Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

National Procedure

Ronapreve 120 mg/mL solution for injection or infusion

casirivimab, imdevimab

PLGB 00031/0925

The Public Assessment Report summarises the initial assessment at the time of approval in August 2021. The text in the original report remains unchanged.

Our advice is regularly updated on the basis of significant new data and our latest advice can be found in the Summary of Product Characteristics.

ROCHE PRODUCTS LIMITED

LAY SUMMARY

Ronapreve 120 mg/mL solution for injection or infusion
casirivimab, imdevimab

This is a summary of the Public Assessment Report (PAR) for Ronapreve 120 mg/mL solution for injection or infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Ronapreve in this lay summary for ease of reading.

For practical information about using Ronapreve, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Ronapreve and what is it used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Ronapreve is used to treat patients with confirmed acute Covid-19 infection and to prevent acute Covid-19 infection.

How does Ronapreve work?
Ronapreve is a combination of two active substances ‘casirivimab’ and ‘imdevimab’. Casirivimab and imdevimab are a type of protein called ‘monoclonal antibodies’. Casirivimab and imdevimab bind to part of the spike protein receptor binding domain (RBD) of SARS-CoV-2. Casirivimab and imdevimab, individually and combined, block RBD binding to the human angiotensin converting enzyme-2 (ACE2) receptor thereby preventing SARS-CoV-2 from entering human cells and consequentially stopping Covid-19 infection.

Ronapreve is intended to compensate/substitute for endogenous antibodies in those individuals who have yet to mount their own immune response to block infection.

How is Ronapreve used?
This medicine is a solution for injection/infusion (sterile concentrate) and the route of administration is intravenous infusion or subcutaneous injection.

The dosage is 600 mg of casirivimab and 600 mg of imdevimab administered together either as a single intravenous (IV) infusion via pump or gravity (where the pressure of gravity delivers Ronapreve into the IV line at a steady and safe rate using a manually operated clamp) or by subcutaneous (SC) injection.

Casirivimab and imdevimab should be given concurrently as soon as possible following exposure to SARS-CoV-2.

For individuals who require repeat dosing for ongoing prevention, i.e. those who have a medical condition making them unlikely to respond to or be protected by vaccination:
- the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by IV infusion or SC injection.

- subsequent doses are 300 mg of casirivimab and 300 mg of imdevimab by IV infusion or SC injection once every 4 weeks.
- repeat dosing regimens for prevention of Covid-19 allow for switching from IV infusion to SC injection or vice versa over the course of treatment.

The rate of infusion may be slowed, interrupted or discontinued if the patient develops any signs of infusion-associated events or other adverse events.

Doses should not be missed and the dosing regimen should be adhered to as closely as possible. If a dose of Ronapreve is missed it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the appropriate interval between doses.

The safety and efficacy of Ronapreve in children < 12 years of age has not yet been established and no data are available. No dosage adjustment is recommended in paediatric individuals ≥ 12 years of age and older and weighing ≥ 40 kg.

For further information on how Ronapreve is used, refer to the Patient Information Leaflet (PIL) and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of Ronapreve have been shown in studies?
In Study COV-20145 Ronapreve was studied in adult outpatients with SARS-Cov-2 infection following a single IV or single subcutaneous dose of Ronapreve. Patients who took Ronapreve had a statistically significant reduction in viral load compared to placebo. The largest reductions in viral load relative to placebo were measured in patients with high viral load.

In Study COV-2067 Ronapreve was studied in adult outpatients with Covid-19 infection who received doses of Ronapreve up to 7 times the recommended dose. All patients had at least one risk factor for severe Covid-19. Patients who took Ronapreve had a 70% relative risk reduction in Covid-19-related hospitalisation or death compared to placebo. The median time to symptom resolution for patients who took Ronapreve was 10 days compared with 14 days for placebo.

In Study COV-2069 Ronapreve was studied in adult patients with a negative Covid-19 RT-PCR test result at enrolment into the study. Patients who took Ronapreve had an 81% relative risk reduction in the development of Covid-19 compared to placebo.

In the same study, Ronapreve was studied in asymptomatic adult patients with a positive Covid-19 RT-PCR test at enrolment into the study. Patients who took Ronapreve had 35% relative risk reduction in the development of Covid-19 compared to placebo.

In Study HV-2093 the effects of repeat SC doses (up to 6 monthly doses) of Ronapreve were studied in adult patients who were not infected with Covid-19 at the point of enrolment. During the 6-month period, patients who took Ronapreve had a 92% relative risk reduction in Covid-19 versus placebo.

What are the possible side effects of Ronapreve?

The most common side effects with Ronapreve (which may affect more than 1 in 10 people) are redness, itching, bruising, swelling, pain or itchy rash at the injection site. For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Ronapreve approved?

Ronapreve has been shown to be effective in the treatment of patients with confirmed acute Covid-19 infection and to prevent acute Covid-19 infection. Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Ronapreve has been authorised with a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.

What measures are being taken to ensure the safe and effective use of Ronapreve?

All new medicines that are approved have a Risk Management Plan (RMP) to ensure they are used as safely as possible. A Risk Management Plan (RMP) has been agreed for Ronapreve in the UK. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

All side effects reported by patients/healthcare professionals are continuously monitored. Any new safety signals identified will be reviewed, and if necessary, appropriate regulatory action will be taken. To facilitate timely patient access to treatment, the MHRA has approved a batch specific variation for cartons of 'casirivimab and imdevimab 120 mg/ml concentrate for solution for infusion', which have been used around the world during the Covid-19 pandemic, for use in the UK under the conditions required for Ronapreve 120 mg/ml solution for injection or infusion. A Direct Healthcare Professional Communication (DHPC) has been agreed as part of this variation to highlight the difference between the labels approved as part of the PLGB conditional marketing authorisation and pandemic labels.

Other information about Ronapreve

A Conditional Marketing Authorisation for Ronapreve was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 19 August 2021. A Regulation 174 is in place to supply Northern Ireland (NI).

The full PAR for Ronapreve follows this summary.

This summary was last updated in October 2022.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Ronapreve 120 mg/mL solution for injection or infusion (PL 00031/0925) could be approved.

The product is approved for the following indication: prophylaxis and treatment of acute Covid-19 infection.

The active substances are casirivimab and imdevimab, which are two neutralising IgG1 recombinant human monoclonal antibodies (mAbs) produced by recombinant DNA technology in Chinese hamster ovary cells.

The casirivimab (IgG1κ) and imdevimab (IgG1λ) antibodies are unmodified in the Fc regions. Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2 with dissociation constants KD = 45.8 pM and 46.7 pM, respectively. Both mAbs, individually and in combination, blocked RBD binding to the human ACE2 receptor with IC50 values of 56.4 pM, 165 pM and 81.8 pM, respectively.

Casirivimab and imdevimab are intended to compensate/substitute for endogenous antibodies in those individuals who have yet to mount their own immune response.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full-dossier application. All non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

This product has received a Conditional Marketing Authorisation (CMA). A temporary Regulatory 174 Authorisation is in place to cover supply in Northern Ireland (NI). Should the European Medicines Agency grant a CMA for Ronapreve, it would apply in NI and the Regulation 174 would no longer be in place.

Conditional MAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks is required, and has been provided for Ronapreve. The CMA for Ronapreve, including the provision of any new information, will be reviewed every year and this report will be updated as necessary.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan MHRA-100052-PIP01-21 and MHRA-100053-PIP01-21. At the time of the submission of the application, the PIPs were not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 5 August 2021 regarding the monitoring of emergence of viral variants and the use of Ronapreve in immunocompromised individuals. It was agreed that the Applicant should further investigate the emergence of viral variants in patients treated with Ronapreve. With regard to immunocompromised individuals, the Applicant plans to submit a retrospective analysis of Ronapreve-treated patients with Covid-19 and primary or secondary immunodeficiency with associated antibody disorders. The Applicant will also capture 'use in immunocompromised patients' and include this important information in the RMP.

A national marketing authorisation was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 19 August 2021.

II QUALITY ASPECTS

II.1 Introduction

This product consists of the active substances casirivimab and imdevimab in the following presentations:

Co-packaged 6 mL single-use vials
Each casirivimab 6 mL vial contains 300 mg of casirivimab per 2.5 mL (120 mg/mL).
Each imdevimab 6 mL vial contains 300 mg imdevimab per 2.5 mL (120 mg/mL).

Co-packaged 20 mL multidose vials
Each casirivimab 20 mL multidose vial contains 1 332 mg of casirivimab per 11.1 mL (120 mg/mL).
Each imdevimab 20 mL multidose vial contains 1 332 mg imdevimab per 11.1 mL (120 mg/mL).

Casirivimab and imdevimab are two neutralising IgG1 recombinant human monoclonal antibodies produced by recombinant DNA technology in Chinese hamster ovary cells.

In addition to casirivimab and imdevimab, this product also contains the excipients L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose and Water for Injection.

The finished product is provided in clear Type 1 glass vials in 20 mL or 6 mL vials.
Each carton contains 2 vials per package:

Ronapreve 120 mg/ml solution for infusion or injection, single-use vial
Pack of two 6 mL clear Type I glass vials with rubber stopper containing one vial of 2.5 mL solution of 300 mg of casirivimab and one vial of 2.5 mL solution of 300 mg of imdevimab.

Ronapreve 120 mg/mL solution for infusion or injection, multidose vials
Pack of two 20 mL clear Type I glass vials with rubber stopper containing one vial of 11.1 mL solution of 1 332 mg of casirivimab and one vial of 11.1 mL solution of 1 332 mg of imdevimab.

II.2 ACTIVE SUBSTANCES

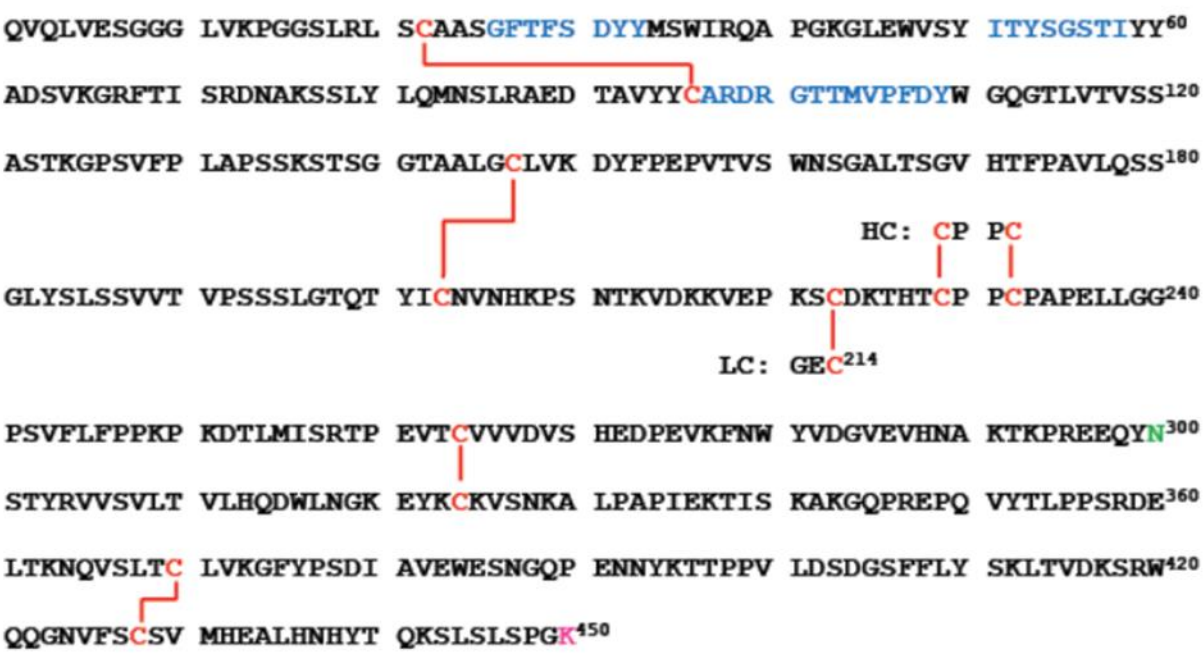
rINN: casirivimab

Chemical Name: Immunoglobulin G1, anti-(severe acute respiratory syndrome coronavirus 2 spike glycoprotein); human monoclonal REGN10933 γ1-heavy chain disulfide with human monoclonal REGN10933 κ-light chain, bisdisulfide dimer

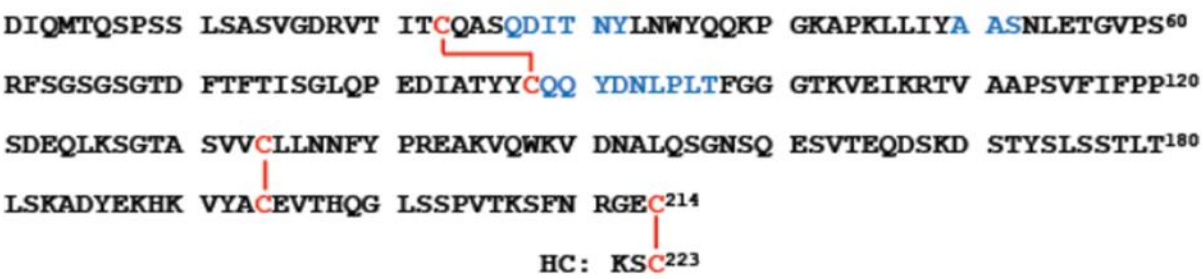
Molecular Formula: $C_{6454}H_{9976}N_{1704}O_{2024}S_{44}$

AA sequence and schematic representation:

REGN10933 Heavy Chain



REGN10933 Light Chain



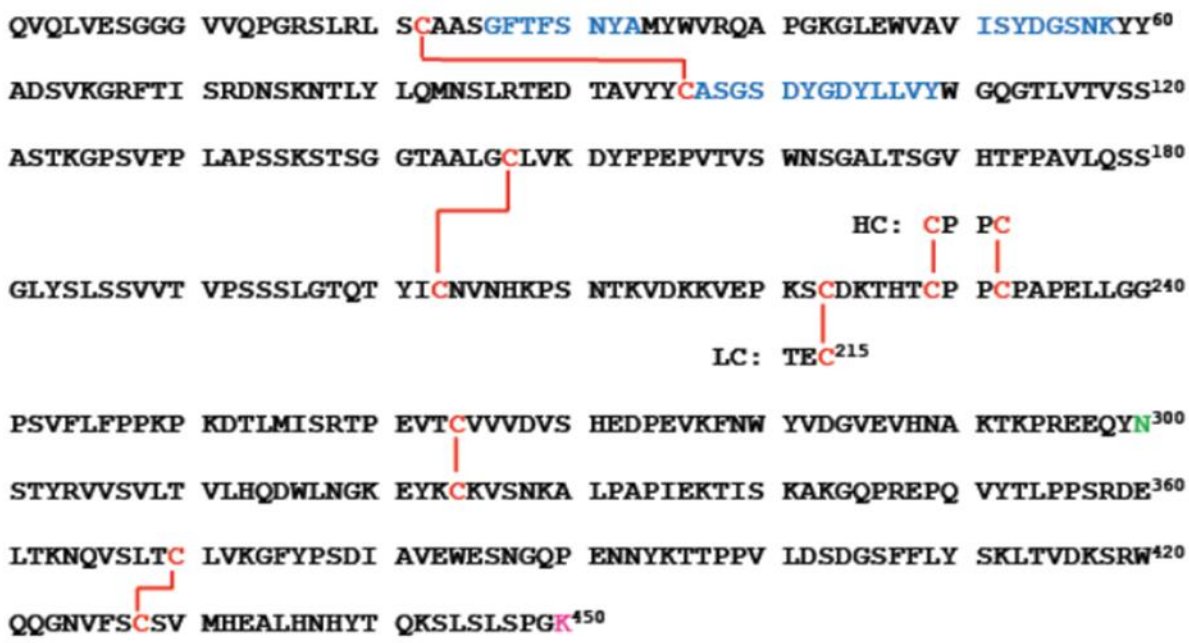
Molecular Weight: 145.23 kDa
Appearance: Colourless to pale yellow liquid
Solubility: At least 183.5 g/L

rINN: **imdevimab**
Chemical Name: Immunoglobulin G1, anti-(severe acute respiratory syndrome coronavirus 2 spike glycoprotein); human monoclonal REGN10987 γ1-heavy chain disulfide with human monoclonal REGN10987 κ-light chain, bisdisulfide dimer

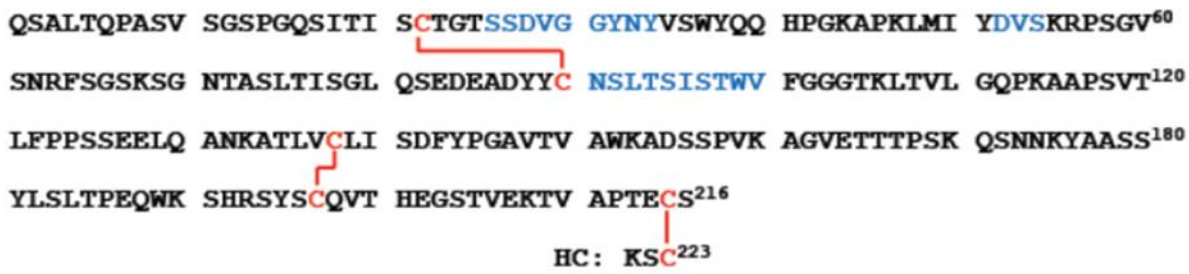
Molecular Formula: $C_{6396}H_{9882}N_{1694}O_{2018}S_{42}$

AA sequence and schematic representation:

REGN10987 Heavy Chain



REGN10987 Light Chain



Molecular Weight:	144.14 kDa
Appearance:	Colourless to pale yellow liquid
Solubility:	At least 182.1 g/L

Casirivimab and imdevimab are not the subject of a European Pharmacopoeia monograph. Casirivimab and imdevimab are each manufactured using the same platform process for Ig molecules.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied.

Appropriate structural characterisation data have been supplied for the active substances. All potential known impurities have been identified and characterised.

Appropriate specifications are provided for the active substances. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. The reference standards used are created in house and adequate tests and specifications are in place to control these.

Suitable specifications have been provided for all packaging used.

Appropriate stability data have been generated supporting the proposed shelf-life when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. There are no novel excipients in this product.

No excipients of animal or human origin are used in the finished products.

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Adequate data from viral clearance studies using a panel of viruses has been provided to show that the manufacturing process is able to remove and inactivate viruses.

Finished Product Specification

The finished product specifications at release and end of shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. The same reference standards are used as described in the drug substance section.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 12 months for the unopened vial with the storage conditions ‘Store in a refrigerator (2 °C - 8 °C). Do not freeze. Do not shake. Keep the vials in the original carton in order to protect from light.’ is acceptable.

The following in-use conditions also apply:

<u>Co-packaged 20 mL multidose vials</u>
After initial puncture: If not used immediately, the product in the vial can be stored for 6 hours at room temperature up to 25 °C or for no more than 24 hours refrigerated between 2 °C to 8 °C. Beyond these times and conditions, in-use storage is the responsibility of the user.

<u>Co-packaged 6 mL single-use vials</u>
After initial puncture: the medicinal product should be used immediately, any remaining product should be discarded.

<u>Diluted solution for IV administration</u>
Solution in vial requires dilution prior to administration. The prepared infusion solution is intended to be used immediately. If immediate administration is not possible, store the

diluted casirivimab and imdevimab infusion solution at 2ºC to 8ºC for no more than 24 hours and at room temperature up to 25°C for no more than 6 hours. Beyond these times and conditions, in-use storage is the responsibility of the user. If refrigerated, allow the IV infusion bag to equilibrate to room temperature for approximately 30 minutes prior to administration.

Storage of syringes for subcutaneous administration
This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes at 2ºC to 8ºC for no more than 24 hours and at room temperature up to 25ºC for no more than 4 hours. Beyond these times and conditions, in-use storage is the responsibility of the user. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 10-15 minutes prior to administration.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

The following non-clinical studies were submitted with this application. In this report, casirivimab and imdevimab are also referred to, respectively, as REGN10933 and REGN10987.

Primary pharmacodynamics
Study r10933-ph-20088-sr-01v1 - determination of kinetic and equilibrium binding parameters for the interaction of REGN10933, REGN10987, and REGN10989 with SARS-CoV-2 spike protein and receptor binding domain.

Study r10933-ph-20089-sr-01v1 - determination of competitive binding properties of REGN10933, REGN10987, and REGN10989 to SARS-CoV-2 spike protein receptor binding domain.

Study r10933-ph-20155-sr-01v1 - characterization of REGN10933 and REGN10987 binding to SARS-CoV-2 receptor binding domain using cryogenic electron microscopy.

Study r10933-ph-20091-sr-01v1 - assessment of REGN10933, REGN10987, and REGN10989 neutralization activities against SARS-CoV-2 virus and vesicular stomatitis virus pseudotyped with SARS-CoV-2 spike protein.

Study r10933-ph-20100-sr-01v1 - assessment of escape mutations in vesicular stomatitis virus encoding SARS-CoV-2 S protein selected in the presence of REGN10933, REGN10987, and REGN10989.

Study r10933-ph-20101-sr-01v1 - assessment of antibody-dependent enhancement of entry of vesicular stomatitis virus pseudotyped with SARS-CoV-2 S protein in the presence of REGN10933, REGN10987, and REGN10989.

Study r10933-ph-20090-sr-01v1 - *in vitro* functional characterization of REGN10933, REGN10987, and REGN10989.

Challenge studies
Study r10933-ph-20161-pd-01v1 - graphical representation and statistical analysis of efficacy of monoclonal antibodies for the treatment and prevention of SARS-CoV-2 infection in Syrian golden hamsters.

Study r10933-ph-20093-sr-01v1 - graphical representation and statistical analysis of efficacy of monoclonal antibodies for the treatment and prevention of SARS-CoV-2 infection in Rhesus Macaques.

Study r10933-ph-20160-sr-01v1 - graphical representation and statistical analysis of prophylactic efficacy of monoclonal antibodies for prevention of SARS-CoV-2 infection in Rhesus Macaques.

Study R10933-PH-21015-SR-01V1 - assessment of antibody-dependent enhancement (ADE) of SARS-CoV-2 infection of primary human macrophages in the presence of REGN10933, REGN10987, and REGN10989.

Study r10933-ph-20192-sr-01v1 - evaluation of antibody dependent enhancement of monoclonal antibodies for the prevention of SARS-CoV-2 infection in Syrian golden hamsters.

Pharmacokinetics
Study r10933-av-20085-va-01v1 – validation of a bioanalytical method for the quantitative measurement of total REGN10933 and REGN10987 in monkey serum.

Study r10933-pk-20071 - a single dose intravenous and subcutaneous pharmacokinetics study with REGN10933 and REGN10987 alone or in combination in Cynomolgus monkeys.

Study r10933-pk-20074 - a single dose intravenous and subcutaneous pilot pharmacokinetic study with REGN10933, REGN10987, REGN10989, and REGN10934 in Cynomolgus monkeys.

Toxicology
Study R10933-tx-20065 - a GLP tissue cross-reactivity study with biotinylated REGN10933 and REGN10987 in normal human and Cynomolgus monkey tissues.

Study r10933-tx-20129 - a GLP tissue cross-reactivity study with biotinylated REGN10933 and REGN10987 in selected foetal human tissues.

Study r10944- tx-20064 - a 4-week intravenous, subcutaneous toxicology study of REGN10933 and REGN10987 in Cynomolgus monkeys followed by an 8-week recovery period.

All studies were conducted in accordance with current Good Laboratory Practice (GLP).

III.2 Pharmacology

Study r10933-ph-20088-sr-01v1
The objective of study r10933-ph-20088-sr-01v1 was to determine binding kinetics of 3 antibodies, REGN10933, REGN10987 and REGN10989, with differing constructs: recombinant monomeric SARS-CoV-2 receptor binding domain, recombinant dimeric SARS-CoV-2 receptor binding domain and recombinant stabilised, trimerised SARS-CoV-2 S protein. The test articles were IgG1 antibodies that target the spike protein from SARS CoV-2 virus.

Surface plasmon resonance (SPR) technology was used to determine the kinetic and equilibrium binding parameters for the interaction of sensor surface-captured REGN10933 (casirivimab) and REGN10987 (imdevimab) with soluble recombinant monomeric or dimeric SARS-CoV-2 RBD protein, and stabilized, trimerized SARS-CoV-2 S protein at pH 7.4 and 25°C.

Table 1: Experimental details for kinetic binding interactions

Recombinant Protein Injected Over Anti-SARS-CoV-2 S Protein mAb Surfaces	Concentration Range (2-Fold Serial Dilution)	Duration of the Dissociation Phase
Monomeric SARS-CoV-2 RBD.mmH	1.56 to 50nM	5 min
Dimeric SARS-CoV-2 RBD.mFc	0.16 to 5nM	10 min
Stabilized, trimerized SARS-CoV-2 S protein	0.78 to 12.5nM	10 min

Results

These experiments showed that REGN10933, REGN10987 and REGN10989 each bound each monomeric and dimeric recombinant SARS-CoV-2 receptor binding domain with nanomolar and picomolar affinities, respectively and bound stabilised, trimerised SARS-CoV-2 S protein with picomolar affinities. Equilibrium dissociation constants (KD) and further details (ka and kd values) are summarised in table 2 for results at 37°C: results at 25°C are shown in table 3 below.

Table 2: Summary of kinetic binding parameters for the interaction of REGN10933, REGN10987 and REGN10989 with SARS-CoV-2 RBD proteins or stabilised, trimerized SARS-CoV-2 S protein at 37°C and pH 7.4

anti-SARS-CoV-2 S Protein mAbs	Protein Injected Over Surface-Captured mAbs	Kinetic Binding Parameters			
		k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (M)	$t_{½}$ (min)
REGN10933	Monomeric SARS-CoV-2 RBD.mmH	3.00E06	1.01E-02	3.37E-09	1.1
	Dimeric SARS-CoV-2 RBD.mFc	6.90E06	9.65E-05	1.40E-11	119.7
	Stabilized, trimerized SARS-CoV-2 S protein	1.90E06	7.90E-05	4.17E-11	146.2
REGN10987	Monomeric SARS-CoV-2 RBD.mmH	8.07E05	3.65E-02	4.52E-08	0.3
	Dimeric SARS-CoV-2 RBD.mFc	9.18E06	2.74E-04	2.98E-11	42.2
	Stabilized, trimerized SARS-CoV-2 S protein	1.34E06	5.74E-05	4.28E-11	201.2
REGN10989	Monomeric SARS-CoV-2 RBD.mmH	3.81E06	1.39E-02	3.65E-09	0.8
	Dimeric SARS-CoV-2 RBD.mFc	8.86E06	1.14E-04	1.29E-11	101.2
	Stabilized, trimerized SARS-CoV-2 S protein	2.38E06	9.82E-05	4.12E-11	117.6

Table 3: Binding affinities for the interaction of REGN10933, REGN10987 and REGN10989 with SARS-CoV-2 protein and receptor binding domain

mAb(s)	Binding Affinities (K_D) [M] at 25°C and pH 7.4		
	Monomeric SARS-CoV-2 RBD	Dimeric SARS-CoV-2 RBD	Stabilized, Trimerized SARS-CoV-2 S Protein
REGN10933	1.83E-09	1.87E-11	4.58E-11
REGN10987	3.15E-08	9.85E-11	4.67E-11
REGN10989	1.31E-09	1.72E-11	5.24E-11

Study r10933-ph-20089-sr-01v1

Study r10933-ph-20089-sr-01v1 determined the ability of REGN10933, REGN10987, and REGN10989 to (1) each bind monomeric SARS-CoV-2 receptor binding domain (RBD); (2)

bind the receptor binding domain individually and as the REGN-COV2 combination and (3) block the interaction of the receptor binding domain with the receptor ACE2 individually and as the REGN-COV2 combination.

The ability of REGN10933 and REGN10987 to simultaneously bind SARS-CoV-2 RBD was assessed in a 2-step binding experiment using SPR technology at 25°C. Surface-immobilized recombinant monomeric SARS-CoV-2 RBD protein was saturated with the first antibody followed by a subsequent injection of second antibody, and binding signals of both antibodies were compared. Both possible orders of addition were tested.

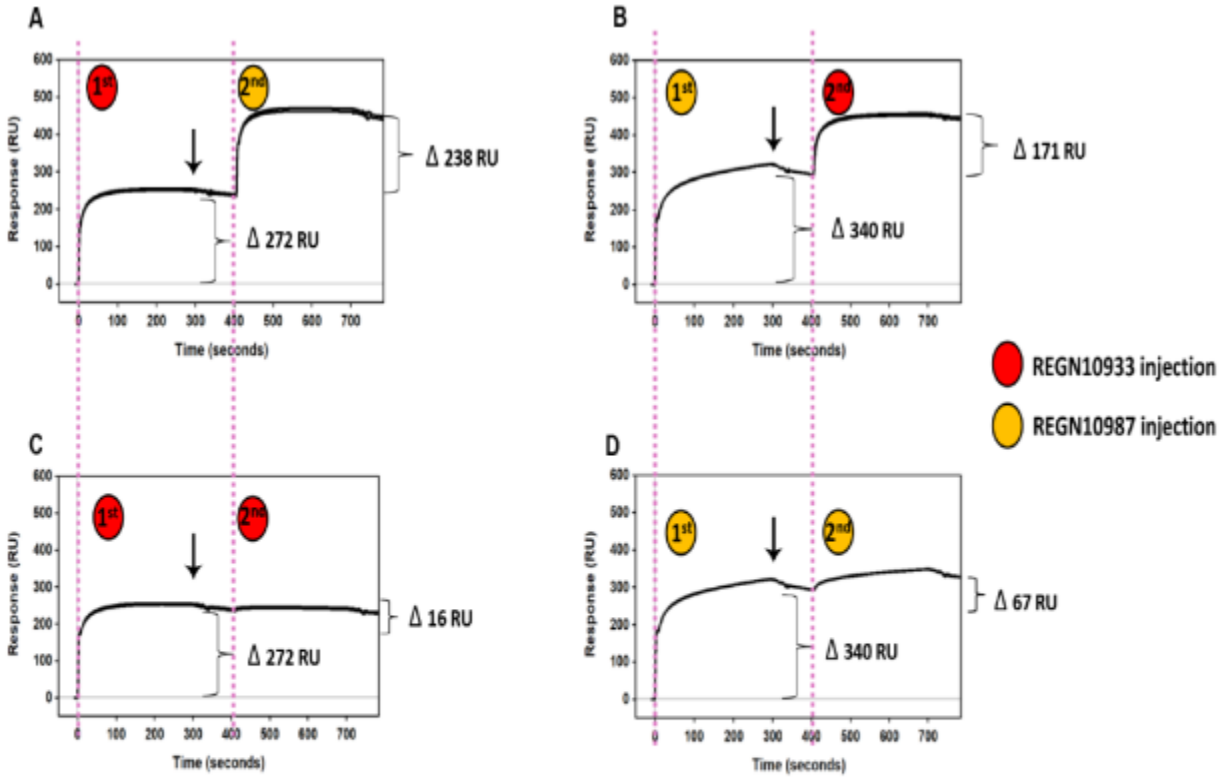
An enzyme-linked immunosorbent assay (ELISA) was used to determine the ability of REGN10933, REGN10987, and REGN-COV2 to bind immobilized recombinant monomeric SARS-CoV-2 RBD protein.

An ELISA was used to determine the ability of REGN10933, REGN10987, and REGN-COV2 to block binding of recombinant dimeric SARS-CoV-2 RBD protein to immobilized recombinant human ACE2 ectodomain protein.

Results
REGN10987 bound to the receptor binding domain protein that was pre-saturated with REGN10933 (figure 1A): REGN10933 bound receptor binding domain protein that was pre-saturated with REGN10987 (figure 1B). REGN10989 competed with REGN10933 and REGN10987 for binding to SARS-CoV-2 receptor binding domain protein. When surfaces were first saturated with REGN10933 (figure 1C) or REGN10989, subsequent injection with REGN10933 or REGN10989, respectively, displayed minimal additional binding. When REGN10987 was the first injection, subsequent injection with REGN10987 resulted in a fraction of additional binding, likely due to partial dissociation of the surface bound REGN10987 from the first injection (figure 1D).

These results are consistent with the view that REGN10933 and REGN10987 bind to non-overlapping epitopes of the SARS-CoV-2 receptor binding domain. REGN10989 competes with REGN10933 and REGN10987 for binding to SARS-CoV-2 receptor binding domain, suggesting that there may be overlap between the epitope bound by REGN10989 and the epitopes bound by REGN10933 and REGN10987.

Figure 1: REGN10933 and REGN10987 bind non-overlapping epitopes on SARS-CoV-2 RBD



Representative sensorgrams showing stepwise increase in binding response, expressed as resonance units (RU), upon sequential injection of REGN10933 and REGN10987 over surface-immobilized RBD.mmH captured on anti-His CM5 sensor surface. Panel A shows REGN10933 as the first mAb injection followed by REGN10987 as the second mAb injection. Panel B shows REGN10987 as the first mAb injection followed by REGN10933 as the second mAb injection. Panels C and D show control experiments where the same mAb was used in both sequential injections: C) REGN10933 and D) REGN10987. The binding response traces are shown in black. The average RU values obtained from duplicate mAb injections are shown on the graphs. The vertical dotted lines denote the time at which each injection took place. The arrows indicate the start of the dissociation phase of the first mAb. The increase in binding signal (Δ RU) following each injection is indicated next to the binding response trace.

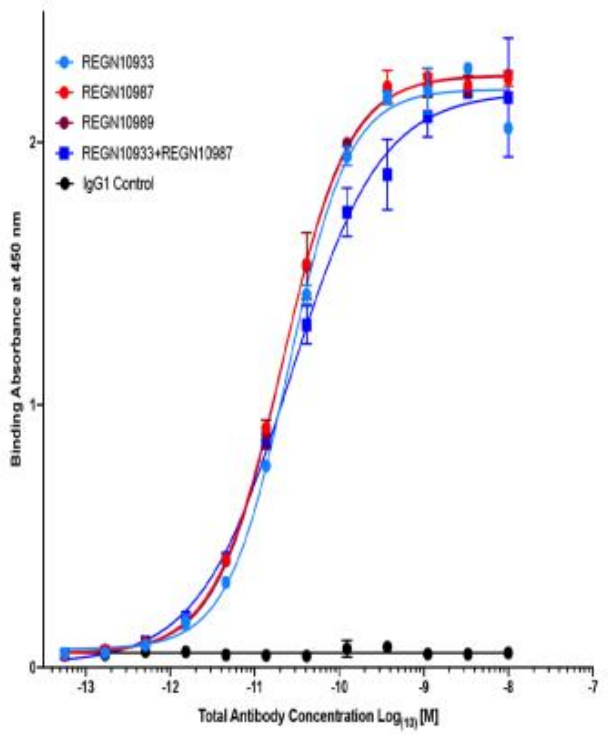
When assessed by ELISA, each of REGN10933, REGN10987, their combination (REGNCOV-2) and REGN10989 were found to bind to SARS-CoV-2 receptor binding domain in a concentration-dependent manner with subnanomolar EC_{50} values, whereas no binding was seen with a control IgG1 antibody (table 4, figure 2). Antibodies were also tested for their ability to block binding between dimeric SARS CoV-2 RBD and human ACE2: first, it was confirmed that dimeric SARS-CoV-2 RBD binds human ACE2: the EC_{50} was 150pM. Each of REGN10933, REGN10987, REGN10989 and REGN-CoV-2 mediated concentration-dependent blocking of this binding with IC_{50}s in the picomolar range, whereas negligible blocking was observed with IgG1 control (figure 3, table 5).

Table 4: Summary of EC_{50} of REGN10933, REGN10987, REGN10989, and REGN-COV2 binding to SARS-CoV-2 RBD.

Antibody	EC_{50} [M]
REGN10933	2.52E-11
REGN10987	2.10E-11
REGN10989	2.13E-11
REGN-COV2 (REGN10933+REGN10987)	2.57E-11
IgG1 Control	ND

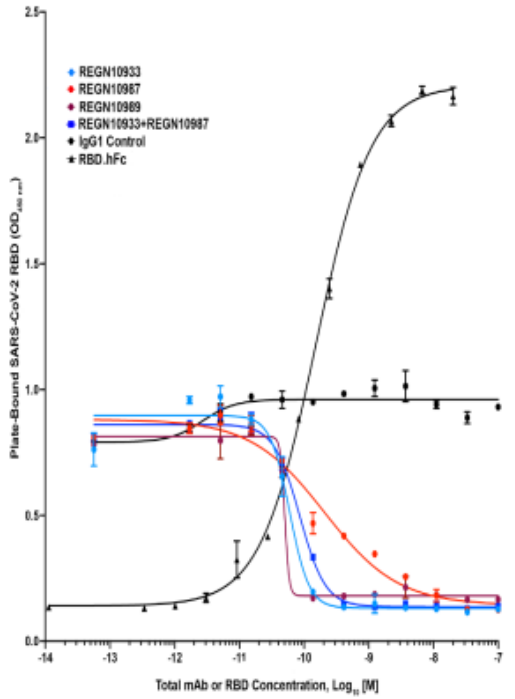
Abbreviation(s): ND, not determined because concentration-dependent binding was not observed

Figure 2: REGN10933, REGN10987, REGN10989, and REGN-COV2 Display Concentration-Dependent Binding to SARS-CoV-2 RBD



Binding of REGN10933, REGN10987, REGN10989, REGN-COV2 (REGN10933+REGN10987), or IgG1 (isotype) control at a range of concentrations (170fM to 10nM) to immobilized RBD.mFH was evaluated by ELISA. The no antibody control condition is shown on the graph at 56fM. The EC_{50} values for binding of each antibody or antibody combination were determined. Data from an assay performed in duplicate wells are plotted as mean ± SD; error bars may be obscured by data symbols. Binding of antibodies was detected using horseradish peroxidase

Figure 3: REGN10933, REGN10987, REGN10989, and REGN-COV2 Block Binding of SARS-CoV-2 RBD to Human ACE2



A constant concentration of RBD.hFc (100pM) was pre-incubated with either REGN10933, REGN10987, REGN10989, REGN-COV2 (REGN10933+REGN10987), or IgG1 (isotype) control at concentrations ranging from 1.7pM to 100nM, including a no-antibody control plotted at 56fM. A dose-response curve of RBD.hFc is shown at concentrations ranging from 340fM to 20nM, including a no-RBD control plotted at 11fM. The antibody-RBD mixtures were then added to wells of an ELISA plate that contained human ACE2.his captured by immobilized Penta-His antibody. Plate-bound RBD.hFc was detected using horseradish peroxidase (HRP)-conjugated anti-hFc and quantified using a colorimetric HRP substrate. OD_{450nm} values were plotted as a function of total mAb concentrations. Data from an assay performed in duplicate wells are plotted as mean ± SD.

Table 5: Summary of IC_{50} and maximum percent blocking of SARS-CoV-2 RBD binding to human ACE2 by REGN10933, REGN10987, REGN10989, and REGN-COV2.

Blockade of 100pM SARS-CoV-2 RBD Binding to Human ACE2		
Antibody	**IC_{50} [M]**	**Maximum % Blockade***
REGN10933	5.64E-11	101
REGN10987	1.65E-10	101
REGN10989	5.00E-11	96
REGN-COV2 (REGN10933+REGN10987)	8.18E-11	100
IgG1 Control	ND	4

*Maximum % blockade is defined as 100 minus the average binding signal observed at the highest antibody concentration tested (100nM) with buffer control subtracted, divided by the binding signal observed at constant concentration of RBD.hFc (100pM) with buffer control subtracted, multiplied by 100.
Abbreviation(s): ND, not determined because concentration-dependent blockade was not observed

Study r10933-ph-20155-sr-01v1

In study r10933-ph-20155-sr-01v1 cryogenic electron microscopy was used to determine the structure of the SARS-CoV-2 RBD in complex with the Fab fragments of REGN10933 and REGN10987, and to structurally characterize the epitope on the RBD for each anti-S protein mAb.

The sequences of publicly available SARS-CoV-2 genomes identified through mid-August 2020 were utilized to assess the degree of variability of the structurally determined epitopes on the RBD for each anti-S protein mAb. The percentage of conservation for each RBD residue found to interact with REGN10933 or REGN10987 was calculated.

Results
Results showed REGN10933 and REGN10987 bind epitopes that do not overlap on the surface of the SARS-CoV-2 receptor binding domain. As no residues are shared by REGN10933 and REGN10987, a single point mutation is unlikely to affect both epitopes.

Study r10933-ph-20091-sr-01v1
In vitro studies tested the ability of REGN10933, REGN10987, REGN-COV2 (i.e. REGN10933+REGN10987) and REGN10989 to neutralise virus through blockade of viral entry into cells.

Vero and Vero E6 cells were selected as they are known to be capable of infection by SARS CoV-2 virus. The ability of antibodies to prevent this infection was tested experimentally: additional testing determined the ability of antibodies to prevent entry of non-replicating vesicular stomatitis virus (VSV) pseudoparticles pseudotyped with different variants of the receptor binding domain SARS-CoV-2 spike protein in circulation.

Non-replicating VSV pseudoparticles pseudotyped with SARS-CoV-2 S protein (aa 14-1255; pVSV-SARS-CoV-2-S), replicating VSV encoding SARS-CoV-2 S protein (aa 1-1255; VSV-SARS-CoV-2-S), and SARS-CoV-2 (USA-WA1/2020 isolate) were pre-incubated with REGN10933, REGN10987, or REGN-COV2and added to Vero (pseudo [p]VSV and VSV) or Vero E6 (SARS-CoV-2) cells. The pVSV, which was engineered to express a fluorescent reporter, was assessed for neutralization using a fluorescence-based assay, VSV neutralization was assessed using immunostaining with polyclonal anti-VSV, and SARS-CoV-2 was assessed for neutralization by plaque reduction assay.

Non-replicating VSV pseudoparticles engineered to express a fluorescent reporter and pseudotyped with SARS-CoV-2 S protein variants were incubated with REGN10933, REGN10987, or REGN-COV2 to assess the capacity of anti-S protein Abs to block pseudoparticle entry into Vero cells. Neutralization capacity was analysed using fluorescence-based assays.

Results
Results showed that each antibody was able to inhibit viral entry whereas a control IgG1 antibody had no effect. REGN10933, REGN10987, REGN-COV2 (REGN10933 + REGN10987) and REGN10989 each mediated concentration-dependent neutralisation into cells of pVSV-SARS-CoV-2-spike (plot A), VSV-SARS-CoV-2-spike virus (plot B) and SARS-CoV-2 (plot C) with half maximal inhibitory concentration (IC_{50}) and 90% inhibitory concentration (IC_{90}) values in the picomolar range. Complete maximal inhibitory concentration (IC_{99}) values for pVSV-SARS-CoV-2-S pseudoparticles and SARS-CoV-2 virus were in the nanomolar (REGN10933, REGN10987, REGN-COV2) or picomolar (REGN10989) range.

