdevimab vs usual care or placebo<br>Treatment Effect: Rate Ratio (RR) or Relative Risk Reduction (RRR) (95% CI); P-Value |
|---|---|
| RECOVERY | |
| **Seronegative population** | Event rate: 24% (396/1633) vs 30% (451/1520)<br>RR: 0.80 (0.7 - 0.91); p = 0.0010 |
| **Overall population** | Event rate: 19% (944/4839) vs 21% (1026/4946)<br>RR: 0.94 (0.86 – 1.03); p = 0.17 |
| **Seropositive population** | Event rate: 16% (411/2636) vs 15% (383/2636)<br>RR: 1.09 (0.95 – 1.26) |
| COV-2066[a] | |
| **Seronegative mFAS** | Event rate: 6.7% (24/360) vs 15.0% (24/160)<br>RRR: 55.6% (24.2%, 74.0%) |
| **High viral load mFAS** | Event rate: 9.2% (43/467) vs 14.4% (33/229)<br>RRR: 36.1% (2.3%, 58.2%) |
| **Overall mFAS** | Event rate: 7.3% (59/804) vs 11.5% (45/393)<br>RRR: 35.9% (7.3%, 55.7%) |
| **Seropositive mFAS** | Event rate: 7% (26/369) vs 9% (18/201)<br>RRR: 21.3% (-40.0%, 55.8%) |

CI = confidence interval; mFAS = modified full analysis set; RR = rate ratio; RRR = relative risk reduction

[a] Combined casirivimab+imdevimab dose groups in pooled Phase 2 Cohort 1 and Phase 3 Cohort 1A, Day 1 to Day 29.

Source: 2.7.4 SCE, Table 19, 20, 21, 27.

**Table 14 Additional Key Efficacy Outcomes (Through 28-Day Analyses)**

| | RECOVERY | | COV-2066 (Pooled Cohort 1 and Cohort 1A) | |
|---|---|---|---|---|
| | Casirivimab+ Imdevimab (8000 mg) | Usual Care | Casirivimab+ Imdevimab Combined Dose (2400 mg and 8000 mg) | Placebo |
| **Seronegative Population** | **n=1633** | **N=1520** | **n= 360** | **n= 160** |
| Discharged from hospital (proportion of patients) | 64% (1046/1633) | 58% (878/1520) | 90% (324/360) | 81.3% (130/160) |
| | RR (95% CI): 1.19 (1.09-1.31) | | RRR (95% CI): -10.8% (-20.2%, -2.0%) | |
| Duration of hospitalization Median time in days (range) | 13 (7 to >28) | 17 (7 to >28) | 4 (2 to 8) | 4.5 (2 to 17) |
| Progression to mechanical ventilation or death (proportion of patients)[a] | 30% (487/1599) | 37% (542/1484) | 10.3% (37/360) | 19.4% (31/160) |
| | RR (95% CI): 0.83 (0.75-0.92) | | RRR (95% CI): 47.0% (17.7%, 65.8%) | |
| **Seropositive Population** | **n=2636** | **N=2636** | **n= 369** | **n= 201** |
| Discharged from hospital (proportion of patients) | 75% (1970/2636) | 77% (2031/2636) | 87.5% (323/369) | 85.6% (172/201) |
| | RR (95% CI): 0.94 (0.88-1.00) | | RRR (95% CI): -2.3% (-9.6%, 4.5%) | |
| Duration of hospitalization Median time in days (range) | -- | -- | 5 (2 to 10) | 4 (3 to 10) |
| Progression to mechanical ventilation or death (proportion of patients)[a] | 19% (456/2449) | 17% (415/2450) | 9.2% (34/369) | 11.4% (23/201) |
| | RR (95% CI): 1.10 (0.97-1.24) | | RRR (95% CI): 19.5% (-32.8%, 51.2%) | |
| **Overall Population** | **n=4839** | **n=4946** | **n=804** | **n=393** |
| Discharged from hospital (proportion of patients) | 70% (3375/4839) | 69% (3413/4946) | 88.8% (714/804) | 84.0% (330/393) |
| | RR (95% CI): 1.01 (0.97-1.07) | | RRR (95% CI): -5.6% (-11.1%, -0.6%) | |
| Duration of hospitalization Median time in days (range) | 10 (6 to >28) | 10 (5 to >28) | 4 (2 to 9) | 4 (3 to 11) |

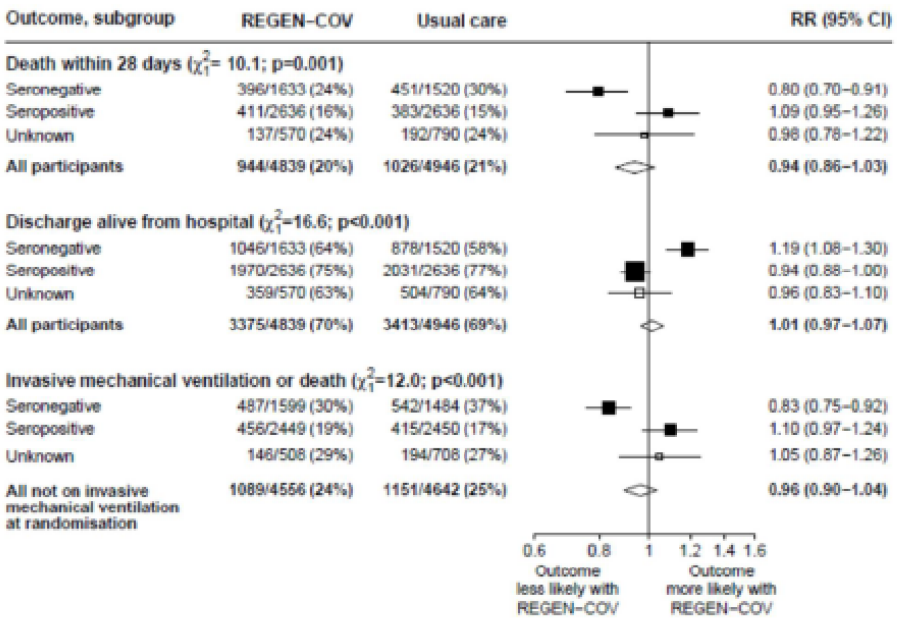
| | RECOVERY | | COV-2066 (Pooled Cohort 1 and Cohort 1A) | |
|---|---|---|---|---|
| | Casirivimab+ Imdevimab (8000 mg) | Usual Care | Casirivimab+ Imdevimab Combined Dose (2400 mg and 8000 mg) | Placebo |
| Progression to mechanical ventilation or death (proportion of patients) [a] | 24% (1089/4556) | 25% (1151/4642) | 10.2% (82/804) | 14.8% (58/393) |
| | RR (95% CI): 0.96 (0.90-1.04) | | RRR (95% CI): 30.9% (5.4%, 49.5%) | |

RR=rate ratio; RRR=relative risk reduction.

[a] For those not on invasive mechanical ventilation at randomization

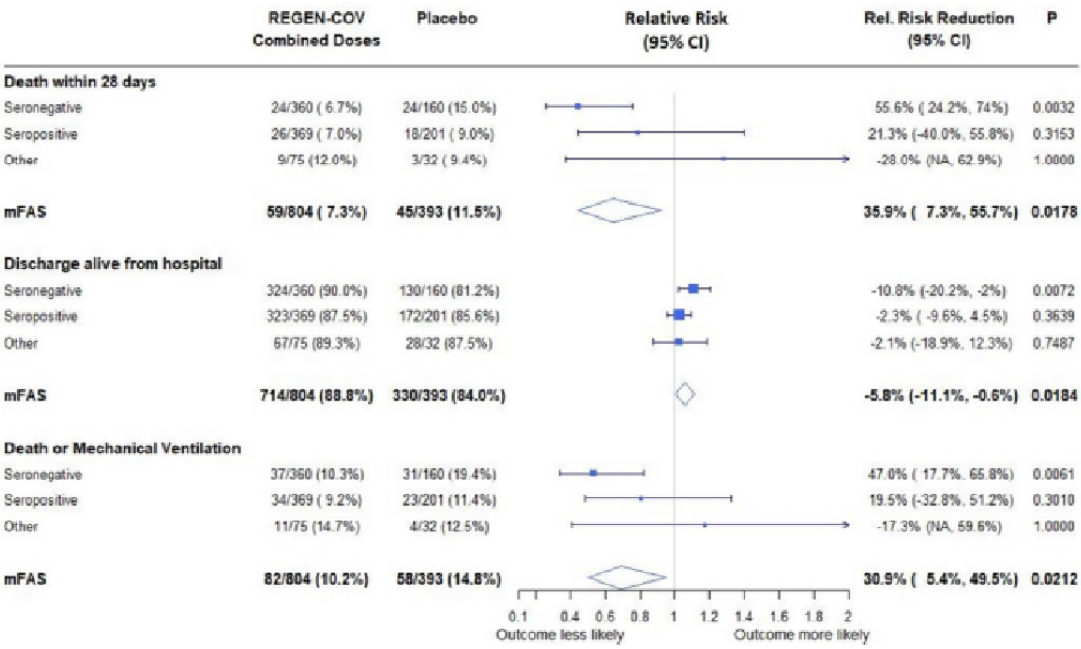
Source: 2.7.3 SCE, Table 27.

**Figure 7 Forest Plots for Endpoints of Death, Discharge, and Death or Mechanical Ventilation in RECOVERY by Baseline Antibody Status**




Source: RECOVERY Collaborative Group, 2021, Figure 3.

**Figure 8 Forest Plots for Endpoints of Death, Discharge, and Death or Mechanical Ventilation in COV-2066 by Baseline Antibody Status: Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A (Combined Doses, mFAS)**




Other" serostatus consists of indeterminate serologic status or missing samples.
Source: t_220_pr_dth_c1c1a_byser.sas, t_220_pr_dth_c1c1a.sas, t_220_pr_disch_c1c1a_byser.sas, t_220_pr_disch_c1c1a.sas, t_220_pr_dthmv_c1c1a_byser.sas, t_220_pr_dthmv_c1c1a.sas.

## *Clinical studies in special populations*

Not applicable

## *Supportive study*

- **Study COV-2066**

COV-2066 was an adaptive Phase 1/2/3 randomized, double-blinded, placebo-controlled study to exclude futility (Phase 1/2) and evaluate efficacy and safety (Phase 3) of casirivimab+imdevimab in hospitalised adult and adolescent patients with COVID-19. The study was the first-in-human clinical trial for the combination mAb therapy product (casirivimab and imdevimab).

On 09 Apr 2021, owing to low recruitment rates, the Sponsor made a decision to close enrolment into the study. The reason for early termination was not based on safety concerns, but due to low recruitment rates over the preceding 3 months. All participants were followed through to their end of study visit according to the protocol, and the last participant last visit date for the main study was 04 Jun 2021.

A subset of cohort 1 and cohort 1A participants at select study sites in the US are enrolled in an ongoing long COVID sub-study. Results from this sub-study will be reported at a later time.

The final CSR is based on a database lock date of 08 Jul 2021. This represents the final data for the main study.

## *Methods and design*

## Study participants

### Key inclusion criteria

- Adult male and female participants ≥ 18 years of age (or the country's legal age of adulthood).
- SARS-CoV-2-positive antigen or molecular diagnostic test (by validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay, using an appropriate sample such as NP, nasal, oropharyngeal [OP], or saliva) ≤72 hours prior to randomization and no alternative explanation for current clinical condition. A historical record of positive result from test conducted ≤72 hours prior to randomization is acceptable.
- Symptoms consistent with COVID-19, as determined by investigator, with onset ≤10 days before randomization
- Hospitalized for ≤72 hours with at least 1 of the following at randomization; patients meeting more than one criterion will be categorized in the most severely affected category:

    a. Cohort 1A: With COVID-19 symptoms but not requiring supplemental oxygen

    b. Cohort 1: Maintains O2 saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or other similar device

    c. Cohort 2*: High-intensity oxygen therapy without mechanical ventilation, where high intensity is defined as receiving supplemental oxygen delivered by 1 of the following devices:

        – Non-rebreather mask (with an SpO2 ≤96% while receiving an oxygen flow rate of at least 10 L/min)

        – High-flow device (eg, AIRVO™ or Optiflow™) with at least 50% FiO2

        – Non-invasive ventilator, including continuous positive airway pressure (CPAP) to treat hypoxemia (excluding isolated use for sleep-disordered breathing)

    d. Cohort 3*: On mechanical ventilation

*Note: Per IDMC recommendation first received on 30 October 2020, and reiterated through19 February 2021, patient enrolment in cohort 2 and cohort 3 has been placed on hold.

The study was initiated before the authorization of COVID-19 vaccines and, after their authorization; enrolment was permitted of vaccinated individuals who had breakthrough COVID-19.

**Key exclusion criteria:**

- In the opinion of the investigator, unlikely to survive for >48 hours from screening
- Receiving ECMO
- Had new-onset stroke or seizure disorder during hospitalization
- Initiated on renal replacement therapy due to COVID-19
- Had circulatory shock requiring vasopressors at randomization (Note: Patients who required vasopressors for sedation-related hypotension or reasons other than circulatory shock may have been eligible in this study)
- Pregnant or breastfeeding women
- Received convalescent plasma, IVIG, or mAbs against SARS-CoV-2 (e.g. bamlanivimab) within 5 months prior to randomization or plan to receive during the study period for any indication

## Treatments

Patients were randomized in each cohort in a 1:1:1 ratio to receive a one-time infusion of casirivimab+imdevimab 8000 mg, casirivimab+imdevimab 2400 mg, or placebo, all given in addition to the local standard of care.

**Standard-of-Care background treatments**

Patients may receive the standard-of-care for the treatment of COVID-19 per local guidelines. Background treatments may include:

- Antiviral therapies (remdesivir or other)

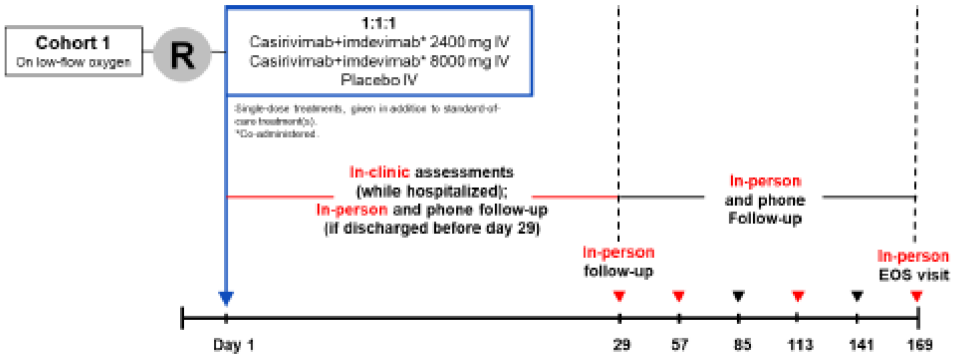
- Immune-based therapies (tocilizumab, sarilumab, steroids, or other)
- Antiviral and immune-based therapies

Patients who have received convalescent plasma, IVIG, or mAbs against SARS-CoV-2 (e.g, bamlanivimab) within 5 months prior to randomization or plan to receive during the study period for any indication were excluded from the study (Exclusion criterion 7).

## Study design

**Phase 1**. In the FIH phase 1 portion of the study, only participants on low-flow oxygen supplementation (cohort 1) were enrolled.

**Figure 1: Study Flow Diagram, Phase 1**

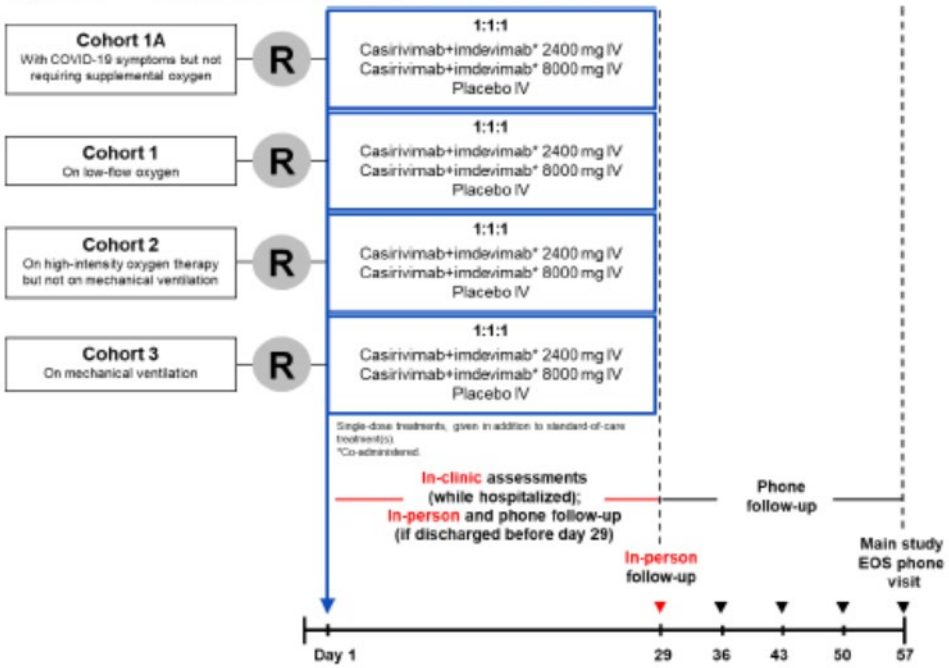



The aim of the Phase 1 portion of the study was to evaluate the safety and tolerability of casirivimab+imdevimab in hospitalized participants; therefore, only participants on low flow oxygen supplementation (Cohort 1 i.e., those on low flow oxygen) were enrolled. Phase 1 included a sentinel safety group where the initial safety data up to Study Day 3 was reviewed by an iDMC. Participants in this sentinel safety group were derived from 2 concurrent first in human studies where the safety and tolerability of casirivimab+imdevimab was evaluated,including COV-2066 (Cohort 1 only) and Study R10933-10987-COV-2067 in outpatients with COVID-19.

### Phase 2 and Phase 3.

Phase 2 was initiated following IDMC clearance of the sentinel safety group and enrolled concurrently with phase 1.

**Figure 2: Study Flow Diagram, Phase 2 and Phase 3**




Phase 2 and Phase 3: This initially included enrolment for Cohort 2 and Cohort 3, and then included enrolment to Cohort 1A following protocol amendment 5.

## Outcomes/endpoints

### Efficacy analysis

For the efficacy analyses, since the overall sample size was smaller than anticipated due to early study termination, study cohorts (Phase 3 Cohort 1 and Phase 2 Cohort 1A) and casirivimab+imdevimab dose groups (2400 mg IV and 8000 mg IV) were pooled for the primary efficacy analysis.

**Table 6 Overview of Efficacy Assessment (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A, mFAS)**

| Endpoint | Definition | Assessment Time Points |
|---|---|---|
| **Primary** | | |
| Virologic: time-weighted average change from baseline viral load in NP sample through Day 7, as measured by RT-qPCR in NP swab sample | Reduction in average (mean) daily viral load for the observation period of Day 1 through Day 7 | Time interval will be 6 days for the observation period Day 1 through Day 7 |
| Clinical: Death or mechanical ventilation | The proportion of patients who died or went on mechanical ventilation from Day 6 through Day 29 and from Day 1 through Day 29[a]. Death or mechanical ventilation was derived based on the patient vital status and the mechanical ventilation use recorded on Clinical status using an Ordinal Scale eCRF. The patients who went on mechanical ventilation were those whose ordinal scale was 2. | Day 6 through Day 29 and from Day 1 through Day 29 |
| **Secondary (Virologic)** | | |
| Time-weighted average change from baseline viral load in NP sample (seronegative mFAS) | | Through Day 11 |
| Time-weighted average change from baseline viral load in NP sample (overall mFAS) | | Through Day 11 |
| Time-weighted average change from baseline viral load in NP sample (high viral load mFAS) | | Through Day 11 |

**Table 6 Overview of Efficacy Assessment (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A, mFAS) (cont.)**

| Endpoint | Definition | Assessment Time Points |
|---|---|---|
| Time-weighted average change from baseline, change from baseline, and percent change from baseline in viral load in NP sample | | Through each post-baseline timepoint until Day 29 |
| **Secondary (Clinical)** | | |
| Proportion of patients who went on mechanical ventilation | | By Day 29 |
| Proportion of patients who were discharged | | By Day 29 |
| Proportion of patients who died | | Day 6 to Day 29 and Day 1 to Day 29 |
| Proportion of patients who died or were readmitted[b] | | By Day 57 (End of Study) |
| Cumulative incidence of death (i.e., overall survival) | | By Day 29 |
| Cumulative incidence of Mechanical Ventilation | | By Day 29 |
| Cumulative incidence of Death or Mechanical Ventilation | | By Day 29 |
| Time to Discharge | | All available follow-up data |

eCRF = electronic case report form; mFAS = modified full analysis set; NP = nasopharyngeal; RT-qPCR = quantitative reverse transcription polymerase chain reaction.

[a] The analysis of the proportion of patients who died or went on mechanical ventilation from Day 1 to 29 was considered a primary clinical endpoint per the statistical hierarchy and was 5th to 7th in the testing order (see Table 7).

[b] Readmission to hospital was also based on what investigators reported on *Hospital – ICU Admission and Discharge* CRF.

The primary endpoints were tested in a hierarchical order.

**Table 8 COV-2066 Hierarchical Testing Order**

| Hierarchy Number | Type of Outcome | Outcome | Analysis Population |
|---|---|---|---|
| 1 | Primary virologic | Time weighted average daily change from baseline in viral load from Day 1 to Day 7 | Seronegative mFAS |
| 2 | Primary clinical | Proportion of patients who died or went on mechanical ventilation from Day 6 to Day 29 | High viral load (>$10^5$ copies/mL) mFAS |
| 3 | | | Seronegative mFAS |
| 4 | | | Overall mFAS |
| 5 | | Proportion of patients who died or went on mechanical ventilation from Day 1 to Day 29 | High viral load (>$10^5$ copies/mL) mFAS |
| 6 | | | Seronegative mFAS |
| 7 | | | Overall mFAS |

## Sample size

### Cohort 1A (phase 2 part)

The sample size of phase 2 cohort 1A was adjusted to approximate 1000 patients based on clinical judgement without statistical justification. However, this target was not reached because the enrollment was prematurely terminated due to slow enrolment rate.

### Phase 3 (Cohort 1)

### Initial estimation

The sample size for phase 3 was initially estimated to be 1350 patients (150 patients per arm across 3 treatment arms in 3 cohorts). Based on the new endpoint of death or mechanical ventilation, the sample size for phase 3 has been re-estimated to be 2505 patients in each of cohort 1 and cohort 1A.

The study was planned to continue enrolling additional patients seamlessly into the phase 3 portion of the study, until an adaptation decision on the dose(s), primary endpoint, and final sample size for

phase 3 is made based on the phase 2 data analysis. A total sample size of approximately 5010 patients was estimated for the phase 3 portion of the study (2505 per cohort, 835 per arm across 3 treatment arms in 2 cohorts). For cohort 1, a total of 241 events (estimated sample size of 2505 patients [835 patients per arm]) would have been needed to provide 90% power at α=0.05 (2-sided) using a log-rank test to detect a risk reduction of 35.8% (i.e., HR=0.642) in the cumulative incidence of patients who died or went on mechanical ventilation, assuming a 12.5% cumulative incidence rate in the placebo group by day 29.

**Final sample size**

Finalization of the sample size and patient population for phase 3 was planned to be subject to change and would be determined after review of phase 2 data. However, enrolment of patients into the study was terminated prematurely by the Sponsor on 09 April 2021 because of extremely slow enrolment in the months preceding the decision. The sample size of phase 3 was not re-estimated.

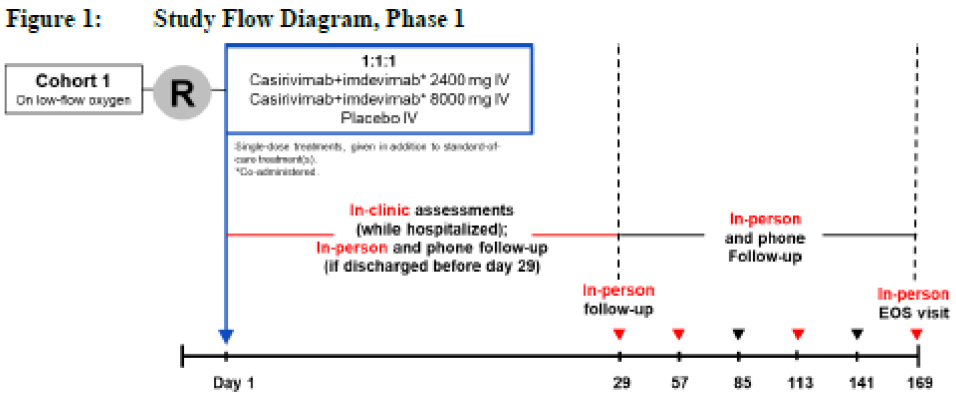
## Randomisation

Patients entering the trial had varying degrees of oxygen support at randomization and this determined their categorization into 1 of 4 cohorts for analyses:

- Patients who required no supplemental oxygen support (Cohort 1A).
- Patients who had O2 saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or another similar device (Cohort 1).
- Patients who required high-intensity oxygen supplementation (Cohort 2). High-intensity oxygen therapy was defined as the use of non-rebreather mask with an oxygen flow rate of at least 10 L/min; use of a high flow device with at least 50% FiO2, or use of non-invasive ventilation to treat hypoxemia.
- Patients who were mechanically ventilated (Cohort 3).

**Phase 1**. In the FIH phase 1 portion of the study, only participants on low-flow oxygen supplementation (cohort 1) were enrolled.

**Figure 1: Study Flow Diagram, Phase 1**

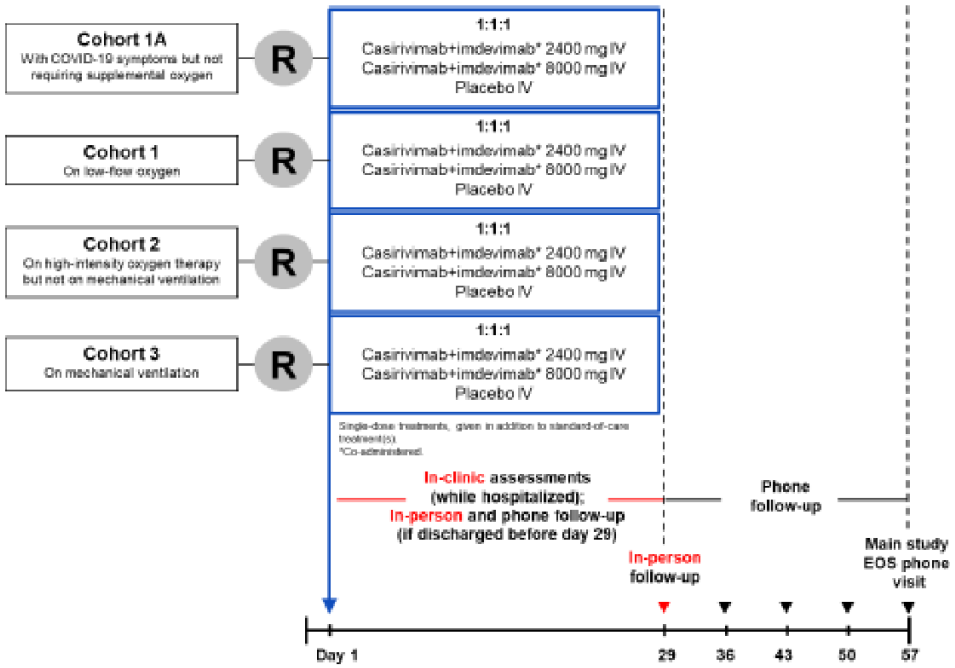



Participants were randomized 1:1:1 to a single intravenous (IV) dose of casirivimab+imdevimab 2400 mg, casirivimab+imdevimab 8000 mg, or matching placebo.

**Phase 2 and Phase 3.**

Phase 2 was initiated following IDMC clearance of the sentinel safety group and enrolled concurrently with phase 1.

**Figure 2: Study Flow Diagram, Phase 2 and Phase 3**




Participants of varying disease severity were randomized 1:1:1 to a single IV dose of casirivimab+imdevimab 2400 mg, casirivimab+imdevimab 8000 mg, or placebo.

Cohort 1 participants who were randomized after 01 Dec 2020 were considered part of phase 3.

Randomization was planned to be stratified by country and type of background standard-of-care being administered for COVID-19 at randomization as follows:

- Those who received antiviral therapies only (e.g., remdesivir, favipiravir)
- All other participants, including those receiving no therapy, non-antiviral therapy for COVID-19 (e.g., systemic corticosteroids or hydroxychloroquine), or antiviral therapy in combination with non-antiviral therapy

## Blinding (masking)

Pharmacist or qualified personnel at the site, not otherwise associated with the conduct of the study, was planned to reconstitute the drug for IV administration. The drug infusion solution must be provided in identical form for active and placebo treatments, so that they remain indistinguishable to both study personnel and patients.

Study patients, the principal investigators, and study site personnel (with the exception of the unblinded pharmacist at each site) were planned to remain blinded to all randomization assignments throughout the study. The Regeneron medical/study director, study monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site were planned to remain blinded to all patient randomization assignments in all phases of the study.

