25 February 2021
EMA/142650/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation (EC) No 726/2004

Regeneron Ireland DAC use of casirivimab and imdevimab for the treatment of COVID-19

INN/active substance: casirivimab and imdevimab

Procedure number: EMEA/H/A-5(3)/1503

Note:

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

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1. Information on the procedure

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus is the causative agent of coronavirus disease 2019 (COVID-19). Early treatment of patients with confirmed COVID-19 presenting only mild symptoms can reduce the number of patients that progress to more severe disease and require hospitalisation or admittance to ICU.

The European Medicines Agency (EMA) is aware of several therapeutic candidates with putative antiviral action which are currently in development for the treatment of these patients.

Amongst those treatments, two fully human, neutralising monoclonal antibodies against SARS-CoV-2 spike protein (casirivimab and imdevimab) were investigated in a double-blind, phase 1–3 trial[1] involving non-hospitalised patients with COVID-19. In that setting, interim results of these antibodies used in a combined cocktail (REGN-COV2) have shown that, in the overall trial population, 6% of the patients in the placebo group and 3% of the patients in the combined REGN-COV2 dose groups reported at least one medically attended visit; among patients who were serum antibody–negative at baseline, the corresponding percentages were 15% and 6% (difference, −9 percentage points; 95% CI, −29 to 11). In this interim analysis, the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline.

These results are of great relevance and their application in the clinical setting before a formal authorisation is considered important in view of the current pandemic situation. In that respect, currently available information on the combination of casirivimab and imdevimab are of significant interest with a view to supporting national decisions on their potential conditions of use.

On 2 February 2021 the Executive Director of the Agency triggered a procedure under Article 5(3) of Regulation EC (No) 726/2004, and requested the CHMP to give a scientific opinion on the currently available quality, preclinical and clinical data on the potential use of casirivimab and imdevimab for the treatment of confirmed COVID-19 in patients that do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.

2. Scientific discussion

2.1. Introduction

Coronaviruses are enveloped RNA viruses and are important human and animal pathogens. In December 2019, a cluster of patients with viral pneumonia of unknown cause was identified in Wuhan, China. A novel coronavirus, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the cause of disease and was subsequently named Coronavirus disease 2019 (COVID-19).

Clinical presentation of COVID-19 can include pneumonia with symptoms including fever, cough, and dyspnoea. In a report from the Chinese Center for Disease Control and Prevention that included 44,500 confirmed infections, the majority (80%) presented with mild COVID-19 (with no or mild pneumonia), while the rest presented with more advanced disease (14% with dyspnoea, hypoxia, or >50% lung involvement on imaging; 5% in respiratory failure, shock, or multiorgan failure). SARS-CoV-2 is transmitted by human-to-human contact and respiratory droplets.

Regeneron Pharmaceuticals, Inc. and F. Hoffman-La Roche, Ltd (Roche) are co-developing two non-competing, high-affinity human IgG1 anti-SARS-CoV-2 monoclonal antibodies (mAbs), REGN10933 and REGN10987, that bind specifically to the receptor binding domain (RBD) of the spike

[1] https://www.nejm.org/doi/full/10.1056/NEJMoa2035002

(S) glycoprotein of SARS-CoV-2, blocking viral entry into host cells. REGN10933 and REGN10987, also referred to as casirivimab and imdevimab (p-INNs), respectively, are both potent neutralizing antibodies that block the interaction between the S protein and its canonical receptor angiotensin-converting enzyme 2 (ACE2). A combination therapy of the 2 anti-SARS-CoV-2 spike antibodies (REGN10933 and REGN10987, also referred to as REGN-COV2) for treatment and prophylaxis of COVID-19 is being evaluated. REGN10933 and REGN10987 are intended to be utilised as a combination treatment and should not be used individually as monotherapy. A combination of antibodies that bind to non-overlapping epitopes may minimize the likelihood of loss of antiviral activity due to naturally circulating viral variants or development of escape mutants under drug pressure.

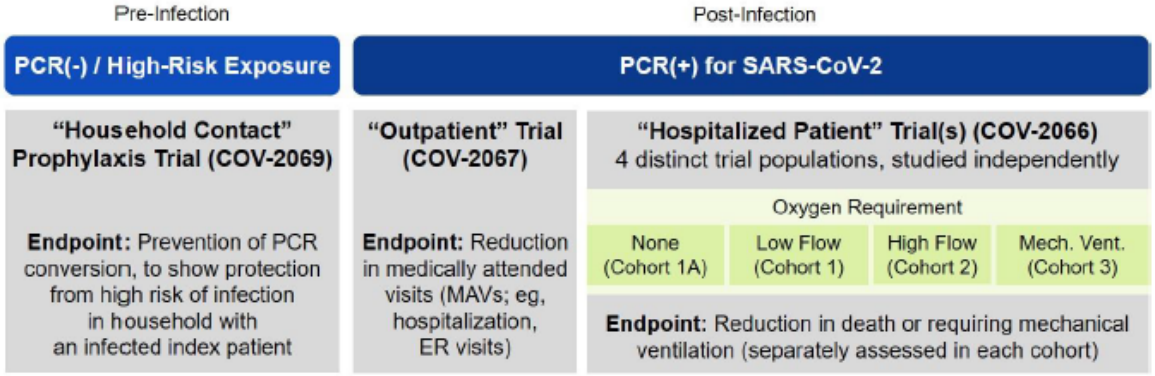
These two fully human, neutralising monoclonal antibodies against SARS-CoV-2 spike protein (casirivimab and imdevimab) were investigated in a double-blind, phase 1–3 trial involving non-hospitalised patients with COVID-19. In that setting, interim results of these antibodies used in a combined cocktail (REGN-COV2) have shown that, in the overall trial population, 6% of the patients in the placebo group and 3% of the patients in the combined REGN-COV2 dose groups reported at least one medically attended visit; among patients who were serum antibody–negative at baseline, the corresponding percentages were 15% and 6% (difference, −9 percentage points; 95% CI, −29 to 11). In this interim analysis, the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline.