Figure 4: REGN10933, REGN10987, REGN-Cov2, and REGN10989 neutralise pVSV-SARS-CoV2-S pseudoparticles, VSV-SARS-CoV-2-S virus, and SARS-CoV-2 isolate in a concentration-dependent manner

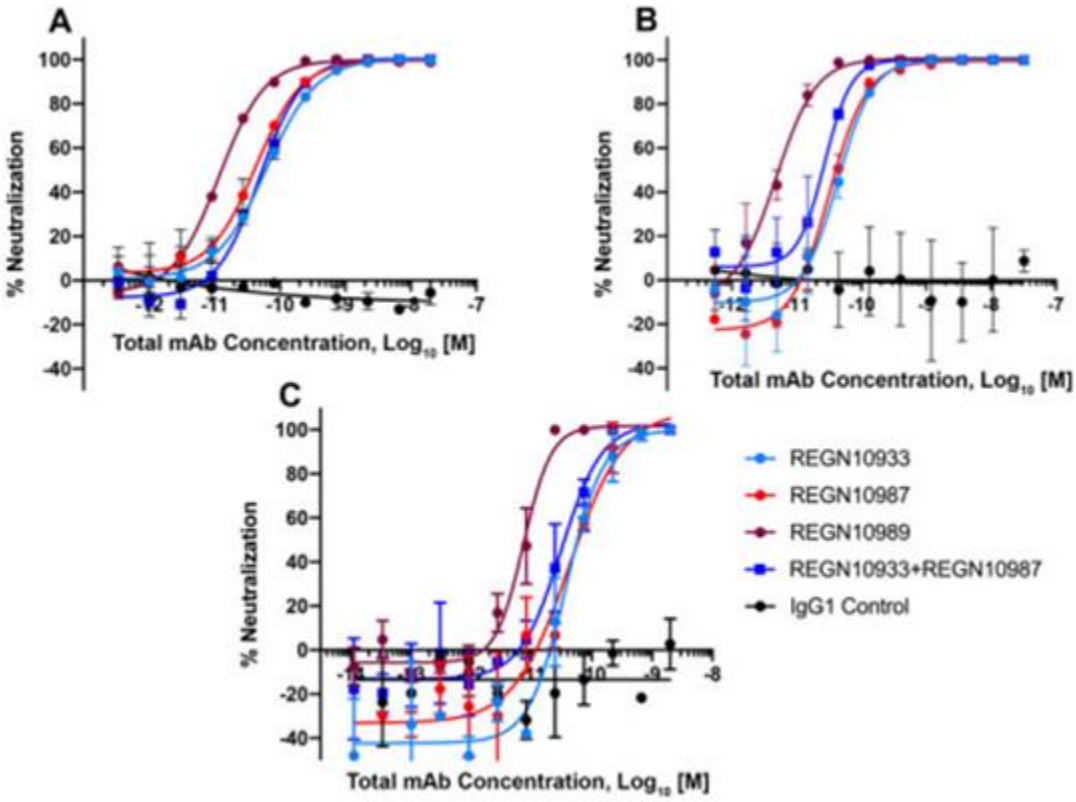


Table 6: Summary of values for REGn10933, REGN10987, REGN-Cov-2, and REGN10989 mediating neutralisation of viral entry into Vero or Vero E6 cells

	pVSV-SARS-CoV-2-S Pseudoparticles			VSV-SARS-CoV-2-S Virus		SARS-CoV-2 Virus		
Antibody Treatment	**IC_{50} [M]**	**IC_{90} [M]**	**IC_{99} [M]**	**IC_{50} [M]**	**IC_{90} [M]**	**IC_{50} [M]**	**IC_{90} [M]**	**IC_{99} [M]**
REGN10933	6.24E-11	4.36E-10	3.63E-09	4.31E-11	1.71E-10	3.74E-11	1.78E-10	9.78E-10
REGN10987	4.30E-11	2.53E-10	1.75E-09	3.13E-11	1.38E-10	4.21E-11	4.30E-10	5.43E-09
REGN10933+REGN10987	4.89E-11	2.60E-10	1.61E-09	2.70E-11	7.70E-11	3.10E-11	1.73E-10	1.14E-09
REGN10989	1.18E-11	2.60E-10	4.83E-10	4.79E-12	2.32E-11	7.38E-12	2.38E-11	8.55E-11
IgG1 Control	ND							

Abbreviations: ND, not determined because a dose-dependent response was not observed

Each of REGN10933, REGN10987, REGN10989 and the combination of REGN10933, REGN10987 neutralised infection of Vero or Vero E6 cells by SARS CoV-2 virus or by the VSV-SARS-CoV-2-S virus and had IC50 and IC90 values in the picomolar range. All were able to prevent infection with virus with all tested variants of the receptor binding domain, including D614G and D614N variants. REGN10987 and REGN10989 demonstrated a >5-fold reduction in neutralisation potency in the presence of 1 variant each, but this was not seen with the REGN-COV2 combination.

Study r10933-ph-20100-sr-01v1

Studies reported in r10933-ph-20100-sr-01v1 assessed risk of development of SARS CoV-2 spike protein escape mutants in the presence of each of REGN10933 and REGN10987, their

combination and REGN10989. Testing also addressed the ability of these antibodies to neutralise pVSV-SARS-CoV-2-spike pseudoparticle putative escape mutants.

Vero E6 cells were infected with fully replicating VSV-SARS-CoV-2-S virus in the presence of a range of concentrations of REGN10933 or REGN10987 (over 2 passages), or REGN-COV2 (over 7 passages [passage 3-7 using Vero cells]) to assess SARS-CoV-2 escape mutant selection. Infected cells were monitored for virus-induced cytopathic effect as a read-out for virus replication. Viral RNA from infected cell supernatants was extracted, sequenced, and analysed after each passage to identify putative escape mutants.

Each putative escape mutant within the RBD identified through sequencing was pseudotyped into non-replicating pVSV-SARS-CoV-2-S pseudoparticles expressing an mNeon fluorescent reporter. The neutralization capacity of REGN10933, REGN10987, and REGN-COV2 against each putative escape mutant was assessed using fluorescence-based assays.

Results
Monotherapy with individual antibodies resulted in rapid selection of viral escape mutants and a functional impact on neutralisation potency of the individual antibodies. In contrast, the combination of REGN109333 and REGN10987 retained potency. It was concluded that a combination of antibodies that bind to non-overlapping epitopes may minimise the likelihood of loss of antiviral activity due to naturally circulating viral variants or development of escape mutants under drug pressure.

Study r10933-ph-20101-sr-01v1
Study r10933-ph-20101-sr-01v1 reported on experiments into risks of antibody-dependent enhancement using *in vitro* methods to assess cellular entry of Vesicular Stomatitis Virus pseudotyped with SARS-CoV-2 spike protein and the effect of antibodies REGN10933, REGN10987, and REGN10989 thereon. Different cell types were used for this characterisation.

Non-replicating pVSV-SARS-CoV-2-S and pVSV-G pseudoparticles were generated for use in viral entry studies. Pseudoparticles were generated using a VSVΔG system in which the VSV glycoprotein was deleted from the genome and in which the VSV was engineered to express an mNeon fluorescent reporter. Pseudoparticles were pseudotyped with either wild-type SARS-CoV-2 S protein (aa 14-1255) or VSV glycoprotein by cloning the synthesised protein into an expression plasmid.

U937, THP1, IM9, K562, and Raji cells, which express Fc gamma receptor (FCGR)1 and/or FCGR2 were incubated with pVSV-SARS-CoV-2 S pseudoparticles expressing an mNeon fluorescent reporter in the presence of a range of concentrations of REGN10933, REGN10987, or REGN-COV2. FCGR-negative Ramos cells served as a negative control. None of the tested cell lines are permissive to infection with pVSV-SARS-CoV-2 S pseudoparticles alone. Viral entry in the presence of antibodies was assessed using flow cytometry.

Results
Cell lines U937, THP1, K5662, Raji and IM9 cells express FCGR2 and do not express FCGR3. U937 and THP1 also express FCGR1. Ramos and Vero cells do not express FCGR1, 2 or 3. All cell lines were permissive to viral entry of pVSV-G pseudoparticles: only Vero cells were permissive to entry of pVSV-SARS-CoV-2. Therefore, all cell lines except Vero cells were then incubated with pVSV-SARS-CoV-2-S pseudoparticles and either REGN10933, REGN10987, and REGN-COV2 to assess ADE of viral entry. FCGR- Ramos

cells were included as a negative control. Results demonstrated that REGN10987 alone or in combination with REGN10933 (REGN-COV2) mediates entry of pVSV-SARS-CoV-2-S pseudoparticles into FCGR2+ Raji and FCGR1+ /FCGR2+ THP1 cells, but not any of the other 3 FCGR+ cell lines tested (table 7). REGN10933 alone did not mediate entry of pVSV-SARS-CoV-2-S pseudoparticles into any of the tested cell lines.

Table 7: Summary of maximum percentage of viral entry into cell lines in the presence of REGN10933, REGN10987, or REGN-COV2

Antibody Treatment	Maximum Infection (%mNeon$^+$ in Total Cells)					
	Ramos	U937	THP1	IM9	K562	Raji
REGN10933+IgG1 Control	0.00	0.00	0.01	0.00	0.01	0.02
REGN10987+IgG1 Control	0.01	0.02	0.24	0.00	0.00	1.34
REGN10933+REGN10987	0.00	0.01	0.06	0.00	0.01	0.69
IgG1 Control	0.00	0.00	0.02	0.00	0.00	0.25

Maximum percentage of viral entry is defined as the highest mean percentage of mNeon$^+$ cells within live/singlets across the tested antibody dose range (3.05pM to 200nM).

Study r10933-ph-20090-sr-01v1

A series of *in vitro* studies assessed the ability of REGN10933, REGN10987, their combination (REGN-COV2) and REGN10989 to mediate antibody-dependent functions against target cells, expressing the against target cells expressing full-length (amino acids [aa] 1-1273) SARS-CoV-2 spike protein.

The effector function potential of REGN10933, REGN10987, and REGN-COV2, was assessed to determine: 1) the ability to mediate antibody-dependent cell mediated phagocytosis (ADCP) of target cells using monocyte-derived macrophages as effector cells; 2) the ability to mediate ADCC of target cells using primary natural killer (NK) cells as effector cells; 3) the ability to activate FCGR3A receptor signalling in an ADCC-surrogate reporter assay; and 4) the ability to mediate complement-dependent cytotoxicity (CDC) of target cells in presence of normal human serum (NHS).

REGN10933, REGN10987, and REGN-COV2 were evaluated for the ability to mediate ADCP of fluorescently labelled target cells engineered to express full-length SARS-CoV-2 S protein (Jurkat/hCD20/SARS-CoV-2-S FL) in the presence of fluorescently labelled primary monocyte-derived macrophage effector cells differentiated with macrophage colony stimulating factor.

REGN10933, REGN10987, and REGN-COV2 were evaluated for the ability to mediate ADCC against Jurkat/hCD20/SARS-CoV-2-S FL target cells using human primary NK cells from 3 independent donors as effector cells.

The ability of REGN10933, REGN10987, and REGN-COV2, to mediate the transcriptional expression of luciferase via activation of FCGR3A (an Fc receptor that mediates ADCC by NK cells) was evaluated in a surrogate ADCC reporter bioassay using reporter Jurkat T cells engineered to express a nuclear factor of activated T cells-luciferase (NFAT-Luc) reporter gene and human FCGR3A (Jurkat/NFAT-Luc/FCGR3A) in the presence of Jurkat/hCD20/SARS-CoV-2-S FL target cells.

REGN10933, REGN10987, and REGN-COV2 were evaluated for the ability to mediate CDC against Jurkat/hCD20/SARS-CoV-2-S FL target cells in the presence of 5% NHS.

Binding to FcRn was also tested in this study using REGN1932, a human IgG1 isotype antibody isolated from its VelocImmune human antibody mouse platform which contains a human light chain variable domain fused to a human kappa constant domain and a human heavy chain variable region fused to a human IgG1 constant domain. It was expected that binding affinities of REGN1932 to Fcγ receptor subtypes and FcRn are representative of the IgG1 isotype antibodies i.e. testing here with REGN1932 is a substitute for what is expected if REGN 10933 and REGN10987 were tested.

Results
ADCP (antibody-dependent cell mediated phagocytosis): REGN10933, REGN10987, their combination (REGN-COV2) and REGN10989 were each shown to mediate concentration-dependent ADCP of target cells expressing the SARS CoV-2 spike protein with EC50 values in the picomolar range. They did not mediate ADCP of Jurkat/hCD20 target cells.

ADCC (antibody-dependent cellular cytotoxicity): REGN10933, REGN10987, and REGN-Cov2 mediate concentration-dependent ADCP with half maximal effective concentration (EC_{50}) values in the picomolar range, and mediate concentration-dependent ADCC against target cells, with EC_{50} values in the low nanomolar to picomolar range, where calculable.

Results from the ADCC-surrogate reporter assay demonstrated that REGN10933, REGN10987, and REGN-Cov2 mediate concentration-dependent increase in activation of reporter cells expressing FCGR3A in the presence of Jurkat/CD20/SARS-CoV-2 FL target cells, with EC_{50} values in the picomolar range.

REGN10933, REGN10987, and REGN-COV2 were not found to mediate CDC against Jurkat/CD20/SARS-CoV-2-S FL target cells in the presence of 5% NHS.

Results from the binding part of the study showed that REGN1932 binding to Fcγ receptor subtypes and FcRn are representative of IgG1 isotype antibodies produced by the company.

Challenge studies
Study r10933-ph-20161-pd-01v1
The aim of study r10933-ph-20161-pd-01v1 was to evaluate the potential for use of antibodies REGN10933 and REGN10987 to prevention and/or treat SARS-CoV-2 infection in Syrian golden hamsters. The impact of FcG receptor engagement by anti-spike antibodies was assessed in both prevention and treatment arms of the study. SARS-CoV-2 replicates in this species and aspects of Covid-19 disease are recapitulated.

A total of 90 male and female Golden Syrian hamsters (6-8 weeks old, ~ 100 g) were assigned to the study. They were randomly assigned to study group based on weight, maintaining an almost even male and female ratio (2:3 or 3:2) when possible.

The hamsters (n=5/group) were randomized to dosing groups with equal distribution across sex and body weight, and given a single IP injection of REGN-COV2 (0.5, 5, or 50 mg/kg [0.25, 2.5, or 25 mg/kg/antibody, respectively]), IgG1 isotype control (50 mg/kg), the same doses of the REGN10993+REGN10943 $IgG4^{P\text{-}GG}$ isotype mAbs or IgG4P-GG isotype control, or placebo 2 days prior to SARS-CoV-2 challenge (prophylactic study arm) or 1 day post-SARS-CoV-2 challenge (therapeutic study arm). In both study arms, hamsters were IN challenged on Day 0 with 2.3E04 plaque-forming units (PFU) of SARS-CoV-2 (USA--WA1/2020).

Body weight was assessed daily throughout the study period (Days 0-7 for prophylaxis and Days 1-7 for treatment) as an indicator of morbidity. A mixed-effects model with repeated measures was used to compare the percentage change in body weight at Day 7 compared with baseline (Day 0 for prophylaxis and Day 1 for treatment). Oral swabs were analysed on Days 2 and 4 to assess viral load. Lung tissue was harvested from hamsters at the end of the study (7 days post-infection) to assess lung pathology and viral load. Lung pathology was assessed by image analysis to measure percentage area of pneumonia and using a 5-point scale of inflammation severity. Viral load was assessed by measuring both gRNA and sgRNA.

Tables 8-11 summarise the study designs. The prevention and treatment arms were run as separate experiments.

Table 8: Treatment study design RGN-20-01

Group	N	mAb Infusion			Challenge	
		mAb	Total Dose (mg/kg)	Timepoint	Material	Route
1	5	10933(25mg/kg)+10987(25mg/kg)	50	1 day after virus challenge via IP route	SARS-CoV-2	0.1ml IN/ 2.34 x10^4 pfu
2	5	10933(2.5mg/kg)+10987(2.5mg/kg)	5			
3	5	10933(0.25mg/kg)+10987(0.25mg/kg)	0.5			
4	5	10993(25mg/kg)+10943(25mg/kg)	50			
5	5	10993(2.5mg/kg)+10943(2.5mg/kg)	5			
6	5	10993(0.25mg/kg)+10943(0.25mg/kg)	0.5			
7	5	REGN1932 (50mg/kg)	50			
8	5	REGN4439 (50mg/kg)	50			
9	5	Placebo	N/A			

Table 9: Prophylaxis study design RGN-20-02

Group	N	mAb Infusion			Challenge	
		mAb	Total Dose (mg/kg)	Timepoint	Material	Route
1	5	10933(25mg/kg)+10987(25mg/kg)	50	2 days prior to challenge via IP route	SARS-CoV-2	0.1ml IN/ 2.34 x10^4 pfu
2	5	10933(2.5mg/kg)+10987(2.5mg/kg)	5			
3	5	10933(0.25mg/kg)+10987(0.25mg/kg)	0.5			
4	5	10993(25mg/kg)+10943(25mg/kg)	50			
5	5	10993(2.5mg/kg)+10943(2.5mg/kg)	5			
6	5	10993(0.25mg/kg)+10943(0.25mg/kg)	0.5			
7	5	REGN1932 (50mg/kg)	50			
8	5	REGN4439 (50mg/kg)	50			
9	5	Placebo	N/A			

Table 10: Treatment study schedule RGN-20-01

DATE	16-Jun	22-Jun	25-Jun	26-Jun	27-Jun	28-Jun	29-Jun	30-Jun	1-Jul	2-Jul
DAY	-9	-3	0	1	2	3	4	5	6	7
Arrival	X									
Ear tag		X								
Grouping		X								
Transfer to ABSL3			X							
Dosing (IP)				X						
Challenge			X							
Bleed (SST)			X							X
Oral Swab			X		X		X			X
Weights[1]			X	X	X	X	X	X	X	X
Clinical Obs[1]			X	X	X	X	X	X	X	X
Lung Tissue Harvest										X

[1] Daily weights and twice daily observations occurred on and post challenge; also, once on timepoints when animals were anesthetized for procedures.

Table 11: Prophylaxis study schedule RGN-20-02

DATE	16-Jun	17-Jun	22-Jun	24-Jun	25-Jun	26-Jun	27-Jun	28-Jun	29-Jun	30-Jun	1-Jul
DAY	-8	-7	-2	0	1	2	3	4	5	6	7
Arrival	X										
Ear tag		X									
Grouping		X									
Transfer to ABSL3				X							
Dosing (IP)			X								
Challenge				X							
Bleed (SST)				X[2]							X
Oral Swab				X[2]		X		X			X
Weights[1]			X	X	X	X	X	X	X	X	X
Clinical Obs[1]			X	X	X	X	X	X	X	X	X
Lung Tissue Harvest											X

[1] Daily Weights and twice daily observations occurred on and post challenge; also, once on timepoints that animals were anesthetized for procedures.
[2] Blood collection and oral swabs collected prior to challenge.

Results

There was one unscheduled death of a hamster who was found dead on day 7 post-challenge, having lost ~13% of its body weight. This was in group 5 (low dose prophylaxis, 10993+10943) which is not the antibody combination that is the subject of this application. Death was attributed to SARS-CoV-2 infection.

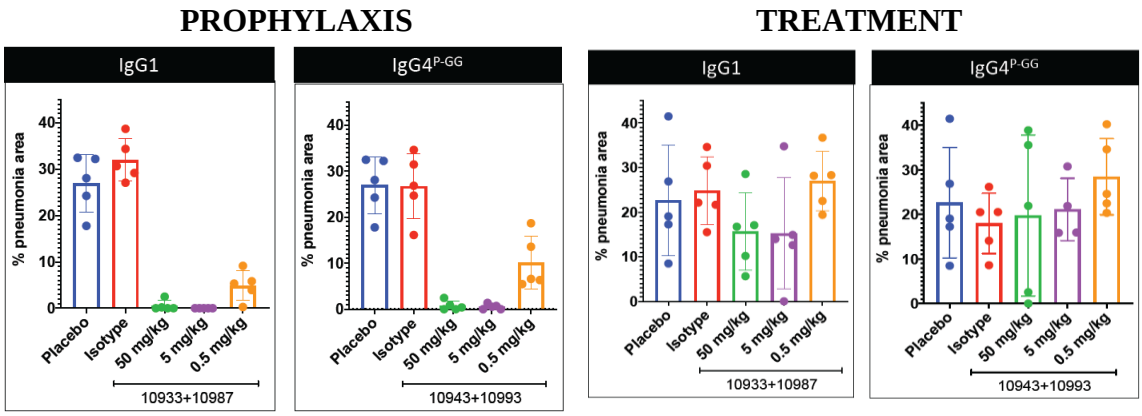
Hamsters that received prophylactic IP REGN-COV2 at 0.5, 5, or 50 mg/kg 2 days prior to SARS-CoV-2 challenge demonstrated similar levels of protection against weight loss throughout the study and protection against weight loss compared to placebo at the end of the study (Day 7).

There were no differences in viral gRNA or sgRNA at all tested doses of REGN-COV2 compared with placebo in oral swabs or in lungs. Although reduction in viral load in lung tissue did not reach statistical significance, there was a clear trend in reduction in all REGN-COV2 dose groups relative to placebo, with many treated animals demonstrating

undetectable viral load. No impact of REGN-COV2 was observed on viral load in oral swabs. No clear differences in efficacy between the IgG1 and IgG4^{P-GG} isotype versions of REGN10933 and REGN10987 were determined

Pathology analyses of lungs indicated that prophylactic administration of IP REGN-COV2 at doses ≥0.5 mg/kg resulted in significantly less pneumonia, measured as percentage area of pneumonia in the lungs and reduced the severity of lung inflammation in a dose-dependent manner compared with placebo. No clear differences in efficacy between the IgG1 and IgG4P-GG isotype versions of REGN10933 and REGN10987 were determined.

Prophylactic dosing of REGN-COV2 at ≥0.5 mg/kg resulted in significantly less pneumonia, compared with placebo, whereas the effect in the therapeutic regimen was much less. As prophylaxis, placebo and IgG1 isotype controls had a mean of 26.96 and 32.01% area of pneumonia, respectively. These values for low, mid and high doses of REGNCOV2 were 4.89, 0 and 0.54, respectively. As treatment, placebo and IgG1 isotype controls had a mean of 22.64 and 24.87% area of pneumonia, respectively. These values for low, mid and high doses of REGNCOV2 were 27.02, 15.25 and 15.64 respectively.



There was no evidence of antibody-dependent disease enhancement (ADE) as no dosing with antibodies resulted in enhanced body weight loss, increased viral loads or more severe lung pathology.

It was concluded that hamsters that had received any prophylactic treatment with SARS-CoV-2 specific antibodies suffered less severe weight loss than did controls. Benefit was less apparent with the treatment regimen and only the those given the highest dose were afforded protection from weight loss. Assessment of viral and subgenomic RNA levels in the lungs generally mirrored these results: subgenomic RNA was drastically reduced in lungs of hamsters given prophylaxis with SARS-CoV-2 specific antibodies: more modest viral load lowering was seen with treatment starting 24 hours post-challenge. Additionally, prophylaxis resulted in less severe lung pathology and was not associated with antibody-dependent enhancement of viral infection.

Study r10933-ph-20093-sr-01v1
The effect of monoclonal antibodies to prevent or to treat infection with SARS CoV-2 was assessed in rhesus monkeys.

The prophylactic and therapeutic efficacy of REGN-COV2 were assessed. Nasopharyngeal and oral swabs were collected to assess for viral load and analysed by RNAseq analysis to assess for the selection of viral escape mutants.

Lung pathology was assessed at the end of the study using a 4-point scale of inflammation severity.

Treatment with test antibodies was either prophylactic and given 3 days prior to the challenge with SARS CoV-2 virus, or therapeutic and given 1 day after challenge. Doses of REGN10933 and REGN10987 were given intravenously once at 0.15 and 0.15 mg/kg respectively, or at 12.5 and 12.5 mg/kg, or at 25 and 25 mg/kg or at 75 and 75 mg/kg. Four monkeys were given REGN10989: approval is not sought in this application for use of this antibody. The dose groups are described in table 12 below.

Table 12: Experimental design

Animal	mAb	ARM	Total dose (mg/kg)	Route	Day of dosing
1	10933 (0.15 mg/kg)+10987 (0.15 mg/kg)	Prophylactic	0.30	IV	-3
2	10933 (0.15 mg/kg)+10987 (0.15 mg/kg)	Prophylactic	0.30	IV	-3
3	10933 (0.15 mg/kg)+10987 (0.15 mg/kg)	Prophylactic	0.30	IV	-3
4	10933 (0.15 mg/kg)+10987 (0.15 mg/kg)	Prophylactic	0.30	IV	-3
5	10933 (25 mg/kg)+10987 (25 mg/kg)	Prophylactic	50	IV	-3
6	10933 (25 mg/kg)+10987 (25 mg/kg)	Prophylactic	50	IV	-3
7	10933 (25 mg/kg)+10987 (25 mg/kg)	Prophylactic	50	IV	-3
8	10933 (25 mg/kg)+10987 (25 mg/kg)	Prophylactic	50	IV	-3
9	Placebo	Prophylactic	N/A	IV	-3
10	Placebo	Prophylactic	N/A	IV	-3
11	10989 (25 mg/kg)	Therapeutic	25	IV	+1
12	10989 (25 mg/kg)	Therapeutic	25	IV	+1
13	10989 (25 mg/kg)	Therapeutic	25	IV	+1
14	10989 (25 mg/kg)	Therapeutic	25	IV	+1
15	10933 (12.5 mg/kg) +10987 (12.5 mg/kg)	Therapeutic	25	IV	+1
16	10933 (12.5 mg/kg) +10987 (12.5 mg/kg)	Therapeutic	25	IV	+1
17	10933 (12.5 mg/kg) +10987 (12.5 mg/kg)	Therapeutic	25	IV	+1
18	10933 (12.5 mg/kg) +10987 (12.5 mg/kg)	Therapeutic	25	IV	+1
19	10933 (75 mg/kg) +10987 (75 mg/kg)	Therapeutic	150	IV	+1
20	10933 (75 mg/kg) +10987 (75 mg/kg)	Therapeutic	150	IV	+1
21	10933 (75 mg/kg) +10987 (75 mg/kg)	Therapeutic	150	IV	+1
22	10933 (75 mg/kg) +10987 (75 mg/kg)	Therapeutic	150	IV	+1
23	Placebo	Therapeutic	N/A	IV	+1
24	Placebo	Therapeutic	N/A	IV	+1

IV – intravenous (saphenous or cephalic, exact location documented on Treatment Administration Worksheet)

Monkeys were followed to day 7 after the challenge. The primary endpoint of this study was the time-weighted average change in viral load (log_{10} copies/ml) from day 1 to day 7, as assessed by nasal pharyngeal swab samples measured by quantitative reverse transcription polymerase chain reaction (qRT-PCR). Results were declared significant at a prespecified 10% alpha level. Secondary endpoints included viral load by saliva, buccal swabs, airway tissue viral load and whole blood viraemia, histology and assessment of a febrile response.

Additional analyses were also conducted into putative SARS-CoV-2 spike escape mutants in rhesus monkeys in this study. RNA was extracted from swabs, reverse transcribed into complementary (c)DNA and cDNA libraries generated for sequencing to identify putative escape mutants with a focus on the genome section encoding the spike protein. The frequency of viral mutations inferred from the sequencing reads was calculated if the proportion of mutated reads were higher than 1% relative to total number of reads.

Results

There were no unscheduled deaths and clinical observations, body weights and body temperatures were either not affected or changes were minor and not considered biologically relevant. Monkeys given the placebo had a higher frequency of a febrile response.

Results from quantitative reverse transcription (qRT-PCR) suggested that prophylactic dosing at 50 mg/kg and therapeutic dosing at 25 and 150 mg/kg (total doses of antibody) decreased viral burden: viral loads declined more rapidly in monkeys given these doses than in controls. Viral replication and viral shedding appeared to decrease more quickly too.

In the prophylactic setting, monkeys given the combination at 0.15 mg/kg had similar amounts of genomic RNA (gRNA) and subgenomic RNA (sgRNA) as did the controls whereas those given the combination at 25 mg/kg (of each antibody) showed robust reductions in gRNA and sgRNA compared with control. In the therapeutic setting, monkeys given the combination at 12.5 and 75 mg/kg showed accelerated clearance of gRNA and sgRNA compared with controls.

Histopathological findings in the lungs suggest that the incidence of lung inflammation was reduced in treated monkeys compared to those given placebo. The frequency of nasal cavity and tracheal lesions was also reduced in both groups given the antibodies compared to placebo controls. No toxicities attributed to the test antibodies were seen.

The findings suggest that REGN10933 + REGN10987 may have effect on viral replication and lung inflammation.

RNAseq analysis demonstrated that no treatment-associated mutations were identified in the SARS-CoV-2 S protein across pooled samples from infected monkeys. All variants identified in the prophylactic and therapeutic groups were also present in the placebo group, with approximately half of these variants already being present in the inoculum.

Study r10933-ph-20160-sr-01v1

This study sought to investigate the potential of REGN10933 and REGN10987 to prevent infection in rhesus monkeys later challenged with SARS CoV-2 challenge virus. Rhesus monkeys were chosen as SARS CoV-2 is known to replicate in this species and monkeys show aspects of Covid-19 disease. Nasopharyngeal swabs and bronchoalveolar lavage fluid (BALF) were collected to assess for viral load and gross lung pathology and histology was assessed. The study design is summarised below.

Table 13: Study summary

Group	Treatment (IV Day -3)	Virus Challenge (Day 0)	Blood Draws	Swab and BAL Collections	Observations	Necropsy- Virus Titers Histopathology
1 (N=6)	10933(25mg/kg)+ 10987(25mg/kg)	SARS-CoV-2 WA/2020 $1.1x10^5$ PFU	Pre, Days 0, 1, 3, 5	Pre, Days 1-5	Days -3, 0 - 5 Clinical Signs, Body Weights, Temps	Day 5 Blood, BAL, Swabs, Respiratory Tract Tissues
2 (N=6)	10993(25mg/kg)+ 10943(25mg/kg)					
3 (N=6)	Placebo					

Table 14: Study design overview

Group N=6	Dosing Material	Dosing Route (Day -3)	Challenge (Day 0)	Necropsy
1	10933(25mg/kg)+ 10987(25mg/kg)	IV	SARS-CoV-2 1.1x10^5 PFU total (5.05x10^4 PFU in 1mL each IN and IT)	Day 5
2	10993(25mg/kg)+ 10943(25mg/kg)	IV		Day 5
3	Placebo	IV		Day 5

Male and female rhesus monkeys (n=6) were randomly assigned to 1 of 2 study groups with an even age distribution in each group. Monkeys were given a single prophylactic IV injection of either 50 mg/kg REGN-COV2 (25 mg/kg/antibody), 50 mg/kg REGN10993+REGN10943 (a different antibody not the subject of this application), or placebo 3 days prior to SARS-CoV-2 challenge. Monkeys were challenged on Day 0 with a total combined inoculum of 1.1E05 PFU of SARS-CoV-2 virus via combined IT/IN, with delivery of 5.05E04 PFU each per route of administration. Nasopharyngeal swabs were collected on Days 1, 2, 3, 4, and 5 and bronchioalveolar lavage fluid (BALF) was collected on Days 1, 3, and 5 to evaluate SARS-CoV-2 infection in the upper and lower airways, respectively. Collected samples were assessed for gRNA and sgRNA as a readout for viral load. Absolute viral load values were graphed as $\log_{10}$ copies/mL. Lung pathology was assessed using a 4-point scale of inflammation severity.

The change in viral load from baseline (Day 1, one day after inoculation) on each day of sample collection (until Day 5) was calculated for individual animals. Statistical analyses were performed comparing the TWA for change in viral load from baseline between REGN-COV2 and placebo dosing groups.

Results

SARS-CoV-2 infection of the rhesus macaque resulted in minimal changes: body weights may have been affected by the repeated use of anaesthetic, but there was no effect of the virus on body weight and none of the monkeys developed a fever. Overt signs of disease were not evident in any of the monkeys.

Monkeys given REGN-COV2 (REGN10933 and REGN10987) prophylactically demonstrate a reduction of viral gRNA and nearly complete ablation of viral sgRNA when compared with those given placebo.

SARS-CoV-2 virus replicated in the upper and lower respiratory tract. Both tested combinations of antibodies (i.e. REGN10933+REGN10987 and REGN10993+REGN10943) protected against viral replication in upper and lower respiratory tract.

Study R10933-PH-21015-SR-01V1

In this study, an assessment of antibody-dependent enhancement (ADE) of SARS-CoV-2 infection of primary human macrophages in the presence of REGN10933, REGN10987, and REGN10989 was undertaken.

In vitro assays with human cells were performed to determine if treatment with REGN10933, REGN10987, REGN10989, or REGN-COV2 resulted in ADE of SARS-CoV-2 infection. Fc gamma receptor-positive monocyte-derived macrophages from 2 human male donors, aged 27 and 32, were incubated with each of the anti-S protein antibodies or a corresponding isotype control (REGN1932), at concentrations of 0.015-1200 ng/ml (or half this

concentration for each antibody in the combination, REGN-COV2) and then infected with SARS-CoV-2: control monocyte-derived macrophages were infected with SARS-CoV-2 in the absence of any antibodies. The percentage of cells infected with SARS-CoV-2 was determined by immunofluorescence imaging of cells after staining with an antibody recognising the SARS-CoV-2 antigen, nucleoprotein.

Results

Images of infected Vero E6 cells were evaluated (not shown here). The % of SARS-CoV-2 N-positive cells was 20% and 15% for an MOI of 1 and 10, respectively (table 15). Monocyte-derived macrophages (MDMs) showed very low expression of SARS-CoV-2 N protein. The number of SARS-CoV-2 N-positive MDMs was reduced by the presence of antibody to viral spike protein and was in the range of that for untreated/infected or isotype control-treated/infected MDMs. The % of N-positive cells was independent of the concentration of the anti-S protein antibody.

Table 15: Percentage of SARS-CoV-2 N-positive MDMs treated with antibodies from 2 donors

Antibody Concentration (ng/mL)	Donor 1								Donor 2							
	IgG1 Control		REGN10933		REGN10987		REGN10933 + REGN10987		IgG1 Control		REGN10933		REGN10987		REGN10933 + REGN10987	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1200	0.10	0.14	0.00	0.00	0.27	0.28	0.16	0.12	0.25	0.17	0.17	0.10	0.26	0.08	0.17	0.05
240	0.11	0.10	0.04	0.03	0.08	0.05	0.16	0.03	0.26	0.13	0.35	0.05	0.51	0.36	0.84	0.71
48	0.03	0.05	0.13	0.15	0.10	0.06	0.28	0.11	0.17	0.08	0.41	0.23	0.19	0.15	0.38	0.19
9.6	0.04	0.01	0.08	0.04	0.04	0.07	0.22	0.23	0.12	0.03	0.26	0.02	0.31	0.08	1.39	0.33
1.92	0.02	0.02	0.08	0.02	0.06	0.02	0.12	0.05	0.09	0.04	0.39	0.33	0.46	0.37	0.39	0.55
0.384	0.05	0.06	0.03	0.02	0.01	0.02	0.10	0.06	0.12	0.11	0.28	0.04	0.18	0.07	0.21	0.04
0.077	0.05	0.05	0.08	0.07	0.04	0.04	0.21	0.25	0.17	0.00	0.12	0.06	0.12	0.07	0.30	0.09
0.015	0.08	0.07	0.02	0.03	0.05	0.06	0.05	0.05	0.26	0.12	0.79	0.19	0.28	0.19	0.42	0.09

Mean values calculated from 3 replicates

The data suggest lack of ADE: there was no evidence of enhancement of viral antigen uptake in the presence of anti-S protein antibodies with REGN10933, REGN10987, REGN10989 and REGN-COV2.

Study r10933-ph-20192-sr-01v1

This study was an evaluation of antibody dependent enhancement of monoclonal antibodies for the prevention of SARS-CoV-2 infection in Syrian golden hamsters. Male hamsters were exposed intranasally to SARS CoV-2 and followed for 7 days and then body weight, viral replication in the respiratory tract and lung histopathology results taken.

Hamsters (n=5 to 7) were given a single intraperitoneal (IP) injection of REGN-COV2 (0.0005, 0.005, 0.05, 0.5, or 5 mg/kg [0.00025, 0.0025, 0.025, 0.25, or 2.5 mg/kg/antibody, respectively]) the same doses of the REGN10993+REGN10943 IgG4P-GG isotype mAbs, or placebo 2 days prior to intranasal (IN) challenge with 1.00E04 PFU SARS-CoV-2 (USA-WA1/2020). Based on a blood volume of ~8.4 ml in an average hamster, the expected antibody concentration in the lung at each dose used is shown below.

Table 16: Expected antibody concentration in lung

Total Dose [mg/kg]	Calculated serum C_{max} [µg/mL]	Anticipated lung concentration [µg/mL]
5	125	18.75
0.5	12.5	1.875
0.05	1.25	0.1875
0.005	0.125	0.01875
0.0005	0.0125	0.001875

Body weight was assessed daily as an indicator of morbidity, with the percentage change in body weight from baseline (day of challenge) graphed. Lung tissue was harvested at the end of the study to assess viral load (log_{10} copies/g), measured by qRT-PCR, and pathology, assessed using a 5-point scale of inflammation severity.

Primary endpoints were the change in body weight at day 7 from baseline (exposure day). Secondary endpoints included viral load ($1og_{10}$ copies/g) in the lungs measured by quantitative reverse transcription polymerase chain reaction (qRT-PCR). The experimental groups are shown below.

Table 17: Experimental design

Iteration	Size	Target Virus Exposure (Day 0)	Treatment mAb (Day -2)	Dose [mg/kg/mAb]
1	7	10,000 PFU SARS-CoV-2, IN	REGN10933+REGN10987	2.5/2.5
1	7			0.25/0.25
2	7			0.025/0.025
2	7			0.0025/0.0025
2	7			0.00025/0.00025
1	7		REGN10943+REGN10993	2.5/2.5
1	7			0.25/0.25
2	7			0.025/0.025
2	7			0.0025/0.0025
2	7			0.00025/0.00025
1	5		Control Article	N/A
1	5	Sterile PBS	Control Article	N/A

PFU – plaque forming units; IN – intranasal; mAb – monoclonal antibody.

Results

Prophylactic administration of REGN-COV2 protected against weight loss and reduced the severity of lung inflammation in a dose-dependent manner. The high dose (5 mg/kg) also reduced the incidences of lung inflammation and secondary changes such as type II pneumocyte hyperplasia. Viral load in lungs was also reduced at 5 mg/kg REGN-COV2 relative to placebo. Importantly, ADE of infection was not observed at a sub-neutralizing dose of REGN-COV2, as indicated by a lack of more severe weight loss, increased inflammation, or enhanced viral load relative to placebo. Likewise, no clear differences in efficacy between the IgG1 and $IgG4^{P-GG}$ isotype versions of REGN10933 and REGN10987 were determined, further supporting lack of FCGR-mediated ADE.

There were no unscheduled deaths and there was no enhancement of lung pathology due to either of treatments at any of the dose levels tested i.e. there was no antibody dependent enhancement (ADE), that is, no group demonstrated greater weight loss, viral load or pathology relative to control.

Figure 5: Mean body weight percent change from baseline (y-axis), days post SARS-CoV-2 exposure (x-axis); group dose concentration are mg/kg/mAb

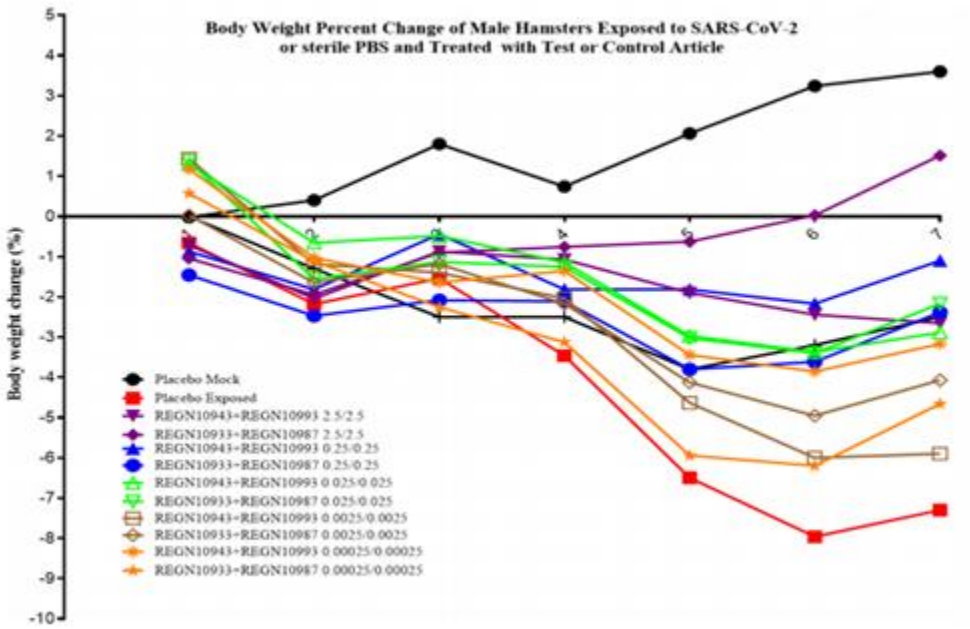
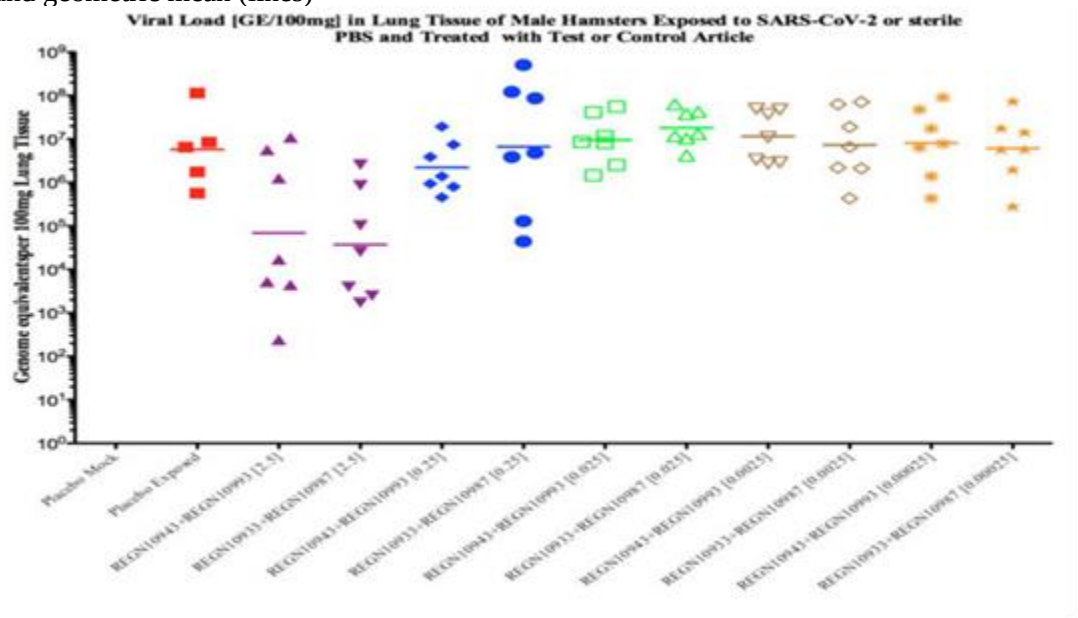


Figure 6: Viral load (genomic) in lung tissue [GE per 100 mg tissue]; individual values (symbols) and geometric mean (lines)



This application also discussed a publication, Copin et al 2021, entitled: *In vitro* and *in vivo* preclinical studies predict REGEN-COV protection against emergence of viral escape in humans (doi: https://www.biorxiv.org/content/10.1101/2021.03.10.434834v4). This addressed concerns that the use in patients of a single antibody might encourage development of resistant variants and how the use of a second antibody in combination could address this risk, even if resistance did develop to one or other of the components.

This paper describes preclinical *in vitro* and *in vivo* (hamsters) experiments attesting to the concept that single antibody use encourages development of resistant variants which does not occur to the same extent with use of the combination. It extends these findings by confirming them in humans; the human aspects are not addressed in this preclinical assessment.

The paper discusses that while only one to two passages led to complete virus resistance against all tested antibodies used as monotherapy, 7 consecutive passages were needed to reach complete resistance to the REGN-COV2 combination, requiring multiple simultaneous mutations impacting each antibody. Rapid escape in the monotherapy setting was independent of the targeted epitope or its sequence conservation. The paper notes that these experiments highlight the inherent risk of monotherapy against SARS-CoV-2 with any anti-spike antibody regardless of the targeted epitope or its conservation.

Secondary pharmacodynamics
No such studies have been done.

Safety pharmacology
No such studies have been done. Safety pharmacology evaluations of vital organ system function including cardiovascular (electrocardiography), respiratory (pulse oximetry) and neurological examinations were included in the general toxicity study. This approach is endorsed.

Pharmacodynamic drug interactions
No such studies have been done.

III.3 Pharmacokinetics

Study r10933-av-20085-va-01v1
A method validation study report has been provided for the measurement of human antibody in monkey serum using an enzyme-linked immunosorbent assay (ELISA). The method was designed to measure the concentration of total human IgG in monkey serum; it did not differentiate between the individual anti-SARS-CoV-2 antibodies. The procedure used a mouse anti-human Ig Fc mAb as the capture reagent. Captured anti-SARS-CoV-2 antibodies were detected using a biotinylated Fab fragment of a different, non-competing mouse anti-human Ig Fc mAb as the detection reagent. The assay had a lower limit of quantitation (LLOQ) of 0.078 µg/mL (78 ng/mL) and an upper limit of quantification of 5 µg/ml in neat monkey serum

Study r10933-pk-20071
The mean concentration-time profiles of total REGN10933 and total REGN10987 when administered alone or in combination as REGN-COV2 in serum were evaluated following a single IV bolus injection of 10 mg/kg REGN10933 or 10 mg/kg REGN10987, or 10 mg/kg/antibody (also referred to as 10/10 mg/kg; total dose of 20 mg/kg) or 50 mg/kg/antibody (also referred to as 50/50 mg/kg; total dose of 100 mg/kg) REGN-COV2, or a single SC injection of 10 mg/kg/antibody (also referred to as 10/10 mg/kg; total dose of 20 mg/kg) REGN-COV2 to male cynomolgus monkeys.