Selected individuals from the Sponsor not involved in the conduct of the study may have access to unblinded phase 1 or phase 2 data as needed for safety review or other data review. The team performing the interim data reviews was planned to be separate from the ongoing study team. No study personnel involved in the day-to-day conduct of the study was planned to have access to any unblinded data before the database is locked for this study.

Anti-drug antibody, drug concentration, and biomarker results were not communicated to the sites, and the Sponsor's blinded operational team was not planned to have access to results associated with patient identification until after the database is locked.

## Statistical methods

Efficacy analyses were performed in the following analysis sets:

- Full Analysis Set (FAS): The FAS included all randomized patients who received at least one dose of the study drug. Analysis of the FAS population was performed according to the treatment allocated (as randomized). The FAS was identical to the Safety Analysis Set.
- Modified Full Analysis Set (mFAS): The mFAS included all FAS patients with a positive RT-qPCR from a central NP swab samples at randomization and analysis was based on the treatment allocated (as randomized).
- Seronegative mFAS: The seronegative mFAS was defined as all randomized patients with documented seronegative status at baseline in mFAS, respectively.
  Note: Seronegativity at baseline required that all non-missing baseline serology test results to be negative for antibodies against SARS-CoV-2 (i.e., anti-S1 IgA, anti-S1 IgG, and anti-N IgG) in order to be considered negative.
- Seropositive mFAS: The seropositive mFAS was defined as all randomized patients with documented seropositive status at baseline in mFAS, respectively.
- High Viral Load mFAS: The High Viral Load mFAS is defined as all patients in mFAS with baseline viral load >106 copies/mL.

Both the FAS and mFAS were used for the summaries of demographic and baseline characteristics and analysis of clinical/biomarker endpoints. The mFAS was used for the analysis of all efficacy endpoints, based on the principle that an anti-viral agent would only be anticipated to provide efficacy in patients with measurable virus at baseline. The Seronegative mFAS and the High Viral Load mFAS were used for the primary analysis and descriptive analysis of certain virologic endpoints and clinical endpoints. Additional analyses were performed in the Seropositive mFAS, as needed.

**Efficacy Analyses**

The efficacy analyses were planned to be performed for the following patients on all efficacy endpoints, separately. The comparisons in all efficacy endpoints were planned to be performed between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo group as well as between each treatment group and placebo group.

- Pooled phase 3 cohort 1 and phase 2 cohort 1A patients
- Phase 3 cohort 1 patients (ie, patients randomized after 01 December 2020 in cohort 1)
- Phase 2 cohort 1A patients

**Analysis of Primary Virologic Efficacy Endpoint**

The primary analysis on the comparison between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo with respect to the virologic endpoint of time-weighted average daily change from baseline in viral load (log10 copies/mL) from day 1 to day 7 and other postbaseline visit timepoint was planned to be performed in the Seronegative mFAS in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. The estimand for the analysis is the difference in means between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. Data collected after use of convalescent plasma therapy or other anti-spike monoclonals were planned to be excluded from efficacy analysis. All other available data were planned to be used in the analysis regardless of intercurrent events such as rescue medication or discontinuation, i.e., treatment policy approach.

The analysis was planned to be based on the observed data with no imputation for missing data except as defined in the SAP for viral load values that are below lower limit of detection (<LLOD), below lower limit of quantification (<LLOQ) or above upper limit of quantification (>ULOQ) of the assay.

The variable was planned to be analyzed using the Analysis of Covariance (ANCOVA) model with treatment group and the type of background standard-of-care as fixed effects, and baseline viral load and treatment by baseline interaction as covariates.

The least squares mean estimates for time-weighted average daily change from baseline in viral load for each treatment group, as well as the difference between the REGN10933+REGN10987 2.4g and 8.0g combined doses and placebo as well as between each individual dose treatment group and placebo, were planned to be provided along with the corresponding two-sided p-value, standard error, and associated 95% confidence interval.

**Analysis of Primary Clinical Efficacy Endpoints**

The primary efficacy analysis was planned to be the comparison between the REGN10933+REGN10987 2.4g and 8.0g combined dose group and placebo in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. The primary clinical endpoint defined in Section 4.1 was to be analyzed using the landmark analysis approach for day 6 through day 29, as well as analyzed for day 1 through day 29 in the order specified below.

The proportion of patients who died or went on mechanical ventilation was planned to be analyzed using either the exact method for binomial distribution or asymptotic normal approximation method. If the number of events is small (eg, $np \leq 5$ or $n(1-p) \leq 5$ in any treatment group, where n is the number of patients in the treatment group and p is the proportion of events), then the Fisher's exact test was planned to be applied. Otherwise, stratified Cochran-Mantel Haenszel (CMH) test, stratified by the type of background standard-of-care (antiviral therapies and non-antiviral therapies), was to be applied. Relative risk and relative risk reduction and corresponding 95% confidence intervals compared to placebo group were planned to be estimated by Farrington-Manning method. Missing data was planned to be considered as non-events.

The analysis was to be performed for the High Viral Load mFAS, the Seronegative mFAS, and the overall mFAS.

**Control of Multiplicity**

The following multiplicity adjustment approach, a hierarchical procedure, was to be used to control the overall Type-1 error rate at 0.05 for the primary virologic and clinical outcome endpoints in comparison between the combined doses of REGN10933+REGN10987 treatment group and placebo group in the pooled phase 3 cohort 1 and phase 2 cohort 1A patients. Each hypothesis was to be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level.

**Table 6: Hierarchical Testing Order**

| Type | Description | Testing Order |
|---|---|---|
| **Primary virologic outcome** | Time-weighted average change from baseline viral load in NP sample through day 7 **in seronegative mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo | 1 |
| **Primary clinical outcome** | Proportion of patients who died or went on mechanical ventilation **from day 6 to day 29 in High Viral Load mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo | 2 |
| | Proportion of patients who died or went on mechanical ventilation **from day 6 to day 29 in Seronegative mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo | 3 |
| | Proportion of patients who died or went on mechanical ventilation **from day 6 to day 29 in overall mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo | 4 |
| | Proportion of patients who died or went on mechanical ventilation **from day 1 to day 29 in High Viral Load mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo | 5 |
| | Proportion of patients who died or went on mechanical ventilation **from day 1 to day 29 in Seronegative mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo | 6 |
| | Proportion of patients who died or went on mechanical ventilation **from day 1 to day 29 in overall mFAS** for comparing the combined doses of REGN10933+REGN10987 versus placebo | 7 |

## *Results*

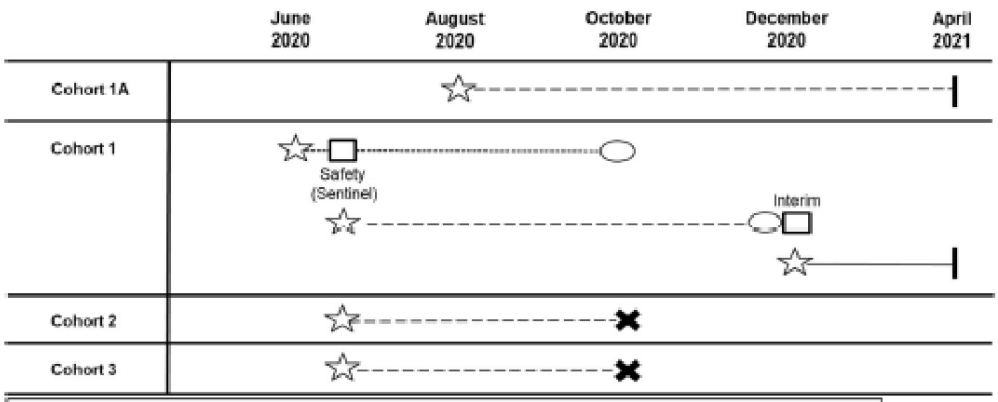
### Recruitment

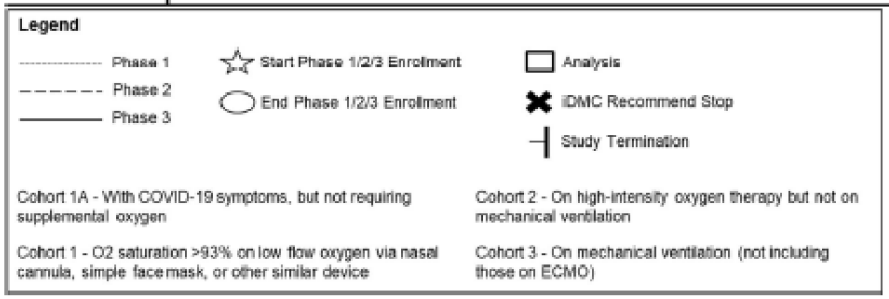
The majority of the patients were enrolled in the United States (87.6%) and the remaining participants were enrolled in Europe (~5% Romania and Moldova), Mexico (~5%) and South America (~4%, Brazil and Chile)

### Conduct of the study

The following describes a timeline of key milestones in the study conduct relevant to the summary of results.

**Figure 1 Timeline of Key Milestones for Study-COV-2066**




- During Phase 2, on 29 Oct 2020, the study iDMC recommended pausing participant enrolment into Cohorts 2 and 3 based on a potential safety imbalance in the incidence of deaths among participants receiving casirivimab+imdevimab compared to the placebo group, while continuing with enrolment in Cohorts 1A and 1. All participants who had been enrolled in Cohorts 2 and 3 up until that point were followed up through to the end of study visit on Study Day 57 as per the protocol. This iDMC recommendation to pause enrolment for Cohorts 2 and 3 was maintained for the duration of the study (Phases 2 and 3).
- A combined Phase 1/2 interim analysis was performed on participants who were randomized through 01 December 2020 in Phase 1 (Cohort 1 only) and Phase 2 (Cohorts 1, 2, and 3). This interim analysis used a data cut-off date of 09 December 2020 and a database lock date of 22 December 2020. The primary objective of the interim analysis was to exclude futility in the seronegative mFAS in Cohort 1, based on α=0.3 (1-sided). Futility was excluded (p=0.23) in Cohort 1. As Phase 2 enrolment of Cohort 2 and 3 was paused per iDMC recommendation, they were not included in the primary objective of the interim analysis. Phase 2 Cohort 1A was not included in the interim analysis as enrolment was still ongoing.
- The sample size for Phase 2 (390 participants per cohort) of the study was originally based on the primary virologic endpoint. Cohort 1 reached its Phase 2 enrolment goal before Cohort 1A did, and as a result, all participants enrolled into Cohort 1 after 01 December 2020 were considered to be part of Phase 3. Enrolment into Phase 2 Cohort 1A occurred concurrently with Phase 3 Cohort 1 enrolment, and the data were handled and overseen in a similar manner.
- On 09 April 2021, the Sponsor made a business decision to close enrolment in this study early due to low recruitment over the preceding 3 months prior to the surge in hospitalizations in the US associated with the emergence of the Delta variant. This early termination was not due to any safety concerns. Accordingly, Phase 3 Cohort 1 and Phase 2 Cohort 1A enrolment were prematurely terminated. All participants were followed up through their end of study visit according to the protocol, and the last participant last visit date for the main study was 04 Jun 2021.

## Baseline data

In the primary efficacy pool (pooled cohort 1 [phase 3] and cohort 1A; n=1197), demography and other baseline disease characteristics were generally balanced across all treatment and placebo groups in the Overall mFAS (see clinical summary: Table 17: Summary of Demographics and Baseline Characteristics (Pooled Cohort 1 [Phase 3] and Cohort 1A; mFAS). The main patient demographic characteristics and baseline disease characteristics are summarised below:

**Demography**

- Most participants were greater than 40 years of age, with an overall median age of 62 years. There were more participants between 40 to 65 years of age in the treatment groups (49.6%) compared to the placebo group (40.5%). Slightly less than half of the participants (45.9%) were female. Most participants were White (62.6%). Black/African Americans (12.1%) and Asians (3.9%) were also represented. Overall, 30.1% of participants were Hispanic or Latino in ethnicity.
- The median body mass index (BMI) was 29.65 kg/m2, with 47.5% of the participants in the obese category (BMI ≥30 kg/m2). Overall, 21.5% of the participants were immunocompromised as having immunological diseases, immunodeficiencies, or being immunosuppressed; examples of medical history for this category include rheumatoid arthritis, solid organ transplantation, HIV, and cancer.

**Baseline disease characteristics**

- Baseline SARS-CoV-2 viral load was similar across all treatment and placebo groups, with an overall median of 6.4 log10 copies/mL and 58.1% of the participants in the high viral load category (>$10^6$ copies/mL).
- Overall, 43.4% of the participants were seronegative at baseline (i.e., with all non-missing baseline serology test results negative for antibodies against SARS-CoV-2 [i.e., anti-S1 IgA, anti-S1 IgG, and anti-N IgG]). The proportion of seronegative participants was slightly higher in the combined treatment group (44.8%) versus the placebo group (40.78%).
- Overall, 47.6% of the participants were seropositive (i.e., with at least one positive anti-SARS-CoV-2 serology test result) at baseline. 71.8% of the seropositive participants were also positive for SARS-CoV-2-neutralizing antibodies, as measured by a cell-based neutralization assay using recombinant vesicular stomatitis virus (VSV) engineered to express the SARS-CoV-2 S protein (Vandergaast, 2020).
- Other baseline disease characteristics (e.g., temperature, respiratory rate, clinical status) were similar across all treatment and placebo groups.

## Numbers analysed

For the primary efficacy analysis population (pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A), a total of 1364 participants were randomized, with 457 participants in the casirivimab+imdevimab 2400 mg IV group, 455 participants in the casirivimab+imdevimab 8000 mg IV arm and 452 participants in the placebo group.

**Table 15 Summary of Analysis Sets (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A, All Randomized Participants) for the Primary Efficacy Analysis**

| | | Casirivimab+Imdevimab IV | | | |
|---|---|---|---|---|---|
| | Placebo (N=452) | 2400 mg (N=457) | 8000 mg (N=455) | Combined (N=912) | Total (N=1364) |
| Participants randomized | 452 (100%) | 457 (100%) | 455 (100%) | 912 (100%) | 1364 (100%) |
| Participants in full analysis set (FAS)[a], n (%) | 445 (98.5%) | 448 (98.0%) | 443 (97.4%) | 891 (97.7%) | 1336 (97.9%) |
| Participants in modified full analysis set (mFAS), n (%) | 393 (86.9%) | 406 (88.8%) | 398 (87.5%) | 804 (88.2%) | 1197 (87.8%) |
| Participants in high viral load modified full analysis set, n (%) | 229 (50.7%) | 231 (50.5%) | 236 (51.9%) | 467 (51.2%) | 696 (51.0%) |
| Participants in seronegative modified full analysis set, n (%) | 160 (35.4%) | 172 (37.6%) | 188 (41.3%) | 360 (39.5%) | 520 (38.1%) |
| Participants in pharmacokinetics (PK) analysis population (PKAS), n (%) | 0 | 419 (91.7%) | 404 (88.8%) | 823 (90.2%) | 823 (60.3%) |
| Participants in anti-drug antibody (ADA) analysis set (AAS), n (%) | 317 (70.1%) | 317 (69.4%) | 316 (69.5%) | 633 (69.4%) | 950 (69.6%) |
| Participants in neutralizing antibody (NAB) analysis set (NAS), n (%) | 317 (70.1%) | 317 (69.4%) | 316 (69.5%) | 633 (69.4%) | 950 (69.6%) |
| Participants excluded from FAS[a], n (%) | 7 (1.5%) | 9 (2.0%) | 12 (2.6%) | 21 (2.3%) | 28 (2.1%) |

IV = intravenous

[a] The FAS is equivalent to a safety analysis set (SAF) in this study.

Source: t_114e_asets_pool.

The number of participants included in each analysis set is summarized in Table 7 for the primary efficacy analysis population (i.e., pooled cohort 1 [phase 3] and cohort 1A).

**Table 7: Summary of Analysis Sets (Pooled Cohort 1 [Phase 3] and Cohort 1A, All Randomized Participants)**

| | | Casirivimab+Imdevimab IV | | | |
|---|---|---|---|---|---|
| | Placebo (N=452) | 2400 mg (N=457) | 8000 mg (N=455) | Combined (N=912) | Total (N=1364) |
| Patients randomized | 452 (100%) | 457 (100%) | 455 (100%) | 912 (100%) | 1364 (100%) |
| Patients in full analysis set (FAS)[1], n(%) | 445 (98.5%) | 448 (98.0%) | 443 (97.4%) | 891 (97.7%) | 1336 (97.9%) |
| Patients in modified full analysis set (mFAS), n(%) | 393 (86.9%) | 406 (88.8%) | 398 (87.5%) | 804 (88.2%) | 1197 (87.8%) |
| Patients in high viral load modified full analysis set, n(%) | 229 (50.7%) | 231 (50.5%) | 236 (51.9%) | 467 (51.2%) | 696 (51.0%) |
| Patients in seronegative modified full analysis set, n(%) | 160 (35.4%) | 172 (37.6%) | 188 (41.3%) | 360 (39.5%) | 520 (38.1%) |
| Patients in pharmacokinetics (PK) analysis population (PKAS), n(%) | 0 | 419 (91.7%) | 404 (88.8%) | 823 (90.2%) | 823 (60.3%) |
| Patients in anti-drug antibody (ADA) analysis set (AAS), n(%) | 317 (70.1%) | 317 (69.4%) | 316 (69.5%) | 633 (69.4%) | 950 (69.6%) |
| Patients in neutralizing antibody (NAB) analysis set (NAS), n(%) | 317 (70.1%) | 317 (69.4%) | 316 (69.5%) | 633 (69.4%) | 950 (69.6%) |
| Patients excluded from FAS[1], n(%) | 7 (1.5%) | 9 (2.0%) | 12 (2.6%) | 21 (2.3%) | 28 (2.1%) |

[1] The FAS is equivalent to a safety analysis set (SAF) in this study. Refer to Section 3.7.1.

Source: PTT 14.1.1.4e

In key efficacy analysis sets, the number of participants and their cohort is shown below:

- Overall mFAS: 667 Cohort 1 participants and 530 Cohort 1A participants
- High Viral Load mFAS: 373 Cohort 1 participants and 323 Cohort 1A participants

- Seronegative mFAS: 232 Cohort 1 participants and 288 Cohort 1A participants

## Outcomes and estimation

**The primary Pooled Phase 3 (Cohort 1) and Phase 2 (Cohort 1A).**

The mFAS was used for the analysis of all efficacy endpoints, based on the principle that an anti-viral agent would only be anticipated to provide efficacy in patients with measurable virus at baseline. The Seronegative mFAS and the High Viral Load mFAS were used for the primary analysis and descriptive analysis of certain virologic endpoints and clinical endpoints. Additional analyses were performed in the Seropositive mFAS, as needed.

**Table 16 Summary of Primary Efficacy Analyses by Statistical Hierarchy (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A, Combined Doses)**

| No | Endpoint | Analysis Set | Treatment Effect | 95% CI | P Value |
|---|---|---|---|---|---|
| **Primary Virologic Outcome** | | | | | |
| 1 | Virologic: Time-weighted average daily change from baseline in viral load from Day 1 to Day 7[a] | Seronegative mFAS | LS mean (SE): -0.28 (0.12) | -0.51, -0.05 | 0.0172 |
| **Primary Clinical Outcomes** | | | | | |
| 2 | Clinical: Proportion of patients who died or went on mechanical ventilation from Day 6 to Day 29[b] | High Viral Load mFAS | RRR: 25.5%; Event rate: 44/445 (9.9%) compared to 28/211 (13.3%) with placebo | -16.2%, 52.2% | 0.2048 |
| 3 | | Seronegative mFAS | RRR: 47.1%; Event rate: 27/341 (7.9%) compared to 22/147 (15.0%) with placebo | 10.2%, 68.8% | 0.0195 |
| 4 | | Overall mFAS | RRR: 24.2%; Event rate: 62/770 (8.1%) compared to 39/367 (10.6%) with placebo | -10.9%, 48.2% | 0.1486 |
| 5 | Clinical: Proportion of patients who died or went on mechanical ventilation from Day 1 to Day 29[b] | High Viral Load mFAS | RRR: 35.0%; Event rate: 57/467 (12.2%) compared to 43/229 (18.8%) with placebo | 6.6%, 54.8% | 0.0249 |
| 6 | | Seronegative mFAS | RRR: 47.0%; Event rate: 37/360 (10.3%) compared to 31/160 (19.4%) with placebo | 17.7%, 65.8% | 0.0061 |
| 7 | | Overall mFAS | RRR: 30.9%; Event rate: 82/804 (10.2%) compared to 58/393 (14.8%) with placebo | 5.4%, 49.5% | 0.0212 |

[a] LS Mean, 95% CI, and p-value for change from baseline on log scale for each treatment group is based on the ANCOVA model with treatment group, the type of background standard-of-care (antiviral therapies and non-antiviral therapies) as fixed effects and baseline viral load and treatment*baseline as covariate. Negative changes imply improvement in viral load.

[b] 95% CI for the relative risk reduction (1 - relative risk) use Farrington-Manning method. P-value was derived through the Cochran-Mantel-Haenszel (CMH) test stratified by the type of background standard-of-care (antiviral therapies and non-antiviral therapies). If np ≤5 or n(1-p) ≤5 in any treatment group, p-value is based on Fisher Exact Test.

Note: The statistical hierarchy was broken after the primary clinical endpoint and p values for all subsequent clinical efficacy endpoints were nominal.

A pre-specified statistical hierarchy was used to test the virologic and clinical efficacy of casirivimab+imdevimab in the combined doses group (2400 mg IV and 8000 mg IV) compared to placebo group, in pooled Cohort 1 (Phase 3) and Cohort 1A (Phase 2).

The first primary endpoint (viral load reduction during the first week after treatment, in the Seronegative mFAS) was met (difference vs placebo of -0.28 log10 copies/mL, p=0.0172), but statistical testing terminated at the first clinical endpoint (reduction in death or mechanical ventilation from Day 6 to Day 29, in the High Viral Load mFAS) as it did not show a statistically significant treatment effect (RRR: 25.5%, p=0.2048).

When the observation period covered the whole efficacy period (Day 1 to Day 29), numeric reductions were observed in the proportion of participants who died or went on mechanical ventilation and all cause mortality in all populations of interest (High Viral Load mFAS, Seronegative mFAS and Overall mFAS).

For the secondary clinical efficacy endpoints of mechanical ventilation, death or readmission and discharge, treatment with casirivimab+imdevimab led to numerically improved outcomes compared to placebo. The secondary virologic outcome of time-weighted average (TWA) change from baseline viral load also indicated numerically greater viral load reductions in the casirivimab+imdevimab treatment.

**Primary Virologic Efficacy Endpoint: Time-weighted average (TWA) daily change from baseline in viral load from Day 1 to Day**

- Casirivimab+imdevimab treatment led to a statistically significant reduction in viral load from Day 1 to 7, compared to placebo, in participants who were seronegative at baseline (difference vs placebo of -0.28 log10 copies/mL [95% CI -0.51, -0.05], p=0.0172)
- Similar virologic efficacy was observed in the Overall mFAS (difference vs. placebo of -0.26 log10 copies/mL [95% CI -0.41, -0.12 copies/mL]). However, the treatment effect was greater in seronegative participants versus seropositive participants (difference vs. placebo of -0.21 log10 copies/mL [95% CI -0.41, -0.02 copies/mL]. Similarly, greater treatment effect was observed in participants with baseline viral load >106 copies/mL (difference vs. placebo of -0.32 log10 copies/mL [95% CI -0.51, -0.13 copies/mL]) than in other subgroups based on varying baseline viral load thresholds (difference vs. placebo of -0.17 log10 copies/mL [95% CI -0.39, 0.05 copies/mL]).
- Consistent results were observed for both individual doses compared to placebo in seronegative participants, indicating the absence of a dose response effect (2400 mg: least squares [LS] mean -0.25 log10 copies/mL [95% CI -0.51, 0.02]; 8000mg: LS mean -0.31 log10 copies/mL [95% CI -0.57, -0.05].

**Primary Clinical Efficacy Endpoint: Progression to death or mechanical ventilation**

**Outcomes for Day 6 to Day 29**

- Among participants treated with casirivimab+imdevimab, greater reductions in the proportion of participants who died or went on mechanical ventilation from Day 6 to Day 29 were observed in the Seronegative mFAS (RRR: 47.1%, 95% CI: 10.2%, 68.8%), and in the overall mFAS (RRR: 24.2%, 95% CI: -10.9%, 48.2%).
- Negligible to moderate numerical differences were observed in seropositive participants (RRR: 1.7%, 95% CI: -83.7%, 47.4%) and those with viral load ≤106 copies/mL (RRR: 21.5 %, 95 % CI: -62.2%, 62.0%)
- When examined by individual doses there were reductions in the primary clinical endpoint for the 2400 mg dose group across all populations of interest (High Viral Load mFAS: RRR: RRR: 45.2%, 95% CI 1.7%, 69.5%; Seronegative mFAS: RRR: 67.0%, 95% CI 28.2%, 84.8%; Overall mFAS: RRR: 48.9%, 95% CI 14.9%, 69.4%) and some smaller trends for benefit in the 8000 mg dose group (High Viral Load mFAS: RRR: 6.2%, 95% CI -52.9%, 42.5%; Seronegative mFAS: RRR: 29.1%, 95% CI -25.9%, 60.0%; Overall mFAS: RRR: -0.7%, 95% CI (-52.5%, 33.4%).

**Outcomes for Day 1 to Day 29**

- Among participants treated with casirivimab+imdevimab, greater reductions in the proportion of participants who died or went on mechanical ventilation were observed in the High Viral Load mFAS (RRR: 35.0%, 95% CI 6.6%, 54.8%), in the Seronegative mFAS (RRR: 47.0%, 95% CI 17.7%, 65.8%), and in the Overall mFAS (RRR: 30.9%, 95% CI 5.4%, 49.5%) (Table 16).

- Numerical reductions were also observed in the Seropositive mFAS treated with casirivimab+imdevimab (RRR: 19.5%, 95% CI: -32.8%, 51.2%) and participants with viral load ≤106 copies/mL (RRR: 18.9 %, 95 % CI -49.6%, 56.0%).
- When examined by individual doses there were reductions in the primary clinical endpoint for the 2400 mg dose group across all populations of interest (High Viral Load mFAS: RRR: 47.0%, 95% CI 15.0%, 66.9%; Seronegative mFAS: RRR: 58.0%, 95% CI 24.0%, 76.8%; Overall mFAS: RRR: 46.6%, 95% CI 19.6%, 64.5% and trends for benefit in the 8000 mg dose group (High Viral Load mFAS: RRR: 23.3%, 95% CI -15.8%, 49.2%; Seronegative mFAS: RRR: 36.9%, 95% CI -3.7%, 61.6%; Overall mFAS: RRR: 14.9%, 95% CI -21.0%, 40.1%).

**Virologic Efficacy Endpoint: Time-weighted average change from baseline viral load in NP samples from Day 1 to Day 11**

For the secondary efficacy endpoints, p-values were not controlled for type I error. Casirivimab+imdevimab treatment (combined and individual doses) led to a reduction in viral load through Day 11, compared to placebo in the Seronegative mFAS, the High Viral Load, and the Overall mFAS.

**Table 17 Summary of Secondary Virologic Efficacy Analyses from Day 1 to Day 11 (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A; mFAS)**

| Endpoint and Analysis Set | Treatment Group | Treatment Effect | 95% CI; P-Value |
|---|---|---|---|
| Time-weighted average daily change from baseline in viral load in the Seronegative mFAS | Placebo (n=160) | | |
| | Casi+imdev 2400 mg (n=172) | LS Mean (SE): -0.58 (0.15) | -0.87, -0.28, p=0.0001 |
| | Casi+imdev 8000 mg (n=188) | LS Mean (SE): -0.61 (0.15) | -0.90, -0.32, p<0.0001 |
| | Casi+imdev combined (n=360) | LS Mean (SE): -0.59 (0.13) | -0.85, -0.34, p<0.0001 |
| Time-weighted average daily change from baseline in viral load in the Overall mFAS | Placebo (n=393) | | |
| | Casi+imdev 2400 mg (n=406) | LS Mean (SE): -0.44 (0.09) | -0.62, -0.25, p<0.0001 |
| | Casi+imdev 8000 mg (n=398) | LS Mean (SE): -0.37 (0.10) | -0.55, -0.18, p=0.0001 |
| | Casi+imdev combined (n=804) | LS Mean (SE): -0.40 (0.08) | -0.56, -0.24, p<0.0001 |
| Time-weighted average daily change from baseline in viral load in the High Viral Load mFAS | Placebo (n=229) | | |
| | Casi+imdev 2400 mg (n=231) | LS Mean (SE): -0.38 (0.11) | -0.60, -0.16, p=0.0008 |
| | Casi+imdev 8000 mg (n=236) | LS Mean (SE): -0.27 (0.11) | -0.49, -0.05, p=0.0164 |
| | Casi+imdev combined (n=467) | LS Mean (SE): -0.32 (0.10) | -0.51, -0.13, p=0.0010 |

LS = least squares; mFAS = modified full analysis set; SE = standard error.
Source: t_200_twachg_c1c1a_byser, t_200_twachg_c1c1a, t_200_twachg_c1c1a_bynp6.

Greater reductions in viral load through Day 29 were observed in casirivimab+imdevimab treated participants (combined and individual doses) compared to placebo in the TWA daily change from baseline.