2.2. Clinical aspects

REGN-COV2 is undergoing clinical investigation in a range of studies across several different clinical settings

The currently proposed indication *"treatment of confirmed COVID-19 in patients 12 years old and over that do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19"* is supported by data from 3 studies, presented in table 1 below:

Table 1. Overview of REGN-COV2 Clinical Programme



The main study in support of the use of this product in the proposed indication was the R10933-10987-COV-2067 study (referred to as COV-2067), a phase 1/2/3 study to evaluate the efficacy and safety of REGN-COV2 in outpatient adult and paediatric patients with COVID-19.

Two further studies provide supportive clinical data:

R10933-10987-COV-2066 (referred to as COV-2066): adaptive phase 1/2/3 study to evaluate the efficacy and safety of REGN-COV2 in hospitalized adult patients with COVID-19;

R10933-10987-COV-2069 (referred to as COV-2069): phase 3 study in adults and paediatric individuals with household exposure to an individual with SARS-CoV-2 infection.

Various dose regimes were evaluated, the dose regimes evaluated in the indication sought are:

- 8000 mg (4000 mg casirivimab and 4000 mg imdevimab) single intravenous (IV) infusion
- 2400 mg (1200 mg casirivimab and 1200 mg imdevimab) single IV infusion

2.2.1. Efficacy

2.2.1.1. Clinical Studies

A. Study COV-2067: Treatment of outpatients who are at high risk of severe coronavirus disease 2019 (COVID-19)

This is an adaptive, phase 1/2/3, randomised, double-blind, placebo-controlled master protocol to evaluate the efficacy, safety, and tolerability of REGN10933 and REGN10987 combination therapy ambulatory patients (i.e., outpatients) with COVID-19.

The key outcomes from the analysis of the first 799 symptomatic patients from Phase 1 and Phase 2 of the COV-2067 study are presented.

i. Dose

Phase 1 and 2

- REGN10933 and REGN10987: 2.4 g (1.2 g of each mAb intravenous [IV] x 1 dose)
- REGN10933 and REGN10987: 8 g (4 g of each mAb IV x 1 dose)
- Placebo IV x 1 dose

Population

Non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2.

The Number of subjects planned were for Phase 1, Up to 100 patients and for Phase 2, Up to 1300 patients (130 patients per arm per cohort):

Asymptomatic Cohort (Combination Therapy)

REGN10933 and REGN10987 (low dose): 130 patients; REGN10933 and REGN10987 (high dose): 130 patients; Placebo: 130 patients

Symptomatic Cohort (Combination Therapy)

REGN10933+REGN10987 (low dose): 130 patients; REGN10933 andREGN10987 (high dose): 130 patients; Placebo: 130 patients**.**

Randomisation

Subjects were randomized in a 1:1:1 manner to receive a single intravenous (IV) infusion of 2,400 mg of casirivimab and imdevimab (1,200mg of each) (n=266), or 8,000 mg of casirivimab and imdevimab (4,000 mg of each) (n=267), or placebo (n=266). An initial analysis based on the first 275 patients (analysis group 1, descriptive and hypothesis generating) was subsequently supplemented with an

additional 524 patients (analysis group 2, prospective confirmation) for a total of 799 patients (analysis group 1/2).

Blinding

Study COV-2067 is an adaptive, phase 1/2/3, randomized, double-blind, placebo-controlled study.

ii. Endpoints (relevant to the submitted analysis)

Primary endpoints

Phase 1

- Proportion of patients with treatment-emergent SAEs through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29
- Time-weighted average change from baseline in viral shedding (log10 copies/mL) from day 1 to day 22, as measured by quantitative reverse transcription quantitative polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples.

Phase 2

The primary endpoint for phase 2 is time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 to day 7, as measured by RT-qPCR in NP swab samples.