Table 17: Experimental design

Group No.	Test Material	Dose Level (mg/kg)	Route	Dose Volume (mL/kg)[a]	Dose Concentration (mg/mL)	No. of Males[b]
1	REGN10933	10	IV	2	5	4
2	REGN10987	10	IV	2	5	4
3	REGN10933/REGN10987	10/10	IV	2/2	5/5[c]	4
4	REGN10933/REGN10987	50/50	IV	2/2	25/25[c]	4
5	REGN10933/REGN10987	10/10	SC	2/2	5/5[d]	4

IV = intravenous bolus injection; SC = subcutaneous injection.
[a] Based on the most recent body weight measurement.
[b] Animals were released from study on Day 72.
[c] REGN10933 and REGN10987 were dosed sequentially, with REGN10933 dosed first followed by an approximate 3 mL flush with sterile saline, then REGN10987 was administered followed by an additional approximate 3 mL flush with sterile saline. Any timed collections were based off completion of the second administration.
[d] REGN10933 (Dose Site 1) and REGN10987 (Dose Site 2) were dosed sequentially, with REGN10933 dosed first. Any timed collections were based off completion of the second administration.
Note: REGN-COV2 represents the combination of REGN10933 and REGN10987 and is used interchangably with REGN10933/REGN10987 is this report.

Serial blood samples were collected predose through Day 71; the resulting serum was analysed for total REGN10933, total REGN10987, and total REGN-COV2 (all measured as total human IgG) concentrations using an ELISA.

Results

The concentration-time profiles of REGN10933, REGN10987, and REGN-COV2 were characterized by an initial brief distribution phase (IV) or absorption phase (SC) followed by a linear elimination phase throughout the 70-day study duration. The mean estimated elimination $t_{1/2}$ ranged from 13.1 to 18.0 days across the various dose groups.

Following IV administration of 10 mg/kg of REGN10933 and REGN10987 individually, mean C_{max} values of 310 and 272 µg/mL, respectively, were observed. Following IV administration of REGN-COV2 (at 10/10 mg/kg or 50/50 mg/kg), mean dose-normalized C_{max} values were within 1.2-fold of C_{max}/dose for either antibody alone, indicating comparable peak concentrations upon individual or REGN-COV2 administration.

Following IV administration of REGN-COV2, a dose-proportional increase in exposure (AUC_{inf}/Dose) was observed between the 10/10 and 50/50 mg/kg dose groups. Comparable dose-normalized exposures with respect to either REGN10933 or REGN10987 when dosed individually (within 1.4-fold across all dose groups) indicates that the individually dosed mAbs behave similarly to each other with regard to kinetics.

Following SC administration of REGN-COV2 at 10/10 mg/kg, a mean dose-normalized C_{max} of 10.3 µg/mL per mg/kg was observed at a t_{max} of 3.75 days. The estimated bioavailability was 81.6%.

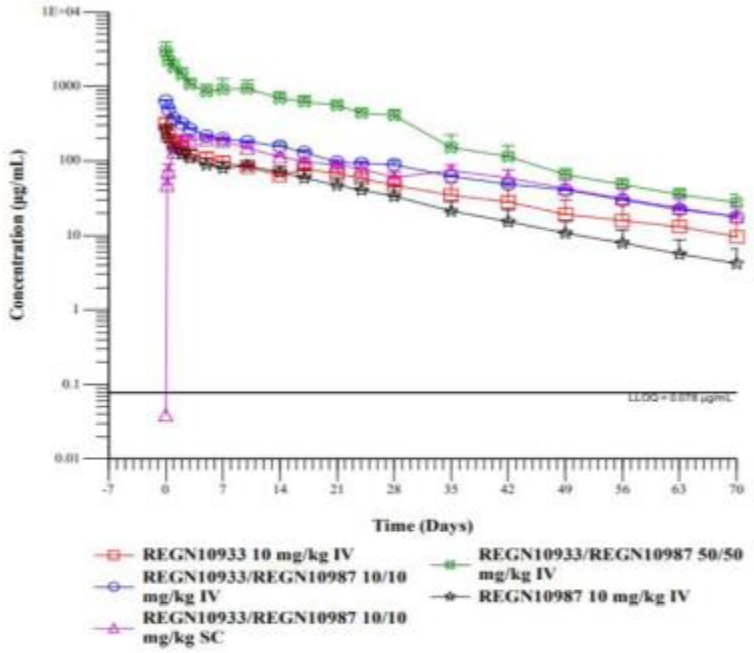
Clearance values were within 1.1- to 1.4-fold across the IV and SC dose groups and the V_{ss} values were between 1.0- to 1.2-fold across the various dose groups. These concentration-independent values indicate the kinetics of REGN10933 and REGN10987 dosed in combination were similar to the kinetics for REGN10933 and REGN10987 dosed individually, indicating no impact on the PK of the individual mAbs when given in combination. These data were consistent with linear PK as would be expected for mAbs directed against an exogenous target. The potential impact of anti-drug antibodies (ADA) was assessed by visual inspection of the individual concentration-time profiles. No evidence of ADA impact on the profiles was observed; thus, no concentration values were excluded from analysis.

Table 18: Mean pharmacokinetic parameters of total REGN1033, REGN10987, and REGN10933+REGN10987 in serum following REGN10933 and REGN10987 administered individually or in combination via a single intravenous or subcutaneous injection to the male cynomolgus monkey

Parameter	Unit	REGN10933 10 mg/kg IV			REGN10987 10 mg/kg IV			REGN10933 + REGN10987 10/10 mg/kg IV			REGN10933 + REGN10987 50/50 mg/kg IV			REGN10933 + REGN10987 10/10 mg/kg SC		
		N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
C_{max}	µg/mL	4	310	74.3	4	272	30.8	4	639	19.4	4	2960	986	4	206	19.3
C_{max}/Dose	(µg/mL)/(mg/kg)	4	31.0	7.43	4	27.2	3.08	4	31.9	0.968	4	29.6	9.86	4	10.3	0.964
t_{max}	h or day	4	0.0833	0.00	4	0.0833	0.00	4	0.0833	0.00	4	0.0833	0.00	4	3.75	1.50
AUC_{inf}	day•(µg/mL)	4	3670	1180	4	2710	695	4	7080	115	4	27700	2100	4	5780	927
AUC_{inf}/Dose	day•(µg/mL)/(mg/kg)	4	367	118	4	271	69.5	4	354	5.76	4	277	21.0	4	289	46.4
$t_{1/2}$	day	4	16.8	5.58	4	13.1	2.50	4	18.0	0.869	4	16.8	2.12	4	16.3	2.42
CL or CL_F	mL/day/kg	4	3.00	1.18	4	3.93	1.26	4	2.82	0.0462	4	3.62	0.265	4	3.53	0.580
V_{ss}	mL/kg	4	68.2	8.91	4	71.3	7.40	4	68.4	2.67	4	63.3	10.2	NC	NC	NC
Bioavailability	%	NC			NC			NC			NC			81.6		

AUC, Area under the concentration-time curve; AUC_{inf}, Area under the concentration-time curve from time zero extrapolated to infinity; C_{max}, Peak concentration; CL, Total body clearance; CL_F, Apparent total body clearance; ELISA, Enzyme linked immunosorbent assay; h, Hours; IV, Intravenous; N, Number of animals; NC, Not calculated; SC, Subcutaneous; SD, Standard deviation; $t_{1/2}$, Elimination half-life; t_{max}, Time to C_{max}; V_{ss}, Volume of distribution at steady state
Note: Bioavailability was calculated as SC mean AUC_{inf}/mean AUC_{inf} at the respective IV dose level x 100%.
ELISA measures total REGN10933 and total REGN10987 as total human IgG.
t_{max} is represented in hours for the IV dose group and in days for the SC dose group.
Dose-normalized parameters for REGN-COV2 combination groups are normalized by total human mAb dose.

Figure 7: Mean (+SD) total REGN10933, total REGN10987, and total REGN10933+REGN10987 concentrations in serum vs time following REGN10933 and REGN10987 administered individually or in combination via a single intravenous or subcutaneous injection to the male cynomolgus monkey



BLQ, Below the limit of quantitation; IV, Intravenous; LLOQ, Lower limit of quantitation; M, Male; N, Number of animals; SC, Subcutaneous
Notes: N=4 animals/group through Day 71.
Concentration values that were considered to be outliers were excluded from 1 animal (3002 M) in the REGN10933+REGN10987 10/10 mg/kg dose group and 1 animal (4001 M) in the REGN10933+REGN10987 50/50 mg/kg dose group (Table 11 and Table 12).
Predtudy serum concentrations were excluded from the plot for the IV groups.
Concentration-time profiles were plotted through the first post dose BLQ result. Concentrations below the LLOQ (<0.078 µg/mL) were imputed as LLOQ/2 (0.039 µg/mL).

Study r10933-pk-20074

In this study a lower dose was used. Following a single IV or SC injection of 1 mg/kg REGN10933, REGN10987, REGN10989, or REGN10934 to male cynomolgus monkeys in this pilot PK study (R10933-PK-20074), the mean concentration-time profiles of total REGN10933 and total REGN10987 were evaluated; REGN10989 and REGN10934 are not the subject of this application and therefore are not discussed in this summary.

Serial blood samples were collected predose through Day 71; the resulting serum was analyzed for total REGN10933 and total REGN10987 (all measured as total human IgG) concentrations using an ELISA. The PK parameters of total REGN10933 and total REGN10987 were estimated by noncompartmental analysis (NCA).

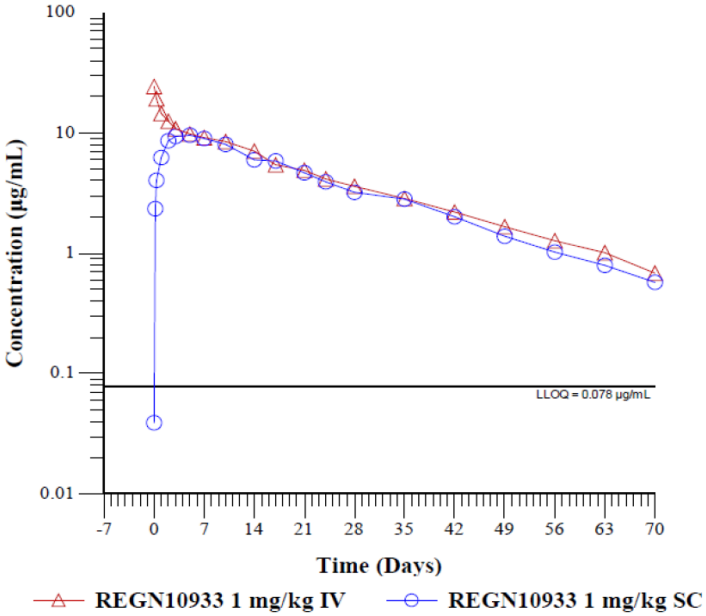
Results

The concentration-time profiles of total REGN10933 and total REGN10987 were characterized by an initial brief distribution phase (IV) or an absorption phase (SC), followed by a single linear elimination phase over the 70-day (10 week) study duration. Total REGN10933 or total REGN10987 mean C_{max} values, following a single IV dose, were 24.3 or 31.9 µg/mL, respectively. After the single SC dose, mean C_{max} values of total REGN10933 or total REGN10987 were 9.57 or 11.7 µg/mL, respectively. Mean t_{max} values following SC administration were 5 and 2.5 days for total REGN10933 and total REGN10987, respectively.

Following the IV dose of REGN10933 or REGN10987, AUC_{inf} values were 304 or 196 day (µg/mL) per mg/kg, respectively. Total body clearance values of total REGN10933 or total REGN10987 were 3.36 or 5.19 mL/day/kg, respectively and the V_{ss} was estimated to be 77.6 mL/kg for total REGN10933 and 53.6 mL/kg for total REGN10987.

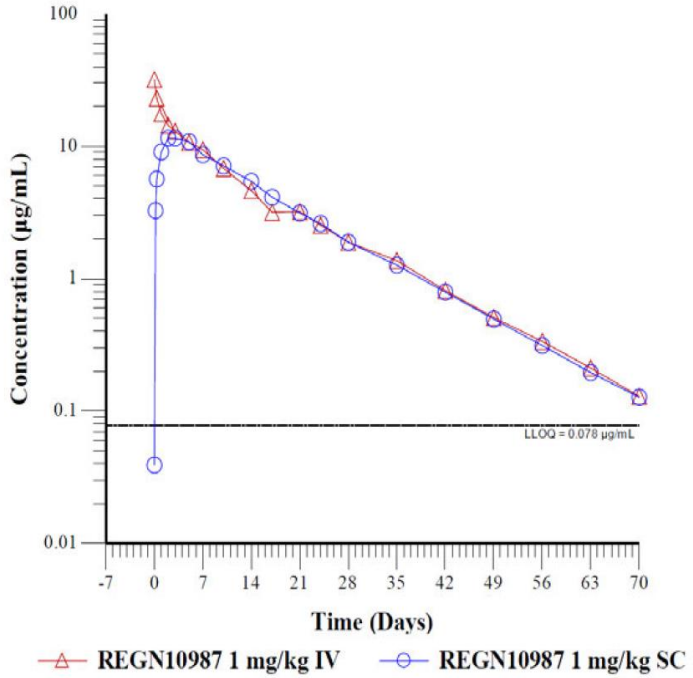
No apparent impact of ADA on total REGN10933 concentration-time profiles was observed. However, there was a precipitous decline in total REGN10987 concentrations observed in one of the 2 (50%) animals in the IV dose group. Impacted concentration values were excluded from mean concentrations and NCA. No apparent impact of ADA on the total REGN10987 concentration-time profiles was observed in the SC dose group.

Figure 8: Mean total REGN10933 concentrations in serum vs time following a single intravenous or subcutaneous injection of REGN10933 in male cynomolgus monkey



BLQ, Below the limit of quantitation, IV, Intravenous; LLOQ, Lower limit of quantitation; N, Number of animals; SC, Subcutaneous
Notes: N=2 animals/group through Day 71.
Prestudy serum concentrations were excluded from the plot for the IV group.
Concentration-time profiles were plotted through the first post dose BLQ result. Concentrations below the LLOQ (<0.078 µg/mL) were imputed as LLOQ/2 (0.039 µg/mL).

Figure 9: Mean total REGN10987 concentrations in serum vs time following a single intravenous or subcutaneous injection of REGN10987



* Concentration values considered to be ADA impacted were excluded from 1 animal (2002) in the 1 mg/kg REGN10987 IV group (Table 18).
ADA, Anti-drug antibody; BLQ, Below the limit of quantitation IV, Intravenous; LLOQ, Lower limit of quantitation; N, Number of animals; SC, Subcutaneous
Notes: N=2 animals/group through Day 71.
Prestudy serum concentrations were excluded from the plot for the IV group.
Concentration-time profiles were plotted through the first post dose BLQ result. Concentrations below the LLOQ (<0.078 µg/mL) were imputed as LLOQ/2 (0.039 µg/mL).

Table 19: Mean pharmacokinetic parameters of total REGN1033 and total REGN1098, in serum following a single intravenous or subcutaneous injection of REGN10933 or REGN10987 in the male cynomolgus monkey

Parameter	Unit	REGN10933 1 mg/kg IV			REGN10987 1 mg/kg IV		
		N	Mean	SD	N	Mean	SD
C_{max}	µg/mL	2	24.3	NC	2	31.9	NC
t_{max}	h	2	0.0833	NC	2	0.0833	NC
AUC_{last}	day•(µg/mL)	2	287	NC	2	186	NC
AUC_{inf}		2	304	NC	2	196	NC
$t_{1/2}$	day	2	17.0	NC	2	7.78	NC
CL	mL/day/kg	2	3.36	NC	2	5.19	NC
V_{ss}	mL/kg	2	77.6	NC	2	53.6	NC
Parameter	**Unit**	**REGN10933 1 mg/kg SC**			**REGN10987 1 mg/kg SC**		
		N	Mean	SD	N	Mean	SD
C_{max}	µg/mL	2	9.57	NC	2	11.7	NC
t_{max}	day	2	5.00	NC	2	2.50	NC
AUC_{last}	day•(µg/mL)	2	247	NC	2	193	NC
AUC_{inf}		2	260	NC	2	195	NC
$t_{1/2}$	day	2	15.9	NC	2	10.3	NC
CL_F	mL/day/kg	2	3.87	NC	2	5.21	NC
Bioavailability	%	85.5			99.5		

ADA, Anti-drug antibody; AUC, Area under the concentration-time curve; AUC_{inf}, Area under the concentration-time curve from time zero extrapolated to infinity; AUC_{last}, Area under the concentration-time curve computed from the time of dosing to the time of the last measurable concentration; C_{max}, Peak concentration; CL, Total body clearance; CL_F, Apparent total body clearance; ELISA, Enzyme linked immunosorbent assay; h, Hours; IV, Intravenous; N, Number of animals; NC, Not calculated; SC, Subcutaneous; SD, Standard deviation; $t_{1/2}$, Elimination half-life; t_{max}, Time to C_{max}; V_{ss}, Volume of distribution at steady state
Note: Bioavailability was calculated as (SC mean AUC_{inf}/mean AUC_{inf} at the respective IV dose level) x 100%.
ELISA measures total REGN10933 and total REGN10987 as total human IgG.

Distribution

No such studies have been done.

Metabolism
There are no studies into metabolism.

Excretion
There are no studies into excretion.

Pharmacokinetic drug interactions
No such studies have been done.

Other pharmacokinetic studies
There are no other studies

III.4 Toxicology
An overview of the toxicology studies is given in table 20 below. The toxicology programme consisted of two cross reactivity studies, one on tissues from adult humans and cynomolgus monkey and one in human foetal tissue, and a repeat-dose toxicity study. No single dose toxicity studies were carried out.

Table 20: Summary of toxicology studies

Study Type and Duration (Compliance)	Study Number	Species	Dose (Administration Route/Frequency)
Repeat-dose Toxicology Study			
4-week study with an 8-week recovery period (GLP)	R10933-TX-20064	Cynomolgus monkey	Control article: 0 mg/kg (IV/SC) REGN10933: 50 mg/kg (IV) REGN10987: 50 mg/kg (IV) REGN10933+REGN10987[a]: 50 and 150 mg/kg/antibody (IV); 150 mg/kg/antibody (SC) (total doses of 100 and 300 mg/kg REGN-COV2, respectively) (once weekly for 4 weeks [total of 4 doses])
Other Studies			
Tissue cross-reactivity study (GLP)	R10933-TX-20065	Normal human and cynomolgus monkey tissues	1 and 10 µg/mL (REGN10933-Bio[b] and REGN10987-Bio[b]) (ex vivo)
Tissue cross-reactivity study (GLP)	R10933-TX-20129	Selected human fetal tissues	1 and 10 µg/mL (REGN10933-Bio[b] and REGN10987-Bio[b]) (ex vivo)

[a] REGN10933+REGN10987 is also referred to as REGN-COV2. REGN10933 and REGN10987 were dosed sequentially, with REGN10933 dosed first.
[b] REGN10933-Bio and REGN10987-Bio refer to the biotinylated antibodies, which were evaluated individually in each study.
GLP, Good Laboratory Practice; IV, Intravenous; SC, Subcutaneous

Tissue cross-reactivity studies
Study R10933-tx-20065
This cross-reactivity study was done in cryosections of tissues from cynomolgus monkeys and humans. Tissues tested are indicated in table 21 below. Testing was applied to tissue from at least 3 different donors. Each of REGN10933 and REGN 10987, prepared by a technique called biotinylation, was applied to tissues at 1 or 10 µg/ml, these concentrations having been selected based on initial testing across a wider concentration range. As a negative control, a biotinylated human IgG1 antibody with different antigenic specificity (termed HuIgG1 Bio) was used. Other controls included lack of any antibody in the assay, use of SARS CoV-2 spike (S) protein UV-resin spot slides (as a positive control to confirm binding to the target antigen) and use of the peptide, human hypercalcaemia of malignancy peptide, amino acid residues 1-34 (as a negative control to conform specificity of any binding). In addition, tissues from both humans and monkey were exposed to labelled polyclonal rabbit antibody to β2-microglobulin to confirm that epitopes could be detected by

immunohistochemical staining methods: β2-microglobulin antigen is expressed on many cell types and is strongly expressed on endothelium.

Table 21: Human tissue (normal) from three separate donors

Adrenal	Kidney (glomerulus, tubule)	Skin
Bladder (urinary)	Liver	Spinal Cord
Blood Cells [a]	Lung	Spleen
Blood Vessels (endothelium) [b]	Lymph Node	Striated Muscle (skeletal)
Bone Marrow	Ovary	Testis
Brain – cerebellum	Pancreas	Thymus
Brain – cerebral cortex	Parathyroid	Thyroid
Breast (mammary gland)	Peripheral Nerve	Tonsil
Eye	Pituitary	Ureter
Fallopian Tube (oviduct)	Placenta	Uterus – cervix
Gastrointestinal (GI) Tract [c]	Prostate	Uterus – endometrium
Heart	Salivary Gland	

[a] Evaluated from peripheral blood smears.
[b] Evaluated from all tissues where present.
[c] Included esophagus, large intestine/colon, small intestine, and stomach (including underlying smooth muscle).

Results
Staining of the positive control material (SARS CoV-2 spike protein UV resin spot slides) was confirmed for both of the concentrations of each of the biotinylated antibodies, REGN10933 and REGN10987. The negative control material (human hypercalcemia of malignancy peptide, amino acid residues 1-34, UV-resin spot slides) did not show staining. The control human IgG antibody did not cross react with either positive or negative controls. All tissues from both humans and monkey showed staining with labelled rabbit antibody to β2-microglobulin which indicates that tissues used in the test did express epitopes that could be detected by immunohistochemical staining (β2-microglobulin antigen is expressed on many cell types and is strongly expressed on endothelium). Based on these findings, the methods applied were judged reliable.

No staining was detected with either REGN10933-Bio or REGN10987-Bio in either human or cynomolgus monkey tissues.

Study r10933-tx-20129
This study examined the binding to human fetal tissues. The test antibodies were biotinylated REGN10933 and biotinylated REGN10987. Testing was done with negative and positive controls.

Results
All evaluated fetal human test tissues stained positive for β2-microglobulin, indicating their suitability for inclusion in the cross-reactivity evaluation. This suggest the results with the test antibody were valid as the assay was sensitive and specific.

Biotinylated -REGN10933 and biotinylated -REGN10987 were tested at 1 and 10 µg/ml. No staining was present in the fetal human tissue panel examined. It was noted that the viral antigen was not expected to be expressed in normal fetal human tissues and these results were anticipated.

Repeat-dose toxicity studies

Study r10944-tx-20064

The aim of this study in cynomolgus monkeys was to determine potential toxicity of REGN10933 and REGN10987 when each was given alone and when given in combination either by intravenous injection or by subcutaneous injection.

Monkeys were dosed on days 1, 8, 15 and 22 and followed to day 85 after their last dose to determine potential for recovery from any toxicity noted. In addition, the toxicokinetic characteristics of REGN10933 and REGN10987 were determined.

Test articles were prepared on each day of dosing by dilution to the appropriate concentration in the diluent. Monkeys were assigned to 1 of 6 groups. Those in group 1 were given the vehicle (histidine, sucrose and polysorbate 80 in saline). Those in groups 2 and 3 were given 50 mg/kg of either REGN10933 or REGN10987 respectively. Those in groups 4 were given both antibodies at 50 mg/kg/antibody: those in groups 5 and 6 were given both antibodies at 150 mg/kg/antibody. Where monkeys were given both antibodies, they first received REGN10933 and then received REGN10987. The antibodies were neither co-formulated nor administered together. Those in group 1 were dosed by each of the intravenous and subcutaneous routes. Those in groups 2, 3, 4 and 5 were dosed intravenously and those in group 6 were dosed subcutaneously with injection sites rotated weekly. Doses were selected to provide exposures higher than that intended in humans and these routes were selected to support their use in humans. The experimental design is outlined in table 22 below. Monkeys were anaesthetised and killed by exsanguination on either days 29 or 85 (7 or 63 days after their last dose).

Table 22: Experimental design

Group No.	Test Material	Dose Level (mg/kg/day)	Route	Dose Volume (mL/kg)[a]	Dose Conc. (mg/mL)	No. of Animals[b]			
						MS		Rec	
						M	F	M	F
1	Control Article	0	IV/SC[c]	2/2	0	3	3	2	2
2	REGN10933	50	IV	2	25	3	3	2	2
3	REGN10987	50	IV	2	25	3	3	2	2
4	REGN10933/ REGN10987[d]	50/ 50	IV	2/2	25/ 25	3	3	2	2
5	REGN10933/ REGN10987[d]	150/ 150	IV	2/2	75/ 75	3	3	2	2
6	REGN10933/ REGN10987[d]	150/ 150	SC	2/2	75/ 75	3	3	2	2

Conc. = concentration; IV = intravenous bolus injection; SC = subcutaneous injection; MS = main study; Rec = recovery.

[a] Based on the most recent body weight measurement.

[b] Main Study animals were euthanized on Day 29. Recovery animals were euthanized on Day 85.

[c] Subcutaneous was administered first followed by IV. All timed collections were based on completion of the IV administration.

[d] Administration of REGN10933 and REGN10987 was sequentially dosed, with REGN10933 dosed first. All timed collections were based off completion of the second administration. For Groups 4 and 5, the REGN10933 dose was followed by approximately 3 mL flush with sterile saline, then REGN10987 was administered followed by an additional approximately 3 mL flush with sterile saline.

Assessment of toxicity was based on the following parameters: clinical evaluations including of the injection sites, food consumption, body weights, ophthalmological examinations, body temperature, heart and respiration rates and blood pressure measurements; clinical pathology (cytokines, haematology, coagulation, serum chemistry and urinalysis) and pathology (gross, microscopic, and organ weights).

Results

There were no unscheduled deaths and no overt clinical signs of toxicity noted. No changes attributed to REGN10933- and/or REGN10987 were noted in haematology.

In all groups, including control, there were transient, minimal to mild increases in CRP on Day 2 and minimal increases in fibrinogen, with or without a minimal decrease in albumin, on Days 2 and/or 7, which returned to within normal range by Day 27. Additionally, there were transient minimal to mild increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and/or lactate dehydrogenase (LDH) in individual animals on Days 2 and 7 that returned within the range of control and/or baseline values by Day 27. Given the transient nature and lack of cytokine correlates (e.g., CRP), low incidence, minimal to mild magnitude of change, lack of dose response, and/or presence of similar changes in controls, the observed changes are considered to be of uncertain relationship to REGN10933 or REGN10987, are possibly related to study procedures, and are not considered to be adverse. On Day 27, clinical pathology changes were limited to a minimal increase in serum globulins at 150 mg/kg/antibody REGN-COV2 IV and SC that were considered related to high doses of immunoglobulin administered during the study and therefore, are of no toxicological significance. There were no macroscopic or microscopic findings or organ-weight changes related to the administration of REGN10933 and/or REGN10987.

All dosing was well tolerated with no toxicity identified: the NOAEL (no-observed-adverse-effect level) was set at 50 mg/kg for each of REGN10933 (C_{max} of 2410 µg/ml/AUC_{tau} of 10,900 day µg/ml) and REGN10987 (C_{max} of 2620 µg/ml/AUC_{tau} of 11,600 day µg/ml); for the combination the NOAEL was set at 150 mg/kg (C_{max} of 12,800 µg/ml/AUC_{tau} of 51,700 day µg/ml).

Interspecies comparison

The aim of interspecies comparison is to understand how exposure shown to be safe in animals compares with that expected in humans.

At the NOAEL dose defined from the monkey general toxicity study, of 150 mg/kg of each antibody, REGN10933 and REGN10987, the dose, on a weight basis, is ~3 times higher than the highest proposed clinical dose of 8 g (or 100 mg/kg [50 mg/kg of each antibody] based on an 80 kg person). At the NOAEL dose, a mean AUC_{cum} (cumulative AUC from initiation of dosing to recovery necropsy) of 242,000 daymg/l was estimated. For a proposed clinical dose of up to 8 g, and in healthy subjects assuming no virus (antigen), a safety margin of at least 4.7-fold was projected prior to human dosing.

Table 23: Mean pharmacokinetic parameters of total REGN10933, total REGN10987, or total REGN10933+REGN10987 in serum following once weekly intravenous or subcutaneous injections administered alone or in combination for 4 weeks in the cynomolgus monkey

Parameter	Unit	Dose	REGN10933 50 mg/kg IV			REGN10987 50 mg/kg IV			COMBINATION 50+50 mg/kg IV			COMBINATION 150+150 mg/kg IV			COMBINATION 150+150 mg/kg SC		
			N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
C_{max}	µg/mL	1	10	1250	197	10	1590	147	10	2680	205	10	7420	662	10	3140	225
		4	10	2410	156	10	2620	217	10	3850	377	10	12800	798	10	7360	955
C_{max}/Dose	(µg/mL)/ (mg/kg)	1	10	25.0	3.93	10	31.8	2.95	10	26.8	2.05	10	24.7	2.21	10	10.5	0.752
		4	10	48.2	3.12	10	52.5	4.35	10	38.5	3.77	10	42.7	2.66	10	24.5	3.18
t_{max}	h or day	1	10	0.0833	0	10	0.0833	0	10	0.0833	0	10	0.0833	0	10	1.80	0.422
		4	10	0.0833	0	10	0.0833	0	10	0.0833	0	10	0.0833	0	10	1.80	0.632
AUC_{tau}	day•(µg/mL)	1	10	4650	404	10	5130	363	10	8790	510	10	26100	1240	10	19000	1540
		4	10	10900	1080	10	11600	1500	10	18000	1810	10	51700	3170	10	43800	6180
AUC_{last}		4	4	33300	8800	4	33300	7680	4	45800	4440	4	140000	10000	4	108000	15600
AUC_{rec}		NA	4	22400	7140	4	20900	5950	4	28600	3320	4	86700	10500	4	67300	14100
AUC_{tau}/Dose		1	10	93.1	8.09	10	103	7.26	10	87.9	5.10	10	87.0	4.14	10	63.3	5.15
		4	10	217	21.7	10	231	30.0	10	180	18.1	10	172	10.6	10	146	20.6
AUC_{last}/Dose	day•(µg/mL)/ (mg/kg)	4	4	667	176	4	666	154	4	458	44.4	4	467	33.3	4	361	52.1
AUC_{rec}/Dose		NA	4	447	143	4	418	119	4	286	33.2	4	289	35.1	4	224	47.1
C_{trough}	µg/mL	1	10	437	35.3	10	469	42.8	10	847	84.2	10	2700	172	10	2620	318
		2	10	598	78.9	10	609	139	10	1140	134	10	3360	344	10	3280	561
		3	10	1070	143	10	1050	121	10	1720	176	10	4800	583	10	4710	779
		4	10	1200	161	10	1230	192	10	2030	304	10	4970	511	10	4900	885
AUC_{cum}	day•(µg/mL)	NA	53500			54400			82200			242000			193000		

AUC, Area under the concentration-time curve; AUC_{cum}, AUC computed from time zero to end of the recovery period, reflecting the overall exposure during the entire study duration; AUC_{last}, AUC computed from time zero to the time of the last detectable concentration; AUC_{rec}, AUC computed during the recovery period; AUC_{tau}, AUC calculated during the dosing interval; C_{max}, Peak concentration; C_{trough}, Concentration measured at the end of a dosing interval; ELISA, Enzyme-linked immunosorbent assay; h, Hours; IV, Intravenous; N, Number of animals; NA, Not applicable; SC, Subcutaneous; SD, Standard deviation; t_{max}, time to C_{max}

Notes: t_{max} is represented in hours for the IV dose group and in days for the SC dose group.

COMBINATION in table title denotes REGN10933 dose + REGN10987 dose (REGN-COV-2)

ELISA measures total REGN10933, total REGN10987 and/or total REGN10933+REGN10987 as total human IgG.

Genotoxicity

No such studies have been done.

Carcinogenicity

No such studies have been done.

Reproductive and developmental toxicity

No such studies have been done. In accordance international guidance, for monoclonal antibodies that target a non-mammalian target, these studies are not required. In cynomolgus monkeys (aged 2.2-4.0 years old), there were no changes in the testes, epididymides, ovaries, uterus or vagina. The study did not identify any potential risks to fertility.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

No such studies have been done.

Local tolerance

No such studies have been done.

Other toxicity studies
No such studies have been done.

III.5 Environmental risk assessment
The company supplied a justification for the absence of an environmental risk assessment: this referred to the 2006 Guideline on Environmental Risk Assessment (ERA) for Non-GMO Human Medicinal Products of the European Medicines Agency (EMEA/CHMP/SWP/4447/00 corr. 2 [1]) which allows, for proteins, that this may consist of a justification for not submitting studies as due to their nature they are unlikely to result in a significant risk to the environment. As applied to this product, proteins are degraded in the patient's body by regular proteolytic mechanisms before excretion, REGN10933 and REGN10987 are unlikely to result in a significant environmental exposure. The document weas supported by an expert with appropriate experience, as required.

This is accepted.

III.6 Discussion on the non-clinical aspects
The expectation for safety studies to support development of an antibody is laid out in international guidance ICH S6 (R1), Preclinical safety evaluation of biotechnology-derived pharmaceuticals. For antibodies that target a non-mammalian antigen, this states that: a short-term safety study in one species (choice of species to be justified by the sponsor) can be considered; no additional toxicity studies, including reproductive toxicity studies, are appropriate. Testing presented in this application is judged to meet this standard.

In respect of the adequacy of the doses used in the general toxicity study, this is accepted. The use of the monkey seems unnecessary as data from a lower species, such as rats, would suffice but in the studies done there were no untoward findings and there are no concerns about data integrity of compliance with Good Laboratory Practice. Increases in liver enzymes were noted in some monkeys but these were not associated with observable toxicity in either liver or skeletal muscle at post-mortem: although the post-mortem data were generated a week after the last dose, allowing the possibility of recovery, the in-life measures did not indicate any toxicity associated with these changes and their magnitude was not such as to cause concern. The tissue cross reactivity studies are not expressly required, according to the guidance, but they did not, insofar as this methodology can, identify binding at an antigen in mammalian tissues.

It is concluded that these data support clinical use of the antibodies and support a decision to grant a licence for the product.

The grant of a conditional marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The following clinical studies were submitted with this application. In this report, casirivimab and imdevimab are sometimes referred to, respectively, as REGN10933 and REGN10987.

Table 24: Overview of clinical studies

Study	Study Population	Dosage and Dosage Regimen	Study Status/ Cut-off date/Data included in application
Treatment Studies			
COV-2067 Phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol.	**Phase 1 and 2:** Adult, non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2. **Phase 3:** Non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2. Cohort 1: ≥18 years of age Cohort 2: 0 to <18 years of age Cohort 3: Pregnant at randomization	**Phase 1 and 2:** Casirivimab+imdevimab IV single dose: • 8000 mg (4000 mg per mAb) • 2400 mg (1200 mg per mAb) Placebo IV single dose **Phase 3:** Cohort 1 and cohort 3 patients ≥18 years: • Casirivimab+imdevimab 1200 mg (600 mg per mAb) IV single dose • Casirivimab+imdevimab 2400 mg (1200 mg per mAb) IV single dose Cohort 2 and cohort 3 patients <18 years: Casirivimab+imdevimab lower-dose and higher-dose treatment arms tiered according to body weight. Cohort 1 and cohort 2[a] • Placebo IV single dose	Phase 1 and 2 complete. Phase 3 cohort 1: Primary analysis complete; follow-up ongoing. Phase 3 cohorts 2 and 3: enrollment ongoing; unblinded data not included in this application. **Cut-off:** 18 Feb 2021[b] **Data included in this application:** • Primary analysis of efficacy data from phase 3 cohort 1 (patients ≥18 years). • Integrated safety data from phase 1/phase 2 symptomatic patients/phase 3 cohort 1 up to the cut-off date. • Blinded safety data from phase 2 asymptomatic patients, phase 3 cohort 2 and phase 3 cohort 3 up to the cut-off date.
Study	**Study Population**	**Dosage and Dosage Regimen**	**Study Status/ Cut-off date/Data included in application**
COV-2066 Phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol.	Hospitalized patients who have a positive diagnostic test for SARS-CoV-2 • **Cohort 1A**: hospitalized patients not requiring oxygen • **Cohort 1**: hospitalized patients requiring low-flow oxygen • **Cohort 2**: hospitalized patients requiring high-flow oxygen • **Cohort 3**: hospitalized patients requiring mechanical ventilation	• Casirivimab+imdevimab: 2400 mg (1200 mg per mAb) IV x 1 dose • Casirivimab+imdevimab: 8000 mg (4000 mg per mAb) IV x 1 dose • Placebo IV x 1 dose	Phase 1, 2 and 3 complete. **Data included in this application:** • Safety data for patients in cohort 1, (phase 1 and 2), cohort 2 (phase 2) and cohort 3 (phase 2). • Efficacy data from cohort 1 (phase 1 and 2).
Prevention Studies			
COV-2069 Phase 3, randomized, double-blind, placebo-controlled study.	Asymptomatic, healthy adults (≥18 years), adolescents (≥12 years to <18 years), and children (<12 years) who are household contacts to the first known household member with a diagnosis of SARS-CoV-2 infection. **Cohort A**: ≥12 years who are SARS-CoV-2 RT-qPCR negative at baseline. **Cohort A1**: <12 years who are SARS-CoV-2 RT-qPCR negative at baseline. **Cohort B**: ≥12 years who are SARS-CoV-2 RT-qPCR positive at baseline. **Cohort B1**: <12 years who are SARS-CoV-2 RT-qPCR positive at baseline	Participants ≥12 years: • Casirivimab+imdevimab: 600 mg of each mAb SC x 1 dose on day 1 • Placebo SC x 1 dose on day 1	Primary analysis of cohort A and cohort B complete; follow-up ongoing. **Data cut-off:** 11 Mar 2021[b] **Data included in this application:** • Efficacy and safety data from subjects randomized by 28 Jan 2021 in cohort A up to the cut-off date. • Blinded safety data from subjects randomized by 28 Jan 2021 in cohort A1 up to the cut-off date. No adolescents were enrolled into cohorts A or B at the time of the data cut off.
HV-2093 Phase 1, randomized, double-blind, placebo-controlled study.	Adult volunteers who are healthy or have chronic but stable and well-controlled medical condition(s), and negative at screening for SARS-CoV-2 infection	• Casirivimab+imdevimab: 1200 mg (600 mg per mAb) SC Q4W x 6 doses • Placebo SC Q4W x 6 doses	Interim analysis complete; study ongoing. **Data cut-off:** 13 Mar 2021[b] **Data included in this application:** • Safety data from all subjects up to the cut-off date

a) Per Independent Data Monitoring Committee (IDMC) recommendation, as of February 25, 2021, patients will no longer be randomized to placebo
b) Cut-off dates for drug concentration and immunogenicity samples are provided in Module 2.7.2.

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

In support of the application, the following studies were submitted which evaluated pharmacokinetics, pharmacodynamics, and immunogenicity for casirivimab+imdevimab.

Table 25: Overview of studies conducted to evaluate pharmacokinetics, pharmacodynamics, and immunogenicity for casirivimab+imdevimab

Study number/ report location/ study status	**Study population/analysis sets**	**PK- and ADA-related objectives**	**Study design and duration**	**Treatment: route of administration, frequency and dose (number of subjects/patients analysed for PK/ADA)**
Clinical studies for the treatment of outpatients with SARS-Cov-2 infection and Covid-19				
COV-2067	**Phase 1 and 2:**	**Phase 1 and 2:**	**Phase 1 and 2:**	**Phase 1 and 2:**

Phase 1 and 2 are Completed	Adult, non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2	Characterize the PK profile of casirivimab+imdevimab in serum over time Assess immunogenicity of casirivimab+imdevimab	Randomized, double-blinded, placebo controlled single-dose study to evaluate the efficacy, safety, and tolerability of casirivimab+imdevimab in ambulatory patients with Covid-19 Duration: 29 days **NP sample collection:** **phase 1 and 2:** baseline (predose), days 3, 5, 7, 9, 11, 13, 15, 18, 22, 25, and 29 (EOS) Dense PK sampling: N=45 Sparse PK sampling: N=458 **PK sample collection:** **phase 1 dense**: baseline, end of infusion, and days 3, 5, 7, 15, and 29 (EOS) **phase 2 sparse:** baseline, end of infusion, and day 29 (EOS)/ET **ADA sample collection:** **phase 1 and 2:** baseline (predose), day 29/ET	IV, single dose: • 8000 mg (4000 mg per mAb) (PK: 257; ADA: 245) • 2400 mg (1200 mg per mAb) (PK: 246; ADA: 231) • Placebo (PK: N/A; ADA: 198)
Primary analysis of phase 3 is completed, follow up ongoing	**Phase 3:** Adult, paediatric, and pregnant patients who have a positive diagnostic test for SARS-CoV-2 and ≥1 risk factor for severe Covid-19 Cohort 1: ≥18 years of age, not pregnant at randomization Cohort 2: 0 to <18 years of age, not pregnant at randomization Cohort 3: Pregnant at randomization At the time of the study data cutoff, Cohort 2 and Cohort 3 data were not available.	**Phase 3:** Further characterize the PK profile of casirivimab+imdevimab in serum over time Assess immunogenicity of casirivimab+imdevimab	**Phase 3:** Randomized, double-blinded, placebo controlled, single-dose study to evaluate the efficacy, safety, and tolerability of casirivimab+imdevimab in ambulatory patients with Covid-19 Duration: 169 days **NP sample collection:** **phase 3:** baseline (predose), days 7, 15, and 29 Sparse PK sampling: N=2421 **PK sample collection:** **phase 3 sparse**: baseline (predose), and days 29 and 120 (Cohort 1, not pregnant at randomization)/ET **ADA sample collection:** **phase 3** baseline (predose), days 29 and 120/ ET	**Phase 3:** Cohort 1: IV, single dose: • 1200 mg (600 mg per mAb) (PK: 291; ADA: 124) • 2400 mg (1200 mg per mAb) (PK: 1214; ADA: 1007) • 8000 mg (4000 mg per mAb (PK: 916; ADA: 877) • Placebo (PK: N/A; ADA: 598)
COV-20145 First-step analysis is completed, follow-up ongoing	**Phase 2**: Adult, non-hospitalized patients who have a positive diagnostic test for SARS CoV-2	**Phase 2**: To assess the concentrations of casirivimab and imdevimab in serum over time. To assess the immunogenicity of casirivimab and imdevimab.	**Phase 2:** Randomized, double-blind, placebo-controlled, parallel group study to assess the dose response profile of single IV or single SC doses of casirivimab+imdevimab in outpatients with SARS-CoV-2 infection Duration: 169 days. **NP sample collection:** Baseline (predose), days 3, 5, 7, 15, 22 Sparse PK sampling: N=685 **PK sample collection:** **sparse:** baseline (predose and postdose), and days 3, 5, 7, and 120/ET **ADA sample collection:**	**Phase 2**: Casirivimab+imdevimab IV, single Dose • 2400 mg (1200 mg per mAb) (PK: 115) • 1200 mg (600 mg per mAb) (PK: 115) • 600 mg (300 mg per mAb) (PK: 113) • 300 mg (150 mg per mAb) (PK: 114) • Placebo (PK: N/A) SC, single Dose • 1200 mg (600 mg per mAb) (PK: 114)

			Baseline (predose) and day 120/ET ADA data were not available for this submission.	• 600 mg (300 mg per mAb) (PK: 114) • Placebo (PK: N/A)
Clinical study for the prevention of SARS-CoV-2 infection in uninfected subjects or Covid-19 disease in subjects with asymptomatic SARS-CoV-2 Infection				
COV-2069 **COV-2069A**: Prevention Study **COV-2069B**: Pre-emptive treatment Primary analysis completed/follow up ongoing	**Phase 3:** Asymptomatic, healthy adults (≥18 years), adolescents (≥12 years to <18 years), and children (<12 years) who are household contacts to the first known household member with a diagnosis of SARS-CoV-2 infection. **COV-2069A:** **Cohort A**: adult and adolescent subjects (≥12 years) who are asymptomatic and SARS-CoV-2 RTqPCR negative at baseline **Cohort A1:** paediatric subjects (<12 years) who are SARS-CoV-2 RTqPCR negative at baseline **COV-2069B:** **Cohort B**: adult and adolescent subjects (≥12 years) who are asymptomatic and SARS CoV-2 RTqPCR positive at baseline **Cohort B1:** paediatric subjects (<12 years) who are SARS-CoV-2 RTqPCR positive at baseline	**Phase 3:** To characterize the concentration-time profiles of casirivimab and imdevimab in serum and selected PK parameters. To assess the immunogenicity of casirivimab and imdevimab.	**Phase 3:** Randomized, double-blind, placebo-controlled single-dose study assessing the efficacy and safety of casirivimab+imdevimab in preventing SARSCoV-2 infection in household contacts of individuals infected with SARS-CoV-2 Duration: 225 days **NP sample collection:** Baseline (predose), days 8, 15, 22, and 29 Dense PK sampling: N=16 subjects Sparse PK sampling: N=152 subjects **PK sample collection:** **Dense (sentinel group)**: baseline (predose), days 2, 4, 8, 15, 22, 29, 57, 85, 113, 141, 169, 197, 225 (EOS)/ET **Sparse (safety group)**: baseline (predose), days 29, 57, 113, 169, 225 (EOS)/ET **ADA sample collection:** Baseline (predose), days 29, 113, and 225 (EOS)/ET	**Phase 3:** Casirivimab+imdevimab SC, single dose Adult and adolescent subjects (≥12 years): • 1200 mg (600 mg per mAb) (PK: 169; ADA: 960 [casirivimab] and 957 [imdevimab]) • Placebo (PK: N/A; AAS: 447 [ADA-10933] and 441 [ADA-10987]) At the time of the data cutoff for the study, no subjects <12 years of age were enrolled in the study.
Clinical study for the prevention of SARS-CoV-2 infection				
HV-2093 Interim analysis completed, study ongoing	**Phase 1:** Adults who are healthy or have chronic but stable and well-controlled medical condition(s), and negative at screening for SARS-CoV-2 infection	**Phase 1:** To assess the concentrations of casirivimab and imdevimab in serum over time after repeated SC administration. Assess immunogenicity for repeated doses of casirivimab and imdevimab administered SC.	**Phase 1:** Randomized, double-blind, placebo-controlled study to assess the safety and tolerability of multiple SC doses of casirivimab+imdevimab Duration 365 days **NP sample collection:** Baseline (predose) only. Post-baseline sample was collected at an unscheduled visit if Covid-19 signs/symptoms were observed Sparse PK sampling: 723 **PK sample collection:** **Sparse**: baseline (predose), days 8, 29, 57, 85, 113, 141, 148, 169, 225, 281, 365 (EOS)/ET **ADA sample collection:** Baseline (predose), days 29, 113, 225, 365 (EOS)/ET	**Phase 1:** Casirivimab+imdevimab SC, multiple dose Q4W for 6 doses • 1200 mg (600 mg per mAb) (PK: 723; ADA: 939) • Placebo (PK: N/A; ADA: 232) Note: Up to Protocol Amendment 2, subjects received 4 doses of study drug

AAS, anti-drug antibody analysis set; ADA, anti-drug antibody; Covid-19, Coronavirus disease 2019; CSR, clinical study report; EOS, end of study; ET, early termination; IV, intravenous; mAb, monoclonal antibody; N/A, not applicable; PD, pharmacodynamics; PK, pharmacokinetics; PKAS, pharmacokinetic analysis set; Q4W, every 4 weeks; RT-qPCR, quantitative reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SC, subcutaneous; Q4W, every 4 weeks.