**Table 18 Summary of Secondary Virologic Efficacy Analyses from Day 1 to Day 29 (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A; mFAS)**

| Endpoint and Analysis Set | Treatment Group | Treatment Effect | 95% CI; P-Value |
|---|---|---|---|
| Time-weighted average daily change from baseline in viral load in the Seronegative mFAS | Placebo (n=160) | | |
| | Casi+imdev 2400 mg (n=172) | LS Mean (SE): -0.81 (0.21) | -1.22, -0.41, p<0.0001 |
| | Casi+imdev 8000 mg (n=188) | LS Mean (SE): -0.96 (0.20) | -1.35, -0.56, p<0.0001 |
| | Casi+imdev combined (n=360) | LS Mean (SE): -0.89 (0.18) | -1.24, -0.54, p<0.0001 |
| Time-weighted average daily change from baseline in viral load in the Overall mFAS | Placebo (n=393) | | |
| | Casi+imdev 2400 mg (n=406) | LS Mean (SE): -0.46 (0.12) | -0.71, -0.22, p=0.0002 |
| | Casi+imdev 8000 mg (n=398) | LS Mean (SE):-0.42 (0.12) | -0.66, -0.18, p=0.0007 |
| | Casi+imdev combined (n=804) | LS Mean (SE): -0.44 (0.11) | -0.65, -0.23, p<0.0001 |
| Time-weighted average daily change from baseline in viral load in the High Viral Load mFAS | Placebo (n=229) | | |
| | Casi+imdev 2400 mg (n=231) | LS Mean (SE): -0.73 (0.18) | -1.08, -0.38, p<0.0001 |
| | Casi+imdev 8000 mg (n=236) | LS Mean (SE): -0.66 (0.18) | -1.01, -0.31, p=0.0002 |
| | Casi+imdev combined (n=467) | LS Mean (SE): -0.70 (0.15) | -1.00, -0.39, p<0.0001 |

LS = least squares; mFAS = modified full analysis set; SE = standard error.

Source: t_200_twachg_c1c1a_byser, t_200_twachg_c1c1a, t_200_twachg_c1c1a_bynp6.

## Secondary Clinical Efficacy Endpoints

**Table 19 Summary of Secondary Clinical Endpoints in the Seronegative mFAS (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A)**

| Secondary Clinical Endpoint | Placebo (N=160) n/N1 (%) | Casirivimab+Imdevimab 2400 mg IV (N=172) n/N1 (%) | Casirivimab+Imdevimab 8000 mg IV (N=188) n/N1 (%) | Casirivimab+Imdevimab 2400 mg +8000 mg IV combined (N=360) n/N1 (%) |
|---|---|---|---|---|
| **All-cause mortality (Day 1 to Day 29)** | | | | |
| Event rate (%) | 24/160 (15.0%) | 9/172 (5.2%) | 15/188 (8.0%) | 24/360 (6.7%) |
| RRR %, 95% CI, nominal p value) | | 65.1% (27.2%, 83.3%, p=0.0040) | 46.8% (2.1%, 71.1%, p=0.0413) | 55.6% (24.2%, 74.0%, p=0.0032) |
| **All-cause mortality (Day 6 to Day 29)** | | | | |
| Event rate (%) | 21/153 (13.7%) | 8/167 (4.8%) | 13/181 (7.2%) | 21/348 (6.0%) |
| RRR %, 95% CI, nominal p value) | | 65.1% (23.5%, 84.1%), p=0.0070) | 47.7% (-1.0%, 72.9%, p=0.0507) | 56.0% (21.9%, 75.2%, p=0.0051) |
| **Mechanical ventilation[a]** | | | | |
| Cumulative incidence % (95% CI) | 10.6% (6.6%, 16.8%) | 6.0% (3.3%, 11.0%) | 7.9% (4.8%, 13.0%) | 7.0% (4.8%, 10.3%) |
| **Death or readmission** | | | | |
| Event rate (%) | 39/160 (24.4%) | 20/172 (11.6%) | 24/188 (12.8%) | 44/360 (12.2%) |
| RRR %, 95% CI, nominal p value) | | 52.3% (21.8%, 70.9%, p=0.0024) | 47.6% (16.8%, 67.0%, p=0.0054) | 49.9% (26.0%, 66.0%, p=0.0005) |
| **Discharge** | | | | |
| Event rate | 130/160 (81.3%) | 155/172 (90.1%) | 169/188 (89.9%) | 324/360 (90.0%) |
| RRR %, 95% CI, nominal p value) | | -10.9% (-21.3%, -1.4%, p=0.0275) | -10.6% (-20.9%, -1.3%, p=0.0223) | -10.8% (-20.2%, -2.0%, p=0.0072) |

CI = confidence interval, IV = intravenous; RRR = relative risk reduction.

[a] For those not on mechanical ventilation at baseline.

Note: N = number of patients in each treatment group; N1= (number of patients in each treatment group - number of patients who died or dropped out from study before Day 6); n = Total number of patients who died on or before day X; % = n/N1.

Source: t_220_pr_dth_c1c1a_byser, t_220_pr_dthd6_c1c1a_byser, t_240_sm_mv_c1c1a_byser, t_220_pr_dthad_c1c1a_byser,

**Table 20 Summary of Secondary Clinical Endpoints in the Overall mFAS (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A)**

| Secondary Clinical Endpoint | Placebo (N=393) n/N1 (%) | Casirivimab+Imdevimab 2400 mg IV (N=406) n/N1 (%) | Casirivimab+Imdevimab 8000 mg IV (N=398) n/N1 (%) | Casirivimab+Imdevimab 2400 mg +8000 mg IV combined (N=804) n/N1 (%) |
|---|---|---|---|---|
| **All-cause mortality (Day 1 to Day 29)** | | | | |
| Event rate (%) | 45/393 (11.5%) | 22/406 (5.4%) | 37/398 (9.3%) | 59/804 (7.3%) |
| RRR %, (95% CI, nominal p value) | | 52.7% (22.7%, 71.0%, p=0.0022) | 18.8% (-22.6%, 46.2%, p=0.3072) | 35.9% (7.3%, 55.7%, p=0.0178) |
| **All-cause mortality (Day 6 to Day 29)** | | | | |
| Event rate (%) | 40/381 (10.5%) | 21/397 (5.3%) | 33/388 (8.5%) | 54/785 (6.9%) |
| RRR %, (95% CI, nominal p value) | | 49.6% (16.2%, 69.7%, p=0.0071) | 19.0% (-25.6%, 47.6%, p=0.3258) | 34.5% (3.2%, 55.6%, p=0.0322) |
| **Mechanical ventilation[a]** | | | | |
| Cumulative incidence % (95% CI) | 9.3% (6.7%, 12.7%) | 5.9% (3.9%, 8.7%) | 8.5% (6.1%, 11.8%) | 7.2% (5.6%, 9.2%) |

**Table 20 Summary of Secondary Clinical Endpoints in the Overall mFAS (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A) (cont.)**

| Secondary Clinical Endpoint | Placebo (N=393) n/N1 (%) | Casirivimab+Imdevimab 2400 mg IV (N=406) n/N1 (%) | Casirivimab+Imdevimab 8000 mg IV (N=398) n/N1 (%) | Casirivimab+Imdevimab 2400 mg +8000 mg IV combined (N=804) n/N1 (%) |
|---|---|---|---|---|
| **Death or readmission** | | | | |
| Event rate (%) | 67/393 (17.0&) | 44/406 (10.8%) | 59/398 (14.8%) | 103/804 (12.8%) |
| RRR %, (95% CI, nominal p value) | | 36.4% (9.4%, 55.4%, p=0.0116) | 13.0% (-19.9%, 36.9%, p=0.3844) | 24.9% (0.3%, 43.4%, p=0.0491) |
| **Discharge** | | | | |
| Event rate (%) | 330/393 (84.0%) | 366/406 (90.1%) | 348/398 (87.4 %) | 714/804 (88.8%) |
| RRR %, (95% CI, nominal p value) | | -7.4% (-13.3%, -1.7%, p=0.0098) | -4.1% (-10.2%, 1.6%, p=0.1531) | -5.8% (-11.1%, -0.6%, p=0.0184) |

CI = confidence interval, IV = intravenous; RRR = relative risk reduction.

[a] For those not on mechanical ventilation at baseline.

Note: N = number of patients in each treatment group; N1= (number of patients in each treatment group - number of patients who died or dropped out from study before Day 6); n = Total number of patients who died on or before day X; % = n/N1.

Source: t_220_pr_dth_c1c1a, t_220_pr_dthd6_c1c1a, t_240_sm_mv_c1c1a, t_220_pr_dthad_c1c1a, t_220_pr_disch_c1c1a.

**Table 21 Summary of Secondary Clinical Endpoints in the High Viral Load mFAS (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A)**

| Secondary Clinical Endpoint | Placebo (N=229) n/N1 (%) | Casirivimab+Imdevimab 2400 mg IV (N=231) n/N1 (%) | Casirivimab+Imdevimab 8000 mg IV (N=236) n/N1 (%) | Casirivimab+Imdevimab 2400 mg +8000 mg IV combined (N=467) n/N1 (%) |
|---|---|---|---|---|
| **All-cause mortality (Day 1 to Day 29)** | | | | |
| Event rate (%) | 33/229 (14.4%) | 17/231 (7.4%) | 26/236 (11.0%) | 43/467 (9.2%) |
| RRR %, (95% CI, nominal p value) | | 48.9% (11.0%, 70.7%, p=0.0174) | 23.5% (-23.6%, 52.7%, p=0.2900) | 36.1% (2.3%, 58.2%, p=0.0454) |
| **All-cause mortality (Day 6 to Day 29)** | | | | |
| Event rate (%) | 29/222 (13.1%) | 16/226 (7.1%) | 23/228 (10.1%) | 39/454 (8.6%) |
| RRR %, (95% CI, nominal p value) | | 45.8% (3.0%, 69.7%, p=0.0383) | 22.8% (-29.3%, 53.9%, p=0.3296) | 34.2% (-3.4%, 58.2%, p=0.0766) |

**Table 21 Summary of Secondary Clinical Endpoints in the High Viral Load mFAS (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A) (cont.)**

| Secondary Clinical Endpoint | Placebo (N=229) n/N1 (%) | Casirivimab+Imdevimab 2400 mg IV (N=231) n/N1 (%) | Casirivimab+Imdevimab 8000 mg IV (N=236) n/N1 (%) | Casirivimab+Imdevimab 2400 mg +8000 mg IV combined (N=467) n/N1 (%) |
|---|---|---|---|---|
| **Mechanical ventilation[a]** | | | | |
| Cumulative incidence % (95% CI) | 11.8% (8.2%, 16.8%) | 6.3% (3.7%, 10.3%) | 9.1% (6.0%, 13.8%) | 7.7% (5.5%, 10.6%) |
| **Death or readmission** | | | | |
| Event rate (%) | 48/229 (21.0%) | 35/231 (15.2%) | 41/236 (17.4%) | 76/467 (16.3%) |
| RRR %, (95% CI, nominal p value) | | 27.7% (-7.3%, 51.3%, p=0.1032) | 17.1% (-20.6%, 43.0%, p=0.3350) | 22.4% (-7.4%, 43.9%, p=0.1314) |
| **Discharge** | | | | |
| Event rate (%) | 184/229 (80.3%) | 206/231 (89.2%) | 205/236 (86.9%) | 411/467 (88.0%) |
| RRR %, (95% CI, nominal p value) | | -11.0% (-20.0%, -2.6%, p=0.0105) | -8.1% (-17.2%, 0.3, p=0.0622) | -9.5% (-17.7%, -1.9%, p=0.0088) |

CI = confidence interval, IV = intravenous; RRR = relative risk reduction.

[a] For those not on mechanical ventilation at baseline.

Note: N = number of patients in each treatment group; N1= (number of patients in each treatment group - number of patients who died or dropped out from study before Day 6); n = Total number of patients who died on or before day X; % = n/N1.

Source: t_220_pr_dth_c1c1a_bynp6, t_220_pr_dthd6_c1c1a_bynp6, t_240_sm_mv_c1c1a_bynp6, t_220_pr_dthad_c1c1a_bynp6, t_220_pr_disch_c1c1a_bynp6.

**Table 22 Summary of Secondary Clinical Endpoints in the Seropositive mFAS (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A)**

| Secondary Clinical Endpoint | Placebo (N=201) n/N1 (%) | Casirivimab+Imdevimab 2400 mg IV (N=191) n/N1 (%) | Casirivimab+Imdevimab 8000 mg IV (N=178) n/N1 (%) | Casirivimab+Imdevimab 2400 mg +8000 mg IV combined (N=369) n/N1 (%) |
|---|---|---|---|---|
| **All-cause mortality (Day 1 to Day 29)** | | | | |
| Event rate (%) | 18/201 (9.0%) | 10/191 (5.2%) | 16/178 (9.0%) | 26/369 (7.0%) |
| RRR %, 95% CI, nominal p value) | | 41.5% (-23.4%, 72.3%, p=0.1169) | -0.4% (-90.8%, 47.2%, p=0.8435) | 21.3% (-40.0%, 55.8%, p=0.3153) |
| **All-cause mortality (Day 6 to Day 29)** | | | | |
| Event rate (%) | 16/196 (8.2%) | 10/188 (5.3%) | 15/176 (8.5%) | 25/364 (6.9%) |
| RRR %, 95% CI, nominal p value) | | 34.8% (-39.9%, 69.7%), p=0.2114) | -4.4% (-104.9%, 46.8%, p=0.9424) | 15.9% (-53.8%, 54.0%, p=0.4557) |
| **Mechanical ventilation[a]** | | | | |
| Cumulative incidence % (95% CI) | 7.7% (4.76%, 12.4%) | 5.4% (3.0%, 9.9%) | 8.2% (5.0%, 13.5%) | 6.8% (4.6%, 10.0%) |

**Table 22 Summary of Secondary Clinical Endpoints in the Seropositive mFAS (Pooled Phase 3 Cohort 1 and Phase 2 Cohort 1A) (cont.)**

| Secondary Clinical Endpoint | Placebo (N=201) n/N1 (%) | Casirivimab+Imdevimab 2400 mg IV (N=191) n/N1 (%) | Casirivimab+Imdevimab 8000 mg IV (N=178) n/N1 (%) | Casirivimab+Imdevimab 2400 mg +8000 mg IV combined (N=369) n/N1 (%) |
|---|---|---|---|---|
| **Death or readmission, RRR %, (95% CI, p value)** | | | | |
| Event rate (%) | 25/201 (12.4%) | 16/191 (9.4%) | 25/178 (14.0%) | 43/369 (11.7%) |
| RRR %, 95% CI, nominal p value) | | 24.2% (-34.3%, 57.3%, p=0.2761) | -12.9% (-89.2%, 32.6%, p=0.7781) | 6.3% (-48.7%, 41.0%, p=0.6787) |
| **Discharge, RRR %, (95% CI, p value)** | | | | |
| Event rate (%) | 172/201 (85.6%) | 169/191 (88.5%) | 154/178 (86.5%) | 323/369 (87.5%) |
| RRR %, 95% CI, nominal p value) | | -3.4% (-11.6%, 4.2%, p=0.2945) | -1.1% (-9.7%,6.8%, p=0.5974) | -2.3% (-9.6%,4.5%, p=0.3639) |

CI = confidence interval, IV = intravenous; RRR = relative risk reduction.

[a] For those not on mechanical ventilation at baseline.

Note: N = number of patients in each treatment group; N1= (number of patients in each treatment group - number of patients who died or dropped out from study before Day 6); n = Total number of patients who died on or before day X (death data will captured from any CRF in the study); % = n/N1.

Source: t_220_pr_dth_c1c1a_byser, t_220_pr_dthd6_c1c1a_byser, t_240_sm_mv_c1c1a_byser, t_220_pr_dthad_c1c1a_byser, t_220_pr_disch_c1c1a_byser.

## All-cause mortality

- Treatment with casirivimab+imdevimab led to a numerical improvement in all-cause mortality from Day 1 through Day 29 in the casirivimab+imdevimab combined dose group compared to placebo in the Seronegative mFAS (RRR: 55.6%; 95% CI: 24.2%, 74.0%) (Table 19), Overall mFAS (RRR: 35.9%; 95% CI: 7.3%, 55.7%) (Table 20), and High Viral Load mFAS (RRR: 36.1%; 95% CI: 2.3%, 58.2%) (Table 21). In participants who were seropositive at baseline, there were numerically fewer deaths through Day 29 in the combined doses group compared to the placebo group (RRR: 21.3%; 95% CI; -40.0%, 55.8%) (Table 22).
- Reductions in the proportion of participants who died from Day 6 to Day 29 for the casirivimab+imdevimab combined doses group compared to the placebo group were observed in the Seronegative mFAS (RRR: 56.0%, 95% CI: 21.9%, 75.2%) (Table 19), the Overall mFAS (RRR: 34.5%, 95% CI: 3.2%, 55.6%) (Table 20), and the High Viral Load mFAS (RRR: 34.2%, 95% CI: -3.4%, 58.2%) (Table 21).
- The individual doses (2400 mg and 8000 mg) compared to placebo for all-cause mortality are presented in Table 19 to 22 for the different analysis populations. Treatment benefit by individual doses shows the 2400 mg dose group had reductions in all-cause mortality across all populations of interest, compared to smaller but numerically fewer deaths with 8000 mg. Consistent with the results of the primary clinical efficacy endpoints, the absence of a dose-related trend suggests there is no meaningful difference in efficacy between the doses and the variability observed between the two doses is due to the small sample size within each dose group.

**Mechanical ventilation**

There was a lower cumulative incidence of patients progressing to mechanical ventilation through Day 29 in the casirivimab+imdevimab combined doses group compared to placebo in the Seronegative mFAS (7.0%, [95% CI: 4.8%, 10.3%] vs. 10.6% [95% CI: 6.6%, 16.8%]) (Table 19). In the overall mFAS, the cumulative incidence in the casirivimab+imdevimab combined doses group was 7.2% (95% CI: 5.6%, 9.2%) compared to 9.3% (95% CI: 6.7%, 12.7%) in the placebo group (Table 20). In the High Viral Load mFAS, the cumulative incidence in the combined doses group was 7.7% (95% CI: 5.5%, 10.6%) compared to 11.8% (95% CI: 8.2%, 16.8%) in the placebo group (Table 21).

**Death or readmission**

For the composite endpoint of death or readmission at Day 29, reductions were observed among participants treated with casirivimab+imdevimab in the combined doses group versus placebo in the Seronegative mFAS (RRR: 49.9%; 95% CI: 26.0%, 66.0%) (event rate 12.2% [44/360] vs. 24.4% [39/160]) (Table 19). The RRR at Day 29 in the Overall mFAS was 24.9% (95% CI 0.3%, 43.4%) (Table 20) and 22.4% (95% CI: -7.4%, 43.9%) in the High Viral Load mFAS (Table 21).

**Discharge**

In the Seronegative mFAS, there were more participants discharged through Day 29 in the casirivimab+imdevimab combined doses group compared to the placebo group, with a RRR of -10.8% and 95% CI: -20.2%, -2.0%) (Table 19). The median time to discharge was 4.0 days across all treatment groups (individual and combined doses) compared to 4.5 days in the placebo group, however the upper quartile (75%) time to discharge was 8.0 days across all treatment groups compared to 17.0 days in the placebo group.

Similarly, in the Overall mFAS and in the High Viral Load mFAS, treatment with casirivimab+imdevimab resulted in more participants discharged through Day 29 and the RRR was -5.8% with 95% CI: -11.1%, -0.6%, and RRR of -9.5% with 95% CI: -17.7%, -1.9%, respectively (Table 20, Table 21).

**Exploratory Analysis of Virologic and Clinical Efficacy Outcomes in Cohort 2**

Due to the IDMC-recommended enrolment pause for cohorts 2 and 3 during phase 2 these cohorts were not fully enrolled, and the sample size is very small. As a result, only limited efficacy data are available. All participants enrolled in cohorts 2 and 3 continued in the study and were followed up through the end of study visit on study day 57.

As cohort 3 included only 33 participants in the Overall mFAS, efficacy data were largely uninterpretable. Accordingly, analyses are presented below for cohort 2 only: viral load through day 11 (Figure 23), all-cause mortality through day 29 (Figure 24), and death or mechanical ventilation through day 29 (Figure 25).

**Figure 23: Mean Viral Load Over Time: Post-Hoc Comparison of Casirivimab+Imdevimab Versus Placebo (Cohort 2; mFAS, N=148)**

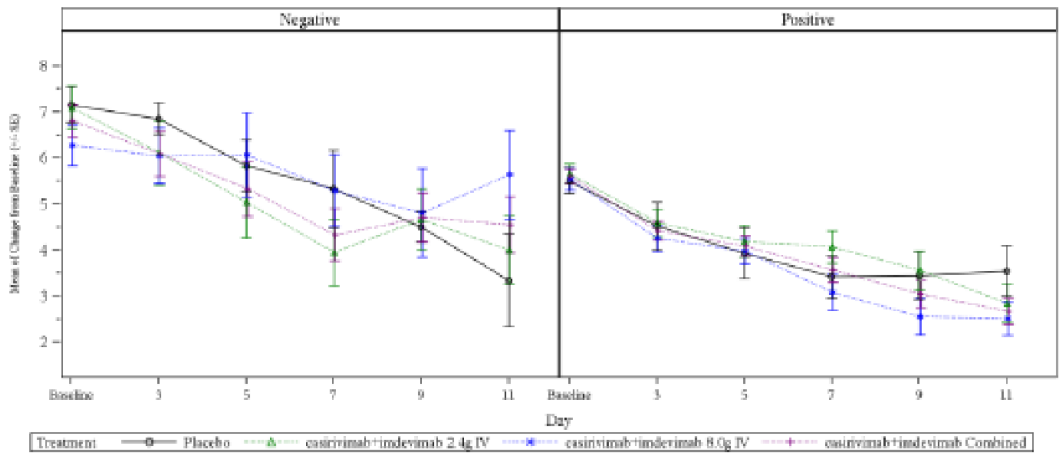
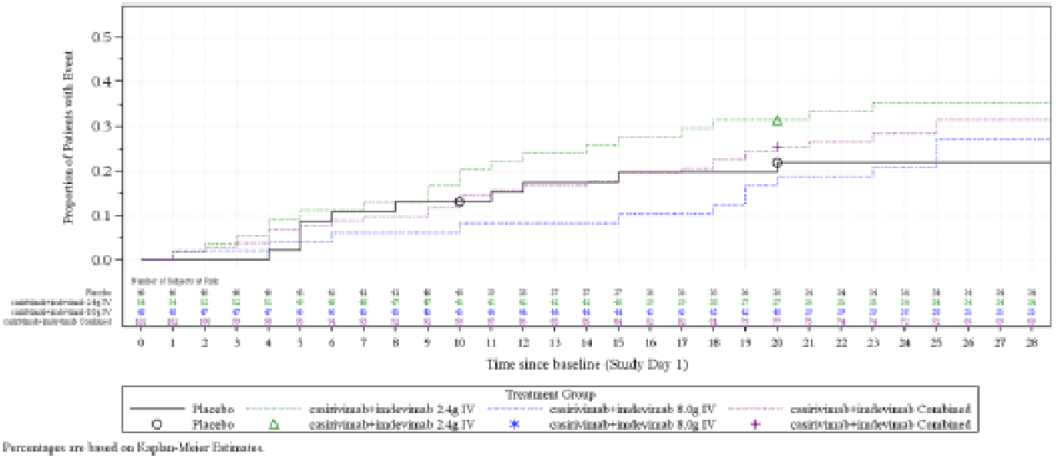
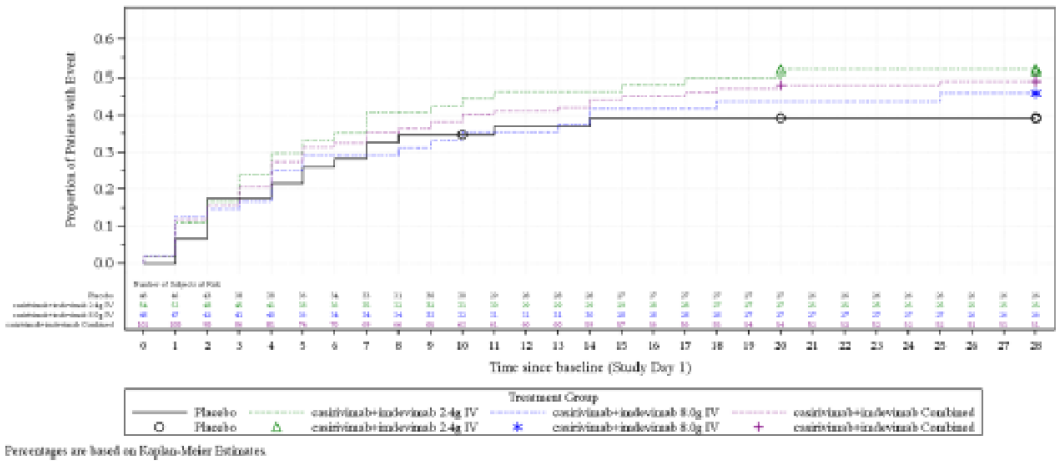


**Figure 24: Kaplan-Meier Curve for Cumulative Incidence of Death: Post-Hoc Comparison of Casirivimab+Imdevimab Versus Placebo (Cohort 2; mFAS, N=148)**




Each symbol represents a censored event.
Source: PTF 14.2.2.5.1.1bm

**Figure 25: Kaplan-Meier Curve for Cumulative Incidence of Death or Mechanical Ventilation: Post-Hoc Comparison of Casirivimab+Imdevimab Versus Placebo (Cohort 2; mFAS, N=148)**




Each symbol represents a censored event.
Source: PTF 14.2.1.1.1.1bm

No meaningful trends for efficacy were observed for any endpoint due to limited sample size in the overall population of either cohort 2 (148 participants total in the Overall mFAS) or cohort 3 (33 participants total in the Overall mFAS). In addition, an imbalance in more participants having do not resuscitate (DNR)/do not intubate (DNI) or comfort care status in casirivimab+imdevimab groups, compared to placebo groups, may have confounded these results.

## 2.4.3. Discussion on clinical efficacy

### Design and conduct of clinical studies

RECOVERY is an investigator-initiated, individually randomized, controlled, open-label platform trial in which several treatments were compared with usual care in patients hospitalized with COVID-19. The multicenter study was conducted in the UK, Indonesia, and Nepal, with 127 hospitals in the UK taking part in the evaluation of casirivimab+imdevimab. The protocol was designed to provide reliable assessments of the effects of multiple different treatments (including re-purposed and novel drugs) on major outcomes in COVID-19 and allowed for treatment arms to be added or removed according to the

emerging evidence. A factorial randomization was utilised to compare the selected treatments with usual care.

To facilitate collaboration, even in hospitals that suddenly become overloaded, patient enrolment (via the internet) and all other trial procedures are greatly streamlined. Informed consent is simple and data entry is minimal.

The inclusion / exclusion criteria are inclusive, no limitation regarding the time of symptom onset a clinically suspected SARS-CoV-2 infection disqualifies the patient for enrolment. This is in contrast to the more restrictive inclusion criteria of Study COV-2066, which aims to enrol patients with early disease. Hospitalised patients with clinically suspected or PCR laboratory-confirmed SARS-CoV-2 infection associated disease and no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial were enrolled.

The study treatment was a single 8000 mg dose (casirivimab 4000 mg and imdevimab 4000 mg) on top of usual care. Patients could also receive between 0 and 4 treatments on top of usual standard of care in an adaptive factorial design, this approach raises some difficulties in interpretation of the outcomes.

There was no pre-specified sample size, and this raises uncertainty. Instead, the DMC repeatedly assessed the primary endpoint and was planned to recommend stopping enrolment if a mortality reduction of at least a 3 to 3·5 standard error was observed in all randomised patients. The study was conducted with relevant uncertainty, and this is understood in the pandemic. The RECOVERY team clarified that no DMC members (who were the only individuals who can review interim unblinded analyses) were involved in the primary endpoint change and Trial Steering Committee meeting minutes, at which the updated SAP was ratified.

Of note, the power considerations are not fully in line with the DMC criterion to consider recommending stopping a treatment early for benefit would require at least a 3 to 3·5 standard error reduction in mortality (see statistical methods). Assuming asymptotic normality of the test statistic, the DMC criterion would correspond to a stricter level than p=0.01, and this observation is consistent with the fact that the DMC did not recommend stopping enrolment.

It should also be noted that at the time when the decision was made to stop enrolment, the trial steering committee considered a benefit in the overall population (i.e., irrespective of serostatus) unlikely to be demonstrated. In conclusion, there is uncertainty due to a lack of pre-specification of the sample size. The initially specified DMC criteria for stopping enrolment were not adhered to.

Since this is an open-label study, the participants and local study staff were not masked to the allocated treatment. This is not optimal, but the primary outcome of 28-day mortality may be considered sufficiently objective to outweigh concerns on lack of blinding. The DMC, which was unblinded, regularly assessed the trial data.

No estimand has been defined. However, it seems clear that the primary analysis of 28-day mortality targets a treatment policy estimand in a seronegative population. Although a treatment policy estimand is of primary interest, restriction to seronegatives does not reflect the intended indication, which is irrespective of serostatus.

Secondary estimands are more complex. In particular it is not obvious how an estimand targeted by the analysis of time to discharge should be described. Particularly difficult is the fact that deceased patients were planned to be censored after day 28, thus assuming that these patients would still be hospitalized at the end of the observation period (see below). Provided an effect on 28-day mortality, this is however not considered critical.