Study 2067

This study was an adaptive, seamless, phase 1/2/3, randomised, double-blinded, placebo-controlled master protocol to evaluate the efficacy, safety, and tolerability of single IV dose casirivimab+imdevimab combination therapy in ambulatory patients (i.e., outpatients) with mild to moderate Covid-19.

Objectives and endpoints for Phase 1/2

Primary objective – To evaluate the virologic efficacy of casirivimab+imdevimab compared to placebo in reducing viral load of SARS-CoV-2.
Endpoint – To assess ability to lower viral load in those infected with Covid-19. This was measured by time weighted average (TWA) daily change from baseline in viral shedding (log_{10} copies/mL0 from day 1 to day 7, as measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples.

Objectives and endpoints for Phase 3

Primary objective – To evaluate the clinical efficacy of casirivimab+imdevimab compared to placebo as measure by Covid-19-related hospitalisations or all cause death.
Endpoint – Proportion of patients with ≥1 Covid-19-related hospitalisation or all-cause death through day 29.

Dose

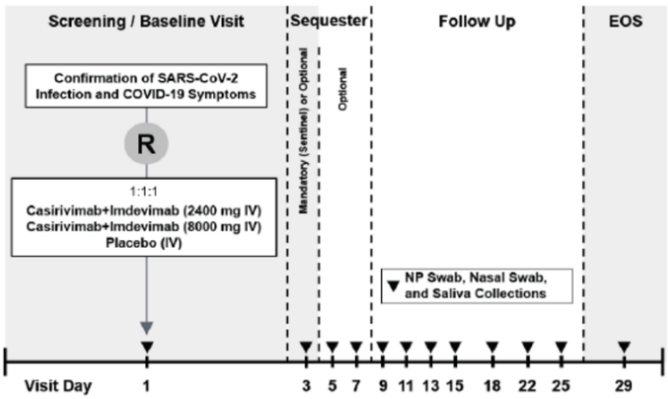
Patients received placebo, 2400 mg, and 8000 mg IV dose of casirivimab + imdevimab in phase 1 and 2, and placebo, 1200 mg, 2400 mg, and 8000 mg IV dose of casirivimab + imdevimab in phase 3, cohort 1. The primary analysis of phase 3 cohort 1 involved patients receiving placebo, 2400 mg, and 1200 mg.

Study design

The primary aim of phase 1 was to evaluate the safety and tolerability of casirivimab+imdevimab and to assess initial virologic efficacy. Patients were randomized 1:1:1 to a single IV dose of casirivimab+imdevimab 2400 mg, casirivimab+imdevimab 8000 mg or placebo.

Nasopharyngeal swabs, nasal swabs, and saliva samples were collected as indicated in figure 10 until day 29 (end of study). The preferred means of collection was NP swab.

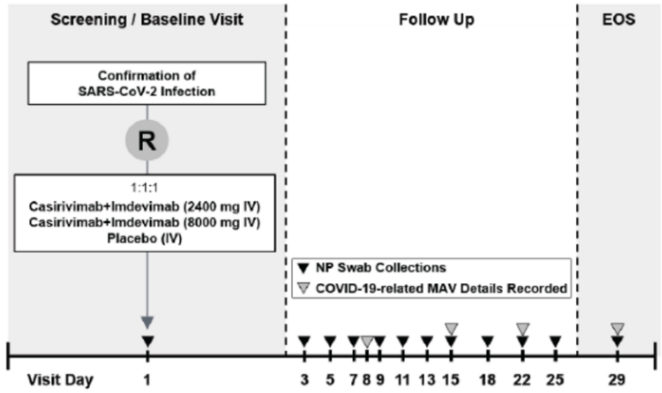
Figure 10: Study design, phase I



The primary aim of phase 2 was to evaluate virologic efficacy and to gain initial insights into the clinical efficacy of casirivimab+imdevimab. Patients were randomized 1:1:1 to a single IV dose of casirivimab+imdevimab 2400 mg, casirivimab+imdevimab 8000 mg, or placebo. Nasopharyngeal swabs and blood draws were collected as indicated in figure 11 until day 29

(end of study).

Figure 11: Study design, phase 2 (and phase 3 prior to the amended portion)



Nasal swabs and saliva samples were not collected in phase 2.

Blood samples for measurement of concentrations of casirivimab and imdevimab, as well as for immunogenicity in serum were collected at the time points specified in table 25. Nasopharyngeal swab samples for SARS-CoV-2 virus were also collected at various time points specified in table 25.

Concentrations of casirivimab, imdevimab, casirivimab+imdevimab combined in serum, concentration-response results for viral load reduction and clinical outcomes, and immunogenicity results for all 3 study phases are presented below.

PK results

Following a single IV dose of 1.2 and 4.0 g, the concentration-time profiles for casirivimab and imdevimab in serum increased in a dose-proportional manner between these 2 dose levels as the difference between the dose normalised C_{max} and AUC did not exceed 25%. The estimated $t_{1/2}$ for the two antibodies ranged between 25 to 37 days.

Figure 12: Mean (+SD) concentration-time profile for REGN10933 and REGN10987 in ambulatory patients with Covid-19

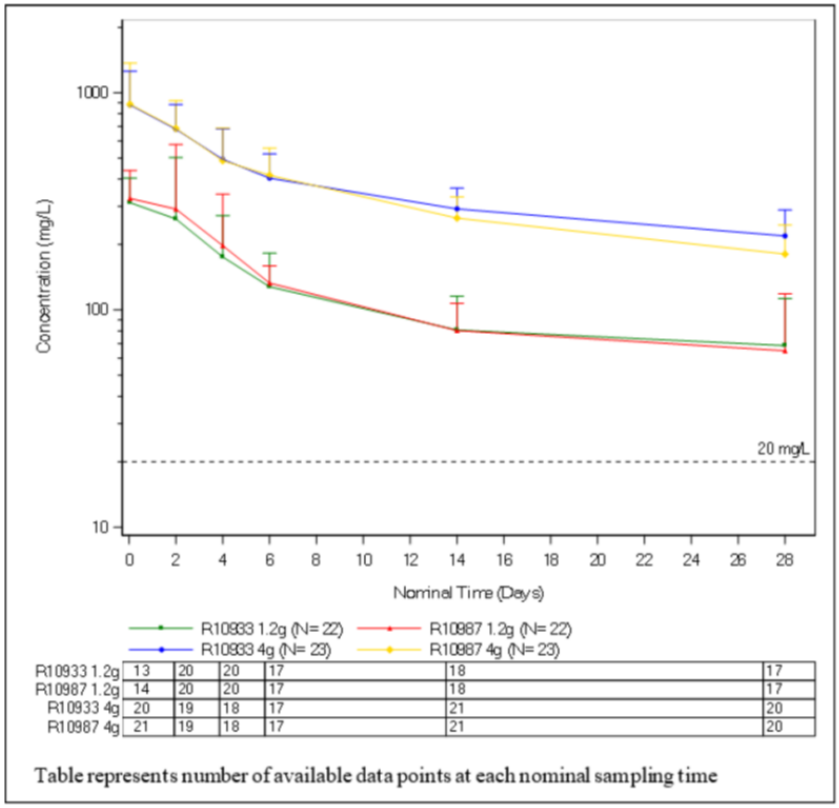


Table 26: Mean (SD) [N][a] pharmacokinetic parameters of REGN10933 and REGN10987 in serum after a single IV dose in ambulatory patients with Covid-19

Pharmacokinetic Parameter	REGN10933		REGN10987	
	1.2 g	4 g	1.2 g	4 g
C_{max} (mg/L)	325 (214) [22]	875 (349) [23]	364 (265) [22]	923 (424) [23]
AUC_{0-28} (mg•day/L)	3393 (1887) [16]	9775 (2464) [19]	3492 (2916) [17]	9218 (2629) [19]
C_{28} (mg/L)[b]	68.0 (45.2) [17]	219 (69.0) [20]	64.9 (53.9) [17]	181 (64.9) [20]
$t_{1/2}$ (days)	37.4 (19.5) [12]	29.1 (9.33)[c,d] [17]	34.4 (25.5) [13]	25.1 (18.1)[c] [18]

[a] Number of observations
[b] Observed concentration 28 days after dosing, ie on day 29
[c] One patient excluded as day 29 concentration was greater than day 14, the resulting positive slope precluded estimation of $t_{1/2}$
[d] One patient with an estimated $t_{1/2}$ of 536 days was identified as an outlier and therefore not reported

The exposure parameters (C_{max}, AUC_{0-28} and C_{28}) have shown moderate to high CV% indicating high interindividual variability, possibly due to flat doses (i.e. not weight adjusted) in subjects with variable body weight.

Study 20145

This was a phase 2 randomized, double-blinded, placebo-controlled, parallel group study to assess the virologic efficacy, safety, and tolerability of casirivimab+imdevimab across different intravenous (IV) and subcutaneous (SC) single-dose regimens in adult, non-hospitalized participants with SARS-CoV-2 infection.

The primary objective was to assess the virologic efficacy of casirivimab+imdevimab across different IV and SC doses compared to placebo.

The primary endpoint is time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in nasopharyngeal (NP) swab samples, in patients who have a central-lab determined RT-qPCR positive test and are seronegative at baseline.

Dose
Patients received a single IV dose of placebo, 300 mg, 600 mg, 1200 mg, or 2400 mg casirivimab+imdevimab, or a single SC dose of placebo, 600 mg or 1200 mg casirivimab+imdevimab.

Study design
A randomized, double-blind, placebo-controlled, parallel group study to assess the dose response profile of single intravenous (IV) or single subcutaneous (SC) doses of REGN10933+REGN10987 in 803 outpatients with SARS-CoV-2 infection. On the day of dosing, patients had NP swabs taken for SARS-CoV-2 RT-qPCR testing and blood drawn for safety, drug concentration, immunogenicity, and serologic analyses. After study drug administration, patients had a post-dose blood collection (either at the end of intravenous infusion or at least 1 hour after subcutaneous administration).

Figure 13: Study design

Study Intervention	Route of Administration	Randomization Ratio
2400 mg (1200 mg each of casirivimab and imdevimab)	IV	2
1200 mg (600 mg each of casirivimab and imdevimab)	IV	2
600 mg (300 mg each of casirivimab and imdevimab)	IV	2
300 mg (150 mg each of casirivimab and imdevimab)	IV	2
Placebo	IV	1

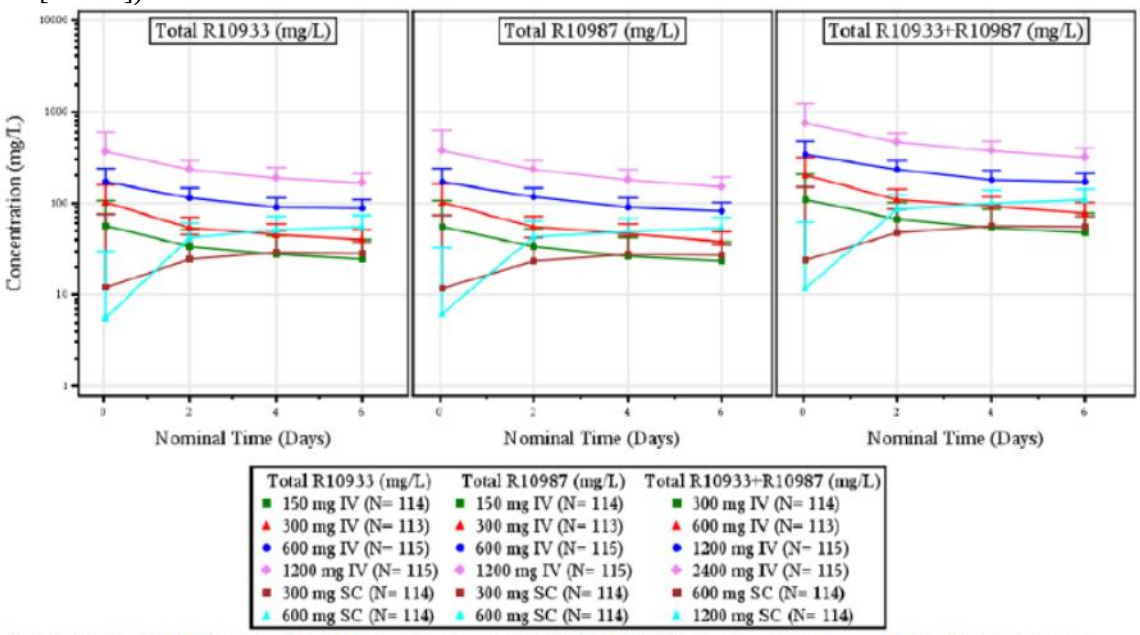
Study Intervention	Route of Administration	Randomization Ratio
1200 mg (600 mg each of casirivimab and imdevimab)	SC	2
600 mg (300 mg each of casirivimab and imdevimab)	SC	2
Placebo	SC	1

IV=intravenous; SC=subcutaneous.

Blood samples for measurement of concentrations of casirivimab and imdevimab, as well as for immunogenicity in serum, were collected at the time points specified in table 25. Nasopharyngeal swab samples for SARS-CoV-2 virus were also collected at various time points specified in table 25.

PK results
Mean casirivimab+imdevimab concentrations increased dose-proportionally for both IV and SC doses indicating linear pharmacokinetics. Casirivimab and imdevimab concentrations were similar over the first 6 days following administration of casirivimab+imdevimab for any given IV or SC dose. No casirivimab+imdevimab concentration or exposure-related differences in the change in viral load at Day 7 were observed, for IV and SC dosing groups.

Figure 14: Mean (+SD) concentrations of casirivimab, imdevimab, and combined casirivimab+imdevimab in serum by time and treatment group (log-scale; pharmacokinetic analysis set [PKAS])



Concentrations below the LLOQ were set to LLOQ/2. Combined concentrations (REGN10933+REGN10987) were calculated only when both the analytes were not missing.
Predose concentrations were not presented, concentration shown at day 0 is an EOI or post dose concentration. Day(s) shown represent the number of day(s) following study drug administrations; study day 1 (as noted in other tables and figures in this report) corresponds to "day 0" in this figure.
EOI=end of infusion; N=number of participants; IV=intravenous; LLOQ=lower limit of quantification; R10933=casirivimab; R10987=imdevimab; R10933+R10987=casirivimab+imdevimab; SC=subcutaneous; SD=standard deviation.

Study COV-2069

This was a phase 3, randomized, double-blind, placebo-controlled study assessing the efficacy and safety of anti-spike SARS-CoV-2 monoclonal antibodies in preventing SARS-CoV-2 infection in household contacts of individuals infected with SARS-CoV-2. The study was conducted in geographic areas with an active Covid-19 outbreak and included 137 sites in Moldova, Romania, and the United States and the clinical trial is ongoing. The study was designed to assess the efficacy of the administration of REGN10933+REGN10987 (REGN-COV2) to reduce the incidence of SARS-CoV-2 infection and prevent the development of disease (symptomaticSARS-CoV-2 infection) after household exposure to individuals with SARS-CoV-2 infection

Study populations

Cohort A analyses evaluated infection prevention in participants who were uninfected at baseline.

- Adult and adolescent subjects (≥12 years) who are SARS-CoV-2-RT-qPCR negative at baseline.

Cohort B focused on early treatment to prevent symptomatic progression in participants with asymptomatic infection at baseline.

- Adult and adolescent subjects (≥12 years) who are SARS-CoV-2-RT-qPCR positive at baseline.

Primary endpoint

Cohort A

The primary efficacy variable was the proportion of subjects who have symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the efficacy assessment period (EAP).

Cohort B

The primary efficacy variable for Cohort B was the proportion of subjects who subsequently

develop signs and symptoms (broad-term) with 1 days of a positive RT-qPCR at baseline or during the EAP.

Dose
For this first-step analysis, a total of 3002 subjects ≥12 years of age were randomized 1:1 to receive a single 1200 mg (600 mg per mAb) SC dose of casirivimab+imdevimab (N=1493) or placebo (N=1509). Of the randomized 3002 subjects, 169 subjects were included in the PK analysis set.

Study design
A phase 3 randomized, double-blind, placebo-controlled study in 3500 adults and adolescents >12yrs and 250 children <12yrs with household contact exposure to individuals with SARS-CoV-2 infection.

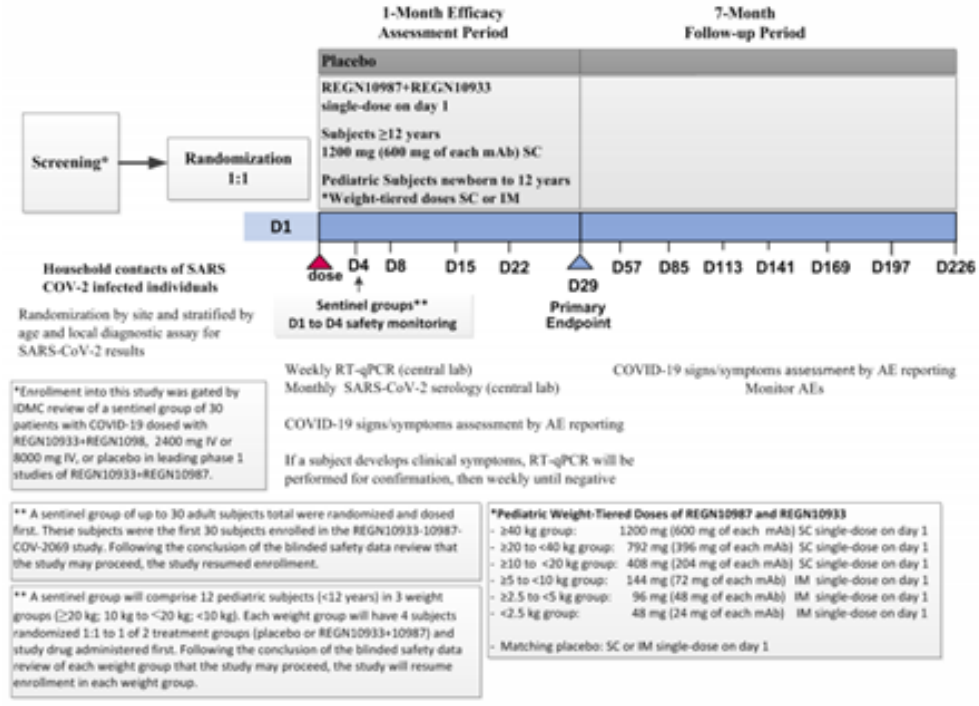
This study was designed to assess the efficacy of the administration of REGN10933+REGN10987 to reduce the incidence of SARS-CoV-2 infection and prevent the development of disease (symptomatic SARS-CoV-2 infection) after household exposure to individuals with SARS-CoV-2 infection.

Eligible subjects were those who were asymptomatic and household contacts with close exposure with the first household member with known SARS-CoV-2 infection (index case) but may be either positive or negative for SARS-CoV-2 during screening, as assessed by central laboratory RT-qPCR performed at baseline.

The index case had a diagnosis of SARS-CoV-2 infection using a diagnostic test e.g. RT-PCR, antigen test, or other test format.

Subjects were randomized in a 1:1 allocation ratio to 1 of 2 treatment groups (placebo or REGN10933+REGN10987). Randomization was performed by individual study subjects, not by households. The first 30 adults and first 12 paediatric subjects formed sentinel groups for additional safety monitoring.

Figure 15: Study flow diagram



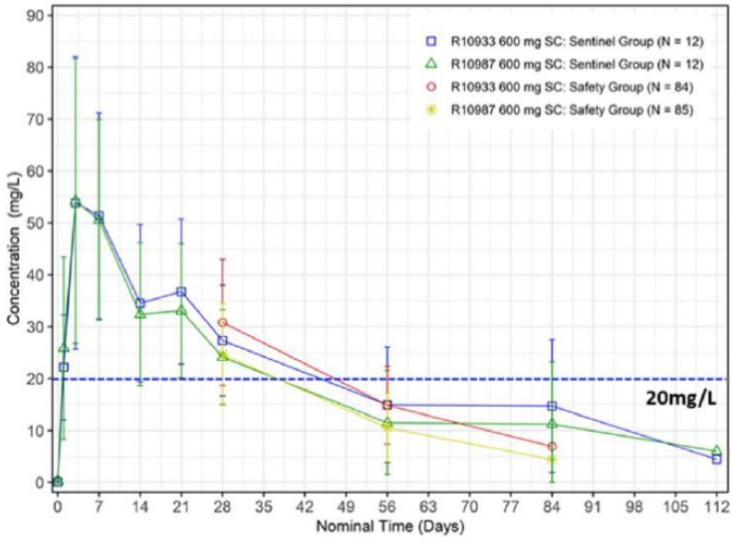
Concentrations of casirivimab and imdevimab were measured in serum, and the presence of ADA was evaluated in serum samples collected from subsets of subjects in COV-2069A (n=152) and COV-2069B (n=14) at pre-dose, and at various times following treatment (table 25). Three subsets of patients (≥18 years of age) were defined to collect drug concentration data: (a) a sentinel subset with dense PK sampling, (b) a safety subset with sparse sampling, and (c) subjects for which no samples for PK were prospectively collected according to the protocol. The PK parameters of casirivimab, imdevimab, and casirivimab+imdevimab were determined by noncompartmental analysis in the sentinel subset (n=16), and descriptive analysis was performed on the sparse samples collected in the safety subset (n=152). Immunogenicity of casirivimab and imdevimab and its relationship to systemic exposure of casirivimab and imdevimab were also assessed in all subsets; in at least 275 subjects who received placebo and at least 925 subjects who received casirivimab+imdevimab. Nasopharyngeal samples were collected for SARS-CoV-2 RT-qPCR test (central laboratory) at pre-dose and at various times throughout the treatment and follow-up periods.

PK results

Following SC administration, casirivimab (REGN10933) and imdevimab (REGN10987) were rapidly absorbed (time to peak concentration in serum ~3 days) and both antibodies exhibited linear elimination (figure 16). Mean (CV%) half-life for casirivimab and imdevimab in evaluable subjects (N=6) was 24.7 (17.1%) days and 19.4 (13.8%) days. A summary of the PK parameters is shown in table 27.

On day 1 following SC administration, serum concentrations of each antibody exceeded the presumed therapeutic threshold of 20 mg/L that, based on preclinical data and modelling, was considered necessary for efficacy. Mean concentration of both mAbs remained >20 mg/L for at least 28 days after dosing.

Figure 16: Mean (SD) concentrations of casirivimab and imdevimab in serum over time for sentinel and safety cohorts after single 1200 mg SC dose (linear scale)



Treatment	0 Day	1 Day	3 Day	7 Day	14 Day	21 Day	28 Day	56 Day	84 Day	112 Day
R10933 600 mg SC: Safety Group	0	0	0	0	0	0	72	38	1	0
R10987 600 mg SC: Safety Group	0	0	0	0	0	0	73	38	1	0
R10933 600 mg SC: Sentinel Group	8	11	11	12	11	12	10	11	10	1
R10987 600 mg SC: Sentinel Group	8	11	11	12	11	12	10	11	10	1

Table 27: Summary of pharmacokinetics parameters for casirivimab and imdevimab after a single 1200 mg SC REGN-COV2 dose in the sentinel cohort

PK Parameter[1]	Casirivimab (REGN10933)	Imdevimab (REGN10987)
C_{max} (mg/L)	56.1 (44) [12]	56.0 (43) [12]
t_{max} (day)[2]	6.85 (2.82, 13.8) [12]	5.77 [2.80, 13.8] [12]
AUC_{inf} (mg•day/L)[3]	2088 (35.8) [6]	1581 (37.2) [6]
Half-life (day)[3]	24.7 (17.1) [6]	19.4 (13.8) [6]

[1]Mean (CV%) [N].
[2]median (range) [N].
[3]value reported for subjects with %AUC_{inf} extrapolated <20%.
Source: Data on file

Study HV-2093

This was a phase 1, randomized, double-blind, placebo-controlled study assessing the safety, tolerability, pharmacokinetics, and immunogenicity of repeated subcutaneous doses of anti-spike (S) SARS-CoV-2 monoclonal antibodies (REGN10933+REGN10987) in adult volunteers.

The primary object was to assess the occurrence of adverse events of special interest (AESIs) in participants treated with repeated SC doses of casirivimab+imdevimab compared to placebo; and to assess the concentrations of casirivimab and imdevimab in serum over time after single and repeated SC administration.

The endpoints were incidence of AESIs that occur within 4 days of SC administration of casirivimab+imdevimab or placebo at baseline and days 29, 57, 85, 113, and 141; and concentrations of casirivimab+imdevimab in serum over time.

Dose

Subjects received placebo or 1200 mg (600 mg per mAb) Q4W for 6 doses.

Study design

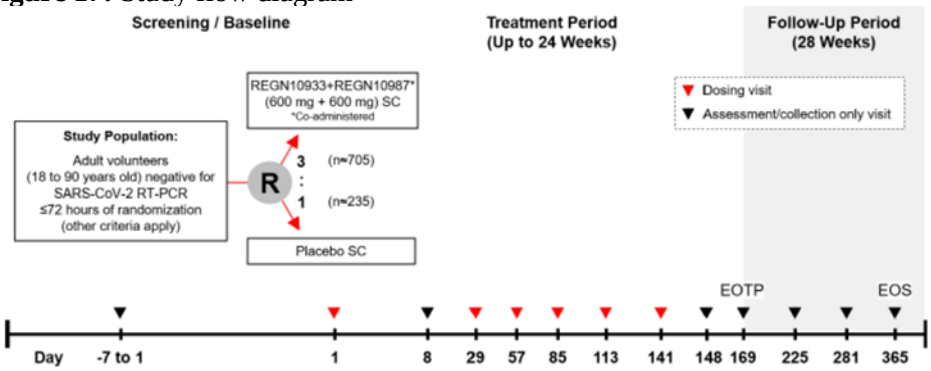
The study is comprised of 3 periods:

- A screening/baseline period of up to 7 days
- A treatment period of 24 weeks
- A follow-up period of 28 weeks

Terms for periods analysed in this study are as follows:

- Treatment period: treatment period of up to 24 weeks
- Entire study period: treatment period of up to 24 weeks and follow up period of up to 28 weeks, up until a participant's Covid-19 vaccination date (if any) or end of study

Figure 17: Study flow diagram



The study was designed to assess the safety and tolerability of multiple SC doses of casirivimab+imdevimab in adult volunteers who are SARS-CoV-2 negative at baseline.

Participants were randomized in a 3:1 ratio to receive up to 6 SC doses of casirivimab+imdevimab combination therapy or placebo.

PK results

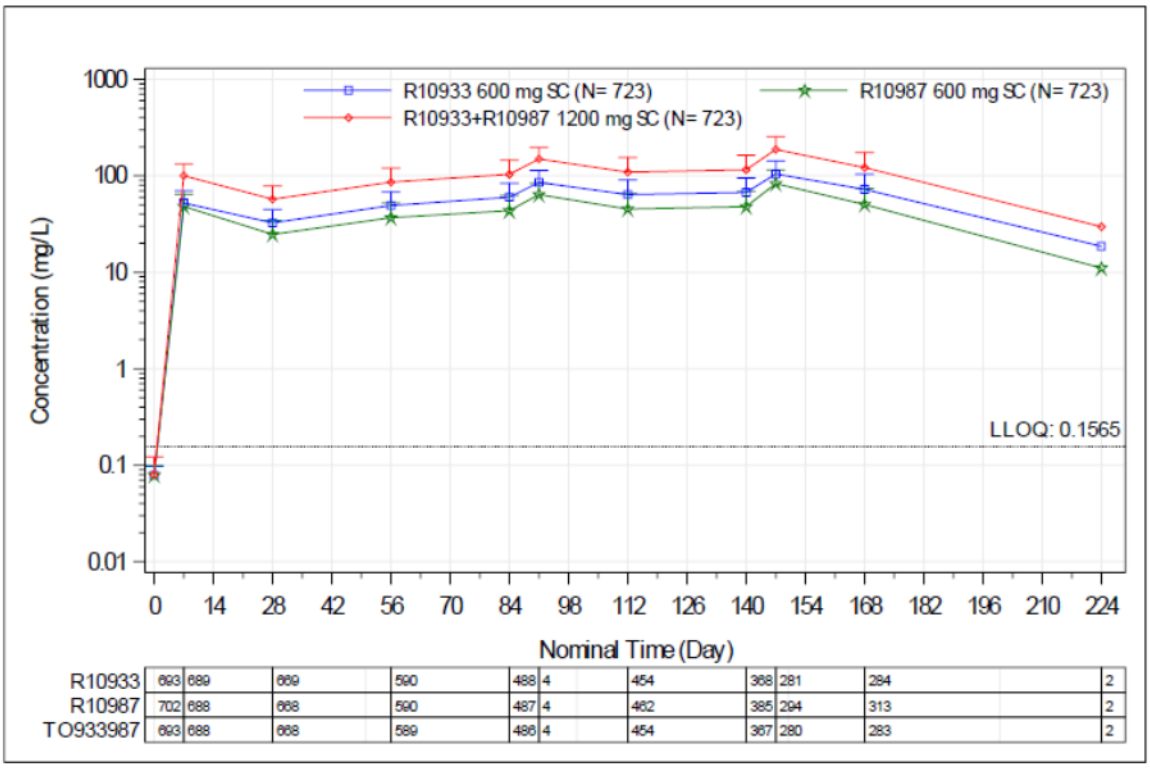
Concentrations of casirivimab and imdevimab over time following repeated administration of casirivimab+imdevimab were similar. Casirivimab and imdevimab reached steady-state following the third casirivimab+imdevimab dose (week 12) and was maintained for the remainder of the 24 week treatment period. Casirivimab and imdevimab concentrations in serum accumulated approximately 2.2-fold and 2-fold, respectively (based on C_{trough}) over the duration of treatment.

Table 28: Summary of concentrations of casirivimab and imdevimab in serum by nominal time (PKAS)

	R10933 600 mg SC (N=723)		R10987 600 mg SC (N=723)		REGN10933+REGN10987 1200 mg SC (N=723)	
Nominal Sampling (Days)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
0	693	0.000815 (0.0215)	702	0.000882 (0.0234)	693	0.00171 (0.0450)
7	689	52.2 (17.7)	688	48.1 (16.5)	688	100 (32.4)
28	669	32.6 (12.1)	668	24.7 (9.60)	668	57.2 (21.0)
56	590	49.2 (19.0)	590	36.8 (15.5)	589	86.1 (33.7)
84	488	60.0 (23.7)	487	43.5 (18.9)	486	104 (41.9)
91	4	85.5 (28.3)	4	63.9 (19.5)	4	149 (47.7)
112	454	63.9 (26.6)	462	45.2 (20.4)	454	109 (46.4)
140	368	67.3 (27.6)	385	47.9 (21.2)	367	116 (48.1)
147	281	105 (37.9)	294	83.0 (31.7)	280	188 (66.9)
168	284	72.4 (31.3)	313	50.5 (23.2)	283	122 (52.9)
224	2	18.6 (---)	2	11.1 (---)	2	29.7 (---)

N = Number of subjects; n = Number of subjects contributing to each timepoint; SD = Standard deviation
Note: BLQs were set to 0. Timepoint Day 91 was removed as of protocol Am 3. Combined concentrations (Total REGN10933+Total REGN10987) were calculated only when both the analytes were not missing.

Figure 18: Mean (+SD) concentrations of casirivimab, imdevimab and casirivimab+imdevimab combined in serum by time in adult volunteers (log-scaled)



N = Number of subjects
Note: Concentrations below the LLOQ (horizontal dashed line) were set to LLOQ/2. Include protocol defined schedule visit only. TO933987= Combined concentration of total casirivimab + total imdevimab. Combined concentrations were calculated only when both the analytes were not missing.

PK conclusion
The dose proposal for treatment and prevention of 1200 mg IV or SC is acceptable for an adult population from a PK standpoint based on the provided exposure data and similar reduction in viral load.

IV.3 Pharmacodynamics

The relationship between plasma concentration and effect was explored in a population exposure/response analysis.

The goal of this analysis was to characterize the relationship between casirivimab+imdevimab concentration and viral load reduction and determine casirivimab+imdevimab doses that are expected to provide near-maximal antiviral activity.

Specific aims included:

- To estimate the population and individual pharmacodynamic parameters related to the viral load reduction effect of casirivimab+imdevimab using data from patients in the R10933-10987-COV-2067, R10933-10987-COV-2069 and R10933-10987-COV-20145 clinical studies.
- To estimate variability and identify clinically relevant covariates of PD parameters related to the viral load reduction effect of casirivimab+imdevimab using data from patients in the aforementioned clinical studies.

Results
The following prespecified covariates were evaluated:

- Baseline endogenous immune response status against the virus (binary covariate): sero-antibody-negative versus sero-antibody-positive/other).
- Baseline high-risk factor for severe Covid-19 illness (binary covariate): presence versus absence.
- Time of symptom onset (continuous variable), not a baseline covariate in a strict sense, was evaluated via a sensitivity analysis by fitting the model to subsets of data split at the median time of symptom onset.

Parameter estimates of the covariate model are presented in table 29. Inhibition of β due to casirivimab+imdevimab was estimated to be 99%. The presence of a high-risk factor for severe Covid-19 illness was associated to a 4.81% decrease of δ; while sero-antibody-positive/other status at baseline was associated to a 110% increase of δ.

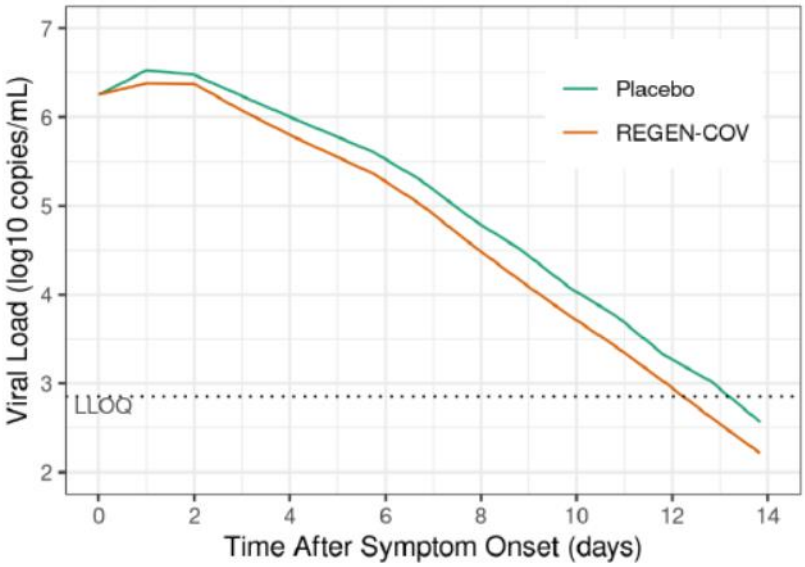
Table 29: Parameter estimates of the covariate model (run 344)

Parameter	Estimate (%RSE)	BSV SD (%RSE)
R_0	9.23 (1.09)	0.5 (FIXED)
delta (day^{-1})	0.878 (9.44)	0.198 (14.3)
p (copies mL^{-1} day^{-1})	2.65e+03 (1.01)	2.35 (5.09)
Drug effect (fractional decrease in beta)	0.99 (5.38)	0.26 (47.1)
WSV SD (log10 copies mL^{-1})	0.932 (12.7)	
Sero-antibody-positive/other at baseline (fractional increase in delta)	1.1 (18.9)	
High-risk factor for severe COVID-19 illness at baseline (fractional decrease in delta)	0.0481 (5.97)	
Correlation BSV delta-p	0.814 (7.66)	
Derived beta (mL $copies^{-1}$ day^{-1})	2.29e-03	
OFV	11073	

BSV = Between subject variability; SD = Standard deviation; OFV = Objective function value; %RSE = Percent relative standard error

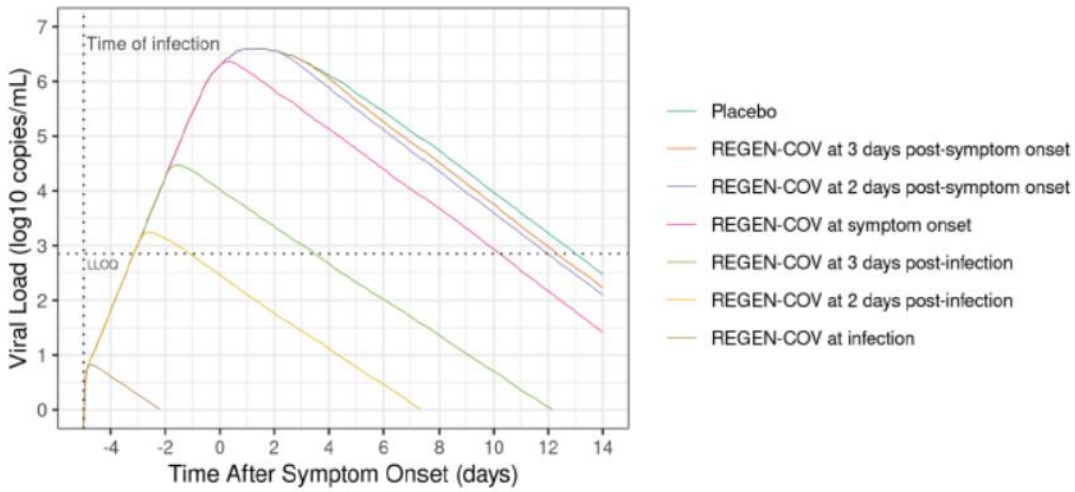
The fit for purpose model (run344) was used to perform stochastic simulations and, hence, (a) predict the viral load-time profile for the analysis dataset (figure 19), and (b) the viral load-time profile assuming various casirivimab+imdevimab treatment start dates (figure 20).

Figure 19: Graphical representation of the predicted viral load over time profile for the analysis dataset



Note: Lines are median of 100 stochastic simulations using the fit-for-purpose model (run344) and the analysis dataset

Figure 20: Graphical representation of the predicted viral load over time profile assuming various treatment start date



Analysis results suggest that the casirivimab+imdevimab dose regimens evaluated here are near maximal antiviral activity, in that (a) an exposure-independent drug effect model fitted the data reasonably well and estimated a 99% inhibition of the infection rate due to casirivimab+imdevimab for casirivimab+imdevimab dose regimens; (b) data did not seem to support the implementation of exposure-dependent drug effect models; and (c) Kaplan Meyer curves of probability of viral clearance over time across the different casirivimab+imdevimab dose regimens nearly overlapped.

Other findings were:

- The presence of a high-risk factor for severe Covid-19 illness was associated to a 4.81% decrease of the elimination rate of the productively infected cells.
- Sero-antibody-positive/other status at baseline was associated to a 110% increase of the elimination rate of the productively infected cells.

PD conclusion
The model estimated a 99% inhibition of infection rate for casirivimab+imdevimab dose regimens. The probability of viral clearance over time across the different casirivimab+imdevimab dose regimens nearly overlapped.

IV.4 Clinical efficacy

The main clinical efficacy studies are Studies COV-2067, COV-2066 and COV-2069 which have been previously outlined in table 25.

Study COV-2067
A randomized, placebo-controlled, multi-centre trial in ambulatory patients with Covid-19 (including, in phase 2, those with asymptomatic SARS-CoV-2 infection).

In support of this application key outcomes have been submitted from the analysis of the first 799 symptomatic patients from Phase 1 and Phase 2 of the COV-2067 study.
- Analysis Group 1 is the first 275 patients from Phase 1/Phase 2 of the study
- Analysis Group 2 is the 524 patients from Phase 2
- Analysis Group 1/2 is for the total of 799 patients.

The study has been briefly described in Section IV.2. The objectives and endpoints are shown in the table below. The primary efficacy endpoint was to assess ability to lower viral load in those infected with Covid-19.

The study evaluated the co-administered REGN10933+REGN10987 as combination therapy at an initial dose level of 2400 mg (1200 mg per mAb) and at a higher dose, 8000 mg (4000 mg per mAb) in the event that a higher dose is required for efficacy.

Only targeted adverse events were collected during the study, consisting of the following:
- All treatment-emergent serious adverse events (SAEs).
- Treatment-emergent adverse events of special interest (AESIs), defined as grade ≥2 infusion-related reactions through day 4 and grade ≥2 hypersensitivity reactions through day 29.
- In phase 1 only, all grade 3 and grade 4 treatment-emergent adverse events (TEAEs)

Table 30: Primary phase 1/2 analysis, objectives and endpoints (efficacy)

Phase 1/2 Objectives	Phase 1/2 Endpoints
Primary	
To evaluate the virologic efficacy of casirivimab+imdevimab compared to placebo in reducing viral load of SARS-CoV-2	• Time weighted average (TWA) daily change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 7, as measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR) in NP swab samples
Secondary	
To evaluate the clinical efficacy of casirivimab+imdevimab compared to placebo	• Proportion of patients with ≥1 COVID-19-related medically-attended visit through day 29
	• Proportion of patients with ≥1 COVID-19-related medically-attended visits consisting only of hospitalizations, emergency room visits, or urgent care visits through day 29 • Proportion of patients with ≥2 COVID-19-related medically-attended visits through day 29 • Total number of COVID-19-related medically-attended visits through day 29 • Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29 • Proportion of patients admitted to a hospital due to COVID-19 by day 29 • Proportion of patients admitted to an ICU due to COVID-19 by day 29 • Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29 • Days of hospitalization due to COVID-19 • Proportion of patients with all-cause mortality by day 29
To evaluate additional indicators of virologic efficacy of casirivimab+imdevimab compared to placebo	• Time weighted average (TWA) daily change from baseline in viral load (log_{10} copies/mL and copies/mL) from day 1 through each visit, as measured by RT-qPCR in NP swabs • Change from baseline in viral load at each visit through day 29, as measured by RT-qPCR in NP swabs
	• Time to negative RT-qPCR in NP swabs with no subsequent positive RT-qPCR • Proportion of patients with high viral load ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL) at each visit • Proportion of patients with viral loads below the limit of detection at each visit • Proportion of patients with viral loads below the lower limit of quantification at each visit

Inclusion and exclusion criteria

A summary of key eligibility criteria for phase 1 and phase 2 symptomatic cohorts is shown below:

- Outpatients (non-hospitalized with O_2 saturation ≥93% on room air).
- Positive diagnostic test for SARS-CoV-2 infection ≤72 hours of randomization.
- Adults (≥18 years or country's legal age of adulthood). Onset of Covid-19 symptoms ≤7 days of randomization; symptoms were determined by the investigator.
- No prior, current, or planned future use of Covid-19 convalescent plasma, mAbs against SARS-CoV-2, intravenous immunoglobulin, systemic corticosteroids, or authorized treatments for Covid-19.
- No pregnancy at randomization; must use highly effective contraception during study.

In phase 1 and phase 2, patients were eligible for enrolment regardless of whether they had one or more risk factors for developing severe Covid-19. In phase 2, randomization was stratified according to risk factors.

A summary of the exclusion criteria is given below. Any patients who met any of the following criteria were excluded from the study:
1. Was admitted to a hospital for Covid-19 prior to randomization or is hospitalized (inpatient) for any reason at randomization.
2. Has participated, or is participating, in a clinical research study evaluating Covid-19 convalescent plasma, mAbs against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or within 5 half-lives of the investigational product (whichever is longer) prior to the screening visit.
3. Prior, current, or planned future use of any of the following treatments: Covid-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG (any indication), systemic corticosteroids (any indication), or Covid-19 treatments (authorized, approved, or investigational). Prior use is defined as the past 30 days or within than 5 half-lives of the investigational product (whichever is longer) from screening.
4. Has known allergy or hypersensitivity to components of study drug.
5. Has been discharged, or is planned to be discharged, to a quarantine centre.
6. Has a known positive SARS-CoV-2 serologic test.
7. Has a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization.
8. Has known active infection with influenza or other non-SARS-CoV-2 respiratory pathogen, confirmed by a diagnostic test.
9. Prior use (prior to randomization), current use (at randomization), or planned use (within 90 days of study drug administration or per current CDC recommendations, as applicable) of any authorized or approved vaccine for SARS-CoV-2.
10. Has participated, is participating, or plans to participate in a clinical research study evaluating any authorized, approved, or investigational vaccine for SARS-CoV-2.

Populations analysed
The number of participants included in each analysis population is shown below.

Table 31: Summary of populations in each analysis set (phase 1/2, combined phase 1 and phase 2)

		REGN10933+REGN10987			
	Placebo (N=266)	**2400 mg IV (N=266)**	**8000 mg IV (N=267)**	**Combined (N=533)**	**Total (N=799)**
Patients randomized	266 (100%)	266 (100%)	267 (100%)	533 (100%)	799 (100%)
Patients in full analysis set (FAS), n(%)	266 (100%)	266 (100%)	267 (100%)	533 (100%)	799 (100%)
First Phase 1/2 Patients, n(%)	93 (35.0%)	92 (34.6%)	90 (33.7%)	182 (34.1%)	275 (34.4%)
Next Phase 2 Patients, n(%)	173 (65.0%)	174 (65.4%)	177 (66.3%)	351 (65.9%)	524 (65.6%)
Patients in modified full analysis set (mFAS), n(%)	232 (87.2%)	219 (82.3%)	220 (82.4%)	439 (82.4%)	671 (84.0%)
First Phase 1/2 Patients, n(%)	81 (30.5%)	74 (27.8%)	74 (27.7%)	148 (27.8%)	229 (28.7%)
Next Phase 2 Patients, n(%)	151 (56.8%)	145 (54.5%)	146 (54.7%)	291 (54.6%)	442 (55.3%)

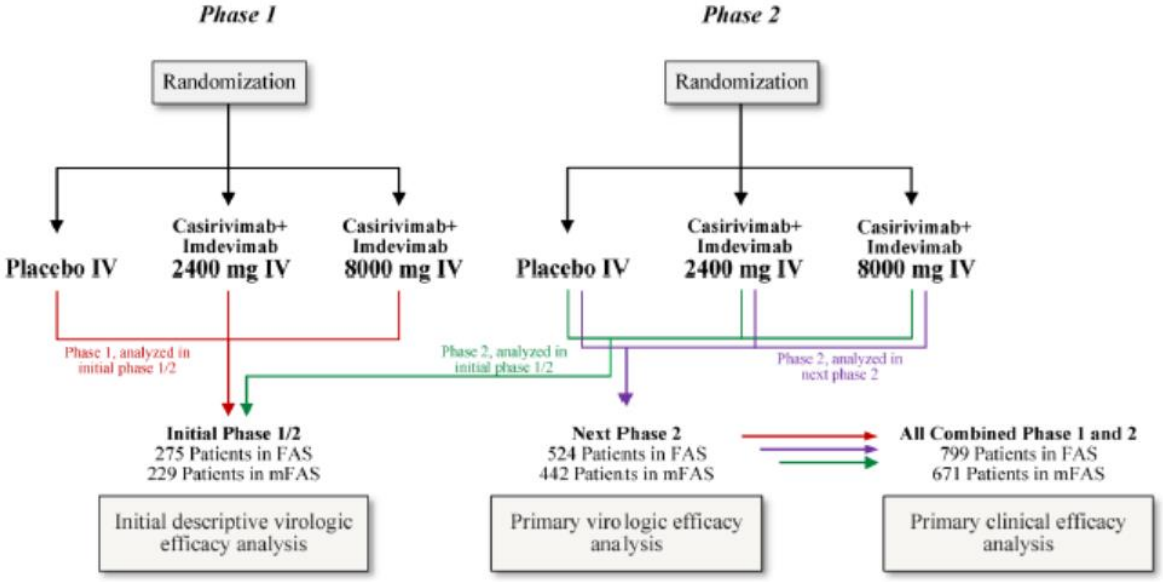
Data cutoff date is 18 Feb 2021.
Source: Phase 1/2 PTT 14.1.1.2

A total of 671 patients (84.0%) met the criteria for the modified full analysis set (mFAS) (positive SARS-CoV-2 RT-qPCR by central laboratory analysis).

An initial descriptive virologic efficacy analysis was conducted on the first 275 symptomatic participants randomized in phase 1/2; the prospective virologic analysis conducted for the phase 1/2 portion of the study included only the subsequent 524 patients randomized in phase 2.

The prospective clinical analysis included all 799 symptomatic participants randomized in phase 1 and phase 2 (the “combined phase 1 and phase 2” population).
A flow diagram depicting the pooling of participants for each analysis is provided below.

Figure 21: Phase 1/2 participant flow and mFAS pooling for efficacy analyses



Patient disposition
Patient disposition is described below.

Table 32: Summary of disposition (phase 1/2, combined phase 1 and phase 2, FAS)

		REGN10933+REGN10987			
	Placebo (N=266)	2400 mg IV (N=266)	8000 mg IV (N=267)	Combined (N=533)	Total (N=799)
Randomized patients	266 (100%)	266 (100%)	267 (100%)	533 (100%)	799 (100%)
Patients who completed the study	252 (94.7%)	251 (94.4%)	255 (95.5%)	506 (94.9%)	758 (94.9%)
Patients ongoing in the study	1 (0.4%)	0	0	0	1 (0.1%)
Patients who discontinued the study	13 (4.9%)	15 (5.6%)	12 (4.5%)	27 (5.1%)	40 (5.0%)
Reasons for study discontinuation:					
Adverse event	0	1 (0.4%)	0	1 (0.2%)	1 (0.1%)
Pregnancy	0	0	0	0	0
Lack of efficacy	0	0	0	0	0
Physician decision	0	0	0	0	0
Sponsor request[1]	2 (0.8%)	2 (0.8%)	2 (0.7%)	4 (0.8%)	6 (0.8%)
Death	0	0	0	0	0
Lost to follow up	8 (3.0%)	4 (1.5%)	3 (1.1%)	7 (1.3%)	15 (1.9%)
Subject decision	3 (1.1%)	8 (3.0%)	7 (2.6%)	15 (2.8%)	18 (2.3%)
Missing reason	0	0	0	0	0

[1] Participants assigned to this category were randomized in error and not treated; in these instances, investigators were instructed to select "Sponsor request".
Data cutoff date is 18 Feb 2021.

Of the 799 patients who were randomized, 758 (94.9%) completed the study (day 29). Only 1 participant discontinued the study due to an AE, in the 2400 mg IV treatment group.

Discontinuations were balanced across the treatment groups and most discontinuations were either lost to follow-up or subject decision. Overall, 905 of subjects completed the study.

Table 33: Summary of overall patient disposition – modified full analysis set (mFAS) – combined all phase 1 and all phase 2 patients

	Placebo (N=231)	R10933+R10987 2.4 g IV (N=215)	R10933+R10987 8.0 g IV (N=219)	R10933+R10987 Combined (N=434)	Total (N=665)
Randomized patients	231 (100%)	215 (100%)	219 (100%)	434 (100%)	665 (100%)
Patients who completed the study	216 (93.5%)	192 (89.3%)	204 (93.2%)	396 (91.2%)	612 (92.0%)
Patients ongoing in the study	5 (2.2%)	15 (7.0%)	9 (4.1%)	24 (5.5%)	29 (4.4%)
Patients who discontinued the study	10 (4.3%)	8 (3.7%)	6 (2.7%)	14 (3.2%)	24 (3.6%)
Reasons for study discontinuation					
Adverse Event	0	1 (0.5%)	0	1 (0.2%)	1 (0.2%)
Pregnancy	0	0	0	0	0
Lack of Efficacy	0	0	0	0	0
Physician Decision	0	0	0	0	0
Sponsor Request	0	1 (0.5%)	1 (0.5%)	2 (0.5%)	2 (0.3%)
Death	0	0	0	0	0
Lost To Follow-Up	8 (3.5%)	3 (1.4%)	2 (0.9%)	5 (1.2%)	13 (2.0%)
Subject Decision	2 (0.9%)	3 (1.4%)	3 (1.4%)	6 (1.4%)	8 (1.2%)
Missing reason	0	0	0	0	0

Demographics for the analysis groups in the full analysis set (FAS) is summarised below.

Table 34: Demographics and baseline characteristics (FAS)

Parameter	Analysis Group 1 (N=275)	Analysis Group 2 (N=524)	Analysis Group 1/2 (N=799)
Mean age years (range)	44 (18-81)	41 (18-89)	42 (18-89)
% over 50 years	32	28	29
% Female	51	54	53
% White	82	87	85
% Black	13	7	9
% Asian	1	2	2
% Hispanic or Latino ethnicity	56	48	50
% ≥1 risk factor for severe COVID-19*	64	59	61
% Obese	42	35	37
Baseline Virologic Parameter			
% Seronegative	**41**	**56**	**51**
Mean log_{10} copies/mL	6.60	6.34	6.41
% Seropositive	**45**	**34**	**38**
Mean log_{10} copies/mL	3.30	3.49	3.43
% Other	14	11	11

* Risk factors defined (per protocol) as follows: age >50 years; obesity, defined as BMI >30; cardiovascular disease, including hypertension; chronic lung disease, including asthma; chronic metabolic disease, including diabetes; chronic kidney disease, including those on dialysis; chronic liver disease; immunosuppressed, based on investigator's assessment.

The FAS population contained 799 subjects in total: mean age 42yrs (SD 15); 93% <65yrs; 47% male; 85% white; mean body mass index 30 kg/m2 (SD 6.7); 62% had a least 1 risk factor associated with Covid-19 disease; mean time from symptom onset to randomisation 3.4 days (SD 2), min 0, max 20. About half subjects were sero-negative at presentation.

Demographics and baseline characteristics for the phase 1/2 mFAS were balanced across the treatment groups. 30.8% of participants were ≥50 years of age and 6.7% were ≥65 years of age. Slightly more females (52.5%) were enrolled versus males (47.5%).

Median concentrations of baseline (pre-dose) C-reactive protein (CRP) were higher among participants randomized to placebo (4.940 mg/L) compared to those randomized to casirivimab+imdevimab (3.390 mg/L). This difference largely occurred among participants who were seropositive at baseline (placebo: 4.030 mg/L; combined active groups: 2.250 mg/L); differences were less prominent in the seronegative group (placebo: 4.855 mg/L; combined active groups: 4.310 mg/L). However, variation within each treatment group was high overall, as indicated by the large within-group standard deviations observed for mean concentrations.

The mFAS population was similar to the FAS population in terms of distribution of features described.

Baseline SARS-Cov-2 virology
Key observations were as follows:

- Baseline viral load (as measured quantitatively in NP swabs) was balanced across treatment groups among those in the mFAS, among those in the mFAS with baseline viral load >106 copies/mL or >107 copies/mL, and among those who were seronegative at baseline (seronegative mFAS). Across all treatment groups in the mFAS, the mean (SD) baseline viral load was 5.83 (1.767) log_{10} copies/mL.
- Patients in the Seronegative mFAS had higher baseline viral load (mean [SD]: 6.78 [1.242] log_{10} copies/mL) compared to the mFAS, and markedly higher than those who were seropositive at baseline (4.32 [1.389] log_{10} copies/mL).

Baseline SARS-Cov-2 serostatus
Key observations were as follows:

- Baseline serostatus was balanced across treatment groups among those in the mFAS and among those in the mFAS with baseline viral load >106 copies/mL or 107 copies/mL.
- 54.2% of participants in the mFAS were seronegative at baseline. 35.2% were seropositive, and 10.6% had a status of ‘other’.

Risk factors
Risk factors are described in table 35.

The frequency of risk factors was balanced across the treatment groups.

A total of 62.3% of patients had at least 1 risk factor severe Covid-19.

Overall, the most common risk factors were obesity, defined as BMI ≥30 kg/m2 (39.5%), age ≥50 years (30.8%) and cardiovascular disease including hypertension (21.0%). Chronic lung disease (including asthma) and chronic metabolic disease (including diabetes) were less common (9.7% and 13.4% respectively). Chronic kidney disease, chronic liver disease and immunocompromised state were uncommon (<2% frequency).

Table 35: Summary of risk factor for hospitalisation – modified full analysis set (mFA) – combined all phase 1 and all phase 2 symptomatic patients

	Placebo (N=232)	R10933+R10987 2.4g IV (N=219)	R10933+R10987 8.0g IV (N=220)	R10933+R10987 Combined (N=439)	Total (N=671)
No risk factor for hospitalization	87 (37.5%)	81 (37.0%)	85 (38.6%)	166 (37.8%)	253 (37.7%)
>=1 risk factor for hospitalization	145 (62.5%)	138 (63.0%)	135 (61.4%)	273 (62.2%)	418 (62.3%)
Risk factor for hospitalization					
Age >=50 years	73 (31.5%)	67 (30.6%)	67 (30.5%)	134 (30.5%)	207 (30.8%)
Obesity, defined as BMI>=30	87 (37.5%)	83 (37.9%)	95 (43.2%)	178 (40.5%)	265 (39.5%)
Cardiovascular disease, including hypertension	51 (22.0%)	43 (19.6%)	47 (21.4%)	90 (20.5%)	141 (21.0%)
Chronic lung disease, including asthma	21 (9.1%)	23 (10.5%)	21 (9.5%)	44 (10.0%)	65 (9.7%)
Chronic metabolic disease, including diabetes	35 (15.1%)	31 (14.2%)	24 (10.9%)	55 (12.5%)	90 (13.4%)
Chronic kidney disease, including those on dialysis	3 (1.3%)	6 (2.7%)	1 (0.5%)	7 (1.6%)	10 (1.5%)
Chronic liver disease	2 (0.9%)	1 (0.5%)	0	1 (0.2%)	3 (0.4%)
Immunocompromised	6 (2.6%)	4 (1.8%)	3 (1.4%)	7 (1.6%)	13 (1.9%)
Immunosuppressed	5 (2.2%)	4 (1.8%)	2 (0.9%)	6 (1.4%)	11 (1.6%)
Taking Immunosuppressants	2 (0.9%)	3 (1.4%)	2 (0.9%)	5 (1.1%)	7 (1.0%)

Data cutoff date is 18Feb2021.
MedDRA (Version 23.0) coding dictionary applied.
A subject who reported 2 or more medical history finding with the same preferred term is counted only once for that term.
A subject who reported 2 or more medical history finding with different preferred terms within the same system organ class is counted only once in that system organ class.
[1]95% CI are based on exact method.

Baseline symptoms were recorded for the mFAS (combined all phase 1 and all phase 2 patients). The most common symptoms found were cough, headache, fatigue and loss of taste and smell.

Randomisation of treatment
Phases 1 & 2
In phases 1 and 2, patients were randomized in a 1:1:1 allocation ratio to one of the following:

- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8000 mg (4000 mg each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose 0.9% sodium chloride for injection

In phase 1, randomization was not stratified.
In phase 2, randomization was stratified by:

- Presence/absence of Covid-19 symptoms (i.e. symptomatic versus asymptomatic cohort)
- Country
- Risk factors for hospitalization due to Covid-19 (no risk factors for hospitalization due to Covid-19 versus ≥1 risk factor for hospitalization due to Covid-19)

Results
Interim analysis
The primary efficacy variable in the primary phase 1/2 analysis was time-weighted average daily change from baseline in viral load (log_{10} copies/mL/day) from day 1 to day 7, as measured by RT-qPCR in nasopharyngeal swab samples.

An initial descriptive virology efficacy analysis was performed on the first 275 symptomatic patients randomized in phase 1 and phase 2, evaluating differences between placebo and the 2400 mg IV and 8000 mg IV treatment groups combined.

This interim analysis found that the casirivimab+imdevimab treatment groups exhibited enhanced reduction of viral load compared to placebo, particularly in seronegative patients and those who had high baseline viral load. The analysis also found that the majority of viral load (regardless of treatment group) had been eliminated in the time points that followed day 7, resulting in a modification to the phase 1/2 primary endpoint.

Phase 1/2 primary efficacy analysis
The virologic analysis reported for the phase 1/2 portion of the study was conducted on the next phase 2 population, which included 524 participants randomized in phase 2 subsequent to the first 275 randomized participants in phase 1 and phase 2.

Virologic endpoint
At baseline, the mean viral load (log_{10} copies/mL) was similar among the casirivimab+imdevimab treatment groups and the placebo group.

Treatment with casirivimab+imdevimab resulted in a statistically significant, greater LS mean reduction in time weighted average daily change from baseline in viral load from day 1 to day 7 when compared to placebo (difference from placebo of -0.35 log_{10} copies/mL for the combined casirivimab+imdevimab doses [p=0.0005]).

The primary efficacy endpoint was shown to be met for subgroups of subjects.

Clinical endpoints
The proportion of participants who had at least 1 Covid-19-related medically-attended visit with the primary reason for the visit being Covid-19 through day 29 was significantly lower in the casirivimab+imdevimab combined treatment group compared to the placebo group (3.0% vs 7.8%, p=0.0065).

The clinical endpoint has been met.

Treatment with REGN-COV2 significantly reduced the risk for Covid-19-related medically-attended visits (MAV) and resulted in fewer patients with MAV for Covid-19 compared to placebo. These effects were similar across both REGN-COV2 dose groups, suggesting the absence of a dose response for this clinical endpoint.

Phase 3
The objectives and endpoints for the phase 3 efficacy analysis are shown below.

The primary and secondary endpoints are acceptable.

This study assessed 2 dose levels of REGN10933+REGN10987, 1200 mg and 2400 mg, in a 1:1 ratio (600 mg and 1200 mg per mAb, respectively).

Table 36: Phase 3 analysis, objectives and endpoints (efficacy)

Phase 3 Objectives	Phase 3 Endpoints
Primary	
To evaluate the clinical efficacy of casirivimab+imdevimab compared to placebo as measured by COVID-19-related hospitalizations or all cause death	• Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29
Secondary (Key)	
To evaluate the clinical efficacy of casirivimab+imdevimab compared to placebo as measured by COVID-19-related hospitalizations or all cause death	• Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29
To evaluate the impact of casirivimab+imdevimab on the resolution of self-reported COVID-19 symptoms compared to placebo	• Time to COVID-19 symptoms resolution
Secondary (Other)	
To evaluate the clinical efficacy of casirivimab+imdevimab compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations, emergency room visits, or all-cause death	• Proportion of patients with ≥1 COVID-19-related hospitalization, emergency room visit, or all-cause death through day 29 • Proportion of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29
	• Proportion of patients with ≥1 COVID-19-related medically-attended visit by type of visit (hospitalization, emergency room, urgent care, and/or physician's office/telemedicine) through day 29 • Proportion of patients with ≥2 COVID-19-related medically-attended visits through day 29 • Cumulative incidence of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 • Cumulative incidence of patients with ≥1 COVID-19-related hospitalization, emergency room visit, or all-cause death through day 29 • Cumulative incidence of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29 • Days of hospitalization due to COVID-19 • Proportion of patients admitted to an intensive care unit due to COVID-19 by day 29 • Proportion of patients requiring supplemental oxygen due to COVID-19 by day 29 • Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29 • Total number of COVID-19-related medically-attended visits through day 29 • Time to all-cause death • All-cause death by day 29, day 120, and day 169
To describe the virologic effects of casirivimab+imdevimab compared to placebo	• Time-weighted average daily change from baseline in viral load (log10 copies/mL) from day 1 to day 7, as measured by RT-qPCR in NP swab samples (patients enrolled prior to protocol amendment 6 only) • Change from baseline in viral load at each visit, as measured by RT-qPCR in NP swab samples

Inclusion and exclusion criteria

Key eligibility criteria for phase 3 cohort 1 are described below.

- Outpatients (non-hospitalized with O_2 saturation ≥93% on room air).
- Positive diagnostic test for SARS-CoV-2 infection ≤72 hours of randomization.
- Adults (≥18 years or country's legal age of adulthood).
- Onset of Covid-19 symptoms ≤7 days of randomization; symptoms were determined by the investigator.
- No prior, current, or planned future use of Covid-19 convalescent plasma, mAbs against SARS-CoV-2, intravenous immunoglobulin, systemic corticosteroids, or treatments for Covid-19 (investigational, authorized, or approved).
- No pregnancy at randomization in cohort 1 (enrolled in a separate cohort); contraception not required during study participation.
- ≥1 risk factor for developing severe Covid-19 (amended portion of phase 3 only).

Risk factors are described below.

Table 37: Risk factors for developing severe Covid-19

Phase 2 Risk Factor Definitions (Stratification)	Phase 3 Risk Factor Definitions (Eligibility)
Age ≥50 years	Age ≥50 years
Obesity, defined as BMI ≥30 kg/m^2	Obesity, defined as BMI ≥30 kg/m^2
Cardiovascular disease, including hypertension	Cardiovascular disease, including hypertension
Chronic lung disease, including asthma	Chronic lung disease, including asthma
Chronic metabolic disease, including diabetes	Type 1 or type 2 diabetes mellitus
Chronic kidney disease, including those on dialysis	Chronic kidney disease, including those on dialysis
Chronic liver disease	Chronic liver disease
Immunocompromised	Immunocompromised

Populations analysed

The phase 3 analysis sets are shown below.

Table 38: Analysis sets, phase 3

Analysis Set	Definition
Full analysis set (FAS)	All randomized participants; based on the treatment allocated (as randomized).
Modified Full Analysis Set (mFAS)	All randomized participants with both of the following: • A qualitatively positive RT-qPCR (via central laboratory) from NP swab samples taken at randomization or collected within 2 hours after study drug infusion was initiated • At least one risk factor for severe COVID-19 at baseline; based on the treatment allocated (as randomized).
Seronegative mFAS	All randomized participants in the mFAS with documented seronegative status at baseline. *Note: serostatus was considered positive if any available anti-SARS-CoV-2 antibody test utilized (eg, anti-SARS-CoV-2 IgA or IgG) was positive, negative if all available tests were negative, and 'other' if serostatus was neither positive or negative (eg, borderline result) or was unknown*

The number of patients included in each analysis population is provided for patients with ≥1 risk factor for severe Covid-19 is shown below.

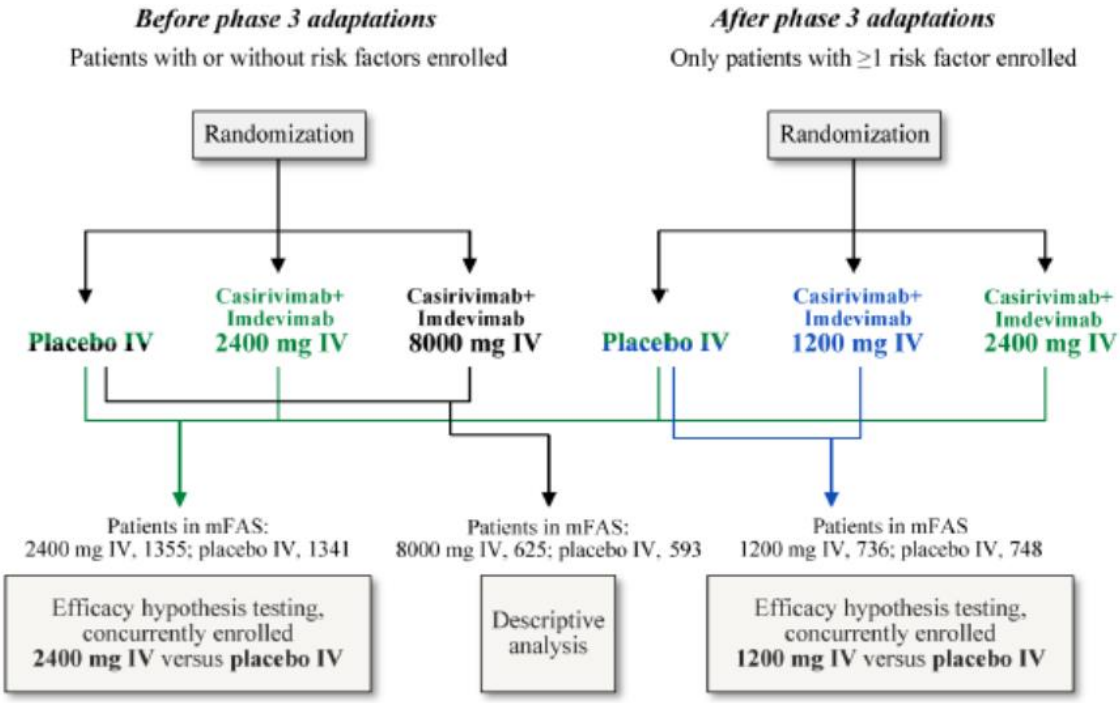
Table 39: Summary of populations in each analysis set (phase 3, 1 risk factor for severe Covid-19)

	Placebo (N=1500)	REGN10933+REGN10987			Total (N=4567)
		1200 mg IV (N=838)	2400 mg IV (N=1529)	8000 mg IV (N=700)	
Patients randomized	1500 (100%)	838 (100%)	1529 (100%)	700 (100%)	4567 (100%)
Patients in full analysis set (FAS), n(%)	1500 (100%)	838 (100%)	1529 (100%)	700 (100%)	4567 (100%)
Patients in modified full analysis set (mFAS), n(%)	1341 (89.4%)	736 (87.8%)	1355 (88.6%)	625 (89.3%)	4057 (88.8%)

Randomized patients through 17 Jan 2021. Data cutoff date is 18 Feb 2021.

A total of 4567 randomized patients had ≥1 risk factor for severe Covid-19 and 4057 (88.8%) met the criteria for the mFAS. In addition, 1040 randomized patients had no risk factors.

Figure 22: Phase 3 participant flow and mFAS for efficacy analyses



Patient disposition

Based on the results of the primary efficacy analysis in phase 1/2, the amended portion of phase 3 required that patients have ≥1 risk factor for severe Covid-19 and the primary analysis in phase 3 was conducted only in patients with ≥1 risk factor. The disposition of randomized study participants in phase 3 is therefore presented only for the 4567 patients with ≥1 risk factor at randomization.

Table 40: Summary of disposition (phase 3, FAS with ≥1 risk factor for severe Covid-19)

	Placebo (N=1500)	REGN10933+REGN10987			Total (N=4567)
		1200 mg IV (N=838)	2400 mg IV (N=1529)	8000 mg IV (N=700)	
Randomized patients	1500 (100%)	838 (100%)	1529 (100%)	700 (100%)	4567 (100%)
Randomized patients but not treated	24 (1.6%)	11 (1.3%)	17 (1.1%)	11 (1.6%)	63 (1.4%)
Patients who completed the study	423 (28.2%)	0	455 (29.8%)	447 (63.9%)	1325 (29.0%)
Patients ongoing in the study	1009 (67.3%)	819 (97.7%)	1029 (67.3%)	219 (31.3%)	3076 (67.4%)
Patients who discontinued the study	68 (4.5%)	19 (2.3%)	45 (2.9%)	34 (4.9%)	166 (3.6%)
Reasons for study discontinuation					
Adverse Event	4 (0.3%)	0	1 (<0.1%)	1 (0.1%)	6 (0.1%)
Pregnancy	0	0	0	0	0
Lack of Efficacy	1 (<0.1%)	0	0	0	1 (<0.1%)
Physician Decision	4 (0.3%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	8 (0.2%)
Sponsor Request	6 (0.4%)	4 (0.5%)	4 (0.3%)	7 (1.0%)	21 (0.5%)
Death	3 (0.2%)	1 (0.1%)	1 (<0.1%)	0	5 (0.1%)
Lost To Follow-Up	19 (1.3%)	1 (0.1%)	13 (0.9%)	11 (1.6%)	44 (1.0%)
Subject Decision	31 (2.1%)	12 (1.4%)	24 (1.6%)	14 (2.0%)	81 (1.8%)

Randomized patients through 17 Jan 2021. Data cutoff date is 18 Feb 2021.

Discontinuations were balanced across the treatment groups among patients with risk factors.

Demographics and baseline characteristics of the mFAS are shown below (table 41).

Demographic characteristics, including age, sex, and race/ethnicity, were balanced across the treatment groups. 51.8% of patients were ≥50 years of age and 13.5% were ≥65 years of age. Slightly more females (51.3%) were enrolled versus males (48.7%). Baseline CRP levels were balanced across all treatment groups.

Baseline virology
Key observations were as follows:

- Baseline viral load was balanced across treatment groups among those in the mFAS.
- Across all treatment groups, the mean (SD) baseline viral load in the mFAS was 6.69 (1.746) $\log_{10}$ copies/mL.
- Patients in the Seronegative mFAS had higher baseline viral load (mean [SD]: 7.20 [1.478] $\log_{10}$ copies/mL) than those who were seropositive at baseline (5.25 [1.681]$\log_{10}$ copies/mL).
- Patients who had ≥1 risk factor for severe Covid-19 (i.e. the mFAS population) had a similar baseline viral load compared to those who did not have risk factors.

Baseline SARS-CoV-2 serostatus
Key observations were as follows:

- Baseline serostatus was balanced across treatment groups among those in the mFAS
- 68.6% of patients in the mFAS were seronegative at baseline. 23.6% were seropositive and 7.8% had a status of 'other'.
- Compared to patients in the mFAS, patients with baseline viral load of >106 copies/mL had higher rates of seronegativity at baseline (81.4%).

Table 41: Demographics and baseline characteristics, excluding virology and serostatus (phase 3, FAS)

	Placebo		REGN10933+REGN10987			Total (N=4057)
	Pooled for 1200 mg IV analysis[1] (N=748)	Pooled for 2400 mg IV analysis[1] (N=1341)	1200 mg IV (N=736)	2400 mg IV (N=1355)	8000 mg IV (N=625)	
Age (Years)						
n	748	1341	736	1355	625	4057
Mean (SD)	47.1 (14.80)	47.8 (14.39)	47.6 (14.73)	49.3 (15.14)	49.7 (14.32)	48.5 (14.72)
Median	48.0	50.0	48.5	50.0	51.0	50.0
Q1 : Q3	35.0 : 57.0	37.0 : 58.0	37.0 : 57.5	39.0 : 60.0	40.0 : 59.0	38.0 : 59.0
Min : Max	18 : 89	18 : 92	18 : 90	18 : 96	18 : 90	18 : 96
Age Group (Years), n (%)						
18 - 44	300 (40.1%)	519 (38.7%)	303 (41.2%)	498 (36.8%)	219 (35.0%)	1539 (37.9%)
45 - 64	360 (48.1%)	678 (50.6%)	340 (46.2%)	643 (47.5%)	309 (49.4%)	1970 (48.6%)
65 - 84	85 (11.4%)	138 (10.3%)	90 (12.2%)	202 (14.9%)	95 (15.2%)	525 (12.9%)
≥85	3 (0.4%)	6 (0.4%)	3 (0.4%)	12 (0.9%)	2 (0.3%)	23 (0.6%)
≥50	356 (47.6%)	678 (50.6%)	357 (48.5%)	715 (52.8%)	351 (56.2%)	2101 (51.8%)
≥65	88 (11.8%)	144 (10.7%)	93 (12.6%)	214 (15.8%)	97 (15.5%)	548 (13.5%)
≥75	20 (2.7%)	37 (2.8%)	31 (4.2%)	59 (4.4%)	23 (3.7%)	150 (3.7%)
Sex, n (%)						
Male	352 (47.1%)	633 (47.2%)	364 (49.5%)	656 (48.4%)	324 (51.8%)	1977 (48.7%)
Female	396 (52.9%)	708 (52.8%)	372 (50.5%)	699 (51.6%)	301 (48.2%)	2080 (51.3%)
Ethnicity, n (%)						
Hispanic or Latino	295 (39.4%)	471 (35.1%)	312 (42.4%)	464 (34.2%)	177 (28.3%)	1424 (35.1%)
Not Hispanic or Latino	449 (60.0%)	862 (64.3%)	417 (56.7%)	875 (64.6%)	444 (71.0%)	2598 (64.0%)
Not Reported	4 (0.5%)	8 (0.6%)	7 (1.0%)	16 (1.2%)	4 (0.6%)	35 (0.9%)
Race, n (%)						
White	611 (81.7%)	1136 (84.7%)	595 (80.8%)	1161 (85.7%)	534 (85.4%)	3426 (84.4%)
Black or African American	38 (5.1%)	66 (4.9%)	38 (5.2%)	67 (4.9%)	33 (5.3%)	204 (5.0%)
Asian	36 (4.8%)	56 (4.2%)	38 (5.2%)	52 (3.8%)	26 (4.2%)	172 (4.2%)
American Indian or Alaska Native	10 (1.3%)	13 (1.0%)	17 (2.3%)	19 (1.4%)	3 (0.5%)	52 (1.3%)
Native Hawaiian or Other Pacific Islander	1 (0.1%)	1 (<0.1%)	2 (0.3%)	4 (0.3%)	0	7 (0.2%)
Unknown	37 (4.9%)	43 (3.2%)	36 (4.9%)	28 (2.1%)	15 (2.4%)	122 (3.0%)
Not Reported	15 (2.0%)	26 (1.9%)	10 (1.4%)	24 (1.8%)	14 (2.2%)	74 (1.8%)
Weight (kg)						
n	748	1338	735	1352	624	4049
Mean (SD)	88.73 (21.804)	89.69 (22.004)	90.21 (23.281)	89.74 (21.180)	92.35 (23.281)	90.21 (22.185)
Median	86.20	87.90	86.20	87.50	89.85	87.80
Q1 : Q3	72.80 : 102.40	74.30 : 103.00	74.40 : 102.10	75.15 : 102.10	76.20 : 106.60	74.80 : 103.00
Min : Max	43.1 : 198.7	43.1 : 198.7	45.1 : 228.6	43.0 : 200.4	47.6 : 195.0	43.0 : 228.6
Height (cm)						
n	748	1338	735	1354	623	4050
Mean (SD)	168.56 (11.289)	169.27 (11.351)	168.96 (11.203)	169.61 (10.622)	169.97 (11.107)	169.43 (11.048)
Median	167.60	168.00	170.00	170.00	170.00	170.00
Q1 : Q3	160.00 : 177.00	161.00 : 177.80	161.00 : 177.00	162.50 : 177.80	162.60 : 177.80	162.00 : 177.80
Min : Max	120.0 : 210.8	114.0 : 219.7	123.0 : 200.7	123.0 : 203.2	123.0 : 203.2	114.0 : 219.7
BMI (kg/m²)						
n	748	1338	735	1352	623	4048
Mean (SD)	31.07 (6.457)	31.19 (6.630)	31.54 (7.309)	31.09 (6.331)	31.90 (7.229)	31.33 (6.761)
Median	30.70	30.80	30.40	30.80	31.20	30.80
Q1 : Q3	26.40 : 34.50	26.40 : 34.70	26.70 : 34.70	26.80 : 34.40	27.00 : 35.30	26.70 : 34.70
Min : Max	17.9 : 65.7	16.2 : 73.8	17.2 : 67.3	15.9 : 66.5	16.4 : 63.9	15.9 : 73.8
Obesity						
BMI < 30 kg/m²	321 (42.9%)	566 (42.2%)	325 (44.2%)	565 (41.7%)	239 (38.2%)	1695 (41.8%)
BMI ≥30 kg/m²	427 (57.1%)	772 (57.6%)	410 (55.7%)	787 (58.1%)	384 (61.4%)	2353 (58.0%)
Missing	0	3	1	3	2	9
C-Reactive Protein (mg/L)						
n	724	1243	713	1242	544	3742
Mean (SD)	13.097 (24.9732)	12.971 (24.5365)	13.244 (23.7685)	11.992 (23.2378)	14.206 (28.0260)	12.877 (24.5170)
Median	4.865	4.940	4.910	4.615	5.065	4.850
Q1 : Q3	2.100 : 11.475	2.090 : 12.070	1.930 : 12.190	1.950 : 11.670	1.885 : 11.585	1.980 : 11.890
Min : Max	0.16 : 227.45	0.10 : 242.73	0.11 : 238.53	0.11 : 354.16	0.18 : 228.07	0.10 : 354.16
Time from symptom onset to randomization (days)						
n	743	1319	727	1334	610	3990
Mean (SD)	3.6 (13.66)	3.5 (10.32)	3.2 (1.84)	6.1 (100.13)	3.4 (1.83)	4.3 (58.21)
Median	3.0	3.0	3.0	3.0	3.0	3.0
Q1 : Q3	2.0 : 4.0	2.0 : 5.0	2.0 : 5.0	2.0 : 5.0	2.0 : 5.0	2.0 : 5.0
Min : Max	0 : 372	0 : 372	0 : 7	-1 : 3660	0 : 7	-1 : 3660

[1] Placebo is presented in two columns, based on those that were concurrently randomized to the 1200 mg and 2400 mg active treatment groups. The placebo group marked as "pooled for 1200 mg IV analysis" is a subset of the placebo group marked as "pooled for 2400 mg IV analysis."

BMI, body mass index; COVID-19, Coronavirus Disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

The frequency of baseline risk factors for severe Covid-19 is provided below (table 42) for patients in the mFAS.

Table 42: Frequency of baseline risk factors for severe Covid-19 (Phase 3, mFAS)

	Placebo		REGN10933+REGN10987			Total (N=4057)
	Pooled for 1200 mg IV analysis[1] (N=748)	Pooled for 2400 mg IV analysis[1] (N=1341)	1200 mg IV (N=736)	2400 mg IV (N=1355)	8000 mg IV (N=625)	
Risk factor for Severe COVID-19						
Age ≥50 years	356 (47.6%)	678 (50.6%)	357 (48.5%)	715 (52.8%)	351 (56.2%)	2101 (51.8%)
Obesity, defined as BMI ≥30 kg/m^2	427 (57.1%)	772 (57.6%)	410 (55.7%)	787 (58.1%)	384 (61.4%)	2353 (58.0%)
Cardiovascular disease, including hypertension	266 (35.6%)	473 (35.3%)	282 (38.3%)	520 (38.4%)	196 (31.4%)	1471 (36.3%)
Chronic lung disease, including asthma	139 (18.6%)	219 (16.3%)	139 (18.9%)	216 (15.9%)	92 (14.7%)	666 (16.4%)
Type 1 or type 2 diabetes mellitus	100 (13.4%)	210 (15.7%)	94 (12.8%)	202 (14.9%)	97 (15.5%)	603 (14.9%)
Chronic kidney disease, including those on dialysis	4 (0.5%)	9 (0.7%)	8 (1.1%)	19 (1.4%)	9 (1.4%)	45 (1.1%)
Chronic liver disease	4 (0.5%)	8 (0.6%)	3 (0.4%)	14 (1.0%)	11 (1.8%)	36 (0.9%)
Immunocompromised	10 (1.3%)	34 (2.5%)	24 (3.3%)	46 (3.4%)	16 (2.6%)	120 (3.0%)
Immunosuppressed	10 (1.3%)	31 (2.3%)	24 (3.3%)	46 (3.4%)	15 (2.4%)	116 (2.9%)
Taking Immunosuppressants	0	11 (0.8%)	0	10 (0.7%)	6 (1.0%)	27 (0.7%)

[1] Placebo is presented in two columns, based on those that were concurrently randomized to the 1200 mg and 2400 mg active treatment groups. The placebo group marked as "pooled for 1200 mg IV analysis" is a subset of the placebo group marked as "pooled for 2400 mg IV analysis."

The most common risk factors were obesity, defined as BMI ≥30 kg/m2 (58.0%), age ≥50 years (51.8%), and cardiovascular disease including hypertension (36.3%).

Chronic lung disease (including asthma) and type 1 or type 2 diabetes mellitus were less common (16.4% and 14.9% respectively). Chronic kidney disease, chronic liver disease and immunocompromised state were uncommon (≤3% frequency).

Randomisation of treatment

In phase 3, patients were randomized in a 1:1:1 allocation ratio to one of the following:

- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose.
- Co-administered REGN10933+REGN10987 combination therapy, 8000 mg (4000 mg each of REGN10933 and REGN10987) IV single dose.
- Placebo IV single dose 0.9% sodium chloride for injection.

Patients in cohort 1 who were enrolled into phase 3 under protocol amendment 6 or 7 were randomized in a 1:1:1 allocation ratio to one of the treatments listed below:

- Co-administered REGN10933+REGN10987 combination therapy, 1200 mg (600 mg each of REGN10933 and REGN10987) IV single dose.
- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose.
- Placebo IV single dose 0.9% sodium chloride for injection.

The placebo arm in phase 3 was dropped in protocol amendment 8 following an iDMC recommendation.

Results

Phase 3 adaptations included discontinuation of the 8000 mg dose, retention of the 2400 mg dose, addition of a lower 1200 mg dose and eligibility criteria requiring at least 1 risk factor for severe Covid-19 (the amended portion of phase 3 i.e. received either casirivimab + imdevimab 2400 mg [N=1355] or 1200 mg [N=736]).

Primary efficacy endpoint

The proportion of participants who had at least 1 Covid-19-related hospitalization or all-cause death through day 29 was significantly reduced with casirivimab+imdevimab 2400 mg compared to placebo (1.3% vs. 4.6%), corresponding to a relative risk reduction of 71.3% ($p<0.0001$).

The proportion of participants who had at least 1 Covid-19-related hospitalization or all-cause death through day 29 was also significantly reduced with casirivimab+imdevimab 1200 mg compared to placebo (1.0% vs. 3.2%), corresponding to a relative risk reduction of 70.4% ($p<0.0024$).
The primary clinical efficacy endpoint was met with an absolute reduction of up to 3.3% in hospitalization or all-cause death up to day 29 when active is compared to placebo.

Sensitivity analyses of the primary endpoint, using the primary efficacy parameters in the FAS population with ≥1 risk factor for severe Covid-19, yielded similar results as the primary analysis population and confirmed that clinical benefit was observed in the overall FAS population with treatment with casirivimab+imdevimab compared to placebo (2400 mg, 1.2% vs 4.2%) and (1200 mg, 0.8% vs 3.0%).

Subgroup analyses based on viral load and sero-status were generally supportive towards the primary endpoint with point estimates favouring active over placebo.