The analysis set, consisting of all subjects randomized, is in principle endorsed, as it adheres to the intent-to-treat principle. However, restriction to seronegative subjects warrants further discussion.

The primary analysis of this open-label study was initially planned to be conducted in all randomized subjects but was restricted to seronegatives in a very late amendment to the SAP (version 3.0) which

was finalised on 21 May 2021, i.e., one day prior to closure of enrolment (on 22 May 2021) and several weeks after the decision to stop enrolment was made by the trial steering committee on 27 April 2021. At the time of this decision, the DMC had conducted several interim analyses and results from previous comparisons in this study were already known. Some of these comparisons included subjects who were also included in the REGN-COV-2 vs control comparison due to the factorial design. It is acknowledged that external data (results from study 2067, not part of this assessment) suggested that seronegatives may have greater benefit, but uncertainty remains on a potentially opportunistic change of primary analysis population.

The SAP states that "Earlier versions of the statistical analysis plan recognised the importance of the seronegative subgroup", however this statement cannot be verified, as only the latest version of the SAP is submitted. The applicant was asked to provide previous versions that were provided.

It is endorsed that the protocol stated that for any pairwise comparison, only concurrent controls would be analysed.

The primary outcome of 28-day mortality was planned to be analysed by means of a log-rank test. It is not fully understood why a time-to-event analysis should be preferred over an analysis of proportions for this rather short-term outcome. Time to death within 28 days does not seem more relevant than the dichotomous version of death until day 28. However, the results are interpretable, and analyses of the binary outcome provide similarly positive results.

The analyses were not adjusted for baseline covariates.

According to the study protocol, patients who were discharged alive from hospital were planned to be assumed as being alive. It was assumed that this means that patients were censored after 28 days after randomisation. The applicant was asked to confirm. In addition, information on the amount of missing values in relevant variables and discuss the robustness of results in the presence of missing data were also requested. The applicant confirmed the mechanisms by which discharged subjects were classified as events or censored and provided further reassurance that there was only very little missing data. This is acknowledged. In the control group as compared to the ronapreve group a slightly higher portion of those patients who were discharged alive died after being discharged. Any interpretation of this finding is limited by the fact that discharge alive is an intercurrent event and depends on survival until discharge.

Statements on the significance level are somewhat inconsistent. Apparently, no significance level was pre-specified in the study protocol, the SAP states a two-sided significance level of 0.05 and the decision to stop enrolment was based on power considerations at the two-sided level of 0.01. The DMC criterion to recommend stopping enrolment (mortality difference of about 3 to 3.5 standard errors) may correspond to yet another level of significance. An ad-hoc interpretation of p-values and estimates may be warranted, and it should be noted that there is relevant uncertainty about type-I-error control.

There were several interim analyses for efficacy through the DMC. The applicant was asked to provide information on the number and timing (in terms of information fraction) of those interim looks and discuss potential bias in estimation due to multiple interim looks, by providing bias adjusted point estimates and multiplicity adjusted confidence intervals. The applicant confirmed that there were 12 interim analyses for efficacy. This number is considered high, especially in an open-label study. The applicant's responses suggest that the sponsor remained blinded towards interim results. Post-hoc considerations on multiplicity were provided. Any such post-hoc discussion is limited as it is may not be unequivocal. The total information was not prespecified and in consequence any information fraction relative to the finally observed information could only be calculated post-hoc. Despite limitations, the applicant's responses provided some reassurance, that the criterion for the DMC to recommend stopping for efficacy was chosen in a way that the increase in type-I-error probability may not be substantial. CHMP concluded that type-I-error was not controlled, and uncertainty remained. The extent of type-I-error inflation was considered limited and needed to be balanced against the observed benefits.

The complex study design added uncertainty. Previous results from this open-label platform study (e.g., through analyses of other treatments, or interim analyses of REGN-COV-2) may have influenced the design of the ongoing study (e.g., through changes in patient selection). It was acknowledged that the study was conducted in a situation with high uncertainty in a quickly changing environment. CHMP concluded that some uncertainties remained due to the complexity of the study design, but results were interpretable.

Multiplicity control across primary and secondary hypotheses was only specified in the SAP, and this is not ideal.

## Efficacy data and additional analyses

A flow chart of participants of the RECOVERY trial is provided. However, the data are not comprehensible e.g., 4839 patients were randomised in the REGN-COV group, 28 withdrew consent but 4839 patients were included in the 28 day ITT. The applicant was requested to provide data on the numbers randomised and numbers actually treated (including specifying how many patients were randomised but not treated. The MAH confirmed that all 4839 participants randomized to the casirivimab+imdevimab arm and all 4946 participants randomized to the usual care alone arm were included in the 28-day intention-to-treat (ITT) analysis, including those who withdrew consent.

The MAH provided further information on the patient flow. Apparently not all randomised patients provided a completed-follow up form, this loss of follow-up is understandable.

The applicant confirmed that approximately 10% of the patients in the ronapreve arm did not receive allocated treatment. While this is not of concern with regard to the validity of the treatment effect estimate (under the alternative it would reduce the estimated effect, under the null it would not matter), the high proportion of approximately 10% was not understood. Reasons were not recorded. In the 28-day intention-to-treat (ITT) analysis, patients who withdrew consent were included. The MAH was invited to comment on this issue. A total of 28/4839 (0.6%) patients in the casirivimab+imdevimab arm and 18/4946 (0.4%) patients in the Usual Care alone arm withdrew consent within 28-days after randomisation. Thus, the numbers of patients who withdrew consent is low. The majority i.e., more than half of the patients in each arm withdrew on or before Day 2 (23 of 28 patients in the casirivimab+imdevimab arm and 10 of 18 patients in the Usual Care alone arm).

In the 28-day intention-to-treat (ITT) analysis, patients who withdrew consent were included. The MAH clarified that inclusion of patients who withdrew consent is in line with the study protocol, which states, "In accordance with regulatory guidance, de-identified data that have already been collected and incorporated in the study database will continue to be used (and any identifiable data will be destroyed)." This approach is accepted.

A portion of participants was included in other study parts (e.g., aspirin vs no additional treatment or baricitinib vs. no additional treatment). The MAH was asked to discuss whether this may have had any impact on results of the comparison of REGN-COV-2 vs no additional treatment, e.g., through respective analyses of treatment combinations in the factorial design in particular for those treatments for which results were already available. The MAH provided information on allocation to other treatments, including an exploratory analysis of potential drug-drug-interactions. There were no apparent baseline imbalances with regard to allocation to other treatments, and that is expected, as all treatments were randomly allocated.

The applicant concluded that there are no meaningful interactions, as interaction p-values are all >0.11 however that was not agreed. Interaction tests are known to have poor statistical properties, and the p-value does not convey information on the clinical relevance of potential differences. The size of estimated interactions was assessed: The reported interaction HRs for Baricitinib and Colchicine are in the range of interactions that may hypothetically neutralize the effect of ronapreve in seronegatives (e.g. the interaction HR for Baricitinib is 1.3 and multiplication with the ronapreve RR=0.79 in

seronegatives results in in neutral effect 0.79*1.30=1.027). Acknowledging that confidence intervals may be wide, the MAH was asked to provide estimates of the effect of ronapreve in subgroups defined by allocation to Baricitinib or Colchicine in the ITT population as well as in the seronegative subgroup and to discuss the plausibility and relevance of observed differences. The MAH provided estimates for the effect of ronapreve in those patients allocated or not allocated to baricitinib or colchicine. It was agreed that a potential interaction with colchicine is of minor importance, given that colchicine is currently considered ineffective as treatment of COVID-19.

However, results suggest a potentially detrimental effect of ronapreve on top of baricitinib in patients not seronegative. Among those allocated to baricitinib, the estimated hazard ratios for ronapreve are 0.89 and 1.20 in the seronegative and overall population respectively. This implies that the estimate in patients not seronegative must be well beyond HR=1.2 (result not provided by the MAH). Credibility of these subgroup findings may be limited. Acknowledging that these findings are post-hoc and any interpretation should be made with great care, they add further uncertainty to the treatment of seropositive patients. They do not raise any concerns in seronegatives. Thus, these findings currently have no implications, but provide support to the finally agreed indication.

A higher portion of subjects in the control arm proceeded to second randomisation. The MAH was asked to discuss whether this observation may support the treatment effect or whether it may imply that in addition to receiving or not receiving REGN-COV-2 there were other differences in patient care between the treatment groups in this open-label study. Also, to provide summary data on the time from first randomisation to second randomisation in these subjects and discuss clinical progression that lead to eligibility for second randomisation. With the data provided, it cannot be excluded that knowledge of the allocated treatment lead to very early inclusion in the tocilizumab part in the control group. The median time to second randomization was 0.4 hours, suggesting that patients were included in the tocilizumab part of the study very shortly after randomization to ronapreve or usual care and thus progression to the tocilizumab part does likely not reflect any effect of treatment in most patients. Knowledge of the allocated treatment in this open-label study appears to be the most plausible explanation for the higher portion of control subjects included in the tocilizumab part. Other treatments appear rather balanced, but this does not fully resolve the uncertainties about potentially different care in the arms of this open-label study. However, there is currently no reason to believe that this might have artificially inflated the treatment effect estimate.

The study was performed in a single country, this might have contributed to some observed differences between the outcome of RECOVERY and COV-2066 (see below).

There were 15 amendments to the protocol, in general addressing the opening and deletion of treatment arms. The factorial design allows testing of different combination of medicines in a short time frame.

The participants' demographic characteristics including age, sex, and race/ethnicity were generally balanced between the treatment groups for the seronegative group and among all randomized participants. The baseline disease characteristics of the seronegative participants were well-balanced between the treatment arms and were mostly similar to those reported for all randomized participants. 1360 (14%) of the study participants had missing SARS-CoV-2 antibody test result. This number is considered relevant. With regard to oxygen report, the majority of patients (60-70 %) were in the combined groups of no oxygen and simple oxygen support, and less than 30% of patients received non-invasive and invasive mechanical ventilation. The type of oxygen support was balanced between the groups.

Quite a substantial proportion of the participants have an unknown serostatus. The MAH was asked to comment under the light of outcome, in particular in light of an observed slightly higher mortality in seropositive participants (16% vs 15%). The MAH provided further analyses to support their view that results in seronegative patients are robust despite the high proportion of patients with unknown serostatus. Despite the fact that there were more patients with unknown serostatus in the control group (12% vs 16% in ronapreve vs usual care, $p<0.001$), there were no apparent strong baseline imbalances between the treatment groups in each of the serostatus subgroups. The effect estimate in

patients with unknown serostatus suggests very little to no effect on all-cause mortality. A pooled analysis was provided by the sponsor based on patients with unknown or negative serostatus, suggesting that the conclusion of a benefit in seronegatives would not have been altered even if all patients with unknown serostatus were truly seronegative. This was further supported by tipping-point analyses. Overall, the treatment effect estimate in seronegative subjects appears to be robust against potential biases due to undetected serostatus in the group with missing serostatus.

The two primary endpoints were 28 days all-cause mortality in patients seronegative at randomisation and in all patients randomised (tested hierarchically).

9785 patients were randomly allocated to receive usual care plus REGEN-COV or usual care alone, including 3153 (32%) seronegative patients, 5272 (54%) seropositive patients and 1360 (14%) patients with unknown baseline antibody status.

Among participants who were seronegative at baseline, there was a statistically significant reduction of 20% in 28-day all-cause mortality among participants in the casirivimab+imdevimab group compared to participants receiving usual care alone. 24 % (396/1633 participants) died in the casirivimab+imdevimab group vs. 30% (451/1520 participants) in the usual care group (rate ratio: 0.80; 95% CI: 0.70–0·91; p=0.001).

Among all randomized participants (including those who were seronegative, seropositive and serostatus unknown), there was no significant difference in 28-day all-cause mortality between the two groups. 20% (944/4839 participants) of participants in the casirivimab+imdevimab group died versus 21% (1026/4946 participants) of participants in the usual care alone group (rate ratio 0.94; 95% CI: 0.86 to 1.03; p=0.17). 28-day mortality was also assessed in participants who were seropositive at baseline. There was little difference in the 28-day all-cause mortality between the two groups: 16% (411/2636) of participants in the seropositive casirivimab+imdevimab group died versus 15% (383/2636) of participants in the usual care alone group (rate ratio 1.09; 95% CI: 0.95 to 1.26). The proportional effect of casirivimab+imdevimab on mortality differed significantly between participants who were seronegative and seropositive at baseline (test for heterogeneity, p=0.001). These findings are in line the hypothesis that patients who had not yet an immune response benefit most from an anti-viral in contrast to patients who already developed an immune response.

Subgroup analyses suggest that both positive serostatus as already explained as well as time from symptom onset >7days might be associated with lack of efficacy. It is observed that seronegatives differed from the overall study population with regard to the time from symptom onset. The applicant was asked to discuss whether one subgroup interaction could mask the other. The MAH was asked to provide respective interaction analyses and investigate different cut-offs for time from symptom onset. Extensive exploratory analyses were provided. Overall, it was noted that time from symptom onset does not provide a clear signal for an interaction with treatment when using two cut-off values (7 and 14 days). No plausible mechanistic reason was found to assume that any interaction between treatment and time from symptom onset would not be monotonous. Thus, it was agreed that it is unlikely that one interaction may mask another in this setting. This is further supported by 2-way and 3-way interaction analyses provided by the MAH.

Minor inconsistencies were observed in reported results of the RECOVERY trial, e.g. between the clinical overview and the material by the RECOVERY investigators. For example, the proportion of patients who died in the regn-cov-2 group in the overall population is presented as either 19% or 20% across different tables and figures, the confidence interval for the effect on discharge alive is presented as either 1.08-1.30 or 1.09-1.31 across different figures and tables. Although these numerical inconsistencies may be minor with regard to the overall interpretation of results, they do raise uncertainty. The MAH was asked to clarify inconsistencies between the documents provided by the applicant and those authored by the RECOVERY investigators and provide an outcome table with correct values. The applicant clarified that there were inconsistencies in previously submitted data because analyses were preliminary. Although it is not understood why two different (and inconsistent)

levels of information were included in the previously submitted dossier, this concern was considered resolved as per the reason above.

**Secondary outcomes**

Secondary endpoints are descriptive, as the second primary endpoint (28-day mortality in the overall population) was not met, and hierarchical testing is discontinued accordingly. P-values <0.05 are considered nominally significant (i.e., in an exploratory sense).

In seronegative patients, the mean duration of hospital stay was shorter in the REGN-COV group than in the SOC group, while in all randomised patients no treatment effect on the hospital stay was observed.

Among seronegative participants, discharge alive within 28 days was nominally significant among participants in the casirivimab+imdevimab group compared with the usual care group (64% vs. 58%; risk ratio: 1.19, 95% CI: 1.08 to 1.30).

Among all randomized participants, there was no meaningful difference observed in the casirivimab+imdevimab group compared with the usual care group in discharge alive within 28 days.

Use of invasive mechanical ventilation or death among patients not on invasive mechanical ventilation at randomisation was reported. The reported death numbers were not in line with the mortality data reported for the primary endpoint e.g., in seronegative patients 396 death were reported for "28 days mortality" while 383 deaths were reported under "use of invasive mechanical ventilation or death among patients not on invasive mechanical ventilation at randomisation". The same applies for the usual care group and all randomised data. The apparent discrepancies in the reported number of deaths for the primary outcome of 28-day mortality and the secondary outcome of 'use of invasive mechanical ventilation or death among participants not on invasive mechanical ventilation at randomization' is clarified to be due to deaths among participants on invasive mechanical ventilation at randomization.

The final conclusion on the importance of the finding is hampered by the small sample size in the RECOVERY study. Of note in Study 2066 Cohort II and III (more diseased patients e.g., on invasive ventilation) were closed early due to futility, and this does not lend support. Nonetheless, the explanation is accepted.

For seronegative participants as well for all patients, the 28-day all-cause mortality in the casirivimab+imdevimab group across pre-specified subgroups (age, sex, ethnicity, days since symptom onset, respiratory support received and use of corticosteroids) was provided. Importantly, regarding the use of corticosteroids both groups i.e., patients receiving corticosteroids and patients receiving no corticosteroids show treatment benefit which was even more pronounced.

Of note, patients > 80 years of seems not to benefit from REGN-COV therapy (reduction in 28-day all-cause mortality and discharge alive from hospital). The MAH was asked to provide a sensitivity analysis and the data of the same age group of study COV-2066. In this regard, the data of the RECOVERY study and Study 2066 are conflicting. Study COV-2066 suggests a potential benefit in patients≥ 80 years in both endpoints i.e., mortality and discharge alive, based on positive point estimates. RECOVERY suggests no benefit in those patients. It should be noted that Study COV-2066 is only supportive and more emphasis is put on RECOVERY in the overall assessment. Sample sizes in RECOVERY are larger also in the subgroup of elderly patients, Study COV-2066 contributes 165 seronegative patients above 80 years of age in total, i.e., pooled over cohorts and study phases. RECOVERY contributes 464 patients above 80 years of age and suggest no effect. It is agreed with the MAH, that a benefit in elderly cannot be excluded based on these data. However, a benefit can also not be concluded and there remains uncertainty.

Given the lack of a mechanistic explanation and some support from COV-2066, it is not seen grounds to restrict the indication, but consider that the prescriber should be informed of the uncertainty.

The MAH was requested to propose an adequate wording for the SmPC section "special population".

For the selected endpoints i.e., 28 days mortality, discharge alive from hospital and invasive mechanical ventilation or death the outcome for seropositive patients / all patients at baseline not only seems less favourable but harmful in the treatment group.

The signal of reduced efficacy in the seropositive patients observed in RECOVERY study remained after clarification. Considering that the benefit-risk-balance is negative in the overall study population, CHMP considered that an extrapolation to a broader indication was not justified. The MAH was asked to propose a new indication wording that restricts to those patients for whom a benefit can be concluded without speculation i.e., seronegative patients. Further in the overall population requiring supplemental oxygen in RECOVERY, there was a reduction in 28-day mortality only in seronegative patients. This conclusion is supported by descriptive results from study COV-2066. The RECOVERY and COV-2066 study results demonstrated clinical benefit of casirivimab+imdevimab in hospitalised patients with COVID-19 who were negative on serology testing.

In addition, it is important to note that with regard to immunocompromised patients:

- Consistent with their underlying immunocompromised state, the immunocompromised patients were more likely to be seronegative for SARS-CoV-2 antibodies (68.7% vs 41.2%, respectively) and to have a higher median viral load (7.21 vs 6.32 log10 copies/mL, respectively) at baseline compared with all study participants.
- Treatment with casirivimab+imdevimab led to a greater reduction in viral load from baseline, with a least-squares mean time weighted average change in viral load difference versus placebo at Day 7 for immunocompromised patients of -0.69 (95% CI: -1.25, -0.14) vs. -0.31 (CI: -0.42, -0.20) for all study patients; treatment benefit persisted through Day 29.
- Although the sample size was small for the immunocompromised patient subset (n=99 [68 seronegative, 25 seropositive, 6 unknown]), trends in clinical outcomes of death or mechanical ventilation at Day 29 (7/64 patients [cumulative incidence 11.0%] casirivimab+imdevimab vs. 6/35 patients [cumulative incidence 17.2%] placebo) were consistent with those in all study patients (200/1307 [cumulative incidence 15.7%] casirivimab+imdevimab vs. 113/633 [cumulative incidence 18.3%] placebo).

The COV-2066 data show the value of treating severely immunocompromised patients with casirivimab+imdevimab and the additional benefits that can be realised in the highest risk patients. With the emergence of new SARS-CoV-2 variants and/or waning immune protection, immunocompromised patients will continue to be at a higher risk of severe outcomes compared to those who are immunocompetent.

For further clarity regarding the RECOVERY data, in addition to the existing results for seronegative patients, the MAH adapted the indication and added summaries of the results for all randomised patients and seropositive patients in Section 5.1 of the SmPC.

Thus, 4.1 is updated with the following indication:

> *Treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg and receiving supplemental oxygen, who have a negative SARS-CoV-2 antibody test result.*

Design and conduct of clinical studies

COV-2066 was an adaptive Phase 1/2/3 randomized, double-blinded, placebo-controlled study to exclude futility (Phase 1/2) and evaluate efficacy and safety (Phase 3) of casirivimab+imdevimab in hospitalised adult and adolescent patients with COVID-19. The study was the first-in-human clinical trial for the combination mAb therapy product (casirivimab and imdevimab).

On 09 Apr 2021, owing to low recruitment rates, the Sponsor made a decision to close enrolment into the study. The reason for early termination was not based on safety concerns, but due to low recruitment rates over the preceding 3 months. All participants were followed through to their end of

study visit according to the protocol, and the last participant last visit date for the main study was 04 Jun 2021.

A subset of cohort 1 and cohort 1A participants at select study sites in the US are enrolled in an ongoing long COVID sub-study. Results from this sub-study will be reported at a later time.

The final CSR is based on a database lock date of 08 Jul 2021. This represents the final data for the main study.

The target population are hospitalised patients early in the course of the disease e.g. onset of symptoms ≤10 days before randomization and hospitalized for ≤72 hours. Patients receiving ECMO, initiated on renal replacement therapy due to COVID-19 or had circulatory shock requiring vasopressors at randomization are excluded from the study. In general, the inclusion / exclusion criteria are stricter than for RECOVERY, this might lead to difficulties in comparing the outcome of the two studies.

Patients entering the trial had varying degrees of oxygen support at randomization and this determined their categorization into 1 of 4 cohorts for analyses:

- Patients who required no supplemental oxygen support (Cohort 1A).
- Patients who had O2 saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or another similar device (Cohort 1).
- Patients who required high-intensity oxygen supplementation (Cohort 2). High-intensity oxygen therapy was defined as the use of non-rebreather mask with an oxygen flow rate of at least 10 L/min; use of a high flow device with at least 50% FiO2, or use of non-invasive ventilation to treat hypoxemia.
- Patients who were mechanically ventilated (Cohort 3).
- Patients were randomised in each cohort in a 1:1:1 ratio to receive a one-time infusion of casirivimab+imdevimab 8000 mg, casirivimab+imdevimab 2400 mg, or placebo, all given in addition to the local standard of care. Patients may receive the standard-of-care for the treatment of COVID-19 per local guidelines. Background treatments may include antiviral therapies (remdesivir or other), immune-based therapies (tocilizumab, sarilumab, steroids, or other) or antiviral and immune-based therapies

In general, the methods are acceptable. In particular, a 1:1:1 ratio is supported, and the number of stratification variables seems feasible. However, there are some unclarities.

However, there are some unclarities, e.g., whether permuted block randomisation or another method was used. However, this is considered of minor importance in light of the early termination and study results.

For the efficacy analyses, since the overall sample size was smaller than anticipated due to early study termination, study cohorts (Phase 3 Cohort 1 and Phase 2 Cohort 1A) and casirivimab+imdevimab dose groups (2400 mg IV and 8000 mg IV) were pooled for the primary efficacy analysis.

The primary endpoints were tested in a hierarchical order.

**Table 8 COV-2066 Hierarchical Testing Order**

| Hierarchy Number | Type of Outcome | Outcome | Analysis Population |
|---|---|---|---|
| 1 | Primary virologic | Time weighted average daily change from baseline in viral load from Day 1 to Day 7 | Seronegative mFAS |
| 2 | Primary clinical | Proportion of patients who died or went on mechanical ventilation from Day 6 to Day 29 | High viral load (>$10^5$ copies/mL) mFAS |
| 3 | | | Seronegative mFAS |
| 4 | | | Overall mFAS |
| 5 | | Proportion of patients who died or went on mechanical ventilation from Day 1 to Day 29 | High viral load (>$10^5$ copies/mL) mFAS |
| 6 | | | Seronegative mFAS |
| 7 | | | Overall mFAS |

The study was prematurely terminated before the planned sample size was reached. Thus, the sample size calculations are of limited relevance. The sample size for phase 2 cohort 1A has no statistical justification, indicating the exploratory character of cohort 1A. Sample size calculations for prior phases of the adaptive study are not discussed in detail. These exploratory phases of the adaptive study were planned to be used as a basis for planning the phase 3 part of the study.

The statistical methods were described and are overall acceptable, but the premature termination and respective ad-hoc modification of the analysis plan may not fully support a confirmatory interpretation.

The study was prematurely terminated and only after the decision to terminate the study, the protocol specified that the exploratory phase 2 cohort 1A and the confirmatory phase 3 cohort 1 would be pooled. This is not fully in line with the concept of a confirmatory study, where the hypotheses should be specified before the study is conducted. Premature termination does not provide reassurance that the sponsor was confident in the hypothesis investigated in the study.

In light of this and in light of the study results (primary clinical endpoint not met), a careful and rather exploratory interpretation is warranted.

Further comments:

*Virology*

The methods for the virologic endpoint are overall acceptable.

It is endorsed that an estimand was defined for the virological endpoint, and this estimand is overall supported.

*Clinic*

It is somewhat unexpected that no estimand was defined for the clinical endpoint. The definition may not be straightforward, e.g., in light of the fact that events occurring before day 6 were to be excluded from the analysis. This adds uncertainty to the interpretation of the primary clinical endpoint. However, given that the endpoint was not met, the assessors do not see any value in a post-hoc discussion on this matter.

The primary analysis set was defined as the High Viral Load mFAS, presumably because a larger effect might have been expected in those patients. It might be questioned whether this analysis set transfers to clinical practise, as it requires a PCR test before treatment initiation.

The primary outcome variable, death or mechanical ventilation from day 6 to day 29, may be prone to biases such as immortal time bias. It is not clear whether subjects who experienced an event prior to

day 6 were planned to be excluded or counted as not having an event. Analyses including events prior to day 6 are considered more robust but were included only later in hierarchy.

The analysis model was specified as a Cochrane-Mantel-Haenszel test stratified for background therapy, with a fisher exact test being the fallback option in case of small event numbers. While a fallback option may in principle be acceptable, the strategy seems to reflect uncertain expectations and in particular the expectation that there may be sparse events (which would not be the optimal basis for assessment of benefit-risk).

The primary analysis was not planned to be adjusted or stratified for country, although this was a stratification factor.

A hierarchical approach to multiplicity control is acceptable. The order of hypotheses might not be ideal, e.g., given concerns on potential biases due to exclusion of early events and a lack of clarity how the respective analyses were planned.

Pooling of cohorts somewhat contradicts the fact that initially the cohorts were planned as separate. It is not obvious whether any heterogeneity was expected. However, results from RECOVERY do not suggest any strong heterogeneity across cohorts of oxygen supply.

## Efficacy data and additional analyses

The majority of the patients were enrolled in the United States (87.6%) and the remaining participants were enrolled in Europe (~5% Romania and Moldova), Mexico (~5%) and South America (~4%, Brazil and Chile).

In general, the demographic characteristics are well balanced between the treatment arms.

The mFAS was used for the analysis of all efficacy endpoints, based on the principle that an anti-viral agent would only be anticipated to provide efficacy in patients with measurable virus at baseline. The Seronegative mFAS and the High Viral Load mFAS were used for the primary analysis and descriptive analysis of certain virologic endpoints and clinical endpoints. Additional analyses were performed in the Seropositive mFAS, as needed. For the purpose of research this approach is acceptable, and the reason provided for the approach by the MAH could be followed. However, in clinical practice this diffrenecation would not be a realistic option.

A pre-specified statistical hierarchy was used to test the virologic and clinical efficacy of casirivimab+imdevimab in the combined doses group (2400 mg IV and 8000 mg IV) compared to placebo group, in pooled Cohort 1 (Phase 3) and Cohort 1A (Phase 2). The combined analysis of the dose groups is accepted for reporting the overall results. Of note, an analysis of the individual dose groups separately can be found under “dose finding studies”.

The results indicated that the first primary endpoint (viral load reduction during the first week after treatment, in the Seronegative mFAS) was met (difference vs placebo of -0.28 log10 copies/mL, p=0.0172). But statistical testing terminated at the first clinical endpoint (reduction in death or mechanical ventilation from Day 6 to Day 29, in the High Viral Load mFAS) as it did not show a statistically significant treatment effect (RRR: 25.5%, p=0.2048).

When the observation period covered the whole efficacy period (Day 1 to Day 29), numeric reductions were observed in the proportion of participants who died or went on mechanical ventilation and all-cause mortality in all populations of interest (High Viral Load mFAS, Seronegative mFAS and Overall mFAS).

For the secondary clinical efficacy endpoints of mechanical ventilation, death or readmission and discharge, treatment with casirivimab+imdevimab led to numerically improved outcomes compared to placebo. The secondary virologic outcome of time-weighted average (TWA) change from baseline viral load also indicated numerically greater viral load reductions in the casirivimab+imdevimab treatment.

Study COV-2066 is considered as supportive study. As expected for an anti-viral REGN-COV treatment led to viral load reduction in the first week after treatment. The most prominent effect was seen in seronegative patients with baseline high viral load. However, the study failed to demonstrate that the anti-viral effect translates in a statically significant clinical benefit i.e., progression to death or mechanical ventilation for Day 6 to Day 29 or Day 1 to Day 29. The results indicate a trend towards a benefit of REGN-COV treatment:

Outcomes for Day 6 to Day 29 showed in the treatment group greater reductions in the proportion of participants who died or went on mechanical ventilation from Day 6 to Day 29 (Seronegative mFAS (RRR: 47.1%, 95% CI: 10.2%, 68.8%), and in the overall mFAS (RRR: 24.2%, 95% CI: -10.9%, 48.2%). Negligible to moderate numerical differences were observed in seropositive participants (RRR: 1.7%, 95% CI: -83.7%, 47.4%) and those with viral load ≤106 copies/mL (RRR: 21.5 %, 95 % CI: -62.2%, 62.0%)

Outcomes for Day 1 to Day 29 showed among participants treated with REGN-COV greater reductions in the proportion of participants who died or went on mechanical ventilation High Viral Load mFAS (RRR: 35.0%, 95% CI 6.6%, 54.8%), Seronegative mFAS (RRR: 47.0%, 95% CI 17.7%, 65.8%), and in the Overall mFAS (RRR: 30.9%, 95% CI 5.4%, 49.5%).

**Secondary endpoints**

Treatment with REGN-COV led to nominally significant improvement in mortality from day 1 through day 29 in the Seronegative mFAS, High Viral Load mFAS, and Overall mFAS. The greatest reduction in relative risk of death based on the proportion of participants who died occurred in participants who were seronegative at baseline with a relative risk reduction (RRR) of 55.6% (nominal p=0.0032). Reduction in the proportion of participants who died from day 6 to day 29 for the combined doses group compared to the placebo group was nominally significant in the seronegative participants (RRR of 56.0%, nominal p=0.0051) and overall population (RRR of 34.5%, nominal p=0.0322), but the trends were not large enough in the high viral load population to reach nominal significance in this study (RRR of 34.2%, nominal p=0.0766)

Potential clinical benefit of treatment with REGN-COV was observed across other secondary clinical endpoints (mechanical ventilation, death or readmission, and discharge) for all populations of interest: Seronegative mFAS, High Viral Load mFAS, and Overall mFAS

Taken together the above, the efficacy results of study COC-2066 are uncertain but point in the same direction as the results observed in RECOVERY.

## Additional analysis

The demonstration of the clinical and virologic efficacy of casirivimab+imdevimab for the treatment of hospitalised participants with COVID-19 consists of data from two studies: the pivotal RECOVERY trial and the supportive COV-2066 study. An integrated analysis of efficacy was not performed across these studies. The MAH laid down that due to the differences in study design e.g., patient population and endpoints an integrated analysis of efficacy was not performed. The reasons provide by the MAH are understandable.

It is accepted that it was aimed to open the access to RECOVERY to participants across the full range of COVID-19 disease severity in the hospitalized population, regardless of the type of respiratory support required while patients in COV-2066 primarily enrolled participants towards the lower end of disease severity that required no supplemental oxygen or low-flow supplemental oxygen. However, in practice the vast majority of participants in RECOVERY were also less diseased patients. i.e., > 70 % of the patients received no oxygen or simple oxygen (see Table 1 Baseline characteristics (seronegative and all participants) by treatment allocation) and thus the participants may be comparable in this respect (see baseline disease characteristics).

However, COV-2066 also had exclusion criteria to prevent the enrolment of participants with more severe disease that may have impacted the interpretation of efficacy and safety data. For example, those requiring additional forms of organ support, such as ECMO, inotropes and vasopressors, or renal replacement therapy were excluded from the study. In RECOVERY, there were no such exclusion criteria for those requiring additional forms of organ support. In order to explain the observed outcome comparing the results (see below) the MAH was requested to perform additional analysis for the RECOVERY study excluding the patients requiring additional forms of organ support, such as ECMO, inotropes and vasopressors, or renal replacement.

The number of patients on ECMO were extremely low i.e. 17 patients, it is remarkable that only 1 patient was seronegative while 9 patients were seropositive (and 7 with unknown serostatus), thus no meaningful data can be provided in this patient group. The MAH provided arguments that given the mode of action no interaction with ECMO would be expected, this argumentation can be followed. However, the concern was that later in the course of disease pathophysiology reflects the host immune response to the virus than damage due to the virus itself, as seropositive patients don't seem to benefit from treatment. However, it is acknowledged that some patients might still be not able to show adequate immune response. Given the favourable safety profile of ronapreve it is acceptable not to exclude these patients from treatment.

The baseline characteristics are compared in the overall population; there are some imbalances in the serostatus, which might be linked to the imbalance in days since symptom onset. Since the main efficacy population is the seronegative population, this difference is not meaningful.

With regard to oxygen support, "simple oxygen" might comparable with supplemental oxygen not requiring high flow. Thus, the populations in the two studies might be similar in this respect. The Applicant can confirm that the simple oxygen respiratory support in RECOVERY is equivalent to the low-flow supplemental oxygen respiratory support group (Cohort 1) in COV-2066. A side-by-side summary of all-cause mortality at Day 28 (RECOVERY) and Day 29 (COV-2066) in seronegative patients on simple oxygen/low-flow supplemental oxygen at randomization is provided for RECOVERY and COV-2066.

Between the two studies, there is a slight imbalance with regard to corticosteroids at baseline in the overall population. However, this does not necessarily reflect the severity of disease; it might just reflect medical practice.

The RECOVERY results are discussed in detail above. In summary a significant reduction in 28-day mortality was observed in seronegative participants receiving casirivimab+imdevimab compared to those receiving usual care alone (24% vs. 30%; RR: 0.80; 95% CI: 0.70-0.91; p=0.001). Among all participants randomized (i.e., those with negative, positive, or unknown serostatus at baseline) the estimated effect of casirivimab+imdevimab on 28-day mortality was small and not significant (20% vs. 21%; RR: 0.94; 95% CI: 0.86-1.03; p=0.17). The respective second primary endpoint 28-day mortality in all randomised participants was not met.

Participants that were seropositive at baseline had no added benefit from treatment with casirivimab+imedvimab compared to usual care alone (16% vs. 15%; RR: 1.09; 95% CI: 0.95-1.26). This estimated effect is substantially different from the effect in seronegatives (heterogeneity p-value, p=0.001). The results from COV-2066 (combined doses) in participants receiving no supplemental oxygen or low-flow supplemental oxygen were directionally consistent but not significant.

With regard to additional key efficacy outcomes and secondary outcomes, the results from COV-2066 were in general directionally consistent.

Results were provided by baseline antibody status. In contrast to RECOVERY, less favourable outcomes under treatment for seropositive patients at baseline were not observed in study COV-2066.

An observed difference in the outcome between the two studies is striking e.g., the mortality in RECOVERY is consistent higher in all groups / populations. A similar observation was made for key efficacy outcomes and secondary endpoints. The MAH provided comprehensive explanation for

observed difference in the outcome between the RECOVERY and Study 2066. The differences are partly due to the design of the studies e.g., eligibility criteria and to the evolving epidemiological situation. The argumentation was accepted. Notable differences in eligibility criteria between the two studies that may have contributed to the overall disease severity of the patient populations and to the differences in mortality rates and effect sizes include the following: Respiratory support, additional organ support, time from symptom onset to randomization, time from hospitalization to randomization.

The presentation of results from RECOVERY and COV-2066 is inconsistent and uses different scales (RR vs RRR). The MAH was asked to provide results on a comparable scale (e.g., RR) in the overall population and in subgroups of serostatus and discuss between-study-heterogeneity in a meta-analytic approach. The applicant provided results from both studies (RECOVERY and COV-2066) on the same scale (RR). Data from study 2066 are now based on the full analysis set (FAS), instead of the mFAS as previously reported. This is endorsed. Study 2066 results now also include other cohorts, which is in principle supported. It does not seem reasonable to exclude subgroups from one study, but not from the other. Recruitment in the cohorts 2 and 3 (high flow oxygen, mechanical ventilation) in study COV-2066 was put on hold following a DMC recommendation. Respective uncertainty should be seen in conjunction with results from RECOVERY and was accepted.

In conclusion, the MAH provided comprehensive explanation for observed difference in the outcome between the RECOVERY and Study 2066. The differences are partly due to the design of the studies e.g., eligibility criteria and also to the evolving epidemiological situation. The argumentation is accepted.

### 2.4.4. Conclusions on the clinical efficacy

RECOVERY is an ongoing investigator-initiated complex randomised controlled, open-label platform trial with a factorial design in which several treatments are compared against control (not receiving the treatment) in patients hospitalized with COVID-19 to investigate their effect on 28-day mortality.

The primary analysis of the REGN-COV-2 part of this open-label study was initially planned to be conducted in all randomized subjects but was restricted to seronegatives in a very late amendment. 28-day mortality was significantly lower in seronegative patients randomised to REGN-COV-2 as compared to control. There was no statistically significant difference in the overall population, and a slightly higher mortality in seropositive participants (16% vs 15%) was observed. A large portion of patients had unclear serostatus (14%). Considering the results, the CHMP proposed an indication limited to patients on supplemental oxygen with a negative SARS-CoV-2 antibody result. This is accepted by the MAH. The adaptive phase 1/2/3 study COV-2066 was prematurely terminated and only after the decision to terminate the study, the protocol specified that the exploratory phase 2 cohort 1A and the confirmatory phase 3 cohort 1 would be pooled. Although the primary virological endpoints were met, the primary clinical endpoint was not met. However, point estimates in the seronegative subgroup are directionally consistent with the results observed in RECOVERY, although of different magnitude.

No integrated analysis of the efficacy data of the two studies is provided, the MAH provided a comparative analysis. A difference in the outcome between the two studies is observed e.g., the mortality in RECOVERY is consistently higher in all groups / populations and the effect estimates are of a somewhat different magnitude. A similar observation was made for key efficacy outcomes and secondary endpoints. The observed differences in the outcome between the RECOVERY and Study 2066 are partly due to the design of the studies e.g., eligibility criteria and also to the evolving epidemiological situation.

## 2.5. Clinical safety

## Introduction

**Table 1 Summary of Studies Contributing to Safety Evaluation**

| Study Number | Study Design | Population | No. of Participants Evaluable for Safety | Dose, Route, and Regimen | Study Duration |
|---|---|---|---|---|---|
| RECOVERY (Phase 3) | Factorial, individually randomized, controlled, open-label, platform trial | Hospitalized children ≥12 years of age and adults with clinically suspected or laboratory-confirmed SARS-CoV-2 infection | Casirivimab+imdevimab plus usual care:<br>4839 participants<br>-Seronegative at baseline: 1633 participants<br>-Seropositive at baseline: 2636 participants<br>-Unknown serostatus at baseline: 570 participants<br>Usual Care:<br>4946 participants<br>-Seronegative at baseline: 1520 participants<br>-Seropositive at baseline: 2636 participants<br>-Unknown serostatus at baseline: 790 participants | Casirivimab+imdevimab plus usual care:<br>Single dose casirivimab+imdevimab 8000 mg (casirivimab 4000 mg and imdevimab 4000 mg) IV infused over 60 minutes<br>Usual Care:<br>Usual standard of care | 18 September 2020 to 22 May 2021[a] |
| COV-2066 (Phase 1/2/3) | Adaptive, randomized, double-blinded, placebo-controlled master study | Adult participants ≥18 years of age, symptomatic for COVID-19 and hospitalized for ≤72 hours with varying degrees of oxygen support at randomization | Casirivimab+imdevimab 2400 mg IV: 757 participants<br>Casirivimab+imdevimab 8000 mg IV: 750 participants<br>Placebo: 745 participants | Casirivimab+imdevimab 2400 mg IV<br>Casirivimab+imdevimab 8000 mg IV<br>Placebo | 10 June 2020 to 9 April 2021[b] (Database lock: 8 June 2021) |

COVID = IV = intravenous, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] This duration reflects the casirivimab+imdevimab evaluation of the 28-day primary endpoint.

[b] This duration reflects the enrollment period for the efficacy evaluation. The study is continuing for the long COVID evaluation.

**RECOVERY Trial**

Patients could receive between 0 and 4 treatments on top of usual standard of care

- azithromycin versus no additional treatment (Part A; 7 April 2020 – 27 November 2020)
- colchicine versus no additional treatment (Part A; 19 November 2020 – 5 March 2021)
- dimethyl fumarate no additional treatment (Part A; 15 February 2021 – ongoing)
- aspirin versus no additional treatment (Part C; 1 November 2020 – 21 March 2021)
- baricitinib versus no additional treatment (Part D; 26 January 2021 – ongoing)

All patients received study medication on top of standard of care. More than > 90 % of the patients received corticosteroids at baseline.

RECOVERY balanced safety data collection with practical considerations to ensure that only key safety outcomes were captured, including the following:

- Targeted safety events in all participants randomized to casirivimab+imdevimab consisting of Suspected serious adverse reactions (SSARs), Suspected unexpected serious adverse reactions (SUSARs), and all deaths and underlying cause of death (Protocol Version 9.1 Section 4.1, Appendix 2). Per the protocol, only events believed with a reasonable possibility to be due to the study treatment were considered as SSARs. Since there were no expected events for casirivimab+imdevimab, all SSARs were considered SUSARs. To streamline data collection and since a matching placebo was not administered, similar events were not collected for the usual care group, making comparative assessment of these events to an appropriate control group, not possible.
- Additional relevant safety data for all participants randomized to either casirivimab+imdevimab or usual care included: all-cause mortality; cause-specific mortality; major bleeding events

(overall and by type, introduced in Protocol Version 10.1); major cardiac arrhythmias (including type of arrhythmia) and non-coronavirus infection (added with Protocol Version 14.0). These data were collected as binary and, therefore, did not include traditional safety collection parameters such as mapping of verbatim terms, duration of events, or severity grade of events or outcomes.

- Early safety data was collected within 72 hours for a subset of participants (ESAF). The focus of data collection was on those events that, based on a single case, were highly likely to be related to the study medication, such as anaphylaxis, Stevens Johnson Syndrome, or bone marrow failure, or events for which there was no other plausible explanation. In addition, specific assessments included binary data collection of: (i) sudden worsening in respiratory status; (ii) severe allergic reaction; (iii) temperature > 39°C or >2°C rise since randomization; (iv) sudden hypotension; (v) clinical haemolysis; (vi) thrombotic event (type of event); (vii) was infusion stopped early; (viii) did participant have a reaction during the infusion and how was the reaction managed. These data were collected both for the casirivimab+imdevimab group and the usual care group. These data did not include traditional safety collection parameters such as mapping of verbatim terms, duration of events or events severity grades or outcome.

Follow-up information was collected on all study participants regardless of whether they completed the scheduled course of allocated study treatment for a period of up to 10 years. The end of the study is expected to be the date of the final data extraction from NHS Digital.

**COV-2066**

Participants were randomized to receive a single IV dose of either 2400 mg (1200 mg of casirivimab plus 1200 mg imdevimab), 8000 mg (4000 mg of casirivimab plus 4000 mg imdevimab) or placebo. All participants received background standard of care treatment for COVID-19 per local guidelines.

The analysis of safety data was performed for Cohort 1 in combined Phases 1, 2 and 3, and Cohorts 1A, 2 and 3 in Phase 2, separately in the full analysis set (FAS).

The study population of hospitalized patients with COVID-19 was expected to have a complicated disease presentation at baseline that could quickly and unexpectedly deteriorate. As such, their TEAE profile was expected to be complex and dynamic. Mainly due to their underlying COVID-19 disease, which affects multiple organ systems and exacerbates concurrent clinical conditions considered risk factors for severe COVID-19. Therefore, a targeted safety data collection was performed, collecting relevant TEAEs in order to reduce background noise and effectively evaluate the safety and tolerability of casirivimab+imdevimab. This included key safety concerns expected for mAbs against exogenous targets and unexpected severe or serious TEAEs. The targeted subset of TEAEs included the following:

- All phases: treatment-emergent AESIs defined as:
  - Grade $\geq$ 2 hypersensitivity through day 29
  - Grade $\varepsilon$ 2 IRRs through day 4
- All phases: treatment-emergent SAEs
- Phase 1 (Cohort 1): Grade $\varepsilon$ 3 TEAEs

The safety analysis was based on the reported SAEs and AESIs and other safety information (clinical laboratory evaluations and vital signs).

## Population analysed

**RECOVERY**

Safety analyses were performed in 2 populations:

- The all randomized patients population, consisting of all randomized patients allocated to either the usual care plus casirivimab+imdevimab group (n=4839) or the usual care group (n=4946) (Table 1).
- Early Safety Population (ESAF), a subset of the All randomized patients population for whom additional safety data were collected within 72 hours after randomization (n=1792 in the casirivimab+imdevimab group and n=1715 in the usual care group) (Table 1). As pre-defined in the protocol, the Data Monitoring Committee (DMC) reviewed early safety data and recommended that this additional data collection was stopped on 17 Feb 2021 (Sandercock, 2021).

**Table 1: Summary of Analysis Population (All Randomized Patients)**

| | Casirivimab + Imdevimab (N=4839) | Usual Care (N=4946) | Total (N=9785) |
|---|---|---|---|
| All Randomized Patients | 4839 | 4946 | 9785 |
| Patients randomized and treatment received | 4298 | 4946 | 9244 |
| Patients randomized and did not receive treatment | 495 | 0 [4] | 495 |
| Patients randomized and unconfirmed if treatment received [1] | 46 | 0 [4] | 46 |
| Early Safety Population (ESAF) [2] | 1792 | 1715 | 3507 |
| Patient received treatment [3] | 1669 (93.1%) | 1715 (100%) | 3384 (96.5%) |

Of all the randomized patients population, 495 patients who were randomized to the casirivimab+imdevimab treatment arm did not receive the assigned treatment and for 46 patients it is unknown whether they were treated due to missing data (Table 1). All analyses are presented for the randomized population, regardless of whether treatment was received.

**COV-2066**

The Safety population (SAF) included all randomized participants who received at least one dose of the study drug. Analysis of the Safety population was done according to the treatment received (as treated).

## *Patient exposure*

The safety evaluation for hospitalized patients is based on 5771 participants in the randomized clinical studies (4298 in RECOVERY (of 4839 participants randomized to casirivimab+imdevimab), 4298 (90%) received the dose and 1473 in COV-2066) who received a single IV dose of casirivimab+imdevimab. Of these participants:

- 5031 (4298 in RECOVERY and 733 in COV-2066) received 8000 mg
- 740 (in COV-2066) received 2400 mg

Overall, the majority of participants in RECOVERY (81.3%; [3495/4298]) had been followed up for at least 4 weeks. Data were only available for up to 4 weeks of follow-up for RECOVERY, while the majority of participants in COV-2066 (73.3% [1080/1473]) had been followed up for at least 8 weeks. A confirmed total of 46 participants (46/6312 [0.7%]) in COV-2066 had been followed up for at least 16 weeks.

## *Adverse events*

**RECOVERY**

Collection of safety parameters in RECOVERY was focused on Suspected serious adverse reactions (SSARs) (which are those events that, based on a single case likely with a reasonable probability to be

related to the study medication) and infusion-related and hypersensitivity reactions, which were collected only in the casirivimab+imdevimab group and not the usual care group since no placebo comparator IV infusion was given.

**Table 3: Suspected Serious Adverse Reactions in the Casirivimab+Imdevimab Group (Randomized and Treated with Casirivimab+Imdevimab)**

| Event | Number of patients (N=4839) |
|---|---|
| Allergic reaction | 3 (<0.1%) |
| Seizure | 2 (<0.1%) |
| Acute desaturation | 1 (<0.1%) |
| Transient loss of consciousness | 1 (<0.1%) |
| Total | 7 (<0.1%) |

Note: Verbatim terms (as recorded on the electronic case report form) are used to describe SSARs.
Source: Appendix 2, Post-text Table 14.3.2.6

Six of these patients experienced SSARs that resolved:

- 3 allergic reaction events (1 IRR and 2 events of acute allergic reactions; occurring within 72 hours, these three events were also considered IRRs and 1 acute allergic reaction was considered a severe allergic reaction
- 2 events of seizure
- 1 event of transient loss of consciousness (unconsciousness).

One patient had experienced a SSAR with an outcome 'unknown':

- 1 acute desaturation (worsening hypoxia)

Three participants experienced events (reported as allergic reaction) that were considered infusion-related reactions during the infusion (see below).

**COV-2066**

**Pooled Analysis (All Phases All Cohorts)**

A higher proportion of participants in the placebo group experienced treatment-emergent SAEs and TEAEs leading to death, compared to the casirivimab+imdevimab groups (combined and individual doses) (Table 7). The incidence of treatment-emergent AESIs (Grade > 2 IRRs and Grade > 2 hypersensitivity reactions) were low in all treatment groups (< 2% in any treatment or placebo group) (Table 7). TEAEs that led to withdrawal from the study and infusion interruption were low (< 0.5% in any treatment or placebo group); TEAEs that led to study infusion discontinuation were also low (< 0.7%) (Table 7).

**Table 7 Overview of Treatment-Emergent Adverse Events (Pooled Phase 1, 2, 3 Cohort 1; Phase 2 Cohort 1A; Phase 2 Cohort 2; Phase 2 Cohort 3, FAS)**

| | Placebo (N=730) | Casirivimab+ imdevimab 2400 mg IV (N=740) | Casirivimab+ imdevimab 8000 mg IV (N=733) | Casirivimab+ imdevimab Combined (N=1473) |
|---|---|---|---|---|
| Total number of TEAE[a] | 383 | 306 | 368 | 674 |
| Total number of Grade 3 or 4 TEAE | 243 | 160 | 208 | 368 |
| Total number of TE SAE | 364 | 265 | 299 | 564 |
| Total number of TE AESI | 11 | 20 | 32 | 52 |
| Total number of TE serious AESI | 5 | 9 | 11 | 20 |
| Participants with any TEAE | 209 (28.6%) | 191 (25.8%) | 201 (27.4%) | 392 (26.6%) |
| Participants with any Grade 3 or 4 TEAE | 139 (19.0%) | 112 (15.1%) | 127 (17.3%) | 239 (16.2%) |
| Participants with any TE SAE | 203 (27.8%) | 177 (23.9%) | 181 (24.7%) | 358 (24.3%) |
| Participants with any TE AESI | 8 (1.1%) | 16 (2.2%) | 21 (2.9%) | 37 (2.5%) |
| Participants with any TE serious AESI | 3 (0.4%) | 7 (0.9%) | 9 (1.2%) | 16 (1.1%) |
| Participants with any TE AESI of infusion-related reactions (Grade ≥2) through Day 4[b] | 6 (0.8%) | 11 (1.5%) | 15 (2.0%) | 26 (1.8%) |
| Participants with any TE AESI of hypersensitivity reactions (Grade ≥2) through Day 4 | 0 | 2 (0.3%) | 6 (0.8%) | 8 (0.5%) |
| Participants with any TE AESI of hypersensitivity reactions (Grade ≥2) through Day 29 | 2 (0.3%) | 5 (0.7%) | 7 (1.0%) | 12 (0.8%) |
| Participants with any SAE TE AESI of infusion-related reactions (Grade ≥2) through Day 4[b] | 1 (0.1%) | 3 (0.4%) | 7 (1.0%) | 10 (0.7%) |

**Table 7 Overview of Treatment-Emergent Adverse Events (Pooled Phase 1, 2, 3 Cohort 1; Phase 2 Cohort 2; Phase 2 Cohort 3, FAS) (cont.)**

| | Placebo (N=730) | Casirivimab+ imdevimab 2400 mg IV (N=740) | Casirivimab+ imdevimab 8000 mg IV (N=733) | Casirivimab+ imdevimab Combined (N=1473) |
|---|---|---|---|---|
| Participants with any SAE TE AESI of hypersensitivity reactions (Grade ≥2) through Day 4 | 0 | 2 (0.3%) | 2 (0.3%) | 4 (0.3%) |
| Participants with any SAE TE AESI of hypersensitivity reactions (Grade ≥2) through Day 29 | 2 (0.3%) | 4 (0.5%) | 2 (0.3%) | 6 (0.4%) |
| Participants with any TEAE leading to death | 107 (14.7%) | 90 (12.2%) | 89 (12.1%) | 179 (12.2%) |
| Participants with any TEAE leading to withdrawal from the study | 0 | 2 (0.3%) | 1 (0.1%) | 3 (0.2%) |
| Participants with any TEAE leading to study infusion interruption[c] | 1 (0.1%) | 1 (0.1%) | 3 (0.4%) | 4 (0.3%) |
| Participants with any TEAE leading to study infusion discontinuation[d] | 0 | 4 (0.5%) | 5 (0.7%) | 9 (0.6%) |

TEAE = Treatment- Emergent Adverse Event. AESI = Adverse Event of Special Interest. SAE = Serious Adverse Event. MedDRA (Version 24.0) coding dictionary applied.

[a] TEAEs collected include TE SAEs, AESIs and Grade 3/4 TEAEs, as well as ad-hoc/voluntarily reported TEAEs by some sites.

[b] TEAEs deemed treatment-related as per investigator assessment.

[c] Infusion interruption: the administration of the infusion was interrupted before being completed, but subsequently was re-started and the full planned dose was administered.

[d] Infusion discontinuation: the administration of the infusion was stopped before being completed, and the full planned dose was not administered.

Notes:

Safety data collection for Study COV-2066 was as follows: All SAEs (all grades), AESIs (Grade 2 or greater IRR through day 4, Grade 2 or greater hypersensitivity reactions through day 29). In addition to this, Grade 3 and 4 TEAEs were collected for Phase 1 (Cohort 1) only.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition.

The Full Analysis Set is identical to the Safety Analysis Set.

Source: t_32_1f_aesum

The frequency of treatment-emergent AEs was 28.6% (209/730 participants) in the placebo group, 25.8% (191/740 participants) in the casirivimab+imdevimab 2400 mg dose group, 27.4% [201/733 participants) in the casirivimab+imdevimab 8000 mg dose group and 26.6% (392/1473 participants) in the combined doses (Table 7).

The SOCs that contained the most frequently reported events which were higher for any casirivimab+imdevimab dose compared to placebo were:

- General disorders and administration site conditions: 3.0% (22/740 participants) in the 2400 mg group, 3.3% (24/733 participants) in the 8000 mg group, and 2.1% (15/730 participants) in the placebo group
- Vascular disorders: 1.5% (11/740 participants) in the 2400 mg group, 2.2% (16/733 participants) in the 8000 mg group, and 1.4% (10/730 participants) in the placebo group

- Gastrointestinal disorders: 1.1% (8/740 participants) in the 2400 mg group, 2.0% (15/733 participants) in the 8000 mg group, and 1.8% (13/730 participants) in the placebo group

The most frequently reported PTs (>2%) where events were higher for any casirivimab+imdevimab dose compared to placebo were:

- Acute respiratory failure: 3.5% (26/740 participants) in the 2400 mg group, 2.3%(17/733 participants) in the 8000 mg group, and 3.3% (24/730 participants) in the placebo group
- COVID-19: 2.4% (18/740 participants) in the 2400 mg group, 4.5% (33/733 participants) in the 8000 mg group, and 4.1% (30/730 participants) in the placebo group

**Adverse Events Related to Treatment**

The number of participants with at least one related TEAE was higher in the casirivimab+imdevimab groups (2.3% in the 2400 mg dose group, 3.1% in the 8000 mg dose group) compared to placebo (1.5%) (Table 8).

**Table 8 Summary of Treatment-Emergent Adverse Events Related to Casirivimab+Imdevimab by System Organ Class (Pooled Phase 1, 2, 3 Cohort 1, Phase 2 Cohort 1A, Phase 2 Cohort 2 and Phase 2 Cohort 3, Full Analysis Set)**

| Primary SOC | Placebo (n=730) | Casirivimab+ imdevimab 2400 mg (n=740) | Casirivimab+ imdevimab 8000 mg (n=733) | Casirivimab+ imdevimab combined (n=1473) |
|---|---|---|---|---|
| Number of related TEAEs | 12 | 20 | 35 | 55 |
| Number of participants with at least one related TEAE | 11 (1.5%) | 17 (2.3%) | 23 (3.1%) | 40 (2.7%) |
| Respiratory, thoracic and mediastinal disorders | 2 (0.3%) | 6 (0.8%) | 7 (1.0%) | 13 (0.9%) |
| General disorders and administration site conditions | 1 (0.1%) | 4 (0.5%) | 6 (0.8%) | 10 (0.7%) |
| Cardiac disorders | 1 (0.1%) | 1 (0.1%) | 3 (0.4%) | 4 (0.3%) |
| Immune system disorders | 0 | 0 | 2 (0.3%) | 2 (0.1%) |
| Nervous system disorders | 0 | 2 (0.3%) | 2 (0.3%) | 4 (0.3%) |
| Psychiatric disorders | 0 | 1 (0.1%) | 3 (0.4%) | 4 (0.3%) |
| Vascular disorders | 0 | 1 (0.1%) | 2 (0.3%) | 3 (0.2%) |

SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Source: t_32_4a_aesocpt, t_32_4b_aesocpt_p2c2, t_32_4c_aesocpt_p2c3, t_32_4d_aesocpt.