Post-hoc analyses by various combinations of risk factor categories showed clinical benefit in reduction in Covid-19-related hospitalization or all-cause death with both doses of casirivimab + imdevimab, regardless of how risk factors were defined. While event numbers were small in some of the risk factor subgroups, generally there was a trend for reduction in Covid-19-related hospitalization or all-cause death with both doses of casirivimab+imdevimab compared to the placebo group, consistent with the protocol-specified primary analysis. Across all subgroups, greater precision was observed with the 2400 mg treatment group due to the larger sample size.

Key secondary efficacy endpoints:

Proportion of participants with ≥1 Covid-19-related hospitalization or all-cause death from day 4 through day 29: There was an 89.2% relative risk reduction for an event in the day 4 through 29 analysis for the casirivimab+imdevimab 2400 mg group compared to placebo (95% CI: 73.0%, 95.7%; $p<0.0001$); the proportion of participants with ≥1 Covid-19-related hospitalization or all-cause death in the casirivimab+imdevimab 2400 mg group compared to placebo was 0.4% vs. 3.4%.

Time to Covid-19 symptoms resolution (participants with ≥1 risk factor for severe Covid-19): Treatment with casirivimab+imdevimab 2400 mg or 1200 mg was associated with a statistically significant 4-day faster time to symptoms resolution (from self-reported SE-C19 assessment) where the median time to resolution of symptoms was 10 days for both casirivimab+imdevimab doses and 14 days for the placebo group.

Virologic secondary efficacy endpoints:

Time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in nasopharyngeal swab samples (participants enrolled prior to the adapted portion of phase 3): Among participants in the mFAS, both the combined treatment group and individual doses (casirivimab + imdevimab IV 2400 mg and 8000 mg) resulted in a greater LS mean daily reduction from baseline in viral load from day 1 to day 7 relative to placebo (difference from placebo of -0.60 log_{10} copies/mL/day for 8000 mg and -0.58 log_{10} copies/mL/day for 2400 mg, nominal $p<0.0001$).

Greater daily reductions relative to placebo were also observed for the casirivimab + imdevimab doses in subgroups regardless of baseline viral load or serologic status.

Most participants were seronegative and/or had a baseline viral load >106 copies/mL at baseline, and these subgroups showed reductions that were greater compared to placebo (nominal p<0.0001).

The magnitude of reduction relative to placebo was not as large for the smaller group of participants with seropositive baseline or ≤106 copies/mL viral load at baseline

Change from baseline in viral load at each visit, as measured by RT-qPCR in nasopharyngeal swab samples: The LS mean daily reduction from baseline in viral load at day 7 was larger than placebo for both the casirivimab + imdevimab 2400 mg group (difference from placebo: -0.86 $\log_{10}$ copies/mL/day, nominal p<0.0001) and the 1200 mg group (difference from placebo: -0.71 $\log_{10}$ copies/mL/day, nominal p<0.0001).

The subgroup of participants who were seropositive or had ≤106 copies/mL viral load at baseline also showed greater LS mean daily reduction in viral load relative to placebo for the casirivimab + imdevimab 2400 mg group (nominal p<0.0001).

There was a trend for benefit for the 1200 mg group which had fewer participants.

Efficacy conclusion for study 2067
Overall, efficacy is considered to outweigh potential harms; the benefit risk profile of the product associated with study 2067 is considered to be positive.

Study COV-2066
An adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master study to evaluate the safety, tolerability, and efficacy of casirivimab+imdevimab in hospitalized adult participants with Covid-19.

Primary objectives:
Phase 1/2 (cohort 1)
The primary objective was to exclude futility of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation. The safety and tolerability of REGN10933+REGN10987 compared to placebo was also evaluated.

Phase 2 (cohort 1A)
The primary objective was to evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation. The safety and tolerability of REGN10933+REGN10987 compared to placebo was also evaluated.

Phase 2 (cohort 2 and cohort 3)
There was no primary objective for cohort 2 and cohort 3 in phase 2 as enrolment was put on hold. All safety and efficacy analyses were secondary.

Phase 3 (cohort 1 and cohort 1A)
The primary objective was to evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation.

Secondary objectives:
Phase 1/2 (cohort 1)
The key secondary objective was to evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation

The other secondary objectives were:
- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2.
- To evaluate (descriptively) additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo.
- To characterize the concentrations of REGN10933 and REGN10987 in serum over time.
- To assess the immunogenicity of REGN10933 and REGN10987.

Phase 2 (cohort 1A)
The secondary objectives were:
- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2.
- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo.
- To characterize the concentrations of REGN10933 and REGN10987 in serum over time.
- To assess the immunogenicity of REGN10933 and REGN10987.

Phase 2 (cohort 2 and cohort 3)
The secondary objectives were:
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by death or mechanical ventilation (as applicable based on the cohort).
- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo.
- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2.
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo.
- To characterize the concentrations of REGN10933 and REGN10987 in serum over time.
- To assess the immunogenicity of REGN10933 and REGN10987.

Phase 3 (cohort 1 and cohort 1A)
The secondary objectives for phase 3 were the same as for phase 1/2.

Primary endpoints:
Phase 1/2 (cohort 1)
Futility: the primary endpoint was death or mechanical ventilation.
Safety and tolerability endpoints were as follows:
- Proportion of patients with treatment-emergent SAEs through end of study
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

Phase 2 (cohort 1A)
Clinical efficacy: the primary endpoint was death or mechanical ventilation.
Safety and tolerability endpoints were as follows:
- Proportion of patients with treatment-emergent SAEs through end of study
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

Phase 2 (cohort 2 and cohort 3)
There were no primary endpoints for cohort 2 and cohort 3 in phase 2.

Phase 3 (cohort 1 and cohort 1A)
The primary endpoint was death or mechanical ventilation.

Key secondary endpoint for phase 1/2 (cohort 1)
Clinical efficacy: the key secondary endpoint was death or mechanical ventilation.

Secondary endpoints:
Key secondary endpoint for phase 1/2 (cohort 1)
Clinical efficacy: the key secondary endpoint was death or mechanical ventilation.

Other secondary endpoints
Phase 1/2 (cohort 1) and phase 2 (cohort 1a)
Virologic efficacy
Clinical efficacy
- All-cause death
- Mechanical ventilation
- Proportion of patients who died or went on mechanical ventilation by day 29
- Proportion of patients who died by day 29 Proportion of patients who went on mechanical ventilation by day 29
- Time to discharge

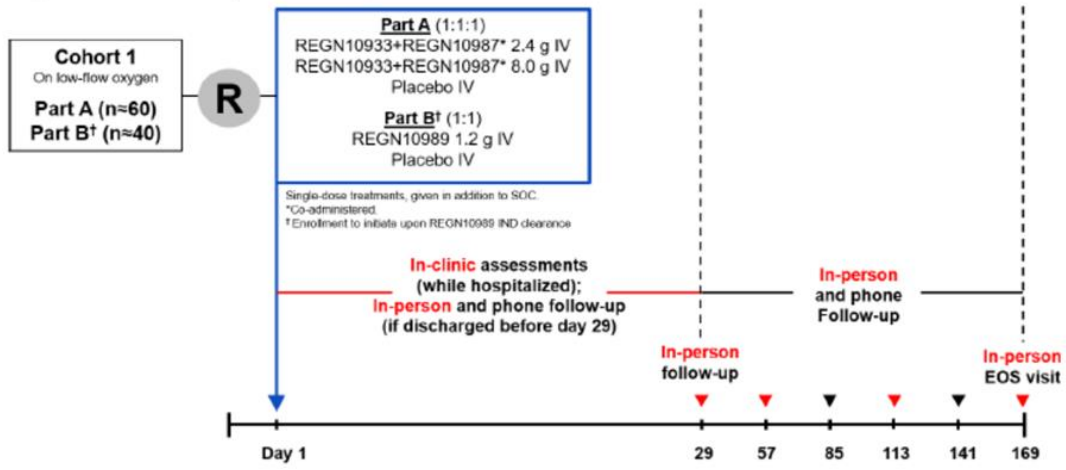
PK/anti-drug antibodies (ADA)
- Concentrations of REGN10987 and REGN10933 in serum and corresponding PK parameters
- Immunogenicity, as measured by ADAs to REGN10933 and REGN10987

Secondary endpoints were also described for phase 2 (cohort 2 and cohort 3) which is currently 'on hold'.

Phase 3 (cohort 1a and cohort 1)
The secondary endpoint(s) were the same as for phase 1/2.

Study design
Phase 1 (cohort 1 only)
Phase 1 assessed the safety, tolerability, and efficacy of REGN10933+REGN10987 in 60 patients from cohort 1. The study design is outlined below.

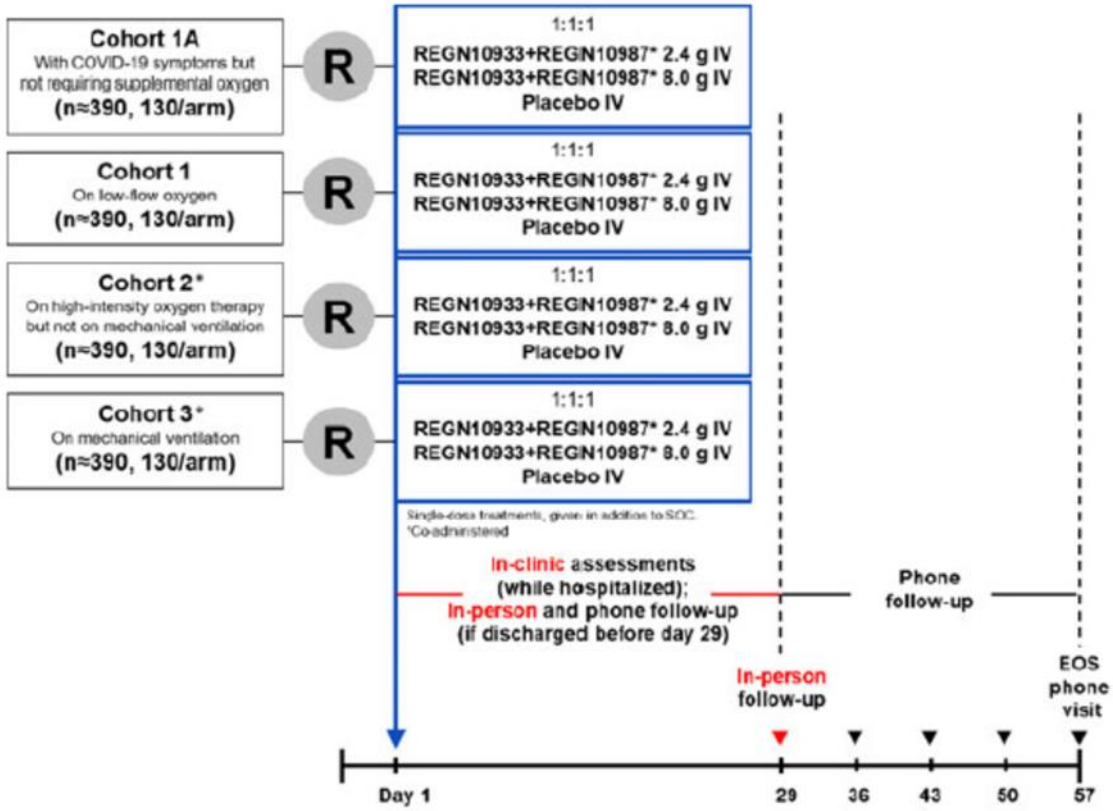
Figure 23: Study flow diagram, phase 1



Phase 2 (cohort 1a, cohort 1, cohort 2, and cohort 3*)*

The phase 2 portion of the study lasted up to 58 days. The study design is outlined below.

Figure 24: Study flow diagram, phase 2



** Per IDMC recommendation received on 30 October, 18 November, and 10 December 2020, patient enrollment in cohort 2 and cohort 3 has been placed on hold (pending IDMC review of further data on patients who are currently enrolled in these cohorts).*

Phase 3

In phase 3, patients were assessed daily up to day 29 for clinical improvement. After day 29, patients were followed-up until end-of-study on day 57.

Study cohorts

Study cohorts are described below.

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	On high-intensity oxygen therapy but not on mechanical ventilation
Cohort 3	On mechanical ventilation

Inclusion and exclusion criteria

A summary of the inclusion criteria is given below:

1. Has provided informed consent (signed by study patient or legally acceptable representative)
2. Male or female adult ≥18 years of age (or country's legal age of adulthood) at randomization

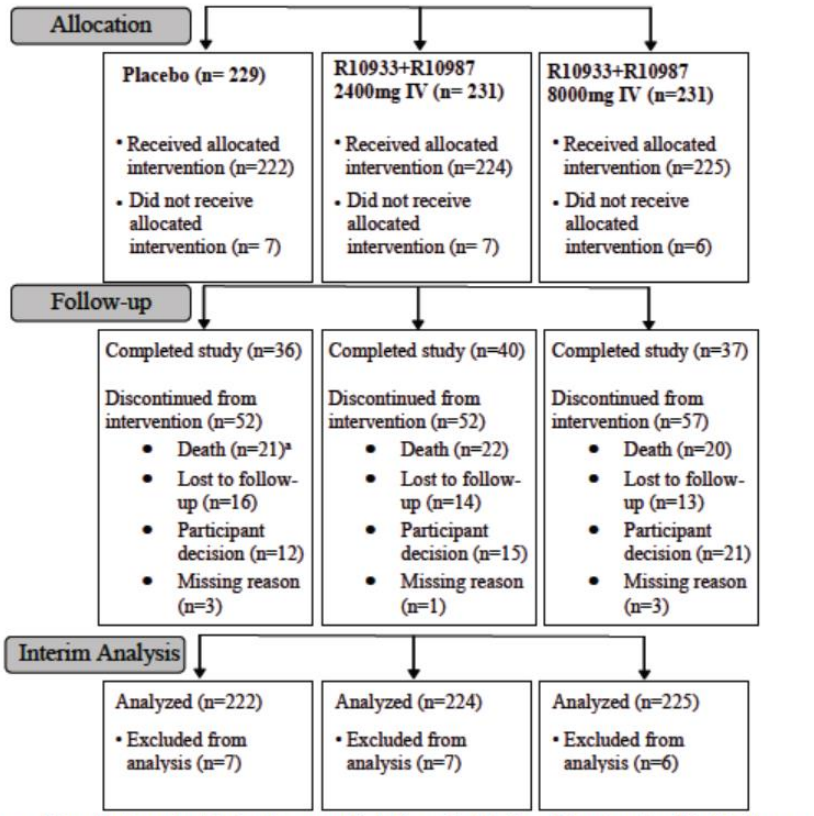
3. Has SARS-CoV-2-positive antigen or molecular diagnostic test (by validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay, using an appropriate sample such as NP, nasal, oropharyngeal [OP], or saliva) ≤72 hours prior to randomization and no alternative explanation for current clinical condition. A historical record of positive result from test conducted ≤72 hours prior to randomization is acceptable.
4. Has symptoms consistent with Covid-19, as determined by investigator, with onset ≤10 days before randomization
5. 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 O_2 saturation >93% on low-flow oxygen via nasal cannula, simple face mask or other similar device
Note: sites located in high-altitude areas (>1500 m above sea level) should get the appropriate high-altitude equivalents for sea-level oxygenation measurements.
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 SpO_2 ≤96% while receiving an oxygen flow rate of at least 10 L/min)
− High-flow device with at least 50% FiO_2
− 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
** Patient enrolment in cohort 2 and cohort 3 has been placed on hold.*

A summary of the exclusion criteria is given below:
1. Phase 1 only: Patients maintaining O_2 saturation >94% on room air
2. In the opinion of the investigator, unlikely to survive for >48 hours from screening
3. Receiving extracorporeal membrane oxygenation (ECMO)
4. Has new-onset stroke or seizure disorder during hospitalization
5. Initiated on renal replacement therapy due to Covid-19
6. Has circulatory shock requiring vasopressors at randomization
Note: Patients who require vasopressors for sedation-related hypotension or reasons other than circulatory shock may be eligible in this study.
7. Patients who have received convalescent plasma, IVIG, or mAbs against SARS-CoV-2 within 5 months prior to randomization or plan to receive during the study period for any indication
8. Participation in a clinical research study, including any double-blind study, evaluating an investigational product within 30 days and less than 5 half-lives of the investigational product prior to the screening visit
Note: The use of remdesivir, hydroxychloroquine, or other treatments (except for Covid-19 convalescent plasma or IVIG) being used for Covid-19 treatments in the context of the local standard-of-care or an open-label study or compassionate use protocol is permitted.
9. Any physical examination findings, history of illness, and/or concomitant medications that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study.
10. Known allergy or hypersensitivity to components of study drug
11. Pregnant or breastfeeding women

Patient disposition cohort 1
For cohort 1, 691 participants were randomized across phase 1 or phase 2, of which 20 participants were randomized in error and not treated and 671 were randomized and treated.

Among participants that were randomized and treated, 113 (16.8%) completed the study, 161 (24%) discontinued from the study early, and the remaining participants were ongoing as of the data cut-off.

Figure 25: Cohort 1, phase 1 and 2 -participant disposition (randomised, n=691)



a: One participant in the cohort 1 placebo group died after end of study and is not captured in this diagram

The reasons for discontinuation from the study included: 63 (9.4%) due to death, 43 (6.4%) lost to follow-up, 48 (7.2%) due to participant decision, and 7 (1.0%) were missing a reason for discontinuation. There were no discontinuations from study due to AEs, lack of efficacy or physician decision.

Patient demographics cohort 1

Cohort 1 demographic characteristics, baseline virology, and disease characteristics in the FAS population were generally similar between patients randomized to the REGN-COV2 treatment groups and the placebo group across the overall population of 671 patients analysed in cohort 1 (table 43).

Table 43: Demographics and baseline characteristics (cohort 1 full analysis set)

Parameter	Placebo (n=222)	2400 mg (n=224)	8000 mg (n=225)	Total (N=671)
Mean age years (range)	62.2 (22 to 100)	62.1 (24 to 95)	61.7 (21 to 95)	62.0 (21 to 100)
% ≥ 65 years	46.8	44.6	44.4	45.3
% Female	44.1	47.3	48.0	46.5
% White	66.7	70.1	64.4	67.1
% Black	16.2	9.8	18.2	14.8
% Hispanic or Latino ethnicity	27.5	25.0	27.1	26.5
% BMI > 30 kg/m^2	60.8	43.3	56.9	53.7
% Sx duration prior to BL, median days	6	6	6	6
% Remdesivir	64.4	63.4	63.6	63.8
% Systemic corticosteroids	73.9	63.8	73.8	72.0
CRP (median mg/L)	69.0	65.5	67.0	67.0
Baseline Virologic Parameter				
% Seronegative	**35.1**	**41.1**	**36.9**	**37.7**
RT-qPCR positive at BL (n)	68	79	70	217
Median log_{10} copies/mL	7.5	7.16	6.77	7.17
Median raw copies/mL	31650000.0	14400000.0	6000000.0	14900000.0
% >6 log_{10} copies/mL	76.9	68.5	65.1	70.0
% Seropositive	**50.9**	**49.1**	**51.1**	**50.4**
RT-qPCR positive at BL (n)	96	86	88	270
Median log_{10} copies/mL	5.31	5.3	5.31	5.31
Median raw copies/mL	202000.0	198000.0	202000.0	202000.0
% >6 log_{10} copies/mL	28.3	28.2	30.4	29.0
% Other	14.0	9.8	12.0	11.9

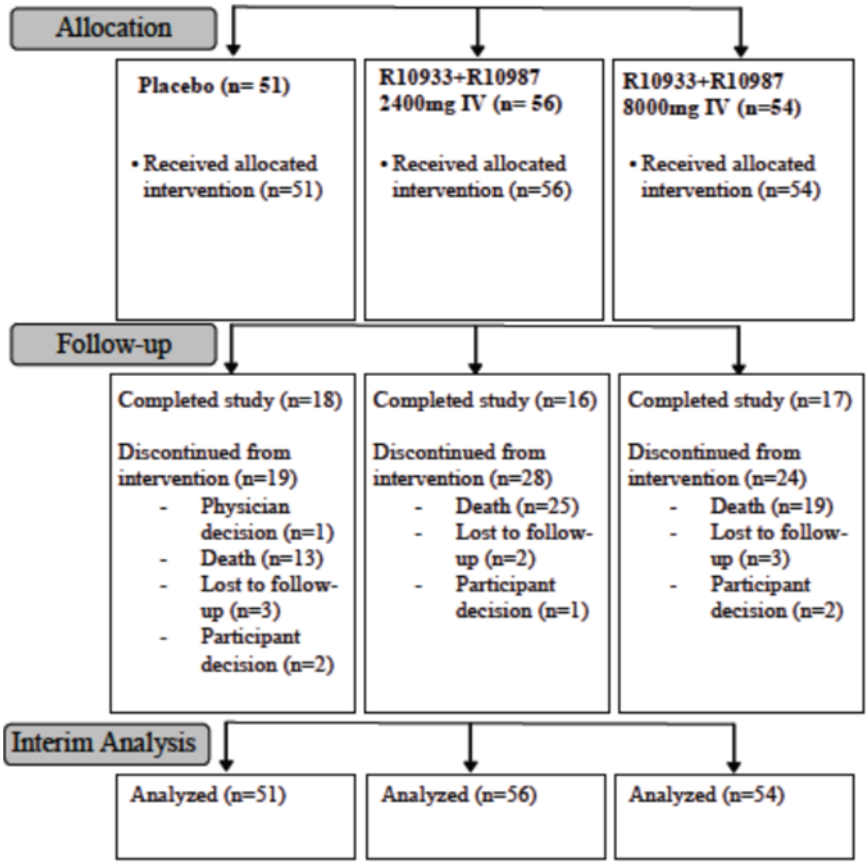
In the FAS population, as shown above, the mean age was 62yrs (SD 16); 45% >65yrs, 23% >75yrs; 54% male; 67% white, 15% black; median body mass index 32kg/m2; 50% seropositive, 38% seronegative, 12% 'other'; 64% administered remdesivir; 72% administered corticosteroids; 98% requiring oxygen supplement.

In the mFAS population, not shown here, the mean age was 62yrs (SD 16); 45% >65yrs, 22% >75yrs; 53% male; 69% white, 14% black; median body mass index 31kg/m2; 1 'missing' RT-PCR result; 51% seropositive, 41% seronegative, 8% 'other'; 64% anti-viral therapy; 98% clinical status requiring oxygen supplement, all but one subject on low-flow oxygen; 9% women of child-bearing age.

The percentage compositions of the FAS and mFAS populations appear similar.

Patient disposition cohort 2
For cohort 2, 161 participants were randomized and treated, of which 51 (31.7%) completed the study, 71 (44.1%) discontinued from the study early and the remaining participants were ongoing as of the data cut-off. A summary is shown in the following figure:

Figure 26: Cohort 1, phase 2 -participant disposition (randomised + dosed, n=161)

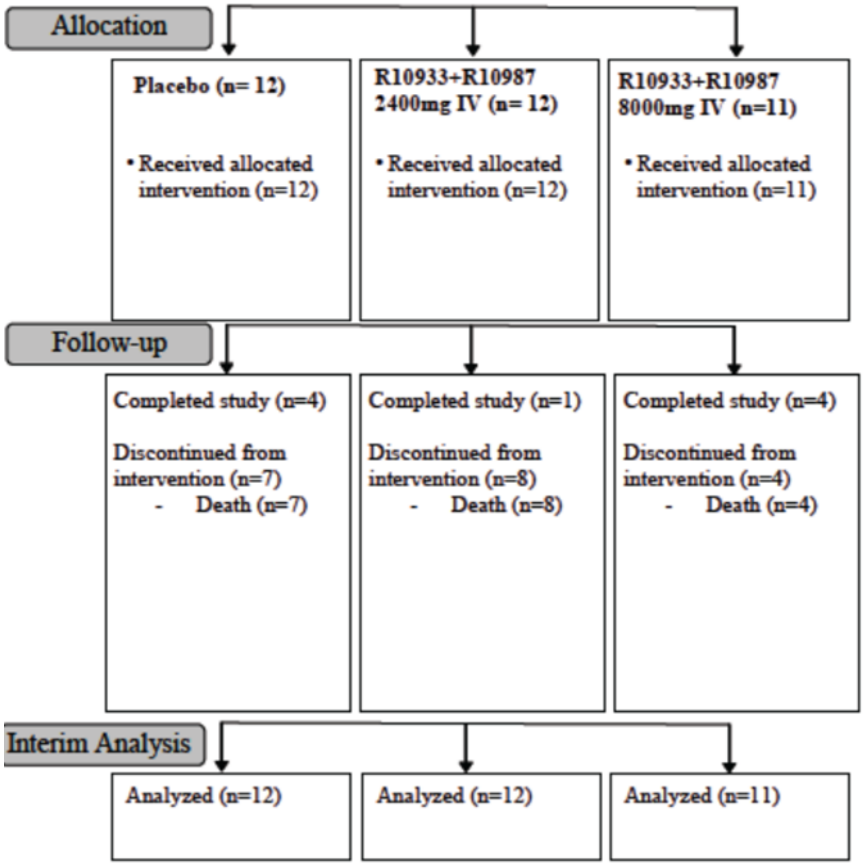


The reasons for discontinuation from the study included: 57 (35.4%) due to death, 8 (5.0%) lost to follow-up, 5 (3.1%) due to participant decision, and 1 (0.6%) due to physician decision. There were no discontinuations from study due to AEs or lack of efficacy.

Patient disposition cohort 3
For cohort 3, 35 participants were randomized and treated, of which 9 (25.7%) participants completed the study, 19 (54.3%) discontinued from the study early and the remaining participants were ongoing as of the data cut-off. A summary is shown in the following figure:

All 19 participants that discontinued did so due to death; there were no discontinuations due to any other reasons.

Figure 27: Cohort 3, phase 2 -participant disposition (randomised + dosed, n=35)



Treatment and randomisation
Phase 1, phase 2, and phase 3

- Co-administered REGN10933+REGN10987 combination therapy 2.4 g (1.2 g of REGN10933 plus 1.2 g of REGN10987) IV single dose
    - 60 patients were randomized in a 1:1:1 allocation ratio
- Co-administered REGN10933+REGN10987 combination therapy 8.0 g (4.0 g of REGN10933 plus 4.0 g of REGN10987) IV single dose
    - For each study cohort patients were randomized in a 1:1:1 ratio
- Placebo IV single dose 0.9% sodium chloride for injection
    - Patients were randomized in a 1:1:1 ratio

Randomization was stratified by type of background standard-of-care being administered for Covid-19 at randomization as follows:

- Antiviral therapies (remdesivir or other)
- Non-antiviral therapies (immune-based therapies, both antiviral and immune-based therapies, or no Covid-19-specific treatment)

Aspects of study flow
Sample collection for RT-qPCR analysis:-
Virologic samples were used to determine presence or absence of SARS-CoV-2 virus, including at baseline, and to measure viral load via RT-qPCR analysis. Only NP swabs were collected for virology testing after phase 1.

Clinical and oxygen status were collected and recorded as follows:-

- Oxygen delivery device status
- Vital status

- Hospitalization status

The type of oxygen delivery device and the most invasive type of oxygen devices used in the past 24 hours were recorded.

Clinical status assessment was made based (7-point ordinal scale) on the clinical and oxygen status, an ordinal scale score was generated automatically and used to assess clinical improvement.

Results

Virologic efficacy

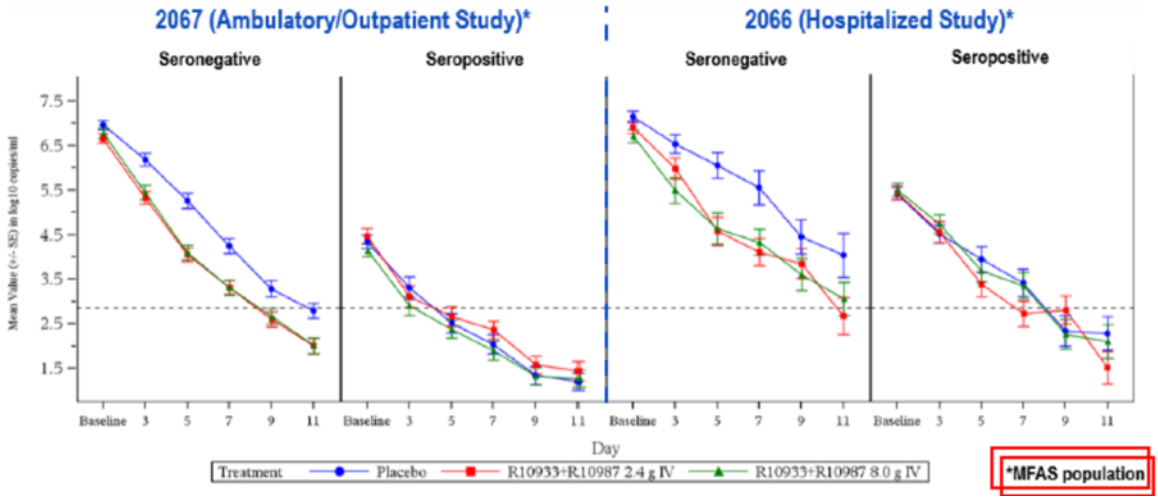
Treatment with REGN-COV2 resulted in a reduction in the time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 through day 7 (mFAS population). Reductions were observed in the overall mFAS population and in other subpopulations, including those with higher baseline viral load (e.g. >106 copies/mL) or who were seronegative at baseline.

There was a lack of dose effect. The antiviral benefit of REGN-COV2 was observed regardless of the background concomitant Covid-19 therapies used, such as remdesivir or dexamethasone.

There was limited antiviral efficacy in patients who already had baseline immunity to the virus (i.e., seropositive), but administering treatment with REGN-COV2 in these patients did not worsen the rate of viral clearance.

The virologic efficacy results observed in COV-2066 were consistent with the virologic efficacy results observed in the outpatient study (COV-2067) and serve as confirmation of the potent antiviral effects of REGN-COV2, as shown:

Figure 28: Reduction in viral load through day 11 (log_{10} copies/mL) by serostatus: COV-2067 and COV-2066



In patients that were seronegative at baseline, there was a -0.54 log_{10} copies/mL difference from placebo for the combined REGN-COV2 dose group in the LS mean time-weighted-average daily change from baseline in viral load through day 7.

By contrast, in patients that were seropositive at baseline, the LS mean time-weighted average daily change from baseline in viral load through day 7 for patients treated with REGN-COV2 was lower compared to the results observed in the seronegative patients (combined REGN-COV2, -0.2 log_{10} copies/mL difference from placebo, p = 0.02; REGN-COV2 8000 mg -0.02 log_{10} copies/mL difference from placebo, p = 0.9).

By visual inspection alone, up to day 11, seronegative subjects showed difference between placebo and active whilst seropositive subjects did not.

The difference between placebo and active was less obvious (if any) beyond day 11 for both seropositive and seronegative subjects, as shown in the following figures:

Figure 29: Line plot LSmean (+/-SE) viral load (log_{10} copies/mL) from baseline at each postbaseline visit through day 29 in nasopharyngeal (NP) samples by baseline serostatus

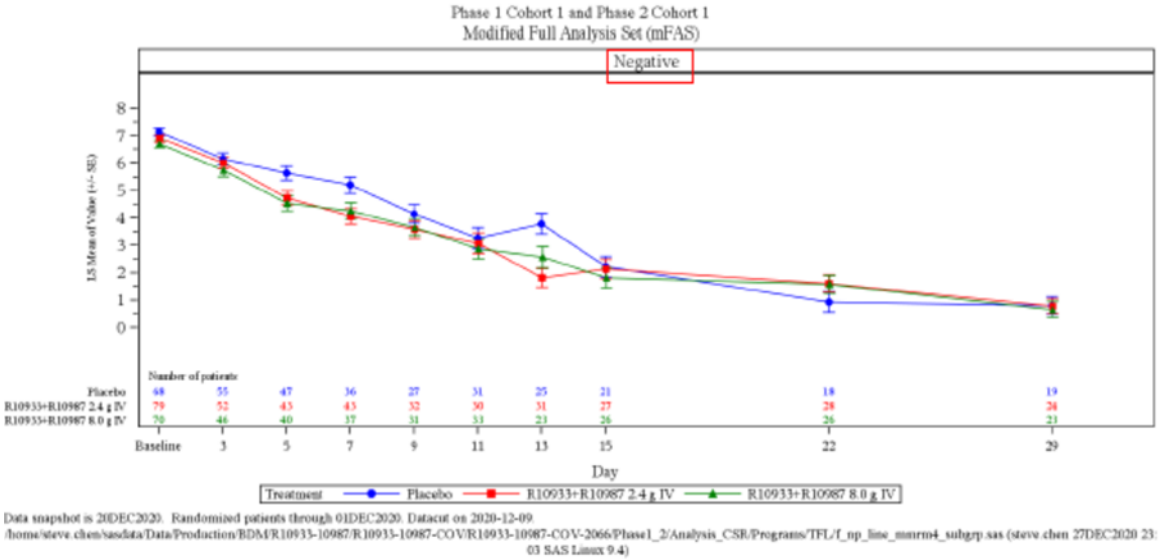
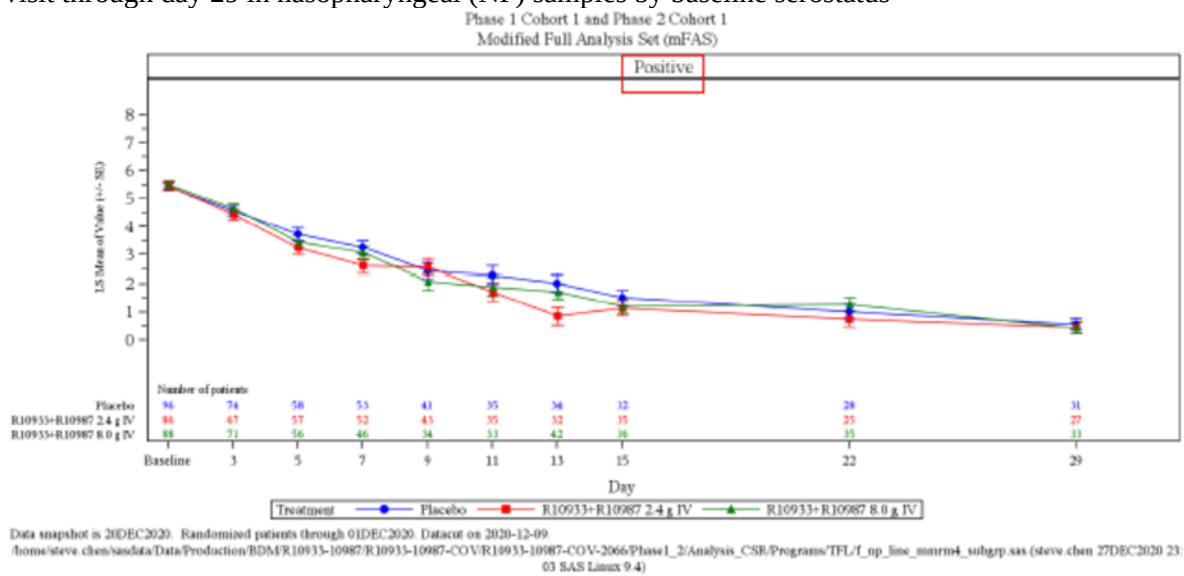


Figure 30: Line plot LSmean (+/-SE) viral load (log_{10} copies/mL) from baseline at each postbaseline visit through day 29 in nasopharyngeal (NP) samples by baseline serostatus

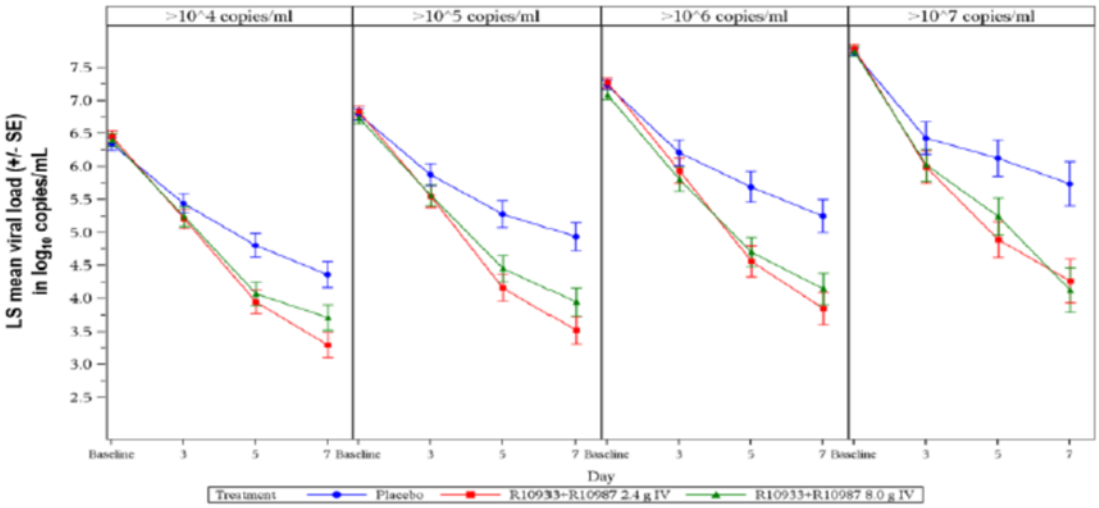


The magnitude of the reduction was greater in patients with greater baseline viral load.

In patients with baseline viral load >4 log_{10} copies/mL, there was a -0.43 log_{10} copies/mL difference from placebo in the least squares (LS) mean time weighted- average daily change from baseline in viral load through day 7 (p <0.0001).

In patients with baseline viral load >6 log_{10} copies/mL, there was a -0.55 log_{10} copies/mL difference from placebo for the combined REGN-COV2 dose group in the LS mean time-weighted-average daily change from baseline in viral load through day 7 (p = 0.0001). Data are shown in figure 31.

Figure 31: Reduction in viral load through day 7 (log_{10} copies/mL) by baseline viral load threshold: comparison of REGN-COV2 versus placebo (mFAS) in cohort 1, phase 1/2



Difference between placebo and active groups was apparent at all viral loads shown from day 3 to day 7. The rate of reduction in viral load in those who received active appears to slow beyond day 5.

Data on the primary and key secondary endpoint of reduction in death or mechanical ventilation in seronegative patients
The data used for these endpoints is summarised in table 44 below.

As the study passed the test of futility the clinical primary endpoint became ‘death or mechanical ventilation’.

For cohort 1, the Kaplan Meier curves (not shown here) for death or mechanical ventilation for seronegative patients of active and placebo crossed over so indicating non-proportional hazard in the data. An analysis carried out to address this suggested that efficacy was gained beyond day 10 with about 30% relative risk reduction in death or mechanical ventilation from day 10 up to day 29.

For cohort 1, seropositive patients did not appear to gain benefit for death or mechanical ventilation by exposure to the active versus placebo.

At the time of this report there were too few patients in cohorts 2 & 3 to make comment on outcomes.

Table 44: Analysis of cohort 1 clinical efficacy endpoints

Analysis	Data Cut 09 Dec 2020*	Data Cut 19 Jan 2021 (Post Hoc)†	Purpose of Test and α
Clinical Efficacy			
Cumulative incidence of death or mechanical ventilation in Seronegative mFAS for comparing the combined (pooled) doses of REGN10933+REGN10987 versus placebo	HR: 0.78 (0.51, 1.21) Risk reduction: 22% (49%, -) P = 0.2316	HR: 0.71 (0.47-1.07) Risk reduction: 29% (53%, -) P=0.1397	Efficacy α = 0.1 (1-sided)
Cumulative incidence of death or mechanical ventilation in Seronegative mFAS for comparing the high dose (REGN10933+REGN10987 8000 mg) versus placebo	HR: 0.92 (0.56, 1.50) Risk reduction: 8% P = 0.4151	HR: 0.83(0.51, 1.33) Risk Reduction: 17 % P= 0.3063	Efficacy α = 0.1 (1-sided)
Cumulative incidence of death or mechanical ventilation in Seronegative mFAS for comparing the low dose (REGN10933+REGN10987 2400 mg) versus placebo	HR: 0.66 (0.39, 1.12) Risk reduction: 34% P = 0.1692	HR: 0.60(0.36, 1.00) Risk Reduction: 40 % P= 0.1068	Efficacy α = 0.1 (1-sided)
Cumulative incidence of death or mechanical ventilation in mFAS patients with baseline viral load $>10^6$ copies/mL for comparing the combined (pooled) doses of REGN10933+REGN10987 versus placebo	HR: 0.74 (0.50, 1.10) Risk reduction: 26% P = 0.1605	HR: 0.66(0.45, 0.97) Risk Reduction: 34 % P= 0.0810	Efficacy α = 0.1 (1-sided)
Cumulative incidence of death or mechanical ventilation in mFAS patients with baseline viral load $>10^7$ copies/mL for comparing the combined (pooled) doses of REGN10933+REGN10987 versus placebo	HR: 0.94 (0.58, 1.54) Risk reduction: 6% P = 0.4381	HR: 0.78(0.49, 1.25) Risk Reduction: 22 % P= 0.2479	Efficacy α = 0.1 (1-sided)

HR = hazard ratio
All p-values in this study are nominal.
*Includes all patients randomized by 01 Dec 2020; with a data cut-off date of 09 Dec 2020 to ensure that patients had at least 8 days of follow-up.†Includes the same patients randomized by 01 Dec 2020; with an updated data cut-off date of 19 Jan 2021 to encompass a full 29 days of follow-up. Not part of hypothesis testing hierarchy; provided as representative information from a more complete dataset.

Study COV-2069

A phase 3, randomized, double-blind, placebo-controlled study assessing the efficacy and safety of anti-spike SARS-CoV-2 monoclonal antibodies in preventing SARS-CoV-2 infection in household contacts of individuals infected with SARS-CoV-2. All subjects in the study were household contacts of the first known household member to be infected with SARS-CoV-2 (index case) but who were themselves asymptomatic (having no active respiratory or non-respiratory symptoms consistent with Covid-19) at the time of screening. This study was intended to demonstrate the efficacy of REGN10933+REGN10987 to prevent SARS-CoV-2 infection (with or without symptoms) in uninfected subjects or prevent symptomatic disease (e.g. pre-emptive therapy) in subjects already infected (i.e. SARS-CoV-2 RT-qPCR positive) at baseline.

For analysis of endpoints, there were 4 defined cohorts based on the subjects' SARS-CoV-2 infection status at baseline, as measured by central lab SARS-CoV-2 RT-qPCR (quantitative reverse transcription polymerase chain reaction):
1. Cohort A: adult and adolescent subjects (≥12 years) who are SARS-CoV-2 RT-qPCR negative at baseline
2. Cohort A1: paediatric subjects (<12 years) who are SARS-CoV-2 RT-qPCR negative at baseline
3. Cohort B: adult and adolescent subjects (≥12 years) who are SARS-CoV-2 RT-qPCR positive at baseline

4. Cohort B1: paediatric subjects (<12 years) who are SARS-CoV-2 RT-qPCR positive at baseline

This study reported on adults only and therefore only descriptions relative to cohorts A and B are given here.

Cohort A primary efficacy objective

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing asymptomatic or symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR

Cohort B primary efficacy objective

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing Covid-19 symptoms (broad-term)

Cohort A secondary objectives

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing a SARS-CoV-2 infection with a high viral load (i.e., viral load >4 (log_{10} copies/mL)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection with a high viral load (i.e., viral load >4 (log_{10} copies/mL)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing asymptomatic or symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of treating the index case with REGN10933+REGN10987 on the incidence of SARS-CoV-2 infection among household contacts in the placebo group (This is a cross-study analysis based on only subjects in placebo group of study R10933-10987-COV-2069 whose index cases participated in study R10933-10987- COV-2067)
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (Center for Disease Control [CDC] definition) confirmed by RT-qPCR
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (strict-term) confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARSCoV-2 RT-qPCR viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 infection: − On health care utilization − On absenteeism from daily responsibilities (where applicable)
- To evaluate the impact of treating any SARS-CoV-2 RT-qPCR positive household member with REGN10933+REGN10987 on the incidence of SARS-CoV-2 infection among their household contacts in placebo group (note: This is a cross-study analysis based on only subjects in placebo group of study R10933-10987-COV-2069 whose index or other household member participated in study R10933-10987-COV-2067 or in cohort B)

- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected PK parameters
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration in seropositive subjects
- To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated seronegative and seropositive subjects compared with placebo-treated subjects
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR (cohort A1)

Cohort B secondary objectives

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing development of:
  - Symptomatic SARS-CoV-2 infection (strict-term)
  - Symptomatic SARS-CoV-2 infection (broad-term; cohort B1)
  - Symptomatic SARS-CoV-2 infection (CDC definition)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection with a high viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 infection:
  - On health care utilization
  - On absenteeism from daily responsibilities (where applicable)
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected PK parameters
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration
- To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated subjects compared with placebo-treated subjects

Cohort A primary endpoint

- Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the efficacy assessment period (EAP)

Cohort A secondary endpoints

- Proportion of participants developing viral load >4 (log_{10} copies/ml) in nasopharyngeal swab samples
- Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term)
- Number of weeks of high viral load >4 (log_{10} copies/mL) in nasopharyngeal swab samples during the efficacy analysis period
- Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the efficacy analysis period

- Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the efficacy analysis period
- Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the efficacy analysis period with an index case participating in study R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 versus placebo in study R1033-10987-COV-2067)

Cohort B primary efficacy endpoint
- Proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP

Cohort B key secondary efficacy endpoints
- Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Number of weeks of high viral load >4 (log_{10} copies/mL) in NP swab samples during the EAP

The study had a 28-day efficacy assessment period (EAP) after the single dose of active study drug or placebo administered SC to capture all infections as detected by SARS-CoV-2 RT-qPCR positivity (both asymptomatic and symptomatic), symptomatic infection (i.e. those individuals that experience symptoms consistent with SARS-CoV-2 infection and progression of Covid-19 disease). [28 days takes into account an incubation period of up to 14 days before onset of symptoms and 14 days for duration of symptoms].

Study design
The study design has been previously described in Section IV.2.

Inclusion and exclusion criteria
A summary of key eligibility criteria is shown below:
1. Adult subjects 18 years of age (irrespective of weight) and above at the signing of informed consent or adolescent subjects ≥12 to <18 years of age, or paediatric subjects <12 years of age at the signing of the assent (parent/guardian sign the informed consent)
2. Asymptomatic household contact with exposure to an individual with a diagnosis of SARS-CoV-2 infection (index case). To be included in the study, subjects must be randomized within 96 hours of collection of the index cases' positive SARS-COV-2 diagnostic test sample
3. Subject anticipates living in the same household with the index case until study day 29
4. Is judged by the investigator to be in good health based on medical history and physical examination at screening/baseline, including subjects who are healthy or have a chronic, stable medical condition

A summary of the exclusion criteria is given below. Any patients who met any of the following criteria were excluded from the study:
1. Subject-reported history of prior positive SARS-CoV-2 RT-PCR test or positive SARS-CoV-2 serology test at any time before the screening
2. Subject has lived with individuals who have had previous SARS-CoV-2 infection or currently lives with individuals who have SARS-CoV-2 infection, with the exception of the index case(s), the first individual(s) known to be infected in the household
3. Active respiratory or non-respiratory symptoms consistent with Covid-19
4. History of respiratory illness with sign/symptoms of SARS-CoV-2 infection, in the opinion of the investigator, within the prior 6 months to screening
5. Nursing home resident

6. Any physical examination findings, and/or history of any illness, concomitant medications or recent live vaccines that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the subject by their participation in the study
7. Current hospitalization or was hospitalized (ie, >24 hours) for any reason within 30 days of the screening visit
8. Treatment with another investigational agent in the last 30 days or within 5 half-lives of the investigational drug, whichever is longer, prior to the screening visit
9. Received an investigational or approved SARS-CoV-2 vaccine
10. Received investigational or approved passive antibodies for SARS-CoV-2 infection prophylaxis (e.g. convalescent plasma or sera, monoclonal antibodies, hyperimmune globulin)

Randomisation of treatment
Subjects were randomized in a 1:1 ratio to receive REGN10987+REGN10933 or placebo according to a central randomization scheme.

Populations analysed
The populations are summarised below:

Table 45: Safety and efficacy analysis sets (randomised population)

	Placebo (N=1522)	REGN10933+REGN10987 (N=1507)	Total (N=3029)
Efficacy analysis sets			
Seronegative mFAS-A	752 (49.4%)	753 (50.0%)	1505 (49.7%)
Seronegative mFAS-B	104 (6.8%)	100 (6.6%)	204 (6.7%)
Safety analysis sets			
Cohort A	1306 (85.8%)	1311 (87.0%)	2617 (86.4%)
Cohort B	156 (10.2%)	155 (10.3%)	311 (10.3%)
Cohort Undetermined	47 (3.1%)	27 (1.8%)	74 (2.4%)

Note: For the first step analysis, all subjects randomized by 28Jan2021 are included. The data cutoff date is 11Mar2021. For efficacy analysis, 554 subjects in cohort A who were in the administrative assessment are excluded.

Patient disposition
A total of 3096 participants were screened. 3029 participants were randomized of whom 3002 were treated, as shown in table 46 below.

Demographics of cohort A (full analysis set & modified analysis set): negative SARS-CoV-2 RT-qPCR status at baseline
For the full set of cohort A, there were 2617 subjects; mean age 43yrs (88 subjects were 12 - 18yrs), 47% male; 83% white; median body mass index 27.7 kg/m2.

For the modified set: there were 1505 subjects; mean age 43yrs (68 subjects were 12 - 18yrs); 46% male; 86% white; median body mass index 27.5 kg/m2.

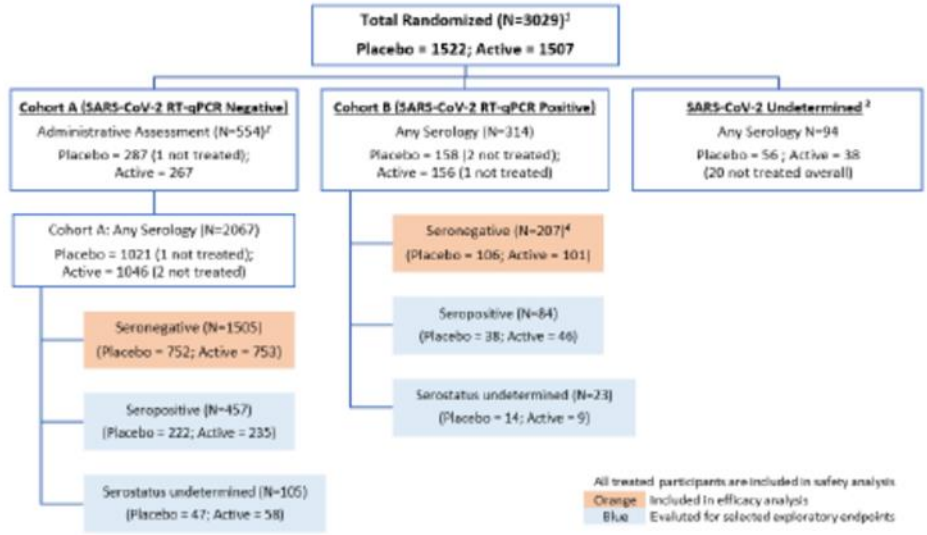
The full and modified sets for cohort A appear comparable with regards to percentage compositions.

Demographics of cohort B (full analysis set & modified analysis set): positive SARS-CoV-2 RT-qPCR status at baseline
For the full set of cohort B, there are 311 subjects; mean age 41yrs (SD 18yrs), 38 subjects were 12 - 18yrs; 48% male; 85% white; median body mass index 27.2 kg/m2.

For the modified set: there were 207 subjects; mean age 41yrs (SD 18yrs), 26 subjects were 12 -18yrs; 45% male; 84% white; median body mass index 27.2 kg/m2.

The full and modified sets for cohort B appear comparable in terms of percentage compositions; this is acceptable.

Figure 32: Summary of study participants (all randomised)



Cohort allocation was based on baseline SARS-CoV-2 RT-qPCR status (based on NP swab samples by central laboratory) and further subdivided by baseline serostatus (by central laboratory), as described in Section 3.1.1.1.

1. Total randomized based on randomization cutoff date for CSR as described in Section 1.1. Randomization to a treatment arm was based on a local diagnostic for SARS-CoV-2 infection at screening.
2. Participants in the administrative assessment were excluded from the primary efficacy analysis but were included in the safety analysis for cohort A.
3. Participants with undetermined SARS-CoV-2 RT-qPCR status (as assessed by central laboratory) were included as a separate group in the safety analysis (SAF-Undetermined).
4. In cohort B, the efficacy analysis included 204 participants as 3 participants who were symptomatic for COVID-19 at baseline were excluded from the analysis.

Table 46: Overview of participant disposition by cohort (all randomised participants)

	Cohort A (N=2621)	Cohort B (N=314)	SARS-CoV-2 Undetermined[1] (N=94)	Total (N=3029)
Randomized subjects	2621 (100%)	314 (100%)	94 (100%)	3029 (100%)
Randomized but not treated	4 (0.2%)	3 (1.0%)	20 (21.3%)	27 (0.9%)
Randomized and treated	2617 (99.8%)	311 (99.0%)	74 (78.7%)	3002 (99.1%)
Complete the efficacy assessment period (EAP) (as derived) [2]	2601 (99.4%)	310 (99.7%)	72 (97.3%)	2983 (99.4%)
Complete the end of study follow-up visit (as per CRF)	15 (0.6%)	3 (1.0%)	0	18 (0.6%)
Did not complete the end of study follow-up visit	2602 (99.4%)	308 (99.0%)	74 (100%)	2984 (99.4%)
Subjects discontinued from the study during EAP	16 (0.6%)	1 (0.3%)	2 (2.7%)	19 (0.6%)
Reason for subjects discontinuing from the study during EAP				
Adverse event	0	0	0	0
Pregnancy	0	0	0	0
Lack of efficacy	0	0	0	0
Physician decision	0	0	0	0
Sponsor request	0	0	0	0
Death	0	0	0	0
Lost to follow-up	7 (0.3%)	0	0	7 (0.2%)
Subject decision	9 (0.3%)	1 (0.3%)	2 (2.1%)	12 (0.4%)

Note: For the first step analysis, all subjects randomized by 28Jan2021 are included. The data cutoff date is 11Mar2021.

1. Cohort allocation for analysis was based on centrally assessed RT-qPCR test result from NP swab sample collected at baseline.
2. Subjects who completed day 29 visit or skipped day 29 visit but still are in the follow-up period were considered as completing the EAP

Risk factors cohort A

The frequency of baseline risk factors for severe Covid-19 is provided below for patients in seronegative mFAS-A. About 30% of baseline-seronegative participants in cohort A had risk factors at baseline for severe Covid-19 if they were to become infected, as summarised:

Table 47: Participants with high-risk factors at baseline (seronegative mFAS-A)

Seronegative	Placebo (N=752)	REGN10933+ REGN10987 (N=753)	Total (N=1505)
Subjects with any high-risk factors at baseline	221 (29.4%)	238 (31.6%)	459 (30.5%)
>= 65 years of age	55 (7.3%)	76 (10.1%)	131 (8.7%)
BMI (kg/m^2) >= 35	104 (13.8%)	99 (13.1%)	203 (13.5%)
Chronic kidney disease	11 (1.5%)	17 (2.3%)	28 (1.9%)
Diabetes	45 (6.0%)	58 (7.7%)	103 (6.8%)
Immunosuppressive disease	2 (0.3%)	5 (0.7%)	7 (0.5%)
Receiving immunosuppressive treatment	11 (1.5%)	4 (0.5%)	15 (1.0%)
>= 55 years of age, and with cardiovascular disease or hypertension or chronic obstructive pulmonary disease	90 (12.0%)	99 (13.1%)	189 (12.6%)

Note: For the first step analysis, the data cutoff date is 11Mar2021.
Note: Data collected from demographics, medical history and concomitant medication eCRF form

Risk factors cohort B

Mean baseline viral load was similar between treatment groups in baseline-seronegative participants in cohort B, and the means were comparable between treatment groups within each baseline serology subgroup.

More than 30% of baseline-seronegative participants in cohort B had baseline risk factors for severe Covid-19 if they were to become infected.

Table 48: Participants with high-risk factors at baseline (seronegative mFAS-B)

Seronegative	Placebo (N=104)	REGN10933+ REGN10987 (N=100)	Total (N=204)
Subjects with any high-risk factors at baseline	34 (32.7%)	31 (31.0%)	65 (31.9%)
>= 65 years of age	13 (12.5%)	8 (8.0%)	21 (10.3%)
BMI (kg/m^2) >= 35	11 (10.6%)	16 (16.0%)	27 (13.2%)
Chronic kidney disease	3 (2.9%)	2 (2.0%)	5 (2.5%)
Diabetes	11 (10.6%)	5 (5.0%)	16 (7.8%)
Immunosuppressive disease	1 (1.0%)	1 (1.0%)	2 (1.0%)
Receiving immunosuppressive treatment	0	3 (3.0%)	3 (1.5%)
>= 55 years of age, and with cardiovascular disease or hypertension or chronic obstructive pulmonary disease	15 (14.4%)	13 (13.0%)	28 (13.7%)

Note: For the first step analysis, the data cutoff date is 11Mar2021.
Note: Data collected from demographics, medical history and concomitant medication eCRF form

Household characteristics and exposure risk were balanced between treatment groups for both cohorts A and B. With regard to prior and concomitant therapies both cohorts A and B were essentially 'healthy volunteer' groups and the pattern of prior and concomitant therapies would not appear able to affect overall outcomes of the study.

Dose in cohorts A and B

REGN10933 and REGN10987, to be co-administered:

- REGN10933: supplied as a 120 mg/mL solution for SC or IM injection, 600mg
- REGN10987: supplied as a 120 mg/mL solution for SC or IM injection, 600mg

- Matching placebo: an aqueous buffer solution at pH 6.0, containing 10 mM histidine, 10% (w/v) sucrose, and 0.1% (w/v) polysorbate 80 supplied as matching solution for SC or IM injection.

All adult or adolescent subjects received 4 SC injections of study drug on day 1, each injection containing 2.5 mL of active study drug or placebo. The REGN10987 and REGN10933 dose was 1200 mg (600 mg of each mAb) SC single dose on day 1.

Results

Cohort A

A total of 2617 participants in cohort A received a dose of study treatment.
In the placebo group, the dose (consisting of 4 injections) was not fully administered in 1/1306 (<0.1%) participant because the individual moved during drug administration preventing a full dose.

In the casirivimab+imdevimab group, the dose was not fully administered in 1/1311 (<0.1%) participant due to an AE of ISR which was mild in severity and resolved on the same day.
Overall, more than 99% of participants were observed for more than 4 weeks.
Approximately 4% have been observed for more than 28 weeks.

The end of study visit occurred at week 32 and data collection is ongoing.

Primary endpoint

Treatment with casirivimab+imdevimab significantly reduced the risk of symptomatic infection by 81.4% compared to placebo in uninfected participants (cohort A) who were seronegative at baseline (p<0.0001).

Table 49: Proportion of participants with symptomatic SARS-CoV-2 infection (broad-term) during the EAP (seronegative mFAS-A)

Criteria: Symptomatic Infection (By Broad-term Definition)	Placebo (N=752)	REGN10933+ REGN10987 (N=753)
Proportion of subjects meeting the criteria based on the central lab or local confirmatory positive RT-qPCR test	59/752 (7.8%)	11/753 (1.5%)
Risk reduction vs Placebo		81.4%
Odds ratio estimate (drug vs placebo) [1]		0.17
95% CI		(0.090 to 0.332)
p-value vs placebo		<0.0001

Note: For the first step analysis, the data cutoff date is 11Mar2021.
1. The CI with p-value is based on the odds ratio (casirivimab+imdevimab group vs placebo group) using a logistic regression model with the fixed categorical effects of treatment group, age group (age in years:>=12 to<50 and >=50), and region (US vs ex-US).

In supportive analyses, a consistent treatment effect was shown regardless of baseline serostatus, with an 82.3% risk reduction in symptomatic infection compared to placebo (OR 0.17 [0.090, 0.312], nominal p<0.0001). A comparable level of reduction was observed when the analysis included only baseline-seropositive participants (81.1% risk reduction vs placebo, OR 0.19 [0.023, 1.682], nominal p=0.1369).

Therefore, although there was apparent reduction in symptomatic infection regardless of baseline sero-status with p<0.0001, when subjects who are seropositive at baseline were analysed separately then difference is not apparent with p = 0.14 (see table 49). Data suggest that the current product bears efficacy only for those subjects in cohort A who are seronegative at baseline.

Treatment benefit was observed as early as 1 day after treatment (table 50) and was maintained through day 29. Most events occurred in the first week, with a 71.9% risk reduction in the casirivimab+imdevimab group compared to placebo during the first week (OR 0.27 [0.126, 0.564], nominal p=0.0005 [post-hoc analysis])

Table 50: Onset of symptomatic infection during EAP (seronegative mFAS-A)

	Placebo (N=752)	REGN10933+ REGN10987 (N=753)	Risk Reduction	Nominal P-value[1]
Number of subjects with symptomatic infection during the EAP	59/752 (7.8%)	11/753 (1.5%)		
First symptomatic infection occurring during:				
Within week 1	32/752 (4.3%)	9/753 (1.2%)	71.9%	0.0005
Weeks 2 to 4	27/752 (3.6%)	2/753 (0.3%)	92.6%	0.0003

Note: For the first step analysis, the data cutoff date is 11Mar2021.
Week 1 corresponds to study day 1 to day 7; weeks 2 to 4 corresponds to day 8 to end of EAP.
1. Odds ratio was provided for the analysis among all participants. The CI with p-value is based on the odds ratio (REGN10933+REGN10987 group vs placebo group) using a logistic regression model with the fixed categorical effects of treatment group, age group (age in years:>=12 to<50 and >=50), and region (US vs ex-US).

Efficacy was apparent up to day 29 and most infections appeared to occur within the first week after administration of product.

Sensitivity analyses and subgroup analyses were generally supportive towards the primary endpoint.

Sensitivity analysis
To assess the impact of participants who may have had an undetected infection prior to dosing, a sensitivity analysis was performed by excluding participants who developed asymptomatic or symptomatic SARS-CoV-2 infection within 72 hours of study drug administration. The results of the sensitivity analysis were consistent with the main analysis (OR 0.18 [0.091, 0.338], nominal p<0.0001) (seronegative mFAS-A).

Subgroup analyses
Subgroup analyses were conducted for the primary endpoint in cohort A to assess the consistency of results in participants with different demographic or other baseline characteristics.

Results demonstrated a consistent treatment effect of casirivimab+imdevimab across subpopulations, including subgroups based on age; race and ethnicity; gender, BMI, and region; risk factors, as defined, and household size.

The various subgroup analyses favour exposure to the current product and are generally supportive towards the primary endpoint. In particular, age does not appear to affect general outcome. Healthcare workers demonstrate wide confidence interval as may be expected for those who are likely exposed to the pathogen.

Key secondary endpoints (seronegative mFAS-A)
Seven key secondary endpoints were assessed during the efficacy assessment period of 29 days, the endpoints are presented below.

1. Proportion of participants developing viral load >4 (log_{10} copies/mL) in nasopharyngeal swab samples
The risk of developing a high viral load infection (>4 log_{10} copies/mL) was reduced by 85.8% in the casirivimab+imdevimab group compared to placebo ($p<0.0001$). Therefore, the key secondary endpoint of reduced proportion of participants developing viral load >4 (log_{10} copies/mL) in nasopharyngeal swab samples during the efficacy analysis period was met [there was a (11.3 – 1.6) = 9.7% reduction in outcome]

2. Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term)
Treatment with casirivimab+imdevimab reduced the cumulative duration of symptomatic infection (by broad-term definition) by 93.1% compared to placebo ($p<0.0001$).

Cumulative duration included the total number of weeks (up to the data cutoff date) for all participants in each treatment arm in which infected participants reported Covid-19 symptoms, and this reduction reflected both a lower incidence and a shorter duration of symptomatic infection.

Of the 59/752 (7.8%) participants in the placebo group and the 11/753 (1.5%) participants in the casirivimab+imdevimab group who had symptomatic infection during the EAP, the mean duration of symptomatic infection per participant was 3.18 weeks and 1.17 weeks, respectively, which corresponded to a difference of approximately 2 fewer weeks for those who received casirivimab+imdevimab.

3. Number of weeks of high viral load >4 (log_{10} copies/mL) in nasopharyngeal swab samples during the efficacy analysis period
The cumulative duration of high viral load infection was reduced by 89.6% in the casirivimab + imdevimab group compared to placebo ($p<0.0001$).

Of the 107/749 (14.3%) participants in the placebo group and the 36/745 (4.8%) participants in the casirivimab+imdevimab group who developed SARS-CoV-2 infection (i.e., had a positive RT-qPCR result) during the EAP, the mean duration of high viral load per participant was 1.27 weeks and 0.39 weeks for placebo and active treatment, respectively. This corresponded to a difference of approximately 6 fewer days for those who received casirivimab+imdevimab.

4. Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the efficacy analysis period
The cumulative duration of detectable SARS-CoV-2 infection (of any magnitude) was reduced by 82.3% in the casirivimab+imdevimab group compared to placebo ($p<0.0001$).

Of the 107/752 (14.2%) participants in the placebo group and the 36/753 (4.8%) participants in the casirivimab+imdevimab group who developed SARS-CoV-2 infection during the EAP, the mean duration of infection per participant was 2.16 weeks and 1.14 weeks, respectively, which corresponded to approximately 1 fewer week for those who received casirivimab+imdevimab.

5. Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the efficacy analysis period

Treatment with casirivimab+imdevimab reduced the overall relative risk of SARS-CoV-2 infection (with or without symptoms) by 66.4% compared to placebo during the EAP ($p<0.0001$).

The cumulative incidence of SARS-CoV-2 infection diverged between the treatment groups by day 8 (i.e., the first post-baseline NP swab sample collection), and a reduced incidence compared to placebo was maintained in the casirivimab+imdevimab group through to day 29.

6. Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the efficacy analysis period with an index case participating in study R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 versus placebo in Study 2067)
Of the participants who developed SARS-CoV-2 infection following exposure to an index case who was participating in Study COV-2067, the proportion of index cases who received treatment with casirivimab+imdevimab vs placebo was balanced within each treatment group (seronegative mFAS-A).

No interaction was observed as the proportion of infected participants in the placebo group in this study was similar regardless of whether the index case received casirivimab+imdevimab or placebo in Study COV-2067 (10/51 [19.6%] vs 23/116 [19.8%] participants, respectively; p=1.0000).

Treatment of the index case with casirivimab+imdevimab in Study COV-2067 therefore did not reduce infections in the household contact participants in the placebo group in cohort A. This endpoint was not met.

Cohort B
A total of 311 participants in cohort B received a dose of study treatment.

In the casirivimab+imdevimab group, the dose (consisting of 4 injections) was not fully administered for 1/155 (0.6%) participant due to an AE of ISR which was mild in severity and resolved on the same day.

Study drug was administered per protocol for all other participants. Overall, more than 99% of participants were observed for more than 4 weeks. Approximately 6% have been observed for more than 28 weeks.

The end of study visit occurred at week 32 and data collection is ongoing.

Primary endpoint
Treatment with casirivimab+imdevimab reduced the risk of progression to symptomatic disease by 31.5% compared to placebo (p=0.0380) (table 51). The primary endpoint was met [there was a (42.3 – 29.0) = 13.3% reduction in outcome, p=0.04; this is acceptable [the p-value is noticeably smaller compared to cohort A].

Table 51: Proportion of participants who subsequently develop signs and symptoms (broad-term) with and onset within 14 days of a positive RT-qPCR at baseline or during the EAP (seronegative mFAS-B)

Symptomatic Infection	Placebo (N=104)	REGN10933+ REGN10987 (N=100)
Broad-term definition, central RT-qPCR test (primary)	44/104 (42.3%)	29/100 (29.0%)
Risk reduction vs Placebo		31.5%
Odds ratio estimate (drug vs placebo) [1]		0.54
95% CI		(0.298 to 0.966)
p-value vs placebo		0.0380

Note: For the first step analysis, the data cutoff date is 11Mar2021.
If a visit with a missing central lab RT-qPCR result had a local confirmatory positive RT-qPCR for a subject with a COVID-19 symptom occurring within 14 days, that visit was considered to have a positive RT-qPCR result.
1. The CI with p-value is based on the odds ratio (casirivimab+imdevimab group vs placebo group) using a logistic regression model with the fixed categorical effects of treatment group, age group (age in years:>=12 to <50 and >=50), and region (US vs ex-US).

A consistent treatment was observed in a post-hoc analysis performed in participants regardless of baseline serology, with a 35.4% risk reduction compared to placebo (OR 0.54 [0.325, 0.894], nominal p=0.0166). A comparable level of reduction was also shown when the analysis included only baseline-positive participants (33.9% risk reduction vs placebo, OR 0.62 [0.147, 2.587], nominal p=0.5079).

It was not possible to accept that efficacy was met by those who were seropositive at baseline because the odds ratio has broad 95% confidence intervals that cross 1.0 and p is >0.5.

Treatment benefit was observed as early as day 4 and was maintained through day 29.

The cumulative symptomatic infection rate (for both active and placebo groups) was noticeably higher than the corresponding analysis for the mFAS cohort A population and the difference between active and placebo groups for the mFAS cohort B population appeared much less apparent than for the mFAS cohort A population. This is not unexpected if the +ve PCR test at baseline for cohort B reflects acute infection (whereas cohort A does not have laboratory evidence of acute infection at baseline).

Sensitivity analysis
The prespecified sensitivity analysis for cohort B was conducted by excluding participants from non-GCP compliant sites; results were consistent with the main analysis (p=0.0410).

Subgroup analyses
Subgroup analyses were conducted for the primary endpoint in cohort B. While event numbers were small in some of the subgroups, results generally showed a consistent treatment effect of casirivimab +imdevimab across subpopulations with different baseline characteristics, including age; race and ethnicity; gender, BMI, and region; risk factors, as defined, and household size. In general, the sensitivity and subgroup analyses support the primary endpoint.

Key secondary endpoints
1. Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the efficacy analysis period
Treatment with casirivimab+imdevimab reduced the duration of symptomatic infection (by broadterm definition) by 45.3% compared to placebo (p=0.0273).

Of the 44/104 (42.3%) participants in the placebo group and the 29/100 (29.0%) participants in the casirivimab+imdevimab group who had symptomatic progression during the EAP, the mean duration of symptomatic infection per participant was 3.9 weeks and 3.1 weeks for placebo and active treatment, respectively. This corresponded to a difference of approximately 5.6 fewer days for those who received casirivimab+imdevimab. The endpoint is met.

2. Number of weeks of high viral load >4 (log_{10} copies/mL) in nasopharyngeal swab samples during the efficacy analysis period
The cumulative duration of high viral load infection was shorter by 39.7% after treatment with casirivimab+imdevimab compared to placebo (p=0.0010). Of the 63/101 (62.4%) participants in the placebo group and the 40/98 (40.8%) participants in the casirivimab+imdevimab group who had high viral loads during the EAP, the duration of high viral load per participant was 1.3 weeks and 1.2 weeks, respectively.

Supportive studies 20145 and HV2093
Study 20145
A randomized, double-blind, placebo-controlled, parallel group study to assess the dose response profile of single intravenous (IV) or single subcutaneous (SC) doses of REGN10933+REGN10987 in 1400 outpatients with SARS-CoV-2 infection. This study has been previously described in table 25.

The primary objective of the study was to assess the virologic efficacy of REGN10933+REGN10987 across different intravenous and subcutaneous doses compared to placebo.

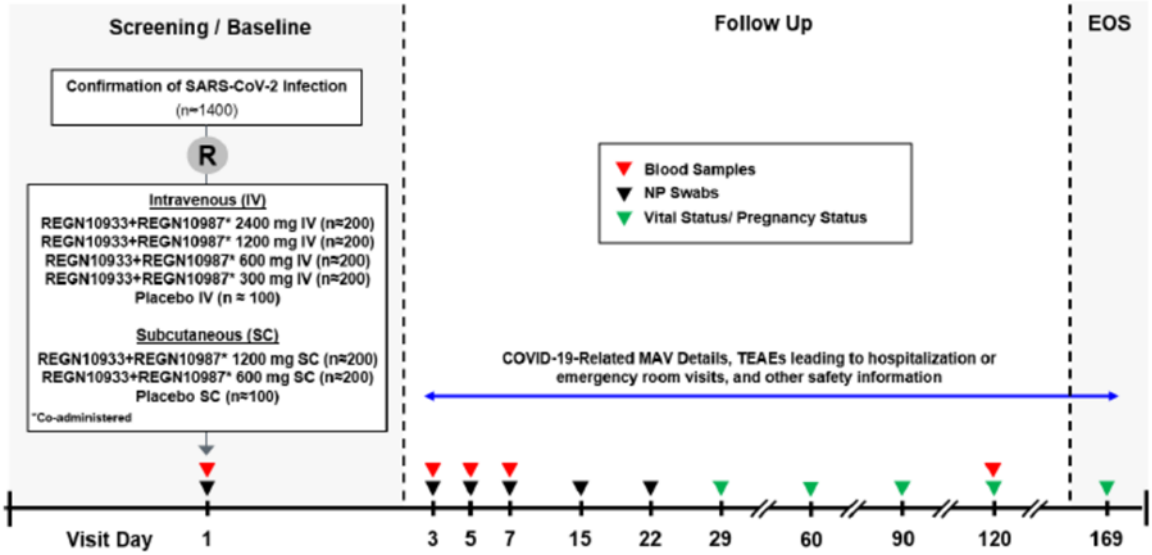
The primary endpoint was time-weighted average daily change from baseline in rial load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in nasopharyngeal (NP) swab samples, in patients who have a RT-qPCR positive test and are seronegative at baseline.

The following treatment arms were included in the study: 2400 mg IV, 1200 mg IV, 1200 mg SC, 600 mg IV, 600 mg SC, 300 mg IV, placebo IV, and placebo SC. Randomization occurred within 72 hours of obtaining a positive SARS-CoV-2 diagnostic test sample.

On the day of dosing, patients had NP swabs taken for SARS-CoV-2 RT-qPCR testing and blood drawn for safety, drug concentration, immunogenicity, and serologic analyses. After study drug administration, patients had a post-dose blood collection (either at the end of intravenous infusion or at least 1 hour after subcutaneous administration).

Demographic characteristics, baseline virology and disease characteristics in the mFAS seronegative patients were similar across all treatment groups. Mean age of participants was about 33yrs, 45% were male and about 96% had a body mass index <30kg/m2.

Figure 33: Study flow diagram



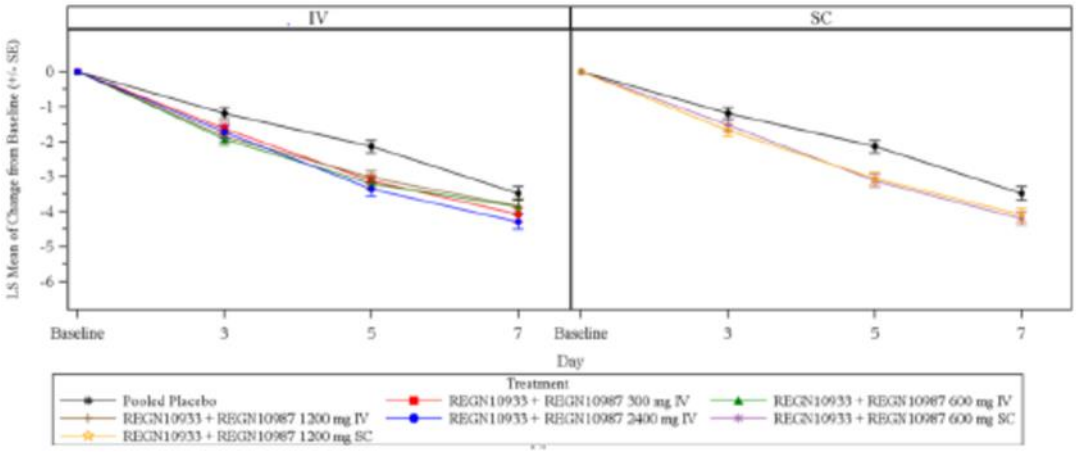
Results

Comparable results for all doses were observed for the primary endpoint of time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in nasopharyngeal (NP) swab samples, in patients with a central-lab determined SARSCoV-2 positive RT-qPCR test and seronegative at baseline. The various presentations appeared to result in comparable outcome in terms of reduction of viral load.

Table 52: Study COV-20145, time-weighted average change in viral load in NP samples from baseline in viral load from day 1 to day 7 (seronegative mFAS)

Comparison	LS Mean	95% CI	p-value
2400 mg IV vs Pooled Placebo (n=61 vs n=74)	-0.71	(-1.05, -0.38)	<0.0001
1200 mg IV vs Pooled Placebo (n=67 vs n=74)	-0.56	(-0.89, -0.24)	0.0007
1200 mg SC vs Pooled Placebo (n=71 vs n=74)	-0.56	(-0.87, -0.24)	0.0007
600 mg IV vs Pooled Placebo (n=66 vs n=74)	-0.66	(-0.99, -0.34)	<0.0001
600 mg SC vs Pooled Placebo (n=71 vs n=74)	-0.56	(-0.88, -0.24)	0.0006
300 mg IV vs Pooled Placebo (n=76 vs n=74)	-0.57	(-0.88, -0.25)	0.0004

Figure 34: COV-20145, LS mean (±SE) change from baseline viral load (log_{10} copies/mL) side-by-side comparison of IV and SC (seronegative mFAS)



Study HV2093

The study was designed to assess the safety and tolerability of multiple SC doses of casirivimab+imdevimab in adult volunteers who are SARS-CoV-2 negative at baseline.

Participants were randomized in a 3:1 ratio to receive up to 6 SC doses of casirivimab+imdevimab combination therapy or placebo.

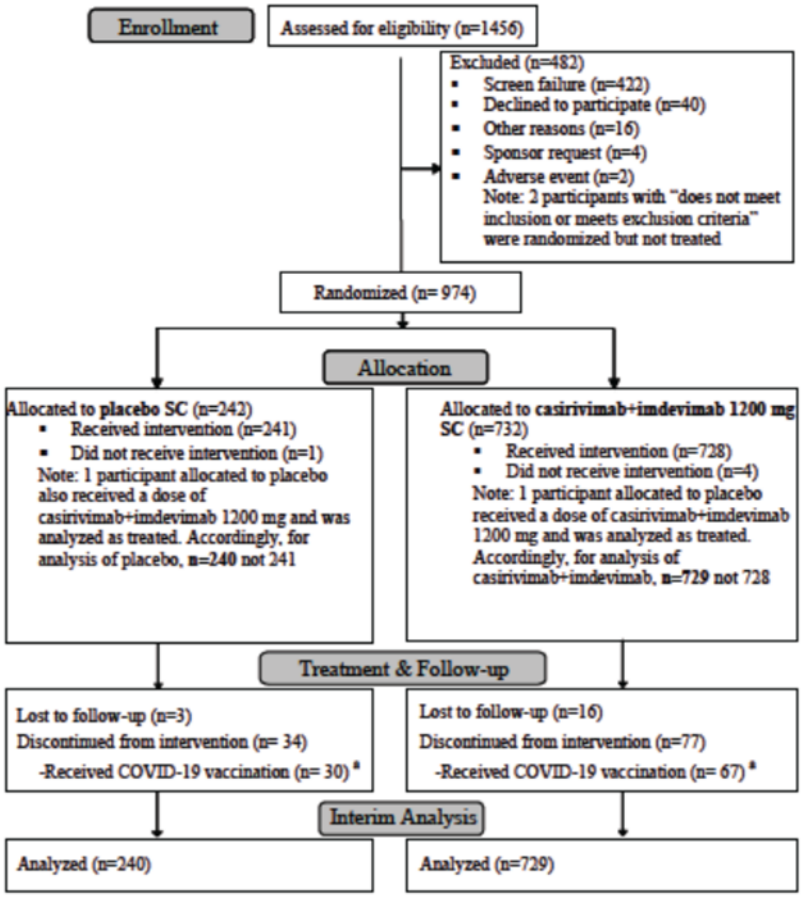
The primary objective was to assess the occurrence of adverse events of special interest (AESIs) in participants treated with repeated SC doses of casirivimab+imdevimab compared to placebo; and to assess the concentrations of casirivimab and imdevimab in serum over time after single and repeated SC administration.

The endpoints were incidence of AESIs that occur within 4 days of SC administration of casirivimab+imdevimab or placebo at baseline and days 29, 57, 85, 113, and 141; and concentrations of casirivimab+imdevimab in serum over time.

The study design has been previously described in table 25 and Section IV.

Population
Healthy adults (or adults with chronic but stable and well-controlled medical condition) who were negative for SARS-CoV-2 infection at screening. A total of 1456 adults were screened. The numbers lost to follow-up or discontinuations appeared similar across groups.

Figure 35: Participant disposition



A total of 111 participants (11.5%) discontinued from study treatment, of which 53 (5.5%) participants discontinued from the study. The most common reason for discontinuation from both study treatment (7.6%) and from study (2.9%) was participant decision.

Demographics
This interim report refers to the safety population of 969 subjects: 240 placebo; 729 active. Mean age of participants was 47yrs (SD 14), 55% male, 87% white and mean body mass

index 29.4 kg/m2 (SD 6.4).

Study treatment
Study drug treatment was administered as 4 SC injections (2.5 mL each) per dose, given Q4W for up to 6 dose administrations during the treatment period. As of the data cut-off for this interim report, approximately 60% of participants in each treatment group had received all 6 doses, and more than 80% of all participants had received at least 5 doses.

The mean treatment duration was approximately 20 weeks and the mean observation period was approximately 24 weeks for both the placebo group and casirivimab+imdevimab 1200 mg group.

Mean study drug administration compliance was high at 96.83% for the placebo group and 97.89% for the casirivimab+imdevimab 1200 mg group.

Results
Incidence of symptomatic SARS-CoV-2 infection during the entire study period
There was a 92.4% relative risk reduction in symptomatic SARS-CoV-2 infection with casirivimab+imdevimab 1200 mg compared to placebo during the entire study period (table 53).

Table 53: Proportion of participants with symptomatic Covid-19 infection during the entire period (SAF)

	Placebo (N=240)	R10933+R10987 1.2g SC (N=729)
Subjects with symptomatic SARS-CoV-2 infections [1]	13 (5.4%)	3 (0.4%)
Risk reduction of symptomatic SARS-CoV-2 infections		92.40 %
Odds ratio estimate (drug vs placebo)		0.07
95% CI [2]		(0.01 to 0.27)
p-value vs Placebo [3]		<.0001

Data cutoff date is 13MAR2021.
[1] Symptomatic SARS-CoV-2 infection was defined clinically by the investigator and reported as an AE; RT-PCR testing was not required
[2] CI: confidence interval; the 95% exact CI is provided
[3] nominal p-value from Fisher's exact test is provided
Included are events that were reported before the COVID-19 vaccination date, if any.

The absolute risk reduction = (5.4 – 0.4) = 5%. Results were similar for the treatment period of the study. It was considered that results support efficacy.

Proportion of baseline anti-SARS-CoV-2 seronegative participants with post- baseline positive serology (anti-N protein) through the end of study
Of those who had an anti-SARS-CoV-2 negative serology test at baseline (approximately 67% in both treatment groups), 8 of 162 (4.9%) participants in the placebo group converted to a positive serology result by the end of the entire study period, whereas none of the 487 participants in the casirivimab+imdevimab group who were seronegative at baseline converted to seropositive, which corresponds to a 100% risk reduction (odds ratio 0.00 [95% CI: 0.00, 0.15]).

Additionally, of those who had a negative SARS-CoV-2-RT-PCR result at baseline, 5 of 238 (2.1%) participants in the placebo group subsequently had a positive SARS-CoV-2-RT-PCR result during the study period, whereas none of the 719 participants in the casirivimab+imdevimab group with a negative baseline SARS-CoV-2-RT-PCR test result

had a positive result during the study period.

Overall, the efficacy data are consistent with the efficacy data of the main clinical studies submitted.

IV.5 Clinical safety

Study 2067

The safety analysis set contained 6311 subjects; mean age 45yrs (SD 15); 90% <65yrs; 49% male; 85% white; mean body mass index 30 kg/m2 (SD 6.8); 65% seronegative, 27% seropositive, 8% 'other'; mean time from symptom onset to randomisation 4 days (SD 47).

Most subjects were <65yrs and 'white'; only 2.8% subjects were >75yrs.

A total of 99% subjects were administered the infusion without interruption and 99% received the total planned dose. The median duration of infusion was 60 minutes and infusion time was balanced across treatment groups.

Treatment-emergent adverse events

A 'targeted' assessment of safety was employed in order to reduce burden during the pandemic. The selected categories of TEAEs to be reported in the study were designed to provide the most relevant safety information to adequately evaluate the safety and tolerability of casirivimab + imdevimab and differed according to study phase; they were modified with protocol amendments and consisted of the following select, targeted safety TEAEs.

- Cohort 1, phase 1 only: all grade ≥3 TEAEs
- All cohorts, all phases: treatment-emergent SAEs, grade ≥2 hypersensitivity reactions, grade ≥2 infusion-related reactions, TEAE that led to a medically attended visit regardless of Covid-19 relatedness.

Table 54: Summary of targeted safety collection described in this report

	Screening/Baseline/ Post-Dose	Through Day 4	Through Day 29	Through Day 169
Serious Adverse Events (SAEs)				
Phase 1	X	X	X	
Phase 2	X	X	X	
Phase 3, pre PA6	X	X	X	
Phase 3, post PA6	X	X	X	X[1]
Adverse Events of Special Interest (AESI): Hypersensitivity Reactions and IRRs				
All phases, Hypersensitivity reactions	X	X	X	
All phases, IRRs	X	X		
AESI: Treatment-Emergent Adverse Events Requiring Medical Attention at a Healthcare Facility (Regardless of COVID-19 Relatedness)				
Phase 3, post PA7	X	X	X	
Grade 3 & 4 Treatment-Emergent Adverse Events (TEAEs)				
Phase 1	X	X	X	

PA, Protocol Amendment

[1] Only SAEs deemed related to study drug as per investigator's assessment.

TEAEs outside of the selected TEAE categories were voluntarily reported for some participants by some sites; these events were retained in the database and are summarized in the overview tables. An overview of TEAEs from day 1 to the last available data is presented below.

Table 55: Overview of treatment-emergent adverse events from last available data – pooled phase 1, 2, and 3 cohort 1 (symptomatic patients) – (SAF)

		R10933+R10987				
	Placebo (N=2105)	1200 mg IV (N=827)	2400 mg IV (N=2107)	8000 mg IV (N=1272)	Combined (N=4206)	Total (N=6311)
Total number of TEAE [1]	328	93	269	131	493	821
Total number of grade 3 or 4 TEAE	85	15	28	25	68	153
Total number of TE SAE	100	12	36	27	75	175
Total number of TE AESI	64	24	31	24	79	143
Total number of TE serious AESI	6	1	1	4	6	12
Patients with any TEAE	205 (9.7%)	59 (7.1%)	155 (7.4%)	91 (7.2%)	305 (7.3%)	510 (8.1%)
Patients with any grade 3 or 4 TEAE	67 (3.2%)	11 (1.3%)	21 (1.0%)	17 (1.3%)	49 (1.2%)	116 (1.8%)
Patients with any TE SAE	80 (3.8%)	9 (1.1%)	28 (1.3%)	19 (1.5%)	56 (1.3%)	136 (2.2%)
Patients with any TE AESI	53 (2.5%)	17 (2.1%)	29 (1.4%)	18 (1.4%)	64 (1.5%)	117 (1.9%)
Patients with TE AESI of infusion-related reactions (grade ≥2) through day 4	1 (<0.1%)	2 (0.2%)	1 (<0.1%)	7 (0.6%)	10 (0.2%)	11 (0.2%)
Patients with at least one TE AESI of hypersensitivity reactions (grade ≥2) through day 4	2 (<0.1%)	0	1 (<0.1%)	0	1 (<0.1%)	3 (<0.1%)
Patients with at least one TE AESI of hypersensitivity reactions (grade ≥2) through last available data	3 (0.1%)	0	1 (<0.1%)	0	1 (<0.1%)	4 (<0.1%)
Patients with at least one TE AESI of hypersensitivity reactions (grade ≥2) from day 30 through last available data	0	0	0	0	0	0
Patients with TE AESI of event that led to a MAV through last available data	50 (2.4%)	15 (1.8%)	27 (1.3%)	11 (0.9%)	53 (1.3%)	103 (1.6%)
Patients with TE AESI of event that led to a MAV from day 30 through last available data	1 (<0.1%)	0	1 (<0.1%)	0	1 (<0.1%)	2 (<0.1%)
Patients with any TE serious AESI	6 (0.3%)	1 (0.1%)	1 (<0.1%)	1 (<0.1%)	3 (<0.1%)	9 (0.1%)
Patients with SAE TE AESI of infusion-related reactions (grade ≥2) [2] through day 4	0	0	0	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Patients with SAE TE AESI of hypersensitivity reactions (grade ≥2) through last available data	0	0	0	0	0	0
Patients with SAE TE AESI of hypersensitivity reactions (grade ≥2) from day 30 through last available data	0	0	0	0	0	0
Patients with SAE TE AESI of event that led to a MAV through last available data	6 (0.3%)	1 (0.1%)	1 (<0.1%)	0	2 (<0.1%)	8 (0.1%)
Patients with SAE TE AESI of event that led to a MAV from day 30 through last available data	1 (<0.1%)	0	0	0	0	1 (<0.1%)
Patients with any TEAE leading to death	5 (0.2%)	1 (0.1%)	1 (<0.1%)	0	2 (<0.1%)	7 (0.1%)
Patients with any TEAE leading to withdrawal from the study	4 (0.2%)	0	2 (<0.1%)	1 (<0.1%)	3 (<0.1%)	7 (0.1%)
Patients with any TEAE leading to study infusion interruption [3]	1 (<0.1%)	1 (0.1%)	0	2 (0.2%)	3 (<0.1%)	4 (<0.1%)
Patients with any TEAE leading to study infusion discontinuation [4]	1 (<0.1%)	0	1 (<0.1%)	3 (0.2%)	4 (<0.1%)	5 (<0.1%)

Randomized patients through 17 Jan 2021. Data cutoff date is 18 Feb 2021.