Related TEAEs were reported at a higher frequency in one or both of the casirivimab+imdevimab dose groups compared to the placebo group in the following SOCs (> 4 participants) (Table 8):

- Respiratory, thoracic and mediastinal disorders: 0.8% (6/740 participants) in the 2400 mg group; 1.0% (7/733 participants) in the 8000 mg dose group; and 0.3% (2/730 participants) in the placebo group
- General disorders and administration site conditions: 0.5% (4/740 participants) in the 2400 mg group; 0.8% (6/733 participants) in the 8000 mg dose group; 0.1% (1/730 participants) in the placebo group
- Cardiac Disorders: 0.1% (1/740 participants) in the 2400 mg group; 0.7% (5/733 participants) in the 8000 mg dose group; 0.3% (2/730 participants) in the placebo group

The most frequently reported PTs (> 2 participants) where events were higher for any casirivimab+imdevimab dose compared to placebo were:

- Dyspnoea (0 in the casirivimab+imdevimab 2400 mg group; 0.5% [4/733 participants] in the casirivimab+imdevimab 8000 mg group; 0 in the placebo group)
- Hypoxia (0.5% [4/733 participants] in the casirivimab+imdevimab 2400 mg group; 0.4% [3/733 participants] in the casirivimab+imdevimab 8000 mg group; 0 in the placebo group)
- Chills (0.3% [2/740 participants] in the casirivimab+imdevimab 2400 mg group, 0.4% [3/733 participants] in the casirivimab+imdevimab 8000 mg group; 0.1% [1/730 participants] in the placebo group)
- Anxiety (0 in the in the casirivimab+imdevimab 2400 mg group; 0.3% [2/733 participants] in the casirivimab+imdevimab 8000 mg group; 0 in the placebo group)
- Pyrexia (0 in the in the casirivimab+imdevimab 2400 mg group; 0.4% [3/733 participants] in the casirivimab+imdevimab 8000 mg group; 0 in the placebo group)
- Flushing: 0 in the in the casirivimab+imdevimab 2400 mg group; 0.3% [2/733 participants] in the casirivimab+imdevimab 8000 mg group; 0 in the placebo group)

**Adverse Events by Intensity**

A total of 17% (378/2203 participants) of all participants had at least one Grade 3 or 4 TEAE (Table 7). A higher percentage of participants in the placebo group experienced Grade 3 or 4 TEAEs (19.0% [139/740 participants]), compared to the casirivimab+imdevimab 2400 mg dose group (15.1% [112/740 participants]), and the casirivimab+imdevimab 8000 mg dose group (17.3% [127/733 participants]) (Table 7).

Grade 3 or 4 TEAEs were reported at a numerically higher frequency in either casirivimab+imdevimab dose group compared to placebo in the following SOCs:

- Vascular disorders: 0.81% (6/740 participants) in the 2400 mg dose group; 1.5% (11/733 participants) in the 8000 mg dose group; 1.1% (8/730 participants) in the placebo group
- Metabolism and nutrition disorders: 0.7% (5/740 participants) in the 2400 mg dose group; 1.1% (8/733 participants) in the 8000 mg dose group; 0.8% (6/730 participants) in the placebo group
- Injury, poisoning and procedural complications: 0.4% (3/740 participants) in the 2400 mg dose group; 1.1% (8/733 participants) in the 8000 mg dose group; 0.8% (6/730 participants) in the placebo group

The most frequently reported PTs (> 2 participants) where events were higher for any casirivimab+imdevimab dose compared to placebo were:

- Hypotension: 0.3% (2/740 participants) in the 2400 mg dose group; 0.7% (5/733 participants) in the 8000 mg dose group; 0.5% (4/730 participants) in the placebo group
- Deep vein thrombosis: 0.1% (1/740 participants) in the 2400 mg dose group; 0.3% (2/733 participants) in the 8000 mg dose group; 0.1% (1/730 participants) in the placebo group
- Acidosis: 0 participants in the 2400 mg dose group; 0.3% (2/733 participants) in the 8000 mg dose group; 0 participants in the placebo group

## *Serious adverse event/deaths/other significant events*

**RECOVERY**

Mortality at 28 days was the primary efficacy endpoint of the RECOVERY study.

**Adverse Events of Special Interest and Selected Adverse Events**

**Early Safety Outcomes (72 hours after randomization) –**

**RECOVERY**

Early safety outcome data were recorded within 72 hours (based on the ESAF) after randomization for the first 1792 casirivimab+imdevimab participants and the first 1715 usual care participants.

**Table 11 Early Safety Outcomes in Seronegative and all Participants by Treatment Group (ESAF)**

| | Seronegative Participants | | Seropositive Participants | | Unknown Participants | | All Randomized Participants | |
|---|---|---|---|---|---|---|---|---|
| | Casirivimab + Imdevimab (N=1633) | Usual Care (N=1520) | Casirivimab + Imdevimab (N=2636) | Usual Care (N=2636) | Casirivimab + Imdevimab (N=570) | Usual Care (N=790) | Casirivimab + Imdevimab (N=4839) | Usual Care (N=4946) |
| Number with form completed | 645 | 528 | 905 | 894 | 242 | 293 | 1792 | 1715 |
| **Sudden worsening in respiratory status** | | | | | | | | |
| No additional support required | 15 (2.3%) | 8 (1.5%) | 9 (1.0%) | 15 (1.7%) | 1 (0.4%) | 6 (2.0%) | 25 (1.4%) | 29 (1.7%) |
| New or increased use of $O_2$ | 103 (16.0%) | 79 (15.0%) | 90 (9.9%) | 76 (8.5%) | 52 (21.5%) | 67 (22.9%) | 245 (13.7%) | 222 (12.9%) |
| New non-invasive respiratory support | 51 (7.9%) | 58 (11.0%) | 43 (4.8%) | 54 (6.0%) | 17 (7.0%) | 33 (11.3%) | 111 (6.2%) | 145 (8.5%) |
| New invasive mechanical ventilation | 25 (3.9%) | 22 (4.2%) | 19 (2.1%) | 21 (2.3%) | 7 (2.9%) | 8 (2.7%) | 51 (2.8%) | 51 (3.0%) |
| Other | 4 (0.6%) | 2 (0.4%) | 0 | 3 (0.3%) | 3 (1.2%) | 2 (0.7%) | 7 (0.4%) | 7 (0.4%) |
| Total: Any sudden worsening in respiratory status | 167 (25.9%) | 140 (26.5%) | 141 (15.6%) | 143 (16.0%) | 61 (25.2%) | 89 (30.4%) | 369 (20.6%) | 372 (21.7%) |
| Persistent worsening | 100 (15.5%) | 92 (17.4%) | 81 (9.0%) | 76 (8.5%) | 46 (19.0%) | 60 (20.5%) | 227 (12.7%) | 228 (13.3%) |
| **Severe allergic reaction** | | | | | | | | |
| Adrenaline required | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Any severe allergic reaction | 1 (0.2%) | 0 | 2 (0.2%) | 1 (0.1%) | 1 (0.4%) | 0 | 4 (0.2%) | 1 (<0.1%) |
| Temperature >39°C or ≥2°C rise above baseline | 48 (7.4%) | 23 (4.4%) | 20 (2.2%) | 20 (2.2%) | 11 (4.5%) | 9 (3.1%) | 79 (4.4%) | 52 (3.0%) |

**Table 11 Early Safety Outcomes in Seronegative and all Participants by Treatment Group (ESAF) (cont.)**

| | Seronegative Participants | | Seropositive Participants | | Unknown Participants | | All Randomized Participants | |
|---|---|---|---|---|---|---|---|---|
| | Casirivimab + Imdevimab (N=1633) | Usual Care (N=1520) | Casirivimab + Imdevimab (N=2636) | Usual Care (N=2636) | Casirivimab + Imdevimab (N=570) | Usual Care (N=790) | Casirivimab + Imdevimab (N=4839) | Usual Care (N=4946) |
| **Sudden hypotension** | | | | | | | | |
| No support required | 20 (3.1%) | 9 (1.7%) | 18 (2.0%) | 8 (0.9%) | 3 (1.2%) | 4 (1.4%) | 41 (2.3%) | 21 (1.2%) |
| New or additional intravenous fluid | 14 (2.2%) | 3 (0.6%) | 0 | 3 (0.3%) | 0 | 2 (0.7%) | 14 (0.8%) | 8 (0.5%) |
| New or additional inotropic/vasopressor support | 8 (1.2%) | 6 (1.1%) | 4 (0.4%) | 7 (0.8%) | 1 (0.4%) | 1 (0.3%) | 13 (0.7%) | 14 (0.8%) |
| Total: Any sudden hypotension | 39 (6.0%) | 17 (3.2%) | 23 (2.5%) | 16 (1.8%) | 4 (1.7%) | 6 (2.0%) | 66 (3.7%) | 39 (2.3%) |
| Persistent change | 9 (1.4%) | 4 (0.8%) | 3 (0.3%) | 7 (0.8%) | 1 (0.4%) | 1 (0.3%) | 13 (0.7%) | 12 (0.7%) |
| **Clinical hemolysis** | | | | | | | | |
| Haemoglobin <100gL | 4 (0.6%) | 2 (0.4%) | 3 (0.3%) | 7 (0.8%) | 0 | 1 (0.3%) | 7 (0.4%) | 10 (0.6%) |
| Bilirubin >50 µmol/L | 0 | 0 | 2 (0.2%) | 1 (0.1%) | 0 | 0 | 2 (0.1%) | 1 (<0.1%) |
| Total: Clinical hemolysis | 14 (2.2%) | 9 (1.7%) | 10 (1.1%) | 21 (2.3%) | 2 (0.8%) | 1 (0.3%) | 26 (1.5%) | 31 (1.8%) |

**Table 11 Early Safety Outcomes in Seronegative and all Participants by Treatment Group (ESAF) (cont.)**

| | Seronegative Participants | | Seropositive Participants | | Unknown Participants | | All Randomized Participants | |
|---|---|---|---|---|---|---|---|---|
| | Casirivimab + Imdevimab (N=1633) | Usual Care (N=1520) | Casirivimab + Imdevimab (N=2636) | Usual Care (N=2636) | Casirivimab + Imdevimab (N=570) | Usual Care (N=790) | Casirivimab + Imdevimab (N=4839) | Usual Care (N=4946) |
| Thrombotic event | | | | | | | | |
| Acute pulmonary embolism | 3 (0.5%) | 4 (0.8%) | 13 (1.4%) | 8 (0.9%) | 2 (0.8%) | 3 (1.0%) | 18 (1.0%) | 15 (0.9%) |
| Deep-vein thrombosis | 1 (0.2%) | 1 (0.2%) | 0 | 2 (0.2%) | 0 | 1 (0.3%) | 1 (<0.1%) | 4 (0.2%) |
| Ischemic stroke | 3 (0.5%) | 0 | 0 | 0 | 1 (0.4%) | 0 | 4 (0.2%) | 0 |
| Myocardial infarction | 4 (0.6%) | 1 (0.2%) | 2 (0.2%) | 1 (0.1%) | 0 | 0 | 6 (0.3%) | 2 (0.1%) |
| Systemic arterial embolism | 0 | 0 | 1 (0.1%) | 0 | 0 | 0 | 1 (<0.1%) | 0 |
| Other | 0 | 1 (0.2%) | 0 | 2 (0.2%) | 1 (0.4%) | 0 | 1 (<0.1%) | 3 (0.2%) |
| Total: Any thrombotic event | 10 (1.6%) | 7 (1.3%) | 17 (1.9%) | 13 (1.5%) | 4 (1.7%) | 4 (1.4%) | 31 (1.7%) | 24 (1.4%) |

Notes:
The first line is the number of participants in the Early Safety Population (ESAF; with a form completed for 72-hour data collection). Percentages are based on these participants.
Multiple selections within categories are possible; therefore, totals may not equal 100%.
Source: t-saf.

No clinically meaningful differences were observed between the casirivimab+imdevimab group and the usual care group among all randomized participants. There were a few imbalances in specific targeted safety outcomes. The early safety outcomes that occurred in a higher (>0.3% difference) proportion of participants in the casirivimab+imdevimab group compared to the usual care group were: new non-invasive use of O2 (6.2% vs. 8.5%), temperature > 39°C or > 2°C rise above temperature at randomization (fever) (4.4% vs. 3.0%), sudden hypotension (3.7% vs. 2.3%), and thrombotic events (1.7% vs. 1.4%), sudden worsening in respiratory status (21.7% vs. 20.6%) and clinical haemolysis (1.8% vs. 1.5%).

Five participants across both treatment groups (4/1792 participants in the ESAF randomized to casirivimab+imdevimab and 1/1715 participants in the ESAF randomized to usual care) experienced a severe allergic reaction.

IRRs were collected for the casirivimab+imdevimab group and not for the usual care group (as treatment did not include infusion).

**Table 12 Summary of Infusion Related Reaction to Casirivimab+Imdevimab (ESAF)**

| | Casirivimab + Imdevimab (N=1792) |
|---|---|
| Number with 72-hr safety form completed | 1792 |
| Received an infusion of Casirivimab + Imdevimab | |
| Yes | 1669 (93.1%) |
| No | 123 (6.9%) |
| Number of participants who stopped infusion early for any reason | 42 (2.3%) |
| Number of participants who had a reaction during the infusion | 20 (1.1%) |
| Reaction Managed by: | |
| No Intervention required | 5 (0.3%) |
| Infusion rate reduced but infusion completed | 1 (<0.1%) |
| Antihistamine given | 7 (0.4%) |
| Steroid given | 2 (0.1%) |
| Adrenaline given | 0 |
| Infusion stopped early | 10 (0.6%) |
| Any of the above | 20 (1.1%) |

Note: Percentages based on participants with a completed 72-hour safety form.
Early Safety Population (ESAF) includes a subset of all randomized participants to part B on whom additional safety data was collected 72 hours after randomization.
Source: t-inf.

Twenty (1.1%) participants had an IRR (Table 12). Of these 20 participants with an IRR, 7 (0.4%) were treated with an antihistamine and 2 (0.1%) were treated with a steroid. None of the participants who had an IRR required adrenaline treatment. Study drug infusion was discontinued early due to an IRR in 10 (0.6%) participants. Data regarding IRRs for participants randomized to the usual care group were not collected. Of the 20 reported IRRs, 3 events were also reported as severe allergic reactions.

**Select safety data for all randomized participants**

An online follow-up form was completed by site staff when participants were discharged, had died, or at 28 days after randomization, whichever occurred first to provide additional safety information. Selected safety data were collected and analysed for 4839 participants randomized to casirivimab+imdevimab and 4946 participants randomized to usual care. These data included the subset of participants from the ESAF. These data were collected as binary outcomes and did not have traditional safety collection parameters such as mapping of verbatim terms or toxicity grading.

**All-cause mortality and cause-specific mortality**

Consistent with treatment benefit, in the seronegative population all-cause 28-day mortality, as well as COVID-19 related mortality, was lower in the casirivimab+imdevimab group compared to the usual care group (24.2% vs. 29.7% and 22.7% vs. 28.4% respectively). This was not observed in the seropositive population.

In the overall population, all cause mortality as well as COVID-related mortality in the casirivimab+imdevimab group compared to the usual care group was 19.5% vs 20.8% and 18.5% vs 20.0%, respectively. The terms for the fatal events reported were consistent with advanced COVID-19 and its complications and worsening comorbid clinical conditions of hospitalised patients.

**Major cardiac arrhythmia**

The frequency of cardiac arrhythmia events was numerically higher in the usual care group compared to the casirivimab+imdevimab group in the overall population (4.4% vs. 3.9%, respectively) and seronegative population (4.5% vs. 3.3%, respectively).

**Thrombosis and major bleeding**

In the overall population, the frequency of any thrombotic event was comparable in the casirivimab+imdevimab and usual care groups (5.2% vs. 5.1% in the in casirivimab+imdevimab and usual care groups) and the frequency of any major bleeding was similar between the groups (1.5% vs. 1.8% casirivimab+imdevimab and usual car groups). In the seronegative population, the frequency of thrombosis (3.6% vs. 4.3%) and major bleeding events (1.3% vs. 1.4%) was similar between the casirivimab+imdevimab and usual care groups.

**COV-2066**

**Death**

A higher percentage of participants in the placebo group experienced TEAEs that led to death (14.7% [107/730]), compared to the casirivimab+imdevimab 2400 mg dose group (12.2% [90/740]), the casirivimab+imdevimab 8000 mg dose group (12.1% [89/733]), and the combined doses group (12.2% [179/1473]).

TEAEs leading to death were reported at a higher frequency in either casirivimab+imdevimab dose group compared to placebo in the following SOC:

- Infections and infestations: 2.8% (21/740 participants) in the 2400 mg dose group; 5.2% (38/733 participants) in the 8000 mg dose group; 4.5% (33/730 participants) in the placebo group

The most frequently reported event PTs (> 2 participants) leading to death and occurring at a higher rate in either casirivimab+imdevimab dose group compared to placebo were:

- Acute respiratory failure: 2.7% (20/740 participants) in the 2400 mg dose group; 1.8% (13/733 participants) in the 8000 mg dose group; 2.1% (15/730 participants) in the placebo group
- COVID-19: 1.5% (11/740 participants) in the 2400 mg dose group; 3.0% (22/733 participants) in the 8000 mg dose group; 2.1% (15/730 participants) in the placebo group
- Multiple organ dysfunction syndrome: 0.4% (3/740 participants) in the 2400 mg dose group; 1.1% (8/733 participants) in the 8000 mg dose group; 0.5% (4/730 participants) in the placebo group
- Cardiac arrest: 0.9% (7/740 participants) in the 2400 mg dose group; 0.5% (4/733 participants) in the 8000 mg dose group; 0.5% (4/730 participants) in the placebo group
- Septic shock: 0.4% (3/740 participants) in the 2400 mg dose group; 0.7% (5/733 participants) in the 8000 mg dose group; 0.5% (4/730 participants) in the placebo group
- Pulmonary embolism: 0.4% (3/740 participants) in the 2400 mg dose group; 0 participants in the 8000 mg dose group; 0.1% (1/730 participants) in the placebo group
- Acute myocardial infarction: 0 participants in the 2400 mg dose group; 0.3% (2/733 participants) in the 8000 mg dose group; 0 participants in the placebo group

In 2.1% (6/286) of participants that had at least 1 TEAE leading to death, the TEAEs leading to death were evaluated by the investigators to be treatment-related: Two participants each in the 2400 mg dose group (one in Cohort 1 [PT Acute respiratory failure] and one in Cohort 2 [PT: Hypoxia), 8000 mg dose group (both in Cohort 1; PTs: Hypoxia, and Respiratory failure), and placebo group (both in Cohort 1; PTs: Hypoxia, and Superinfection bacterial). Of note, none of these 6 events were considered by the Sponsor to be treatment-related.

Phase 2 enrolment of Cohort 2 and 3 was paused per iDMC recommendation due to an observed imbalance of deaths in the treatment groups compared to placebo. The Sponsor conducted a thorough

assessment of these deaths and it was determined not to be treatment related, but considered primarily due to worsening COVID-19 disease and participants' concurrent medical conditions.

**Cohort 2**

A greater percentage of participants in the casirivimab+imdevimab groups compared to the placebo group experienced at least 1 TEAE leading to death. The percentages of participants with at least 1 TEAE leading to death was 44.6% (25/56) in the casirivimab+imdevimab 2400 mg dose group, 35.2% (19/54) in the casirivimab+imdevimab 8000 mg dose group, and 25.5% (13/51) in the placebo group.

The majority of TEAEs that led to death were in the Infections and infestations and Respiratory, thoracic and mediastinal disorders SOC, which was consistent with the participant population having advanced COVID-19 disease and progression of COVID-19 infection, resulting in respiratory failure and a fatal outcome (Table 45). A higher percentage of participants experienced death in the casirivimab+imdevimab groups compared to the placebo group due to TEAE PTs including COVID-19, COVID-19 pneumonia, Acute respiratory failure, Acute respiratory distress syndrome, Cardiac arrest, and Multiple organ dysfunction syndrome.

All but 1 of the TEAEs that led to death were considered not related to study drug by the investigator, and were assessed to be caused by advanced and progressive COVID-19 disease, participants' underlying clinical comorbidities, or demographic characteristic such as older age. One participant in the casirivimab+imdevimab 2400 mg group had a TEAE of worsening hypoxia (PT: Hypoxia) leading to death >14 days after treatment, that was considered related to study treatment by the investigator but not by the Sponsor. This participant's status had recently been changed to DNI, and the participant was transferred to comfort care measures. The Sponsor considered the event as secondary to progression of underlying COVID-19.

**Table 45: Summary of Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term (Cohort 2; FAS)**

| | | Casirivimab+Imdevimab IV | | |
|---|---|---|---|---|
| Primary System Organ Class<br>Preferred Term | Placebo<br>(N=51) | 2400 mg<br>(N=56) | 8000 mg<br>(N=54) | Combined<br>(N=110) |
| Number of patients with at least one TEAE leading to death | 13 (25.5%) | 25 (44.6%) | 19 (35.2%) | 44 (40.0%) |
| Infections and infestations | 6 (11.8%) | 9 (16.1%) | 10 (18.5%) | 19 (17.3%) |
| COVID-19 | 2 (3.9%) | 6 (10.7%) | 7 (13.0%) | 13 (11.8%) |
| COVID-19 pneumonia | 3 (5.9%) | 2 (3.6%) | 3 (5.6%) | 5 (4.5%) |
| Septic shock | 1 (2.0%) | 1 (1.8%) | 0 | 1 (0.9%) |
| Respiratory, thoracic and mediastinal disorders | 5 (9.8%) | 13 (23.2%) | 4 (7.4%) | 17 (15.5%) |
| Acute respiratory failure | 0 | 7 (12.5%) | 3 (5.6%) | 10 (9.1%) |
| Respiratory failure | 4 (7.8%) | 3 (5.4%) | 1 (1.9%) | 4 (3.6%) |
| Acute respiratory distress syndrome | 0 | 1 (1.8%) | 0 | 1 (0.9%) |
| Hypoxia | 1 (2.0%) | 1 (1.8%) | 0 | 1 (0.9%) |
| Respiratory distress | 0 | 1 (1.8%) | 0 | 1 (0.9%) |
| Cardiac disorders | 1 (2.0%) | 2 (3.6%) | 3 (5.6%) | 5 (4.5%) |
| Cardiac arrest | 1 (2.0%) | 2 (3.6%) | 2 (3.7%) | 4 (3.6%) |
| Cardiac disorders | | | | |
| Bradycardia | 0 | 0 | 1 (1.9%) | 1 (0.9%) |
| General disorders and administration site conditions | 0 | 1 (1.8%) | 1 (1.9%) | 2 (1.8%) |
| Multiple organ dysfunction syndrome | 0 | 1 (1.8%) | 1 (1.9%) | 2 (1.8%) |
| Nervous system disorders | 0 | 0 | 1 (1.9%) | 1 (0.9%) |
| Cerebrovascular accident | 0 | 0 | 1 (1.9%) | 1 (0.9%) |
| Gastrointestinal disorders | 1 (2.0%) | 0 | 0 | 0 |
| Intestinal ischaemia | 1 (2.0%) | 0 | 0 | 0 |

Note: The Full Analysis Set (FAS) is identical to the Safety Analysis Set (SAF).
MedDRA (Version 24.0) coding dictionary applied.
A patient who reported 2 or more adverse events with different preferred terms within the same system organ class is counted only once in that system organ class.
A patient who reported 2 or more adverse events with the same preferred term is counted only once for that term.
Primary System Organ Classes (SOCs) are sorted according to decreasing order of frequency of the combined treatment group.
Within each SOC, Preferred Terms are sorted by decreasing frequency.
Source: PTT 14.3.3.3.1b

**Cohort 3**

A greater percentage of participants in the casirivimab+imdevimab groups compared to the placebo group experienced TEAE leading to death: The percentages of participants with at least 1 TEAE leading to death was 66.7% (8/12) in the casirivimab+imdevimab 2400 mg dose group compared to the placebo group (58.3% [7/12]), and casirivimab+imdevimab 8000 mg dose groups (36.4% [4/11].

On analysis of TEAEs that resulted in a fatal outcome, the following 6 TEAEs (by PT) were experienced by ≥2 participants in any casirivimab+imdevimab treatment groups: respiratory failure, acute respiratory failure, COVID-19, and cardiac arrest.

**Table 46: Summary of Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term (Cohort 3; FAS)**

| | | Casirivimab+Imdevimab IV | | |
|---|---|---|---|---|
| Primary System Organ Class<br>Preferred Term | Placebo<br>(N=12) | 2400 mg<br>(N=12) | 8000 mg<br>(N=11) | Combined<br>(N=23) |
| Number of patients with at least one TEAE leading to death | 7 (58.3%) | 8 (66.7%) | 4 (36.4%) | 12 (52.2%) |
| Respiratory, thoracic and mediastinal disorders | 4 (33.3%) | 4 (33.3%) | 1 (9.1%) | 5 (21.7%) |
| Respiratory failure | 1 (8.3%) | 3 (25.0%) | 0 | 3 (13.0%) |
| Acute respiratory failure | 2 (16.7%) | 1 (8.3%) | 1 (9.1%) | 2 (8.7%) |
| Respiratory arrest | 1 (8.3%) | 0 | 0 | 0 |
| Infections and infestations | 2 (16.7%) | 2 (16.7%) | 2 (18.2%) | 4 (17.4%) |
| COVID-19 | 2 (16.7%) | 1 (8.3%) | 2 (18.2%) | 3 (13.0%) |
| Viral cardiomyopathy | 0 | 1 (8.3%) | 0 | 1 (4.3%) |
| Cardiac disorders | 0 | 1 (8.3%) | 1 (9.1%) | 2 (8.7%) |
| Cardiac arrest | 0 | 1 (8.3%) | 1 (9.1%) | 2 (8.7%) |
| Renal and urinary disorders | 0 | 0 | 1 (9.1%) | 1 (4.3%) |
| Renal impairment | 0 | 0 | 1 (9.1%) | 1 (4.3%) |
| Vascular disorders | 0 | 1 (8.3%) | 0 | 1 (4.3%) |
| Haemorrhage | 0 | 1 (8.3%) | 0 | 1 (4.3%) |
| General disorders and administration site conditions | 1 (8.3%) | 0 | 0 | 0 |
| Sudden cardiac death | 1 (8.3%) | 0 | 0 | 0 |

Note: The Full Analysis Set (FAS) is identical to the Safety Analysis Set (SAF).
MedDRA (Version 24.0) coding dictionary applied.
A patient who reported 2 or more adverse events with different preferred terms within the same system organ class is counted only once in that system organ class.
A patient who reported 2 or more adverse events with the same preferred term is counted only once for that term.
Primary System Organ Classes (SOCs) are sorted according to decreasing order of frequency of the combined treatment group.
Within each SOC, Preferred Terms are sorted by decreasing frequency.
Source: PTT 14.3.3.3.1c

**Serious adverse events**

A post-hoc pooled safety analysis across all cohorts and all phases showed that 25.5 (561/2203) of all participants had at least 1 treatment-emergent SAE. The frequency of treatment-emergent SAEs was higher in the placebo group (27.8% [203/730 participants]) compared to the casirivimab+imdevimab 2400 mg dose group (23.9% [177/740 participants]), the casirivimab+imdevimab 8000 mg dose group (24.7% [181/733 participants]), and the combined doses (24.3% [358/1473 participants]).

The most frequently reported SOCs where treatment-emergent SAEs were numerically higher for any casirivimab+imdevimab dose compared to placebo were:

General disorder and administration site conditions: 2.4% (18/740 participants) in the 2400 mg group, 1.9% (14/733 participants) in the 8000 mg group, and 1.9% (14/730 participants) in the placebo group

Vascular disorders: 0.9% (7/740 participants) in the 2400 mg group, 1.5% (11/733 participants) in the 8000 mg group, and 1.2% (9/730 participants) in the placebo group

The most frequently reported PTs (> 2 participants) where events were higher for any casirivimab+imdevimab dose compared to placebo were:

- Multiple organ dysfunction syndrome (0.4% [3/740 participants] in the 2400 mg dose group; 1.1% [8/733 participants] in the 8000 mg dose group; 0.7% [5/730 participants] in the placebo group)

- Death (0.7% [5/740 participants] in the 2400 mg dose group; 0.1% [1/733 participants] in the 8000 mg dose group; 0.5% [4/730 participants] in the placebo group)
- Chest pain 0.4% [3/740 participants] in the 2400 mg dose group; 0.3% [2/733 participants] in the 8000 mg dose group; 0.1% [1/730 participants] in the placebo group)

**Adverse events of special interest and selected adverse events**

Treatment-emergent AESIs (serious and non-serious) were defined as:

- Grade ≥ 2 IRRs through Day 4
- Grade ≥ 2 hypersensitivity reactions through Day 29

A post-hoc pooled safety analysis across all cohorts and all phases showed that 2.0% (45/2203) of all participants experienced at least 1 treatment emergent AESI. More participants in the casirivimab+imdevimab 2400 mg dose group (2.2% [16/740]) and 8000 mg dose group (2.9% [21/733]) had at least 1 treatment emergent AESI, compared to the placebo group.

**Grade ≥2 infusion-related reactions through Day 4**

Overall, 32 participants experienced AESIs of Grade ≥2 IRRs through Day 4. A higher proportion of participants experienced Grade ≥2 IRRs in the casirivimab+imdevimab 8000 mg dose group (2.0%) and 2400 mg dose group (1.5%) compared to the placebo group (0.8%).

The AESI PTs that were most frequently (> 2 participants) reported in the casirivimab+imdevimab dose groups compared to placebo were:

- Hypoxia: 0.4% (3/740 participants) in the 2400 mg dose group; 0.4% (3/733 participants) in the 8000 mg dose group; 0.1% (1/730 participants) in the placebo group
- Chills: 0 participants in the 2400 mg dose group; 0.3% (2/733 participants) in the 8000 mg dose group; 0.1% (1/730 participants) in the placebo group

**Grade ≥2 hypersensitivity reactions through Day 29**

Overall, 14 participants experienced AESIs of Grade > 2 hypersensitivity, through

Day 29. A higher proportion of participants experienced Grade > 2 hypersensitivity reactions in the casirivimab+imdevimab 8000 mg dose group (1.0%) and 2400 mg dose group (0.7%) compared to the placebo group (0.3%).