TEAE = Treatment- Emergent Adverse Event. AESI = Adverse Event of Special Interest. SAE = Serious Adverse Event, MAV=Medically attended visit includes physician's office visit, telemedicine, urgent care visit, hospitalizations, or emergency room (ER) visit regardless of whether the visit was related to COVID-19. MedDRA (Version 23.1) coding dictionary applied.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the observation period which is from the time of study drug administration to the last study visit.

[1] TEAEs collected include TE SAEs, AESIs and grade 3/4TEAEs, as well as ad-hoc/voluntarily reported TEAEs by some sites.

[2] TEAEs deemed treatment-related as per investigator assessment.

[3] Infusion interruption: the administration of the infusion was interrupted before being completed, but subsequently was re-started and the full planned dose was administered.

[4] Infusion discontinuation: the administration of the infusion was stopped before being completed, and the full planned dose was not administered

Overall, a higher percentage of participants in the placebo group than in any casirivimab+imdevimab group experienced a grade 3 or 4 TEAE, treatment-emergent SAE, or TEAE leading to a medically attended event regardless of Covid-19 relatedness.

Across all treatment groups, ≤0.2% of participants experienced AESIs of grade 2 or greater hypersensitivity reaction or infusion related reaction, fatal SAEs, or TEAEs that led to withdrawal from the study, study infusion interruption, or study infusion discontinuation.

The percentage of participants who experienced any treatment-emergent AESI was also numerically higher in the placebo group compared to the casirivimab+imdevimab treatment groups. However, more participants in the casirivimab+imdevimab 8000 mg group experienced a greater number of treatment-emergent AESIs of infusion-related reactions (IRR) (grade ≥2) relative to any other casirivimab+imdevimab treatment group and relative to the placebo group.

Table 56: Summary of grade 3 and grade 4 treatment-emergent adverse events by system organ class and preferred term from day 1 to day 169 experienced by >1 participant in any treatment group – pooled phase 1, 2, and 3 cohort 1 (symptomatic patients) (SAF)

		R10933+R10987				
Primary System Organ Class Preferred Term	**Placebo (N=2105)**	**1200 mg IV (N=827)**	**2400 mg IV (N=2107)**	**8000 mg IV (N=1272)**	**Combined (N=4206)**	**Total (N=6311)**
Number of grade 3/4 TEAEs	85	15	28	25	68	153
Number of patients with at least one grade 3/4 TEAE	67 (3.2%)	11 (1.3%)	21 (1.0%)	17 (1.3%)	49 (1.2%)	116 (1.8%)
Infections and infestations	45 (2.1%)	4 (0.5%)	11 (0.5%)	9 (0.7%)	24 (0.6%)	69 (1.1%)
COVID-19 pneumonia	15 (0.7%)	1 (0.1%)	5 (0.2%)	4 (0.3%)	10 (0.2%)	25 (0.4%)
COVID-19	17 (0.8%)	1 (0.1%)	3 (0.1%)	3 (0.2%)	7 (0.2%)	24 (0.4%)
Pneumonia	17 (0.8%)	3 (0.4%)	1 (<0.1%)	1 (<0.1%)	5 (0.1%)	22 (0.3%)
Respiratory, thoracic and mediastinal disorders	16 (0.8%)	1 (0.1%)	4 (0.2%)	7 (0.6%)	12 (0.3%)	28 (0.4%)
Dyspnoea	5 (0.2%)	1 (0.1%)	0	2 (0.2%)	3 (<0.1%)	8 (0.1%)
Acute respiratory failure	4 (0.2%)	0	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)	6 (<0.1%)
Hypoxia	6 (0.3%)	0	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)	8 (0.1%)

Randomized patients through 17 Jan 2021. Data cutoff date is 18 Feb 2021.
TEAE = Treatment-Emergent Adverse Event. MedDRA (Version 23.1) 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 ordered by decreasing frequency in Combined active treatment column. Within each SOC, Preferred Terms are sorted by decreasing frequency.

Grade 3 or 4 TEAE were 3.2% in the placebo group and 1.2% in the combined group.

Deaths
Overall, the incidence of deaths was low, with more participants in the placebo group compared to any casirivimab+imdevimab groups experiencing a fatal event from day 1 to last available data cut (5 in the placebo group and 1 each in the 1200 mg and 2400 mg group).

Most deaths (5 of 7) occurred prior to day 29. All were considered not related to study treatment by the investigator and most were considered related to advanced and progressive Covid-19 disease or due to complications of participant-specific concurrent medical conditions.

Serious adverse events
The incidence of serious TEAEs from day 1 to last available data cut was higher in the placebo group compared to the casirivimab+imdevimab groups (3.8% in placebo versus 1.1% in casirivimab + imdevimab 1200 mg group, 1.3% in casirivimab+imdevimab 2400 mg group, and 1.5% in casirivimab + imdevimab 8000 mg group). This was driven by a higher incidence of TEAEs in the infections and infestations SOC, with a higher incidence of Covid-19, Covid-19 pneumonia, and pneumonia in the placebo group compared to any casirivimab+imdevimab group, and by a higher incidence TEAEs in the respiratory, thoracic and mediastinal disorders SOC, driven by a higher incidence of dyspnoea and hypoxia in the placebo group compared to any casirivimab+imdevimab groups

Most SAEs were considered not related to study treatment; only 2 participants reported treatment-emergent SAEs from day 1 to day 29 that were considered related to study treatment: nausea, vomiting, hyporesponsive to stimuli, hyperhidrosis in another participant. No treatment-related SAEs were reported after day 29.

Adverse events of special interest
Throughout the study, treatment-emergent AESI (serious and nonserious), were defined as:
- Grade ≥2 infusion-related reactions (IRRs), up to study day 4
- Grade ≥2 hypersensitivity reactions, up to study day 29

The incidence of grade 2 infusion-related reactions was more common in the active arm.

A total of 3 participants (0.1%) experienced a grade ≥2 hypersensitivity reaction in the placebo group, compared to only 1 participant (<0.1%) in the combined casirivimab+imdevimab treatment group (casirivimab+imdevimab 2400 mg group).

Subgroup analysis of TEAEs
Using the safety population, subgroup analyses of safety data were performed for SAEs and AESIs for the following parameters: baseline age group, gender, ethnicity, race, baseline obesity status, baseline status for kidney disease, liver disease, diabetes, cardiovascular disease, chronic respiratory conditions, immunosuppressive disease and concomitant immunosuppressive treatment.

Serious TEAEs were more common in those >65yrs and those with a body mass index >30kg/m2 who were administered placebo. Similarly, those with kidney disease, liver disease, cardiovascular disease and immunosuppressive disease are more likely to experience a serious TEAE (related to Covid-19 disease) when administered placebo compared to active [with the caveat that the numbers of patients reported upon is small].

Safety conclusion
The main element of safety relates to infusion-related reactions; it is considered that the safety profile may be managed from a clinical perspective.

Study COV-2066
Only select TEAEs were collected in this study (cohort 1, phase 1 only: all grade ≥3 TEAEs; all cohorts, all phases: treatment-emergent SAEs, treatment-emergent grade ≥2 hypersensitivity reactions and grade ≥2 infusion-related reactions). Grade 3 and 4 TEAEs in cohorts 2 and 3 were either reported voluntarily or were SAEs.

Adverse events of special interest (AESI) were: grade ≥2 hypersensitivity reactions and grade ≥2 infusion-related reactions.

The study population of hospitalized participants with Covid-19 was expected to have a complicated disease presentation at baseline that could quickly and unexpectedly deteriorate. Accurately collecting a large volume of TEAEs expected from this population could impose unnecessary burden on an already over-strained healthcare system; therefore, the selected categories of TEAEs to be reported were expected to provide the most relevant safety information to adequately evaluate the safety and tolerability of casirivimab+imdevimab.

Cohort 1, phases 1 and 2 - overview of treatment-emergent adverse events
Adverse events of special interest were more evident in those exposed to active versus placebo. In other respects, the safety profile of active appeared similar to placebo (in this focused collection of safety data).

Table 57: Cohort 1, phases 1 and 2 - overview of treatment-emergent adverse events (SAF) for the safety analysis population

	Placebo (N=222)	R10933+R10987 2400 mg IV (N=224)	R10933+R10987 8000 mg IV (N=225)	R10933+R10987 Combined (N=449)	Total (N=671)
Total number of TEAE	104	84	111	195	299
Total number of grade 3 or 4 TEAE	72	51	65	116	188
Total number of SAE	97	73	84	157	254
Total number of AESI	6	5	11	16	22
Total number of serious AESI	3	1	4	5	8
Patients with any TEAE	59 (26.6%)	53 (23.7%)	56 (24.9%)	109 (24.3%)	168 (25.0%)
Patients with any grade 3 or 4 TEAE	45 (20.3%)	34 (15.2%)	36 (16.0%)	70 (15.6%)	115 (17.1%)
Patients with any SAE	54 (24.3%)	45 (20.1%)	47 (20.9%)	92 (20.5%)	146 (21.8%)
Patients with any AESI	4 (1.8%)	4 (1.8%)	7 (3.1%)	11 (2.4%)	15 (2.2%)
Patients with any serious AESI	1 (0.5%)	1 (0.4%)	3 (1.3%)	4 (0.9%)	5 (0.7%)
Patients with infusion-related reactions (grade >=2) through day 4	3 (1.4%)	2 (0.9%)	6 (2.7%)	8 (1.8%)	11 (1.6%)
Patients with hypersensitivity reactions (grade >=2) through day 4	0	0	1 (0.4%)	1 (0.2%)	1 (0.1%)
Patients with hypersensitivity reactions (grade >=2) through day 29	1 (0.5%)	2 (0.9%)	2 (0.9%)	4 (0.9%)	5 (0.7%)
Patients with any TEAE leading to death	22 (9.9%)	21[a] (9.4%)	20 (8.9%)	41 (9.1%)	63 (9.4%)
Patients with any TEAE leading to withdrawal from the study	0	0	2 (0.9%)	2 (0.4%)	2 (0.3%)
Patients with any TEAE leading to study infusion interruption	0	0	1 (0.4%)	1 (0.2%)	1 (0.1%)

a. One participant had an AE leading to death that started prior to treatment and hence was not captured as a TEAE.
Data snapshot is 20DEC2020. Randomized patients through 01DEC2020. Data cutoff on 09DEC2020.
TEAE = Treatment- Emergent Adverse Event. AESI = Adverse Event of Special Interest. SAE = Serious Adverse Event.
Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the observation period which is from the time of study drug administration to the last study visit.
MedDRA (Version 23.0) coding dictionary applied.

Grade 3 and 4 treatment-emergent adverse events. cohort 1 (phases 1 and 2)
A greater percentage of participants in the placebo group (20.3% [45/222]) experienced grade 3 and 4 TEAEs than in any casirivimab+imdevimab dose group (2400 mg: 15.2% [34/224]; 8000 mg: 16.0% [36/225]). The imbalance in grade 3 and grade 4 TEAEs was driven by more participants in the placebo group (4.5% [10/222]) experiencing Hypoxia compared to participants in either casirivimab+imdevimab dose group (2400 mg: 2.2% [5/224] and 8000 mg: 2.2% [5/225]).

TEAEs leading to death cohort 1 (phases 1 and 2)
In cohort 1 (phases 1 and 2), the percentages of participants with at least 1 TEAE leading to death was numerically higher in the placebo group (9.9% [22/222]) compared to the casirivimab+imdevimab 2400 mg (9.4% [21/224]) and casirivimab+imdevimab 8000 mg dose groups (8.9% [20/225].

The majority of the TEAEs reported were in the Respiratory, thoracic and mediastinal disorders and Infections and infestations system organ class (SOC), which was consistent with the participant population having advanced Covid-19 disease and rapid progression resulting in cardio-respiratory failure and a fatal outcome.

Serious adverse events cohort 1 (phases 1 and 2)
In cohort 1 (phases 1 and 2), the frequency of SAEs was higher in the placebo group compared to the casirivimab+imdevimab 2400 mg and 8000 mg groups. The incidence of Respiratory failure and Hypoxia were comparatively higher in the placebo group compared to the casirivimab+imdevimab groups (table 58). The SAEs reported were generally suggestive of advanced and progressive Covid-19 disease, its complications, or worsening of participants' concurrent medical conditions due to Covid-19.

Table 58: Cohort 1, phases 1 and 2 - overview of treatment-emergent serious adverse events by SOC and PT in >1 participant (SAF)

Primary System Organ Class Preferred Term	Placebo (N=222)	R10933+R10987 2400 mg IV (N=224)	R10933+R10987 8000 mg IV (N=225)	R10933+R10987 Combined (N=449)	Total (N=671)
Number of Serious TEAEs	97	73	84	157	254
Number of patients with at least 1 Serious TEAE	54 (24.3%)	45 (20.1%)	47 (20.9%)	92 (20.5%)	146 (21.8%)
Respiratory, thoracic and mediastinal disorders	29 (13.1%)	22 (9.8%)	22 (9.8%)	44 (9.8%)	73 (10.9%)
Acute respiratory failure	6 (2.7%)	8 (3.6%)	6 (2.7%)	14 (3.1%)	20 (3.0%)
Respiratory failure	9 (4.1%)	4 (1.8%)	6 (2.7%)	10 (2.2%)	19 (2.8%)
Hypoxia	8 (3.6%)	3 (1.3%)	7 (3.1%)	10 (2.2%)	18 (2.7%)
Pulmonary embolism	2 (0.9%)	4 (1.8%)	1 (0.4%)	5 (1.1%)	7 (1.0%)
Acute respiratory distress syndrome	2 (0.9%)	1 (0.4%)	1 (0.4%)	2 (0.4%)	4 (0.6%)
Dyspnoea	1 (0.5%)	1 (0.4%)	0	1 (0.2%)	2 (0.3%)
Infections and infestations	24 (10.8%)	17 (7.6%)	19 (8.4%)	36 (8.0%)	60 (8.9%)
COVID-19	5 (2.3%)	4 (1.8%)	9 (4.0%)	13 (2.9%)	18 (2.7%)
Pneumonia bacterial	3 (1.4%)	4 (1.8%)	2 (0.9%)	6 (1.3%)	9 (1.3%)
Septic shock	3 (1.4%)	3 (1.3%)	2 (0.9%)	5 (1.1%)	8 (1.2%)
Pneumonia	4 (1.8%)	0	3 (1.3%)	3 (0.7%)	7 (1.0%)
Sepsis	4 (1.8%)	1 (0.4%)	2 (0.9%)	3 (0.7%)	7 (1.0%)
COVID-19 pneumonia	2 (0.9%)	3 (1.3%)	1 (0.4%)	4 (0.9%)	6 (0.9%)
Urinary tract infection	2 (0.9%)	0	0	0	2 (0.3%)
Cardiac disorders	7 (3.2%)	8 (3.6%)	4 (1.8%)	12 (2.7%)	19 (2.8%)
Atrial fibrillation	3 (1.4%)	1 (0.4%)	2 (0.9%)	3 (0.7%)	6 (0.9%)
Cardiac arrest	1 (0.5%)	3 (1.3%)	1 (0.4%)	4 (0.9%)	5 (0.7%)
Tachycardia	0	2 (0.9%)	0	2 (0.4%)	2 (0.3%)
Gastrointestinal disorders	5 (2.3%)	2 (0.9%)	4 (1.8%)	6 (1.3%)	11 (1.6%)
Abdominal pain	1 (0.5%)	2 (0.9%)	0	2 (0.4%)	3 (0.4%)
Retroperitoneal haemorrhage	1 (0.5%)	0	1 (0.4%)	1 (0.2%)	2 (0.3%)
Renal and urinary disorders	4 (1.8%)	3 (1.3%)	4 (1.8%)	7 (1.6%)	11 (1.6%)
Acute kidney injury	2 (0.9%)	3 (1.3%)	4 (1.8%)	7 (1.6%)	9 (1.3%)
Vascular disorders	2 (0.9%)	4 (1.8%)	5 (2.2%)	9 (2.0%)	11 (1.6%)
Hypotension	2 (0.9%)	3 (1.3%)	3 (1.3%)	6 (1.3%)	8 (1.2%)
Shock haemorrhagic	1 (0.5%)	1 (0.4%)	0	1 (0.2%)	2 (0.3%)
Metabolism and nutrition disorders	2 (0.9%)	3 (1.3%)	3 (1.3%)	6 (1.3%)	8 (1.2%)
Hypernatraemia	1 (0.5%)	0	1 (0.4%)	1 (0.2%)	2 (0.3%)
Nervous system disorders	3 (1.4%)	2 (0.9%)	3 (1.3%)	5 (1.1%)	8 (1.2%)
Encephalopathy	1 (0.5%)	1 (0.4%)	2 (0.9%)	3 (0.7%)	4 (0.6%)
Psychiatric disorders	2 (0.9%)	0	1 (0.4%)	1 (0.2%)	3 (0.4%)
Confusional state	1 (0.5%)	0	1 (0.4%)	1 (0.2%)	2 (0.3%)

Data snapshot is 20DEC2020. Randomized patients through 01DEC2020. Data cutoff on 09DEC2020.
MedDRA (Version 23.0) 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 all treatment groups combined. Within each SOC, Preferred Terms are sorted by decreasing frequency.

Infusion interruptions and discontinuations due to adverse events cohort 1 (phases 1 and 2)
In cohort 1 (phases 1 and 2), 2 participants in the casirivimab+imdevimab 8000 mg group experienced TEAEs that led to discontinuation from the study: One participant discontinued (back pain and chills) due to grade 2 infusion-related reaction and 1 participant discontinued due to grade 3 Hypoxia.

A dose-dependent safety signal was not observed.

Cohorts 2 & 3
In cohort 2 and cohort 3 (phase 2), there was more evidence of death in those who experienced a TEAE.

Enrolment into cohorts 2 and 3 was paused on 30 Oct 2020.

A review of complete follow-up data for the participants enrolled in these cohorts did not show clear treatment associated trends for death or mechanical ventilation. The higher number of deaths in participants on high flow oxygen may be primarily due to worsening Covid-19 disease and its complications with contribution from participant's concurrent medical conditions and considered not related to study drug. The imbalance in more participants in the casirivimab+imdevimab groups compared to placebo group in both cohorts 2 and 3 having a DNR/DNI or comfort care status may have also compounded these results; however, overall, the sample size was too small to draw definitive conclusions about safety in the study population in these cohorts.

Safety conclusion
For cohort 1, adverse events reported were as common in the placebo group as the active group and appear to be a function of advanced/progressing Covid-19 disease.

Data are not yet available for cohorts 2 & 3.

Study COV-2069
Cohort A (negative SARS-CoV-2 RT-qPCR status at baseline)
The safety analysis population for cohort A consisted of 2617 randomized participants who were uninfected at baseline (i.e., negative SARS-CoV-2 RT-qPCR) and who had received study treatment. Of these participants, 88 were adolescents (age ≥12 to <18 years).
Among participants who were uninfected at baseline (cohort A), fewer participants in the casirivimab + imdevimab group reported TEAEs during the overall study period.

Table 59: Overview of TEAEs during the overall study period (SAF-A)

	Placebo (N=1306)	R10933+R10987 (N=1311)
Number of TEAEs	709	556
Number of non-COVID-19 TEAEs	481	483
Number of TEAEs with grade >= 3	25	21
Number of serious TEAEs	17	14
Number of AESIs	0	0
Number of TEAEs resulting in study drug withdrawn	0	0
Number of TEAEs resulting in death	2	2
Subjects with at least one TEAE	379 (29.0%)	265 (20.2%)
Subjects with at least one non-COVID-19 TEAE	215 (16.5%)	210 (16.0%)
Subjects with at least one TEAE with grade >= 3	22 (1.7%)	11 (0.8%)
Subjects with at least one serious TEAE	15 (1.1%)	10 (0.8%)
Subjects with at least one AESI	0	0
Subjects with at least one TEAE resulting in study drug withdrawn	0	0
Subjects with any TEAE resulting in death	2 (0.2%)	2 (0.2%)

AESI, adverse event of special interest; COVID-19, Coronavirus Disease 2019; REGN10933, casirivimab; REGN10987, imdevimab; SAF-A, safety analysis set for cohort A; TEAE, treatment-emergent adverse event

Overall, the majority of TEAEs were mild or moderate in severity (grade 1 or grade 2). Fewer than 2% of participants in either treatment group experienced SAEs or severe (grade 3 or grade 4) TEAEs.

Incidences were comparable between treatment groups.

Deaths
As of the data cut-off date, 2 (0.2%) participants in each treatment group in cohort A died during the study. All 4 deaths occurred during the follow-up period.

Table 60: Summary of TEAEs leading to death by primary SOC and PT: overall study period (SAF-A)

Primary System Organ Class Preferred Term	Placebo (N=1306)	R10933+R10987 (N=1311)
Subjects with at least one TEAEs leading to death	2 (0.2%)	2 (0.2%)
Cardiac disorders	1 (<0.1%)	1 (<0.1%)
Cardiac failure congestive	0	1 (<0.1%)
Cardiac arrest	1 (<0.1%)	0
General disorders and administration site conditions	0	1 (<0.1%)
Sudden death	0	1 (<0.1%)
Injury, poisoning and procedural complications	1 (<0.1%)	0
Gun shot wound	1 (<0.1%)	0

Note: For the first step analysis, the data cutoff date is 11Mar2021.
MedDRA (Version 23.1) coding dictionary applied.
A subject who reported 2 or more TEAEs with the same preferred term is counted only once for that term.
A subject who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.

Serious adverse events
As of the data cut-off date, 15/1306 (1.1%) participants in the placebo group and 10/1311 (0.8%) participants in the casirivimab+imdevimab group experienced an SAE during the overall study period in cohort A.

With the exception of Covid-19 and Covid-19 pneumonia, no other SAE was experienced by more than 1 subject in each treatment group. No participant in the casirivimab+imdevimab group experienced a Covid-19-related SAE.

Covid-19 infection/Covid-19 pneumonia was more common in the placebo group suggesting efficacy for the active in prevention of Covid-19 infection/Covid-19 pneumonia.

Frequency of adverse events
During the overall study period in cohort A, fewer participants in the casirivimab+imdevimab group reported TEAEs compared to the placebo group, which was consistent with a higher incidence of Covid-19-related TEAEs in placebo-treated participants.

In cohort A, TEAEs with an incidence >2% in each treatment group were:
- placebo group: asymptomatic Covid-19, Covid-19, and Headache
- casirivimab+imdevimab group: injection site reaction (ISR) and Asymptomatic Covid-19

Regardless of baseline serology in cohort A, Asymptomatic Covid-19 was the most frequently reported TEAE during the overall study period in the placebo group, whereas Injection site reaction was the most frequently reported TEAE for the casirivimab+imdevimab group.

Table 61: Summary of serious treatment-emergent adverse events (TEAEs) by primary SOC and PT: overall study period (SAF-A)

Primary System Organ Class Preferred Term	Placebo (N=1306)	R10933+R10987 (N=1311)
Subjects with at least one serious TEAE	15 (1.1%)	10 (0.8%)
Infections and infestations	9 (0.7%)	4 (0.3%)
Gastroenteritis	0	1 (<0.1%)
Pneumonia	1 (<0.1%)	1 (<0.1%)
Sepsis	0	1 (<0.1%)
Soft tissue infection	0	1 (<0.1%)
Appendicitis	1 (<0.1%)	0
COVID-19	4 (0.3%)	0
COVID-19 pneumonia	2 (0.2%)	0
Scrotal abscess	1 (<0.1%)	0
Urinary tract infection	1 (<0.1%)	0
Cardiac disorders	1 (<0.1%)	1 (<0.1%)
Acute myocardial infarction	0	1 (<0.1%)
Cardiac failure congestive	0	1 (<0.1%)
Cardiac arrest	1 (<0.1%)	0
Gastrointestinal disorders	1 (<0.1%)	1 (<0.1%)
Abdominal pain upper	0	1 (<0.1%)
Abdominal pain	1 (<0.1%)	0
General disorders and administration site conditions	0	1 (<0.1%)
Sudden death	0	1 (<0.1%)
Hepatobiliary disorders	0	1 (<0.1%)
Cholecystitis acute	0	1 (<0.1%)
Injury, poisoning and procedural complications	1 (<0.1%)	1 (<0.1%)
Ankle fracture	0	1 (<0.1%)
Foot fracture	0	1 (<0.1%)
Tibia fracture	0	1 (<0.1%)
Gun shot wound	1 (<0.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<0.1%)	1 (<0.1%)
Cervix carcinoma recurrent	0	1 (<0.1%)
Breast cancer	1 (<0.1%)	0
Respiratory, thoracic and mediastinal disorders	0	1 (<0.1%)
Respiratory failure	0	1 (<0.1%)
Psychiatric disorders	2 (0.2%)	0
Mania	1 (<0.1%)	0
Suicidal ideation	1 (<0.1%)	0
Vascular disorders	1 (<0.1%)	0
Essential hypertension	1 (<0.1%)	0

Note: For the first step analysis, the data cutoff date is 11Mar2021.
MedDRA (Version 23.1) coding dictionary applied.
A subject who reported 2 or more TEAEs with the same PT is counted only once for that term.
A subject who reported 2 or more TEAEs with different PTs within the same SOC is counted only once in that SOC.

Adverse events in adolescents
In cohort A, the proportion of adolescent participants with TEAEs of Asymptomatic Covid-19 and Covid-19 were higher in the placebo group than the casirivimab+imdevimab group. Conversely, the proportion of adolescent participants with TEAEs of Injection site reaction was higher in the casirivimab+imdevimab group compared to placebo.

Overall, the types of TEAEs experienced by adolescent participants in cohort A were similar to those observed in the adult population.

Adverse events by severity
The majority of TEAEs in cohort A were mild or moderate in severity (i.e. grade 1 or grade 2). During the study, fewer than 2% of participants in either treatment group experienced grade 3 or grade 4 TEAEs. Adverse events were more common in the placebo group, mainly due to more events at grade 1.

Severity of adverse events by baseline serology
Among baseline-seronegative and baseline-seropositive participants in cohort A, fewer than 2% in either treatment group experienced a grade 3 or grade 4 TEAE.

Severity of adverse events in adolescents
No adolescent participant (age ≥12 to ≤18 years) in cohort A reported grade 3 or grade 4 TEAEs during the overall study period. Overall, the types and severity of TEAEs experienced by adolescent participants were similar to those experienced by adults in the study.

Treatment-related adverse events
Compared to the placebo group, more cohort A participants in the casirivimab+imdevimab group reported treatment-related TEAE during the overall study period, consistent with a higher incidence of ISR in this treatment arm. Injection site reaction was the most frequently reported treatment-related TEAE in both treatment groups.

All injection site reactions and hypersensitivity reactions
Few (<5%) participants in cohort A reported ISRs during the EAP and none met criteria for AESI.

The majority of ISRs were mild in severity and the remaining were moderate. More participants in the casirivimab+imdevimab group reported ISRs but a greater proportion of participants in the placebo group reported a duration >4 days. The 2 most frequently reported signs or symptoms of ISR were Erythema and Pruritus.

Discontinuations due to adverse events
As of the data cut-off date, no participant experienced a TEAE that led to study treatment discontinuation in cohort A.

Clinical laboratory evaluation (SAF-A)
Laboratory data did not reveal any particular concern

Adverse events of special interest
None.

Adverse event profile after receiving a Covid-19 vaccine
During the study, Covid-19 vaccines became available for emergency use, and the protocol was amended to allow study participants to receive Covid-19 vaccines after the completion of efficacy assessments in the study.

A total of 175 participants in cohort A received vaccinations against Covid-19, and the number of participants receiving vaccines was comparable between the treatment groups

The majority of these participants received their Covid-19 vaccine after day 29, with a mean time to first vaccination of 85.3 days. Three participants in the placebo group and 6 in the casirivimab + imdevimab group received Covid-19 vaccination before day 29, and none of these participants experienced TEAEs after vaccination.

After vaccination, fewer of those in the casirivimab+imdevimab group experienced TEAEs compared to placebo. No participant in the casirivimab+imdevimab group had grade ≥3 TEAEs, SAEs, and AESIs. No unexpected safety signal was observed in either treatment group.

Serious adverse events occurring after Covid-19 vaccination were reported by 2 participants, both in the placebo group (Covid-19 pneumonia and Breast cancer).

Although the numbers reported are small, the data reported here does not give rise to any particular concern.

Study COV-2069

Cohort B (positive SARS-CoV-2 RT-qPCR status at baseline)

The safety analysis population for cohort B consisted of 311 randomized participants with asymptomatic infection at baseline (i.e., positive SARS-CoV-2 RT-qPCR) and who had received study treatment. Of these participants, 38 were adolescents (age ≥12 to <18 years). Among participants with asymptomatic infection at baseline (cohort B), fewer participants in the casirivimab+imdevimab group reported TEAEs during the study period, and the number and proportion of participants reporting non-Covid-19 TEAEs were also smaller in the casirivimab+imdevimab group compared to the placebo group.

Table 62: Overview of TEAEs during the overall study period (SAF-B)

	Placebo (N=156)	R10933+R10987 (N=155)
Number of TEAEs	109	67
Number of non-COVID-19 TEAEs	42	26
Number of TEAEs with grade >= 3	5	1
Number of serious TEAEs	4	0
Number of AESIs	0	0
Number of TEAEs resulting in study drug withdrawn	0	0
Number of TEAEs resulting in death	0	0
Subjects with at least one TEAE	75 (48.1%)	52 (33.5%)
Subjects with at least one non-COVID-19 TEAE	25 (16.0%)	17 (11.0%)
Subjects with at least one TEAE with grade >= 3	4 (2.6%)	1 (0.6%)
Subjects with at least one serious TEAE	4 (2.6%)	0
Subjects with at least one AESI	0	0
Subjects with at least one TEAE resulting in study drug withdrawn	0	0
Subjects with any TEAE resulting in death	0	0

Note: For the first step analysis, the data cutoff date is 11Mar2021.

Deaths

As of the data cut-off date, there were no deaths in cohort B.

Serious adverse events

As of the data cut-off date, 4/156 (2.6%) participants in the placebo group and none in the casirivimab+imdevimab group experienced an SAE in cohort B. No SAE was considered related to study treatment.

Table 63: Summary of serious treatment-emergent adverse events (TEAEs) by primary SOC and PT: overall study period (SAF-B)

Primary System Organ Class Preferred Term	Placebo (N=156)	R10933+R10987 (N=155)
Subjects with at least one serious TEAE	4 (2.6%)	0
Gastrointestinal disorders	1 (0.6%)	0
Pancreatitis acute	1 (0.6%)	0
Infections and infestations	3 (1.9%)	0
COVID-19	2 (1.3%)	0
COVID-19 pneumonia	1 (0.6%)	0

Note: For the first step analysis, the data cutoff date is 11Mar2021.
MedDRA (Version 23.1) coding dictionary applied.
A subject who reported 2 or more TEAEs with the same PT is counted only once for that term.
A subject who reported 2 or more TEAEs with different PTs within the same SOC is counted only once in that SOC.

Frequency of adverse events

During the overall study period in cohort B, fewer participants in the casirivimab+imdevimab group reported TEAEs compared to the placebo group. Covid-19 was the most frequently

reported TEAE in both treatment groups, with a higher incidence in the placebo group compared to the casirivimab+imdevimab group.

Adverse events by baseline serology
Regardless of baseline serology in cohort B, Covid-19 was the most frequently reported TEAE during the overall study period and was reported in more participants in the placebo group compared to the casirivimab+imdevimab group.

Adverse events in adolescents
Regardless of age group in cohort B, the incidence of Covid-19 was higher in the placebo group than the casirivimab+imdevimab group during the EAP. No unexpected safety trends were observed between adolescent (N=38) and adult (N=273) participants.

Adverse events by severity
The majority of TEAEs in cohort B were mild or moderate in severity. Few (<3%) participants experienced grade ≥3 TEAEs during the overall study period. No participant in either treatment group experienced a grade 4 or 5 TEAE.

Severity of adverse events by baseline serology
Regardless of baseline serology in cohort B, the majority of TEAEs were mild or moderate in severity.

Severity of adverse events in adolescents
No adolescent participant (age ≥12 to ≤18 years) in cohort B reported grade ≥3 TEAEs during the overall study period. Overall, the types and severity of TEAEs experienced by adolescent participants were similar to those experienced by adults in the study.

Treatment-related adverse events
Fewer than 5% of participants in either treatment group in cohort B reported treatment-related TEAE during the overall study period, and incidence was comparable between treatment groups. The most often reported treatment-related TEAE was ISR in the casirivimab+imdevimab group and Covid-19 in the placebo group. No other treatment-related TEAE was experienced by more than 1 participant in either treatment group.

Discontinuations due to adverse events
As of the data cut-off date, no participant experienced a TEAE that led to study treatment discontinuation in cohort B.

Clinical laboratory evaluation (SAF-B)
Laboratory data did not reveal any particular concern

Adverse events of special interest
None.

All injection site reactions and hypersensitivity reactions
Few (<5%) participants in cohort B reported ISRs during the EAP. All were mild in severity and none met criteria for AESI. The 2 most frequently reported signs or symptoms of ISR were Erythema and Ecchymosis.

Adverse event profile after receiving a Covid-19 vaccine
During the study, Covid-19 vaccines became available for emergency use, and the protocol was amended to allow study participants to receive Covid-19 vaccines after the completion of

efficacy assessments in the study.

A total of 12 participants in cohort B received vaccinations against Covid-19 during the study, with 9 vs 3 participants receiving vaccine in the placebo and casirivimab+imdevimab groups, respectively. All of these participants received their Covid-19 vaccine after day 29, with a mean time to first vaccination of 106.0 days.

After vaccination, 1 placebo-treated participant reported 2 TEAEs (Asymptomatic Covid-19 [i.e., a second positive infection] and Rash), compared to none in the casirivimab+imdevimab group. No participant had a grade ≥3 TEAE. No participant had SAEs or AESIs after receiving a Covid-19 vaccine. No unexpected safety signal was observed in either treatment group.

Cohorts A & B - immunogenicity
The anti-drug antibody (ADA) analysis sets were based on the actual treatment received and included all treated participants who received study treatment and had at least 1 non-missing ADA result after study treatment administration.

The incidence of anti-casirivimab antibodies and anti-imdevimab antibodies was low (<3%).

Supportive study
Study HV2093
The study was designed to assess the safety and tolerability of multiple SC doses of casirivimab+imdevimab in adult volunteers who are SARS-CoV-2 negative at baseline. This study has been previously described, only safety results are presented here.

Results
A greater percentage of participants experienced at least 1 TEAE during the entire study period in the casirivimab+imdevimab 1200 mg group (52.7%) than in the placebo group (46.3%). This imbalance is mainly due to the higher incidence of injection site reactions experienced by participants treated with casirivimab+imdevimab 1200 mg (34.7%), compared to placebo (15.8%).

Table 64: Summary of TEAEs during the entire study period (SAF)

	Placebo (N=240)	R10933+R10987 1200 mg SC (N=729)
Number of TEAEs	313	2054
Number of TEAEs with grade >= 3	2	13
Number of serious TEAEs	1	7
Number of AESIs	0	0
Number of TEAEs resulting in study drug withdrawn	14	11
Number of TEAEs resulting in death	0	1
Subjects with at least one TEAE	111 (46.3%)	384 (52.7%)
Subjects with at least one TEAE with grade >= 3	2 (0.8%)	7 (1.0%)
Subjects with at least one serious TEAE	1 (0.4%)	5 (0.7%)
Subjects with at least one AESI	0	0
Subjects with at least one TEAE resulting in study drug withdrawn	12 (5.0%)	9 (1.2%)
Subjects with any TEAE resulting in death	0	1 (0.1%)

MedDRA (Version 23.1) coding dictionary applied.
Data cutoff date is 13MAR2021.
Included are events that were reported before the COVID-19 vaccination date, if any.
TEAE: Treatment-Emergent Adverse Events

Deaths
None.

Serious adverse events
Five of 729 participants in the casirivimab+imdevimab 1200 mg group and 1 of 240 participants in the placebo group experienced at least 1 treatment-emergent serious adverse event during the entire study period. No deaths were reported.

Table 65: Participants with serious treatment-emergent adverse events in the entire study period (SAF)

Primary System Organ Class Preferred Term	Placebo (N=240)	R10933+R10987 1200 mg SC (N=729)
Subjects with at least one serious TEAE	1 (0.4%)	5 (0.7%)
Cardiac disorders	0	1 (0.1%)
Angina pectoris	0	1 (0.1%)
Injury, poisoning and procedural complications	0	1 (0.1%)
Post laminectomy syndrome	0	1 (0.1%)
Procedural pain	0	1 (0.1%)
Metabolism and nutrition disorders	0	1 (0.1%)
Diabetic complication	0	1 (0.1%)
Musculoskeletal and connective tissue disorders	0	1 (0.1%)
Spinal osteoarthritis	0	1 (0.1%)
Psychiatric disorders	0	1 (0.1%)
Major depression	0	1 (0.1%)
Post-traumatic stress disorder	0	1 (0.1%)
Gastrointestinal disorders	1 (0.4%)	0
Enteritis	1 (0.4%)	0

MedDRA (Version 23.1) coding dictionary applied. TEAE: treatment-emergent adverse event; SOC: System organ class; PT: preferred term; ISR: injection site reaction.
Data cutoff date is 13MAR2021.

All injection site reactions
The 2 most common symptoms of the injection site reactions were Erythema and Pruritus in the casirivimab+imdevimab group, and Erythema and Ecchymosis in the placebo group.

Approximately half of all injection site reactions resolved within 2 days after each injection for both treatment groups. The median time to resolution was 1.9 days in the casirivimab+imdevimab 1200 mg group (with a minimum of <1 day and a maximum of 42.0 days) and 1.6 days in the placebo group (with a minimum of <1 day and a maximum of 27.9 days).

A minority of participants who experienced injection site reactions received any treatment for the event e.g. simple analgesia, antihistamine.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

A brief discussion of the benefit/risk conclusions of treatment with Ronapreve, at this interim stage, is given below.

The overall benefit-risk of Ronapreve is considered to be positive in the treatment of adults and adolescents aged 12-18yrs in the community with acute Covid-19 infection and who are seronegative at the time of presentation [and who are not in receipt of supplemental oxygen for the management of acute Covid-19 infection]. The overall benefit-risk may also be considered positive in the same overall population yet who are seropositive at the time of presentation.

The overall benefit-risk of Ronapreve is considered to be positive in the post-exposure prophylaxis of adults and adolescents aged 12-18yrs in the community with acute Covid-19 infection and who are seronegative at the time of presentation [and who are not in receipt of supplemental oxygen for the management of acute Covid-19 infection]. A positive benefit-risk has not been established for this same overall population yet who are seropositive at the time of presentation.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product in the prophylaxis and treatment of acute Covid-19 infection

Ronapreve has been authorised with a Conditional Marketing Authorisation (CMA) in Great Britain. The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	Estimated due date
The company will provide final reports for submitted clinical studies (2066, 2067, 2069, HV-2093, now submitted at the interim stage) and also final report for the RECOVERY trial.	End 2022
The company will re-evaluate the PIL user test with a view to either conducting a new test on the updated PIL or providing a bridging exercise.	End 2021
The company will revise the population PK model and provide agreed simulations.	End 2021
The Applicant will re-evaluate and, where appropriate, tighten the DS and DP specifications when further additional manufacturing data becomes available in the future.	End Q1 2022

Catalent will not supply the UK until after completion of qualification at the secondary package site in Q1 2022. Initial supply will come from HTO. On that basis, several specific obligations (SOBs) have been raised. These obligations can be addressed post-authorisation (and prior to Catalent supply).	End Q1 2022
The company will submit a revised RMP which will capture the final approved indication, any issues of relevance from the Paediatric Investigation Plan, a PLGB-specific annex which will capture systemic hypersensitivity reactions (SHRs, including acute infusion-related reactions [IRRs]and/or injection site reactions [ISRs]) as an AESI, and a targeted follow-up form to follow up any such reported cases.	To align with with EU RMP
The company will provide a full study protocol for the COVID-19 International Drug Pregnancy Registry.	End October 2021
The company will provide the comparison of the incidence of Injection Site Reactions (ISRs) with single exposures versus repeated exposures once the final results of study HV-2093 are available in the PGLB-specific annex.	End October 2021
The company will add 'Use in immunocompromised patients' as missing information in a PLGB specific annex of the RMP.	End October 2021
The company will submit a retrospective analysis of Ronapreve-treated patients with Covid-19 and primary or secondary immunodeficiency with associated antibody disorders. The company will discuss the data with reference to the scope and focus of study in areas of missing information with regard to efficacy in immunocompromised individuals. The MHRA reserves the right to request further study from the company should the aforementioned gaps become apparent in these discussions.	End October 2021
The Applicant commits to providing cumulative reviews of all Serious Hypersensitivity Reactions (including IRRs and ISRs) in the PSURs going forward. The review will include both a presentation and critical appraisal of data received in the interval period and cumulatively.	Ongoing

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPCs and PILs for these products are available on the MHRA website.

The following text is the currently approved label text. Full-colour label mock-ups have been provided.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ronapreve 120 mg/mL solution for injection or infusion
Casirivimab/imdevimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One multidose vial contains 1 332 mg/11.1 mL of casirivimab (120 mg/mL).
One multidose vial contains 1 332 mg/11.1 mL of imdevimab (120 mg/mL).

3. LIST OF EXCIPIENTS

L-histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80, Sucrose, Water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection or infusion
120 mg/mL
2 multidose vials of 11.1 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For intravenous or subcutaneous use
For IV, casirivimab and imdevimab must be administered together
For SC, casirivimab and imdevimab must be administered consecutively

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C). Do not freeze. Do not shake. Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Products Limited
6 Falcon Way, Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PLGB 00031/0925

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CASIRIVIMAB VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ronapreve 120 mg/mL solution for injection or infusion
casirivimab

2. METHOD OF ADMINISTRATION

For intravenous or subcutaneous use (Read the package leaflet before use)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 332 mg/11.1 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

IMDEVIMAB VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ronapreve 120 mg/mL solution for injection or infusion
imdevimab

2. METHOD OF ADMINISTRATION

For intravenous or subcutaneous use (Read the package leaflet before use)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 332 mg/11.1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ronapreve 120 mg/mL solution for injection or infusion
Casirivimab/imdevimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 300 mg/2.5 mL of casirivimab (120 mg/mL).
One vial contains 300 mg/2.5 mL of imdevimab (120 mg/mL).

3. LIST OF EXCIPIENTS

L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection or infusion
120 mg/mL
2 vials of 2.5 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For intravenous or subcutaneous use
For IV, casirivimab and imdevimab must be administered together
For SC, casirivimab and imdevimab must be administered consecutively
For single-use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C). Do not freeze. Do not shake. Keep the vials in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Products Limited
6 Falcon Way, Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PLGB 00031/0925

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CASIRIVIMAB VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ronapreve 120 mg/mL solution for injection or infusion
casirivimab

2. METHOD OF ADMINISTRATION

For intravenous or subcutaneous use (Read the package leaflet before use)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg/2.5 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

IMDEVIMAB VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ronapreve 120 mg/mL solution for injection or infusion
imdevimab

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg/2.5 mL

6. OTHER

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**