The AESI PTs that were most frequently (> 2 participants) reported in the casirivimab+imdevimab dose groups compared to placebo were:

- Chills: 0.3% (2/740 participants) in the 2400 mg dose group; 0.1% (1/733 participants) in the 8000 mg dose group; 0 in the placebo group
- Dyspnoea: 0.3% (2/740 participants) in the 2400 mg dose group; 0.1% (1/733 participants) in the 8000 mg dose group; 0.1% (1/730 participants) in the placebo group
- Headache: 0 participants in the 2400 mg dose group; 0.3% (2/733 participants) in the 8000 mg dose group; 0 participants in the placebo group
- Nausea: 0 participants in the 2400 mg dose group; 0.3% (2/733 participants) in the 8000 mg dose group; 0 participants in the placebo group

## *Laboratory findings*

The RECOVERY trial did not collect data to evaluate haematology, clinical chemistry or immunogenicity. No clinically relevant changes in the available laboratory data and vital signs were observed in COV-2066. Also, no new safety signal was identified based on the review of data.

**COV-2066**

**Haematology**

**Table 9 Summary of Participants with at least One Treatment-Emergent Potentially Clinically Significant Abnormal Value for Hematology during the Study Period (Pooled Phase 1, 2, 3 Cohort 1, Phase 2 Cohort 1A, Phase 2 Cohort 2 and Phase 2 Cohort 3, Full Analysis Set)**

| Parameter (unit) | Placebo (n=730) | Casirivimab+ imdevimab 2400 mg (n=740) | Casirivimab+ imdevimab 8000 mg (n=733) | Casirivimab+ imdevimab combined (n=1473) |
|---|---|---|---|---|
| Patients with at least one treatment emergent PCSV – Red Blood Cells and Platelets | 188/650 (28.9%) | 180/671 (26.8%) | 169/659 (25.6%) | 349/1330 (26.2%) |
| Patients with at least one treatment emergent PCSV – White Blood Cells | 207/649 (31.9%) | 194/671 (28.9%) | 198/657 (30.1%) | 392/1328 (29.5%) |
| Patients with at least one treatment emergent PCSV – Coagulation | 24/611 (3.9%) | 13/615 (2.1%) | 21/600 (3.5%) | 34/1215 (2.8%) |

PCSV = potentially clinical significant value.

Source: t_353_1a_lb_pcsv_rbc, t_353_1b_lb_pcsv_rbc, t_353_1c_lb_pcsv_rbc, t_353_1d_lb_pcsv_rbc, t_354_1a_lb_pcsv_oth, t_354_1b_lb_pcsv_oth, t_354_1c_lb_pcsv_oth, t_354_1d_lb_pcsv_oth, t_359_1a_lb_pcsv_oth, t_359_1b_lb_pcsv_oth, t_359_1c_lb_pcsv_oth, t_359_1d_lb_pcsv_oth.

The most frequently reported PCSVs among the hematologic parameters were as follows:

- Red blood cells and platelets: decrease of ≥20 g/L in haemoglobin values
- White blood cells: abnormal monocyte values t
- Coagulation: abnormal activated partial thromboplastin time and abnormal prothrombin time

**Chemistry**

Treatment-emergent PCSVs compared to baseline were generally similar across all treatment and placebo groups for electrolytes (placebo: 9.6%, casirivimab+imdevimab 2400 mg group: 7.9%, casirivimab+imdevimab 8000 mg group: 7.9%) and liver function (placebo: 11.2%, casirivimab+imdevimab 2400 mg group: 11.1%, casirivimab+imdevimab 8000 mg group: 12.3%). Treatment-emergent PCSVs for metabolic function during the study compared to baseline were slightly higher in the casirivimab+imdevimab 8000 mg group compared to the placebo and slightly lower in casirivimab+imdevimab 2400 mg group compared to placebo (placebo: 44.9%, casirivimab+imdevimab 2400 mg group: 43.3%, casirivimab+imdevimab 8000 mg group: 50.5%. Treatment-emergent PCSVs for renal function during the study period compared to baseline were slightly higher in the placebo group compared to either treatment group and both treatment groups combined (placebo: 23.8%, casirivimab+imdevimab 2400 mg group: 19.6%, casirivimab+imdevimab 8000 mg group: 19.6%) (Table 10).

**Table 10 Summary of Participants with at Least One Treatment-Emergent Potentially Clinically Significant Abnormal value for Chemistry During the Study Period (Pooled Phase 1, 2, 3 Cohort 1, Phase 2 Cohort 1A, Phase 2 Cohort 2 and Phase 2 Cohort 3, Full Analysis Set)**

| Treatment-emergent PCSV category, n (%) | Placebo (n=730) | Casirivimab+ imdevimab 2400 mg (n=740) | Casirivimab+ imdevimab 8000 mg (n=733) | Casirivimab+imdevimab combined doses (n=1473) |
|---|---|---|---|---|
| Patients with at least one treatment emergent PCSV – Metabolic function | 298/663 (44.9%) | 295/682 (43.3%) | 341/675 (50.5%) | 636/1357 (46.9%) |
| Patients with at least one treatment emergent PCSV – Electrolytes | 63/657 (9.6%) | 53/675 (7.9%) | 53/671 (7.9%) | 106/1346 (7.9%) |
| Patients with at least one treatment emergent PCSV – Renal function | 157/659 (23.8%) | 133/678 (19.6%) | 132/672 (19.6%) | 265/1350 (19.6%) |
| Patients with at least one treatment emergent PCSV – Liver function | 73/650 (11.2%) | 74/665 (11.1%) | 80/651 (12.3%) | 154/1316 (11.7%) |

PCSV = potentially clinical significant value.

Source: t_355_1a_lb_pcsv_oth, t_355_1b_lb_pcsv_oth, t_355_1c_lb_pcsv_oth, t_355_1d_lb_pcsv_oth, t_356_1a_lb_pcsv_oth, t_356_1b_lb_pcsv_oth, t_356_1c_lb_pcsv_oth, t_356_1d_lb_pcsv_oth, t_357_1a_lb_pcsv_oth, t_357_1b_lb_pcsv_oth, t_357_1c_lb_pcsv_oth, t_357_1d_lb_pcsv_oth, t_358_1a_lb_pcsv_oth, t_358_1b_lb_pcsv_oth, t_358_1c_lb_pcsv_oth, t_358_1d_lb_pcsv_oth.

Overall, there were 6 participants (4 participants in the placebo group, 1 participant in the casirivimab+imdevimab 2400 mg group and 1 participant in the casirivimab+imdevimab 8000 mg group) with liver enzyme elevations that met the criteria for Hy's Law (maximum post-baseline total bilirubin > 2x upper limit of normal (ULN) within 30 days after maximum post-baseline alanine transaminase or aspartate aminotransferase > 3x ULN, without findings of cholestasis, defined as alkaline phosphatase > 2x ULN) (l_300_hylaw). The participants in the casirivimab+imdevimab treated groups both had relevant medical history including viral infections (Hepatitis and HIV)Considering the participants' relevant comorbidities, the liver enzyme elevations are considered likely related to underlying medical conditions and/or COVID-19, and not related to casirivimab+imdevimab treatment.

**Immunogenicity**

The majority of participants in this study were ADA negative for casirivimab and imdevimab. Of the patients with treatment-emergent or treatment-boosted ADA, greater than 95% of patients dosed with casirivimab+imdevimab had low (<1,000) maximum titre, with no high titre responses observed. There was no impact of immunogenicity on concentrations of casirivimab and imdevimab in serum. Concentrations in serum for casirivimab and imdevimab at Day 28 (i.e., Study Day 29) were similar between ADA negative and ADA-positive patients, with the majority of samples being ADA-negative.

## *Safety in special populations*

### RECOVERY

### Age

**Table 17 Summary of 72-hour Safety Outcomes by Age Group among all Randomized Participants Treated w Casirivimab+Imdevimab and Usual Care who completed the Early Safety Form (Early Safety Popula**

| | Casirivimab+Imdevimab Group | | | Usual Care Group | | |
|---|---|---|---|---|---|---|
| | <18 years (N=4) | ≥18 to ≤65 years (N=2912) | >65 years (N=1923) | <18 years (N=7) | ≥18 to ≤65 years (N=3018) | >65 years (N=1921) |
| Number with form completed | 2 | 973 | 817 | 3 | 951 | 761 |
| Sudden worsening in respiratory status, n (%) | 0 | 180 (18.5%) | 189 (23.1%) | 1 (33.3%) | 190 (20.0%) | 181 (23.8%) |
| Severe allergic reaction, n (%) | 0 | 2 (0.2%) | 2 (0.2%) | 0 | 0 | 1 (0.1%) |
| Temperature >39°C or ≥ 2°C rise above baseline (Grade ≥ 2), n (%) | 0 | 41 (4.2%) | 38 (4.7%) | 0 | 32 (3.4%) | 20 (2.6%) |
| Sudden hypotension, n (%) | 0 | 26 (2.7%) | 40 (4.9%) | 0 | 20 (2.1%) | 19 (2.5%) |
| Clinical hemolysis, n (%) | 0 | 12 (1.2%) | 14 (1.7%) | 0 | 20 (2.1%) | 11 (1.4%) |
| Thrombotic event, n (%) | 0 | 15 (1.5%) | 16 (2.0%) | 0 | 12 (1.3%) | 12 (1.6%) |

Source: t-saf-age.

There were 11 adolescent participants (ages ranging from 12 to 17 years) in the RECOVERY trial (4 randomized to the casirivimab+imdevimab and 7 to standard care). There were no deaths, SUSARs or SSARs reported among this group. Five of the 11 adolescent patients were in the subset of participants who had early safety assessments. Of the five patients, 2 were in the casirivimab+imdevimab group and neither experienced an allergic reaction, fever, sudden hypotension, thrombotic events or clinical haemolysis.

The incidence of severe allergic reaction was the same between participants who were >65 years of age and those who were >18 to <65 years of age (0.2% in both groups) (Table 17). In the casirivimab+imdevimab group, the overall incidence of sudden worsening in respiratory status, temperature > 39°C or > 2°C rise above baseline, sudden hypotension, clinical haemolysis and thrombotic event was higher (> 0.3% difference) among participants who were >65 years of age compared to those who were >18 to <65 years of age (Table 17). This was expected, as the >65 years age group is at higher risk of complications/progression to severe COVID-19 infection and are observed in patients with severe COVID-19 infection.

In the usual care group, the incidence of sudden worsening in respiratory status, sudden hypotension, and thrombotic events was higher (>0.3% difference) among participants who were < 65 years of age compared to those who were >18 to < 65 years of age; while, the incidence of temperature > 39°C or >2° C rise above baseline and clinical haemolysis was higher (>0.3% difference) among participants who were >18 to <65 years of age compared to those who were >65 years of age.

**Gender**

**Table 18 Summary of 72-hour Safety Outcomes by Gender among all Randomized Participants Treated with Casirivimab+Imdevimab and Usual Care who Completed the Early Safety Form (Early Safety Population)**

| | Casirivimab+Imdevimab Group | | Usual Care Group | |
|---|---|---|---|---|
| | Men (N=3033) | Women (N=1806) | Men (N=3095) | Women (N=1851) |
| Number with form completed | 1120 | 672 | 1073 | 642 |
| Sudden worsening in respiratory status, n (%) | 235 (21.0%) | 134 (19.9%) | 225 (21.0%) | 147 (22.9%) |
| Severe allergic reaction, n (%) | 3 (0.3%) | 1 (0.1%) | 1 (<0.1%) | 0 |
| Temperature >39°C or ≥2°C rise above baseline (Grade ≥ 2), n (%) | 53 (4.7%) | 26 (3.9%) | 33 (3.1%) | 19 (3.0%) |
| Sudden hypotension, n (%) | 39 (3.5%) | 27 (4.0%) | 18 (1.7%) | 21 (3.3%) |
| Clinical hemolysis, n (%) | 16 (1.4%) | 10 (1.5%) | 17 (1.6%) | 14 (2.2%) |
| Thrombotic event, n (%) | 17 (1.5%) | 14 (2.1%) | 17 (1.6%) | 7 (1.1%) |

Source: t-saf-sex.

In the casirivimab+imdevimab group, the incidence of sudden worsening in respiratory status and temperature > 39°C or > 2°C rise above baseline, were higher (≥0.3% difference) in men compared to women, while the incidence of sudden hypotension and thrombotic event was higher (≥0.3% difference) in women compared to men. The incidence of severe allergic reaction and clinical haemolysis was comparable between men and women (Table 18).

In the usual care group, the incidence of thrombotic event was higher (≥0.3% difference) in men compared to women, while the incidence of sudden worsening in respirator status, sudden hypotension, and clinical haemolysis was higher (≥0.3% difference) in women compared to men. The incidence of severe allergic reaction and temperature >39°C or > 2°C rise above baseline was comparable between men and women (Table 18).

**Ethnicity**

**Table 19 Summary of 72-hour Safety Outcomes by Ethnicity among all Randomized Participants Treated with Casirivimab+Imdevimab and Usual Care who Completed the Early Safety Form (Early Safety Populati**

| | Casirivimab+Imdevimab Group | | | Usual Care Group | | |
|---|---|---|---|---|---|---|
| | White (N=3779) | Black, Asian, and Minority Ethnic (N=596) | Unknown (N=464) | White (N=3822) | Black, Asian, and Minority Ethnic (N=697) | Unknown (N=427) |
| Number with form completed | 1429 | 191 | 172 | 1334 | 231 | 150 |
| Sudden worsening in respiratory status, n (%) | 300 (21.0%) | 38 (19.9%) | 31 (18.0%) | 305 (22.9%) | 43 (18.6%) | 24 (16.0%) |
| Severe allergic reaction, n (%) | 4 (0.3%) | 0 | 0 | 1 (<0.1%) | 0 | 0 |
| Temperature >39°C or ≥2°C rise above baseline (Grade ≥ 2), n (%) | 63 (4.4%) | 7 (3.7%) | 9 (5.2%) | 42 (3.1%) | 7 (3.0%) | 3 (2.0%) |
| Sudden hypotension, n (%) | 52 (3.6%) | 10 (5.2%) | 4 (2.3%) | 30 (2.2%) | 6 (2.6%) | 3 (2.0%) |
| Clinical hemolysis, n (%) | 23 (1.6%) | 3 (1.6%) | 0 | 20 (1.5%) | 7 (3.0%) | 4 (2.7%) |
| Thrombotic event, n (%) | 28 (2.0%) | 2 (1.0%) | 1 (0.6%) | 19 (1.4%) | 3 (1.3%) | 2 (1.3%) |

Source: t-saf-race.

In the casirivimab+imdevimab group, the incidence of sudden worsening in respiratory status, severe allergic reaction and thrombotic event was higher (>0.3% difference) among White people compared to Black, Asian, and Minority Ethnic and unknown (Table 19). The incidence of sudden hypotension was higher (>0.3% difference) in the Black, Asian, and Minority Ethnic group compared to the White and Unknown groups (Table 19). The incidence of temperature > 39°C or > 2°C rise above baseline was higher (>0.3% difference) in the unknown group compared to the White and Black, Asian, and Minority Ethnic groups. The incidence of clinical haemolysis was equivalent between the White and Black, Asian, and Minority Ethnic groups (Table 19).

In the usual care group, the incidence of sudden worsening in respiratory status was higher (>0.3% difference) in the White people compared to Black, Asian, and Minority Ethnic and unknown (Table 19). The incidence of sudden hypotension and clinical haemolysis was higher (>0.3% difference) in the Black, Asian, and Minority Ethnic group compared to the White and Unknown groups. The incidence of temperature > 39°C or >2°C rise above baseline was comparable between the White and the Black, Asian, and Minority Ethnic groups (Table 19); while the incidence of severe allergic reaction and thrombotic event was comparable between all 3 ethnic groups (Table 19).

**Pregnancy and lactation**

By-participant data was collected for participants who were pregnant at baseline and included the day of hospital discharge or death, but not outcomes. There were 26 participants that were pregnant at randomization; 18 pregnant participants in the casirivimab+imdevimab group (3 were not treated) and 8 pregnant participants in the usual care group (4 were not treated). Of these participants, all but 2 were discharged from the hospital. One participant was recorded as having a fatal outcome (in the usual care group on Study Day 12) and there was no discharge information for the other participant (usual care group). Further details on pregnancy outcome are not available in the safety database.

**COV-2066**

**Age**

**Table 20 Incidence of TEAEs by Baseline Age Group among Casirivimab+Imdevimab-Treated Participants**

| | 18 to <65 years | | ≥ 65 years | |
|---|---|---|---|---|
| | 2400 mg IV (N=424) | 8000 mg IV (N=413) | 2400 mg IV (N=316) | 8000 mg IV (N=320) |
| Patients with any TEAE, n (%) | 81 (19.1%) | 85 (20.6%) | 110 (34.8%) | 116 (36.3%) |
| Patients with any TE SAE, n (%) | 70 (16.5%) | 73 (17.7%) | 107 (33.9%) | 108 (33.8%) |
| Patients with any TE AESI of infusion-related reactions[a] (Grade ≥ 2) through Day 4, n (%) | 7 (1.7%) | 6 (1.5%) | 4 (1.3%) | 9 (2.8%) |
| Patients with any TE AESI of hypersensitivity reactions (Grade ≥ 2) through Day 29, n (%) | 3 (0.7%) | 6 (1.5%) | 2 (0.6%) | 1 (0.3%) |
| Patients with any TEAE leading to death, n (%) | 29 (6.8%) | 23 (5.6%) | 61 (19.3%) | 66 (20.6%) |

TE = treatment-emergent; TEAE – treatment-emergent adverse event; TE AESI = treatment-emergent adverse event of special interest; TE SAE = treatment-emergent serious adverse event.

[a]TEAEs deemed infusion-related reaction as per investigator assessment.

Source: t_321_1_aesum_age.

Among the pooled phases and cohorts, the incidence of TEAEs, TE SAEs, and TEAEs leading to death was higher in the >65 years age subgroup compared to the 18 to < 65 years age group in both the casirivimab+imdevimab 2400 mg and 8000 mg dose groups (Table 20). The incidence of TE AESI of IRRs (Grade >2) through Day 4 was slightly higher in the 18 to < 65 years age group compared to the >65 years age group for the casirivimab+imdevimab 2400 mg dose group (1.7% vs. 1.3%, respectively) and higher in the >65 years age subgroup compared to the 18 to < 65 years age group in the 8000 mg dose group (2.8% vs. 1.5%, respectively) but the number of participants with these events was small. The incidence of TE AESI of hypersensitivity reactions (Grade >2) through Day 29 was comparable between the age groups in the 2400 mg dose group (0.3% vs. 0.2% in the 18 to < 65 years vs. >65 years age groups, respectively) but was higher in the 18 to < 65 years age group compared to the >65 years age subgroup in the 8000 mg dose group (1.5% vs. 0.3% respectively) (Table 20).

**Gender**

**Table 21 Incidence of TEAEs by Gender among Casirivimab+Imdevimab Treated Participants**

| | Male | | Female | |
|---|---|---|---|---|
| | 2400 mg IV (N=411) | 8000 mg IV (N=399) | 2400 mg IV (N=329) | 8000 mg IV (N=334) |
| Patients with any TEAE, n (%) | 113 (27.5%) | 106 (26.6%) | 78 (23.7%) | 95 (28.4%) |
| Patients with any TE SAE, n (%) | 106 (25.8%) | 98 (24.6%) | 71 (21.6%) | 83 (24.9%) |
| Patients with any TE AESI of infusion-related reactions[3] (Grade ≥ 2) through Day 4, n (%) | 6 (1.5%) | 8 (2.0%) | 5 (1.5%) | 7(2.1%) |
| Patients with any TE AESI of hypersensitivity reactions (Grade ≥ 2) through Day 29, n (%) | 4 (1.0%) | 5 (1.3%) | 1 (0.3%) | 2 (0.6%) |
| Patients with any TEAE leading to death, n (%) | 52 (12.7%) | 52 (13%) | 38 (11.6%) | 37 (11.1%) |

TE = treatment-emergent; TEAE – treatment-emergent adverse event; TE AESI = treatment-emergent adverse event of special interest; TE SAE = treatment-emergent serious adverse event.

[3]TEAEs deemed infusion-related reaction as per investigator assessment.

Source: t_321_3_aesum_gender.

**Gender**

Among the pooled phases and cohorts, the incidence of TEAEs, TE SAEs, TE AESI of hypersensitivity reactions (Grade >2) through Day 29 and TEAEs leading to death was higher among males compared to females in both the casirivimab+imdevimab 2400 mg and 8000 mg dose groups (Table 21). The incidence of TE AESI of infusion-related reactions (Grade >2) through Day 4 was comparable between males and females in both the 2400 mg dose group (Males: 1.5% [6/411 participants]; Females: 1.5% [5/329 participants]) and the 8000 mg dose group (Males: 2.0% [8/399 participants]; Females: 2.1% [7/334 participants]) (Table 21).

**Race**

Among the pooled phases and cohorts, the incidence of TEAEs, TE SAEs, TE AESI of hypersensitivity reactions (Grade >2) through Day 29, TE AESI of infusion-related reactions (Grade >2) through Day 4 and TEAEs leading to death was higher among White people compared to all other race categories in the casirivimab+imdevimab 2400 mg dose group and 8000 mg dose group. It should be noted that the majority of the participants in COV-2066 were White. The incidence of TEAEs, TE SAEs, TE AESI of hypersensitivity reactions (Grade >2) through Day 29, TE AESI of infusion related reactions (Grade > 2) through Day 4 and TEAEs leading to death was comparable among those whose race was unknown or not reported between both dose groups (Table 22).

**Table 22 Incidence of TEAEs by Race among Casirivimab+Imdevimab-Treated Participants**

| | White | | Black or African American | | Asian | | American Indian or Alaska Native | | Native Hawaiian or Other Pacific Islander | | Unknown | | Not reported | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2400 mg (N=472) | 8000 mg (N=475) | 2400 mg (N=94) | 8000 mg (N=103) | 2400 mg (N=30) | 8000 mg (N=22) | 2400 mg (N=10) | 8000 mg (N=15) | 2400 mg (N=3) | 8000 mg (N=3) | 2400 mg (N=48) | 8000 mg (N=36) | 2400 mg (N=83) | 8000 mg (N=79) |
| Patients with any TEAE, n (%) | 127 (26.9%) | 134 (28.2%) | 23 (24.5%) | 30 (29.1%) | 9 (30%) | 4 (18.2%) | 2 (20.0%) | 4 (26.7%) | 0 | 2 (66.7%) | 14 (29.2%) | 12 (33.3%) | 16 (19.3%) | 15 (19.0%) |
| Patients with any TE SAE, n (%) | 121 (25.6%) | 121 (25.5%) | 19 (20.2%) | 26 (25.2%) | 7 (23.3%) | 3 (13.6%) | 2 (20.0%) | 4 (26.7%) | 0 | 2 (66.7%) | 14 (29.2%) | 12 (33.3%) | 14 (16.9%) | 13 (16.5%) |
| Patients with any TE AESI of infusion-related reactions[a] (Grade ≥ 2) through Day 4, n (%) | 4 (0.8%) | 11 (2.3%) | 2 (2.1%) | 3 (2.9%) | 3 (10.0%) | 1 (4.5%) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.4%) | 0 |

**Pregnancy and lactation**

Pregnancy was an exclusion criterion for COV-2066; however, there were 2 cases of pregnancy reported during the study:

- The first case concerned a woman who was diagnosed with COVID-19 and randomized to receive casirivimab+imdevimab treatment. On the day she signed the informed consent, she received casirivimab+imdevimab and subsequently took her first urine pregnancy test with a positive result for pregnancy. At the time of treatment, she was in the second trimester of pregnancyt. She delivered a healthy female baby with no complications.
- The second case concerned a female participant who became pregnant while enrolled in COV-2066. Upon admission to hospital, she had a negative urine pregnancy test. She received casirivimab+imdevimab prior to becoming pregnant; however, she was still enrolled in the study. The pregnancy is currently ongoing.

## *Safety related to drug-drug interactions and other interactions*

No formal drug-drug interaction studies have been performed. Casirivimab and imdevimab are monoclonal antibodies, which are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

## *Discontinuation due to adverse events*

**RECOVERY**

Three participants experienced infusion-related events (PT: Hypersensitivity [2 participants]; PT Infusion-related reaction [1 participant]). All 3 events resulted in treatment discontinuation and were reported as a SSAR.

**COV-2066**

**Infusion discontinuations**

Four participants in the casirivimab+imdevimab 2400 mg dose group (0.5% [4/740 participants], with reported PTs: Chest pain, Infusion site extravasation, and Chills [2 participants]) and 5 participants in the casirivimab+imdevimab 8000 mg dose group (0.7% [5/733 participants], with reported PTs: Infusion related reaction, Hypoxia, Anxiety, Pruritus in 1 participant each; Dyspnoea and Tachypnoea in 1 participant), experienced TEAEs leading to infusion discontinuation. There were no TEAEs leading to infusion discontinuation in the placebo group.

**Infusion interruptions**

Overall, TEAEs leading to infusion interruption were observed in 1 participant in the placebo group (0.1% [1/730]; PT: Hypoxia), 1 participant in the casirivimab+imdevimab 2400 mg dose group (0.1% [1/740]; with reported PT: Arthralgia), and 3 participants in the casirivimab+imdevimab 8000 mg dose group (0.4% [1/733]; with reported PTs: Dyspnoea, Tachycardia and Hypoxia).

**Withdrawal from Study**

Two participants in the casirivimab+imdevimab 2400 mg dose group (1 participant with a reported PT of Acute Respiratory Failure also had a fatal outcome; 1 participant with the reported PT: Fall) and 1 participant in the casirivimab+imdevimab 8000 mg group (PT: Pruritus; also lead to infusion discontinuation), experienced TEAEs leading to study withdrawal. There were no TEAEs leading to study withdrawal in the placebo group

**Dose Modification**

Since this was a single dose study, dose modifications were not permitted.

## *Post marketing experience*

As of 30 November 2021, Ronapreve has been approved for treatment or prophylaxis of COVID-19 in several countries, as well as EUAs in other countries.

In order to ensure a comprehensive safety assessment of available data from outside of the Ronapreve clinical trial program, non-interventional study/EUA/Compassionate use data were evaluated and combined with the post-marketing data from Japan and the UK.

A search of the Roche Global Safety Database up to 30 November 2021, retrieved a total of 8748 events corresponding to 3117 cases (spontaneous: 824 cases; literature: 47 cases; non-interventional study/program: 2228 cases). Of the 3117 cases, 1138 cases were serious (1043 medically confirmed) and 1961 cases were non-serious (1253 medically confirmed).

Overall, the 5 most frequently reported SOCs were: General disorders and administration site conditions (2352 events); Respiratory, thoracic and mediastinal disorders (949 event); Nervous system disorders (876 events); Injury, poisoning and procedural complications (840 events); and Gastrointestinal disorders (714 events).

The most frequently reported PTs (>150 events) were: Pyrexia (581 events); No adverse event (352 events); Chills (311 events); Nausea (271 events); Dyspnoe (263 events); Off label use (244 events); Oxygen saturation decreased (203 events); Headache (183 events); Dizziness (155 events).

**Hypersensitivity**

A total of 452 cases (575 events) of Hypersensitivity were identified as having PTs falling within Hypersensitivity SMQ (narrow).

The most frequently reported Hypersensitivity reactions PTs (>15 events) were: Rash (115); Urticaria (109 events); Infusion related reaction (70 events); Hypersensitivity (36 events); Rash pruritic (25 events); Anaphylactic reaction (22 events); and Lip swelling (17 events).

Of the 452 cases, 140 cases were serious. Of these, 4 cases (Distributive shock [1 case]; Skin necrosis [1 case]; Anaphylactic reaction [2 cases]) involved a fatal outcome. The event of skin necrosis occurred more than 2 months after administration of Ronapreve and was considered unrelated to Ronapreve by the Applicant. The event of Distributive shock was considered to be most likely due to underlying medical condition of the patient. Of the 2 remaining reports of anaphylactic reaction, both patients had risk factors for severe COVID-19. For one report, time from the initial COVID-19 symptoms to administration of Ronapreve was not reported.

**Lack of efficacy**

A total of 36 cases involving lack of efficacy have been reported up to 30 November 2021. The cases were identified by review of relevant PTs within the HLT of Therapeutic and non-therapeutic responses. The PTs within the cases were: Drug ineffective (30 events); Treatment failure (2 events); Therapeutic product effect decreased (2 events); Therapy non-responder and Therapeutic response decreased (1 event each).

Half of the cases (50%; 18/36) reported a lack of efficacy within 1 day of administration of Ronapreve. Of the remaining 18 cases, 4 cases had limited information and no information regarding time of COVID-19 onset and administration of Ronapreve; and 1 case involved neutropenia without response to Granulocyte colony-stimulating factor (GCSF), hence was not a lack of efficacy case for Ronapreve.

For the remaining 13 cases, time from administration to reporting of lack of efficacy was not provided.

**Pregnancy**

Data from 171 pregnant patients (age range: 17 to 44 years) were available from clinical studies that allowed enrolment of pregnant women (COV-2066, COV-2067, COV-2069 and COV-20145), the RECOVERY trial, and from patients administered casirivimab+imdevimab under the non-interventional study/EUA/compassionate use program and from the post-marketing setting.

There were 16 SAEs reported in patients receiving casirivimab+imdevimab; none of the SAEs were considered related to study drug (Ronapreve).

Based on current data, the following outcomes were reported: 53 live births without congenital anomaly, 1 live birth with congenital anomaly, 5 premature births, 2 ectopic pregnancies, 3 stillbirths without foetal defects, 9 elective abortions (no foetal defects or unknown) and 7 spontaneous abortions. Sixty-seven cases were still awaiting outcome data and 24 cases had an unknown outcome. There were 14 cases with a reported SAE (including spontaneous abortion). The safety profile in pregnant patients was consistent with the known safety profile of Ronapreve.

There are no available data on the presence of casirivimab and/or imdevimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk.

## 2.5.1. Discussion on clinical safety

The safety data base includes 5771 hospitalised patients; the majority, 5031 patients received the 8000 mg dose and 740 patients received the 2400 mg dose. The observation period is depending on the study 4 to 8 weeks, with a few patients followed for 16 weeks. Give that this acceptable for a single dose application directed towards an exogenous target.

The safety data collection addresses in RECOVERY deviated from traditional safety data collection. It was aimed to balanced safety data collection with practical considerations to ensure that only key safety outcomes were captured. Given the circumstances of the study, which was conducted in a challenging situation for the health care system, this is acceptable.

Since the safety profile in hospitalised patients was expected to be complex and dynamic due the COVID-19 disease, which affects multiple organ systems and exacerbates concurrent clinical conditions considered risk factors for severe COVID-19, a targeted safety data collection was performed in study COV-2066, collecting relevant TEAEs in order to reduce background noise. This approach is acceptable.

**RECOVERY**

**Adverse events**

Collection of safety parameters was focused on suspected serious adverse reactions (SSARs) (which are those events that, based on a single case likely with a reasonable probability to be related to the

study medication) and infusion-related and hypersensitivity reactions, which were collected only in the casirivimab+imdevimab group and not the usual care group since no placebo comparator IV infusion was given. The reported events were consistent with IRRs or hypersensitivity reactions (identified risks of casirivimab+imdevimab treatment) or associated with COVID-19 and its complication.

**Serious adverse event/deaths/other significant events**

Mortality at 28 days was the primary efficacy endpoint of the RECOVERY study.

Early safety outcome data were recorded within 72 hours (based on the ESAF) after randomization for the first 1792 casirivimab+imdevimab participants and the first 1715 usual care participants.

No clinically meaningful differences were observed between the casirivimab+imdevimab group and the usual care group among all randomized participants. A few imbalances in specific targeted safety outcomes were observed; these were consistent with advanced COVID-19 and its complications.

IRRs were collected for the casirivimab+imdevimab group and not for the usual care group (as treatment did not include infusion).

An online follow-up form was completed by site staff when participants were discharged, had died, or at 28 days after randomization, whichever occurred first to provide additional safety information. Selected safety data (all-cause mortality and cause-specific mortality, major cardiac arrhythmia and thrombosis and major bleeding) were collected and analysed for 4839 participants randomized to casirivimab+imdevimab and 4946 participants randomized to usual care. The events reported are consistent with advanced COVID-19 and its complications and worsening comorbid clinical conditions of hospitalized patients.

**Age, gender and ethnicity**

72-hour safety outcomes defined as sudden worsening in respiratory status, severe allergic reaction, temperature > 39°C or > 2°C rise above baseline, sudden hypotension, clinical haemolysis and thrombotic event, were summarised by subgroups i.e., age, gender and ethnicity among all randomised participants treated with casirivimab+imdevimab in the early safety population.

The number of subjects who were <18 years was too low in both the casirivimab+imdevimab group and the usual care group to allow for any meaningful comparisons or conclusions to be drawn. However, although the data is limited in this patient group as casirivimab and imdevimab are directed towards an exogenous target, no difference in safety profile is expected between this population and patients ≥18 years.

An imbalance with a slightly higher incidence of events in the >65-year age group as compared to the > 18 to <65 year age group for some safety outcomes was observed. A similar trend was observed in the usual care group.

Regarding gender and ethnicity, there were slight imbalances in safety outcomes, but these were also observed with the usual care group.

Overall, no specific pattern or trend for concern was observed in casirivimab+imdevimab group for age, gender and/or ethnicity.

**COV-2066**

The Safety population (SAF) included all randomized participants who received at least one dose of the study drug. Analysis of the Safety population was done according to the treatment received (as treated).

The proportion of participants reporting TEAEs was similar in casirivimab+imdevimab 2400 mg (25.8%), 8000 mg (27.4%) and the placebo group (28.6%). The most frequently reported event preferred terms (PTs) (>2%) which were higher for any casirivimab+imdevimab dose compared to placebo were: acute respiratory failure (2400mg: 3.5%; 8000mg: 2.3%; placebo: 3.3%) and COVID-19 (2400mg: 2.4%; 8000mg: 4.5%; placebo: 4.1%).

A total of 17% (378/2203 participants) of all participants had at least one Grade 3 or 4 TEAE. A higher percentage of participants in the placebo group experienced Grade 3 or 4 TEAEs (19.0%), compared to the casirivimab+imdevimab 2400 mg (15.1%) and the 8000 mg dose group (17.3%).

A higher proportion of participants in the placebo group experienced treatment-emergent SAEs and TEAEs leading to death, compared to the casirivimab+imdevimab groups (combined and individual doses).

A post-hoc pooled safety analysis across all cohorts and all phases showed that 25.5 (561/2203) of all participants had at least 1 treatment-emergent SAE. The frequency of treatment-emergent SAEs was higher in the placebo group (27.8% [203/730 participants]) compared to the casirivimab+imdevimab 2400 mg dose group (23.9% [177/740 participants]), the casirivimab+imdevimab 8000 mg dose group (24.7% [181/733 participants]), and the combined doses (24.3% [358/1473 participants]). The treatment-emergent SAEs reported are consistent with advanced and progressive COVID-19 disease, its complications, or worsening of participants' concurrent medical conditions due to COVID-19.

Treatment-emergent AESIs (serious and non-serious) were defined as: Grade ≥ 2 IRRs through Day 4 or Grade ≥ 2 hypersensitivity reactions through Day 29. The pooled safety analysis across all cohorts and all phases showed that 2.0% (45/2203) of all participants experienced at least 1 treatment emergent AESI. More participants in the casirivimab+imdevimab dose groups (2400 mg: 2.2%; 8000 mg: 2.9%) had at least 1 treatment emergent AESI, compared to the placebo group (1.1%). The numbers were low and consistent with the expected safety profile.

Phase 2 enrolment of Cohort 2 and 3 was paused per iDMC recommendation due to an observed imbalance of deaths in the treatment groups compared to placebo. The Sponsor conducted a thorough assessment of these deaths and it was determined not to be treatment related but considered primarily due to worsening COVID-19 disease and participants' concurrent medical conditions.

Among the pooled phases and cohorts, TEAEs leading to infusion discontinuation, to infusion interruption or to withdrawal from the study were uncommon.

**Age, gender and ethnicity**

TEAEs, TESAEs and TE AESIs were summarised by subgroups i.e., age, gender and ethnicity among pooled phases and cohorts (FAS) in the 2400 mg dose group and 8000 mg dose group. The overall safety profile of casirivimab+imdevimab was comparable across all groups.

**Post marketing experience**

The post marketing data do not reveal new safety signals.

Data from 171 pregnant patients were available from clinical studies that allowed enrolment of pregnant women. There were 16 SAEs reported in patients receiving casirivimab+imdevimab; none of the SAEs were considered related to Ronapreve. No safety new concerns in pregnant women were observed

## 2.5.2. Conclusions on clinical safety

The events were either due to COVID-19/COVID-19 progression or worsening of the patients' concurrent/background clinical condition, or in line with the known safety profile of Ronapreve. No dose dependency of the events was observed.

No new signals/safety concerns were identified.

## 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicine's web-portal.

## 2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable.

The CHMP endorsed this advice without changes.

### Safety concerns

| Summary of safety concerns | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | Use in pregnancy |

### Pharmacovigilance plan

| Study Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Date(s) |
|---|---|---|---|---|
| **Category 3**↓Required additional pharmacovigilance activities | | | | |
| COVID-PR (COVid-19 International Drug Pregnancy Registry)<br><br>Ongoing | To estimate the effect specific newly developed medications indicated for mild to severe COVID-19 have on the risk of obstetric, neonatal, and infant outcomes compared to the effects of repurposed treatments for COVID-19 | Use in pregnancy | Annual report | Progress reports on enrolment and intermediate analysis results will be provided yearly |
| | | | Final report | 31/12/2027 |

COVID-19 = Coronavirus disease 2019

### *Risk minimisation measures*

| Safety Concern | Risk Minimization Measure(s) | Pharmacovigilance Activities |
|---|---|---|
| Use in pregnancy | **Routine risk-minimization measures:**<br>EU SmPC Section 4.6: Fertility, pregnancy and lactation<br>EU SmPC Section 5.3: Preclinical safety data<br>PL Section 2<br><br>**Other risk minimization measures beyond the Product Information:**<br>Medicine's legal status:<br>The combination of casirivimab and imdevimab is a prescription only medicine<br><br>**Additional risk minimization measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>Presentation of periodic and cumulative data in PBRERs<br><br>**Additional pharmacovigilance activities:**<br>COVID-PR (COVid-19 International Drug Pregnancy Registry)<br>Final study report due date: 31/12/2027 |

COVID-PR = COVid-19 International Drug Pregnancy Registry; PBRER = Periodic benefit-risk evaluation report; PL = Package Leaflet

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 ,4.9, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Labelling Package Leaflet have been updated accordingly.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

There are not significant changes impacting key safety messaging in terms of safe use.

There are not significant changes impacting the readability of the PL.

### 2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ronapreve (casirivimab / imdevimab) is included in the additional monitoring list as:

- it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Infection with SARS-CoV-2 may be asymptomatic or it may cause a wide spectrum of illness, ranging from a mild upper respiratory tract infection to severe acute respiratory distress syndrome and multiple organ failure (Wiersinga et al. 2020). Mortality in the most severe subgroup (i.e., those requiring mechanical ventilation) is reported to be as high as 40-50% when health care systems are overwhelmed (Wiersinga et al. 2020; Gray et al, 2021).

The majority of patients with SARS-CoV-2 infection exhibit relatively mild symptoms or are asymptomatic (Hu, 2020; Oran et al. 2020), especially considering the widespread vaccination efforts and high efficacy of currently available vaccines, suggesting that most cases can be managed in an outpatient setting. However, vaccines are not 100% effective and there have been reports of breakthrough infections that result in hospitalization. Although it is expected that the majority of breakthrough infections are likely to be mild to moderate, those considered high risk or those coming to the end of their vaccine immunity remain susceptible to severe disease. Furthermore, those that choose not to be vaccinated remain at risk with higher levels of morbidity and mortality.

Approximately 15% of COVID-19 patients develop severe symptoms characterized by the same clinical signs of mild to moderate COVID-19 and with one of the following: respiratory rate (≥30 breaths/minute); severe respiratory distress; or hypoxia requiring hospitalization and oxygen support (WHO 2020a) (Cascella et al. 2021). In approximately 5% of infected patients, the severe form of interstitial alveolar damage may rapidly progress to critical manifestations of the disease characterized by respiratory failure associated with acute respiratory distress syndrome that necessitates mechanical ventilation and support in an ICU. Complications include sepsis, septic shock and/or multi-organ failure including acute kidney and cardiac injury, and even death (WHO 2020a).

Studies among hospitalized patients have found that high SARS-CoV-2 viral load is associated with worse outcomes, including increased mortality rates (Magleby et al.2020) (Westblade et al. 2020). Community-based studies in non-hospitalized patients show symptomatic patients have higher viral load across both adults and children compared to asymptomatic individuals (Chung et al. 2021).).

SARS-CoV-2 variants of the S protein have continued to emerge, with variants of concern including the Alpha (B.1.1.7 lineage/United Kingdom origin), Beta (B.1.351/South Africa origin), Gamma (P.1/Brazil origin), Delta (B.1.617.2/India origin) variants and, the Omicron (B.1.1.529) variant. Irrespective of the country of initial reporting, these variants have driven waves of infection globally and are currently present in many countries, areas, or territories. These variants have led to significant changes in the virus and disease characteristics, such as increased transmissibility and/or virulence, and/or decreased effectiveness of vaccines and therapeutics. They continue to present a challenge for treatment and prophylaxis against the disease.

### 3.1.2. Available therapies and unmet medical need

Remdesivir (Veklury) is approved for the treatment of COVID-19 in the EU for adults and adolescents (≥12 years old and weighing ≥40 kg) with pneumonia requiring supplemental oxygen (low or high flow oxygen or other non-invasive ventilation at start of treatment). Other treatments include Kineret but only in adult patients with pneumonia requiring supplemental oxygen (low or high flow) who are at risk of progressing to severe respiratory failure determined by plasma concentration of suPAR ≥6 ng/mL. RoActemra is indicated in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. Finally, dexamathesone has been shown to be efficacious in those receiving oxygen alone or invasive mechanical ventilation via the RECOVERY trial and has since been implemented in multiple national guidelines for hospitalized patients.

Despite these approvals, there remains a significant unmet medical need for COVID-19 treatments in hospitalized patients. A broad hospitalized population, including adult and adolescent patients, could benefit from treatment with a single dose of casirivimab+imdevimab.

Additionally, emerging viral variants pose a very real threat to natural and vaccine immunity and therapeutic efficacy, highlighting the need to have as many treatment options available as possible.

### 3.1.3. Main clinical studies

RECOVERY is an investigator-initiated, individually randomized, controlled, open-label platform trial in which several treatments were compared with usual care in patients hospitalized with COVID-19. The multicenter study was conducted in the UK, Indonesia, and Nepal, with 127 hospitals in the UK taking part in the evaluation of casirivimab+imdevimab.

Table 2 Overview of Clinical Studies Contributing Efficacy and Safety Data to this Application (cont.)

| Study Population | Study Design | Number of Randomized Participants | Dose, Route, and Regimen | Study Duration/ Study Status |
|---|---|---|---|---|
| COV-2066 | | | | |
| Adult and adolescent patients ≥18 years of age, hospitalized for ≤72 hours at screening, who have a positive diagnostic test for SARS-CoV-2, on varying degrees of oxygen support at randomization. | Phase 1/2/3 adaptive, randomized, double-blinded, placebo-controlled master study. | Casirivimab+imdevimab 2400 mg IV: 757 patients<br>Casirivimab+imdevimab 8000 mg IV: 750 patients<br>Placebo: 745 patients | Phase 1, 2 and 3: In addition to background standard of care, patients in each cohort were randomized in a 1:1:1 allocation ratio to one of the following:<br>• casirivimab+imdevimab 2400 mg (1200 mg of each mAb) IV single dose<br>• casirivimab+imdevimab 8000 mg (4000 mg of each mAb) IV single dose<br>• Placebo IV single dose | 10 June 2020 to 9 April 2021[b]<br>Phase 1/2 safety and efficacy data were previously described in an abbreviated interim CSR (COV-2066 Abbreviated Interim CSR, 2021) finalized on 15 Jun 2021. The interim analysis was performed on patients who were randomized through 1 December 2020 in Phase 1 (Cohort 1 only) and Phase 2 (Cohorts 1, 2, and 3), using a data cut-off date of 9 December 2020 and a database lock date of 22 December 2020.<br>The final CSR (COV-2066 Final CSR, 2021) describes results from the final analyses of the study, including all phases and all cohorts based on a database lock date of 08 June 2021. This represents the final data for the main study. |

CSR = clinical study report; IV = intravenous; mAb = monoclonal antibody.

[a] For the casirivimab+imdevimab treatment evaluation. All randomized patients were to be followed-up until death, discharge from hospital, or 28 days after randomization (whichever occurred sooner). Additional information on longer term outcomes after 28-days post randomization could have been collected through review of medical records or linkage to medical databases where available, but this data was not available at the time of this submission.

[b] A subset of patients from Cohorts 1 and 1A at select study sites were enrolled in an ongoing long COVID sub-study, but this data was not available at the time of this submission.

COV-2066 was an adaptive Phase 1/2/3 randomized, double-blinded, placebo-controlled study to exclude futility (Phase 1/2) and evaluate efficacy and safety (Phase 3) of casirivimab+imdevimab in hospitalised adult and adolescent patients with COVID-19. The study was the first-in-human clinical trial for the combination mAb therapy product (casirivimab and imdevimab).

Table 2 Overview of Clinical Studies Contributing Efficacy and Safety Data to this Application

| Study Population | Study Design | Number of Randomized Participants | Dose, Route, and Regimen | Study Duration/ Study Status |
|---|---|---|---|---|
| RECOVERY | | | | |
| Hospitalized patients ≥12 years of age with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Pregnant or breastfeeding women were eligible for study inclusion. | Phase 3, adaptive, factorial, randomized, controlled, open-label, platform trial. | Casirivimab+imdevimab plus Usual Care N=4839<br>1. Seronegative at baseline: n=1633<br>2. Seropositive at baseline: n=2636<br>3. Unknown serostatus at baseline: n=570<br>Usual Care alone: n=4946<br>4. Seronegative at baseline: n=1520<br>5. Seropositive at baseline: n=2636<br>Unknown serostatus at baseline: n=790 | Casirivimab+imdevimab plus Usual Care: Casirivimab+imdevimab 8000 mg (4000 mg of each mAb), single dose IV infusion over 60 minutes.<br>Usual Care alone:<br>Usual standard of care. | 18 September 2020 to 22 May 2021[a]<br>Upon recommendation from the Trial's Steering Committee, recruitment into the casirivimab+imdevimab comparison was stopped on 22 May 2021. Based on the number of patients recruited and the overall number of events observed for the primary and secondary outcome measures, it was determined that the trial had sufficient power to detect plausible treatment effects. Casirivimab+imdevimab was subsequently removed from the protocol on 5 July 2021 (Amendment 16.0). |

## *3.2. Favourable effects*

Main results from the studies:

**RECOVERY**

**28-day all-cause mortality**

- All randomized participants (including those who were seronegative, seropositive and serostatus unknown): 20% (944/4839 participants) of participants in the casirivimab+imdevimab group died versus 21% (1026/4946 participants) of participants in the usual care alone group (rate ratio 0.94; 95% CI: 0.86 to 1.03; p=0.17)
- Participants seronegative at baseline: 24 % (396/1633 participants) died in the casirivimab+imdevimab group vs. 30% (451/1520 participants) in the usual care group (rate ratio: 0.80; 95% CI: 0.70–0·91; p=0.001)

**COV-2066**

**Mortality by day 29**

- Overall population (i.e., regardless of baseline serostatus) who were treated with casirivimab+imdevimab compared to placebo showed a relative risk reduction in mortality by day 29 (7.3% vs. 11.5%; relative risk reduction (RRR): 35.9%; 95% CI: 7.3%, 55.7%).
- Seronegative participants with casirivimab+imdevimab treatment compared to placebo showed a relative risk reduction in mortality by day 29 (6.7% vs. 15%; relative risk reduction: 55.6%; 95% CI: 24.2%, 74.0%).

**Discharged from hospital alive**

**RECOVERY**

- Seronegative participants with casirivimab+imdevimab treatment compared to those receiving usual care alone showed significant results with regard to this item (64% vs. 58%; rate ratio 1.19, 95% CI 1.08 to 1.30). The additional benefit with casirivimab+imdevimab was no longer observed in all randomized participants or in seropositive participants.

**COV-2066**

- Seronegative with casirivimab+imdevimab compared to placebo showed significant RRR with regard to this item (discharged from hospital alive) (90% vs. 81.3%; relative risk reduction: -10.8%; 95% CI -20.2%,-2.0%).

- In the case of the overall population when casirivimab+imdevimab was compared to placebo the RRR was -5.8% (88.8% vs. 84%; relative risk reduction: -5.8%; 95%: CI -11.1%, -0.6%). Seropositive participants had no additional benefit of being discharged alive from hospital with casirivimab+imdevimab.

## *3.3. Uncertainties and limitations about favourable effects*

RECOVERY is an ongoing investigator-initiated adaptive randomised controlled, open-label platform trial with a factorial design in which several treatments are compared with control (not receiving the treatment) in patients hospitalized with COVID-19, to investigate their effect on 28-day mortality. The primary analysis of the REGN-COV-2 part of this open-label study was initially planned to be conducted in all randomized subjects, but was restricted to seronegatives in a very late amendment to the SAP (i.e. one day prior to closure of enrolment and several weeks after the decision to stop enrolment was made by the trial steering committee. At the time of this decision, the DMC had conducted several interim analyses and results from previous comparisons of other treatments in this study were already known. Some of these comparisons included subjects who were also included in the REGN-COV-2 vs control comparison due to the factorial design.

The mortality related outcomes reached statistical significance only in seronegative participants, while a slightly higher mortality in seropositive participants (16% vs 15%) was observed. The majority of the patients in the trial received some form of oxygen therapy. No strong heterogeneity was observed in the treatment effect across the different subgroups of respiratory status.

Moreover, 14% of study participants had an unclear serostatus.

COV-2066 was prematurely terminated and only after the decision to terminate the study, the protocol specified that the exploratory phase 2 cohort 1A and the confirmatory phase 3 cohort 1 would be pooled.

Although the primary virological endpoints were met, the primary clinical endpoint was not met.

The data are considered exploratory.

## *3.4. Unfavourable effects*

**RECOVERY**

Five participants across both treatment groups (4/1792 participants in the ESAF randomized to casirivimab+imdevimab and 1/1715 participants in the ESAF randomized to usual care) experienced a severe allergic reaction.

Twenty (1.1%) participants had an IRR.

**COV-2066**

32 participants experienced AESIs of Grade ≥2 IRRs through Day 4. A higher proportion of participants experienced Grade ≥2 IRRs in the casirivimab+imdevimab 8000 mg dose group (2.0%) and 2400 mg dose group (1.5%) compared to the placebo group (0.8%).

Overall, 14 participants experienced AESIs of Grade > 2 hypersensitivity, through Day 29. A higher proportion of participants experienced Grade > 2 hypersensitivity reactions in the casirivimab+imdevimab 8000 mg dose group (1.0%) and 2400 mg dose group (0.7%) compared to the placebo group (0.3%).

**Post-marketing**

A total of 452 cases (575 events) of hypersensitivity were identified as having PTs falling within Hypersensitivity SMQ (narrow).

A total of 36 cases involving lack of efficacy were reported.

## 3.5. Uncertainties and limitations about unfavourable effects

The safety data collection addresses in RECOVERY deviated from traditional safety data collection. It was aimed to balance safety data collection with practical considerations to ensure that only key safety outcomes were captured. Given the circumstances of the study, which was conducted in a challenging situation for the health care system, this is acceptable.

Since the safety profile in hospitalised patients was expected to be complex and dynamic due the COVID-19 disease, which affects multiple organ systems and exacerbates concurrent clinical conditions considered risk factors for severe COVID-19, a targeted safety data collection was performed in study COV-2066, collecting relevant TEAEs in order to reduce background noise.

The reasons to restrict the collection of safety data is understandable. However, the safety profile in the fragile population cannot be fully established.

## 3.6. Effects Table

**Effects Table for Ronapreve treatment of coronavirus disease 2019 in hospitalized adults**

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| **Mortality by day 28** | RECOVERY All randomised pts | % | 20 | 21 | Large sample size (9785)<br>Complex open-label platform study<br>not stat. significant<br>Initially planned as primary EP | RECOVERY medRxiv preprint |
| | RECOVERY Seronegative pts | % | 24 | 30 | Large sample size (3153) in seronegative subgroup<br>Stat. significant primary EP (late amendment)<br>14% of study participants with unclear serostatus<br>Slightly higher mortality in seropositive pts (16% vs 15%) | RECOVERY medRxiv preprint |
| **Mortality by day 29** | COV-2066 All randomised PCR-positive pts (mFAS) | % | 7.3 | 11.5 | Exploratory<br>Study prematurely terminated, primary clinical endpoint not met | COV-2066 study report |
| | COV-2066 Seronegative subgroup | % | 6.7 | 15 | Exploratory<br>Study prematurely terminated, primary clinical endpoint not met | COV-2066 study report |
| **Discharge alive by day 28** | RECOVERY All randomised pts | % | 70 | 69 | | RECOVERY medRxiv preprint |
| | RECOVERY Seronegative pts | % | 64 | 58 | | RECOVERY medRxiv preprint |
| | COV-2066 All mFAS | % | 89 | 86 | | COV-2066 study report |
| | COV-2066 Seronegative subgroup | % | 90 | 81 | | COV-2066 study report |

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Unfavourable Effects** | | | | | | |
| IRR | Grade ≥2 infusion-related reactions through Day 4 | % | 2.0 (8000 mg dose group)<br><br>1.5 (2400 mg dose group) | 0.8 | | COV-2066 study report |
| IRR | Grade ≥2 hypersensitivity reactions through Day 29 | % | 1 (8000 mg dose group)<br><br>0.7 (2400 mg dose group) | 0.3 | | |
| IRR | Infusion related reaction | % | 20 (1,1 %) | | | RECOVERY medRxiv preprint |
| Allercic reaction | | N | 4/ 1792 | 1/1715 | | RECOVERY medRxiv preprint |
| Hypersensitivity reactions | | N | 452 cases (575 events) | | | PM data clinical summary safety |
| Lack of efficacy | | N | 36 cases | | | PM data clinical summary safety |

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

In hospitalised seronegative patients, a benefit regarding 28-day all-cause mortality and discharged from hospital alive by day 28 was observed in RECOVERY. In seropositive patients and in the overall population such a benefit was not seen, even slightly higher mortality in seropositive participants (16% vs 15%) was observed.

In COV-2066-point estimates in the seronegative subgroup are directionally consistent with point in the same direction as the results observed in RECOVERY, although of different magnitude.

The reduction in mortality related outcomes is clinically meaningful.

However due to the methodological uncertainties as discussed in the report, the RECOVERY data are not as robust as usually expected for a confirmatory trial. Data of COV-2066 cannot be considered confirmatory as well, however the data are considered supportive.

Beside a low number of IRR, the safety events were either due to COVID-19/COVID-19 progression or worsening of the patients' concurrent/background clinical condition, or in line with the known safety profile of Ronapreve. No dose dependency of the events was observed.

The post-marketing did not reveal new signals/safety concerns.

### 3.7.2. Balance of benefits and risks

The efficacy data show a clinical benefit in a subgroup of COVID-19 patients i.e., seronegative COVID-19 patients that were hospitalised. Given the main disease manifestation of COVID-19, it is likely that patients were hospitalised because of respiratory distress as indicated by the need for oxygen supplementation in the majority of patients.

In response to the CHMP comments, the MAH provided a revised proposal for the indication restricting to patients on supplemental oxygen that are either seronegative for SARS-CoV-2 or moderately to severely immunocompromised. The MAH provided of number of arguments to support the view that restricting the indication to seronegative patients may not capture all patients that may benefit from therapy. While some of the arguments may indeed be correct (e.g., seropositivity does not reflect neutralizing capacity, changes in epidemiology) there are no convincing data within RECOVERY to support this view and therefore the indication should reflect the recruited patient population to the extent possible.

As regards the argument to alternatively (instead of SARS-CoV-2 serostatus) include patients that are immunocompromised there are not data from the RECOVERY trial to support this view. Data from COV-2066 show a trend for reduced death/mechanical ventilation in immunocompromised but this is not surprising as immunocompromise was associated with seronegativity in the trial.

The initially proposed qualifier of "hospitalisation" was removed from the indication following the CHMP comments. While hospitalisation was an inclusion criterion for RECOVERY it is an ambiguous characterisation of eligible patients considering medical practice in Europe overall.

The majority of patients in RECOVERY had respiratory compromise and therefore oxygen supplementation (and more intensive respiratory support) is a good reflection of the patient population in addition to SARS-CoV-2 seronegativity.

The MAH has proposed a posology that increases the dose with perceived increasing severity of COVID-19. Even though the justification for the high dose of 8000 mg is not convincing it is most sensible to use the dose employed in RECOVERY for the new indication since the data from RECOVERY are the basis for the application. While the effort by the MAH to propose differential dosing across the disease spectrum/severity is acknowledged, a posology that is not backed by the data from the RECOVERY trial was not accepted. Currently it is not clear what distinguishes the small subgroup from RECOVERY that did not require supplemental oxygen from the already approved treatment population that would justify a different posology and therefore a specific posology based on a baseline characteristic "hospitalisation" was not agreed. In summary, one posology for patients on supplemental oxygen would be acceptable. The SmPC is updated accordingly.

The safety profile is favourable.

### 3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

## *3.8. Conclusions*

The overall B/R of Ronapreve is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |

Extension of indication to include treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg and receiving supplemental oxygen, who have a negative SARS-CoV-2 antibody test result for Ronapreve; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SmPC are updated.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

## *Additional market protection*

The MAH submitted at the start of the procedure a request for consideration that the new indication brings significant benefit in comparison to existing therapies in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. During the assessment, the CHMP raised questions concerning the significant benefit. Prior to the adoption of the CHMP opinion, the company withdrew its request for additional market protection. As a result of the MAH withdrawal of this ancillary request, no opinion on the additional market protection is adopted by CHMP.

# 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

## *Scope*

Please refer to the Recommendations section above.

## *Summary*

Please refer to Scientific Discussion ‘Ronapreve-H-C-005814-II-002