Key Secondary Endpoints

Phase 1: Virologic

- Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 to day 22, as measured by RTqPCR in saliva samples
- Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 to day 22, as measured by RTqPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (NP swabs, nasal swabs, saliva)
- Change from baseline in viral load at each visit through day 29, 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 saliva samples
- Change from baseline in viral load at each visit through day 29, as measured by RT-qPCR in nasal swabs
- Correlation and concordance of RT-qPCR results across different sample types (NP, nasal, and saliva)
- Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 to post-baseline study days (e.g., day 5, 7, 15, and 29)

Phase 1: Clinical

- Medically-attended visits (MAVs) described as:

- Proportion of patients with ≥1 COVID-19-related medically attended visit 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 admitted to a hospital due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29

Phase 2: Virologic

- Time to negative RT-qPCR in NP swabs with no subsequent positive RT-qPCR change from baseline in viral load at each visit, as measured by RT-qPCR in NP samples
- Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 to post-baseline study days
- Proportion of patients with high viral load (>104 copies/mL, >105 copies/mL, >106 copies/mL, >107 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 quantitation at each visit

Phase 2: Clinical

- Medically attended visits described as
  - Proportion of patients with ≥1 COVID-19-related medically attended visit 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 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 with ≥1 outpatient or telemedicine visit 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
- Time to first onset of symptoms consistent with COVID-19 (asymptomatic cohort only)
- Duration of symptoms consistent with COVID-19
- Proportion of patients with treatment-emergent SAEs through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

It was noted by the CHMP that the primary endpoints in both phases include a virological endpoint. This is acceptable for the early development of the anti-viral antibodies.

There are a variety of clinical endpoints related to COVID-19 disease and its severity. The reported efficacy data summarises the "proportion of patients with ≥1 COVID-19 Related Medically-Attended Visits Through Day 29". No direct relationship has been established between not having a MAV and having a clinical benefit from treatment. Therefore, results related to the following clinical endpoints,proportion of patients requiring mechanical ventilation due to COVID-19 by day 29, proportion of patients with all-cause mortality by day 29, time to first onset of symptoms consistent with COVID-19 (asymptomatic cohort only), duration of symptoms consistent with COVID-19, are of more interest and are expected to be included in the final clinical study report.

Statistical methods

Outcome variables

Virological endpoints were analysed as time-weighted average change from baseline in viral load through day 7.

Medically-Attended Visits (MAVs) for COVID-19 were defined as hospitalisations, emergency room (ER) or urgent care visits, or physician office or telemedicine visits with the primary reason for the visit being COVID-19. MAVs for reasons other than COVID-19 were not recorded.

Regarding the populations, the phase 1 subjects are referred to as analysis group 1. The phase 2 subjects are referred to as analysis group 2. Analyses of the pooled population are referred to as analyses of group 1/2.

Analyses of virologic endpoints for the phase 2 analysis were conducted using mFAS of Analysis Group 2 (n=437 patients).

Analyses of MAVs utilised all available data from the study in the mFAS of Analysis Group 1/2 (n=665 patients).

Details on the analysis model (model specification, adjustment for covariates, pre-specification, etc.) were not reported.

Multiplicity and results

Analyses of phase I are descriptive.

In phase II (analysis of group 2), a hierarchical testing procedure was conducted with 8 virological endpoints being tested hierarchically based on group 2, followed by an analysis of clinical endpoints based on pooled data from phase I and II (see the following table for the ordering). Tests are conducted at a two-sided significance level of 0.05.

Treatment was initiated within 3 days of obtaining a positive SARS-CoV-2 viral infection determination. Subjects were randomized in a 1:1:1 manner to receive a single intravenous (IV) infusion of 2,400 mg of casirivimab and imdevimab (1,200mg of each) (n=266), or 8,000 mg of casirivimab and imdevimab (4,000 mg of each) (n=267), or placebo (n=266). An initial analysis based on the first 275 patients (analysis group 1, descriptive and hypothesis generating) was subsequently supplemented with an additional 524 patients (analysis group 2, prospective confirmation) for a total of 799 patients (analysis group 1/2).

Baseline Demographic and Disease Characteristics

The demographics and baseline characteristics of these 3 analysis groups are provided in table 2 below.

Table 2: Demographics and Baseline Characteristics

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
% over 65 years	7	7	7
% Female	51	54	53
% White	82	87	85
% Black	13	7	9
% Asian	1	2	2
% Hispanic or Latino ethnicity	56	48	50
% High Risk [a] (≥1 risk factors for severe COVID-19)	64	59	61
% Obese	42	35	37
Median duration of symptoms (days)	3	3	3
Baseline Virologic Parameter			
% Seronegative	41	56	51
Mean log10 copies/mL	6.60	6.34	6.41
% Seropositive	45	34	38
Mean log10 copies/mL	3.30	3.49	3.43
% Other	14	11	11

[a] The study COV 2067 defined high risk patients with 1 or more of the following risk factors: Age >50 years; BMI > 30 kg/m^2 collected via vital signs CRF; Cardiovascular disease, including hypertension; Chronic kidney disease, including those on dialysis; Chronic lung disease, including asthma; Chronic metabolic disease, including diabetes; Chronic liver disease; and Immunosuppressed, based on investigator's assessment.

Demographic characteristics, baseline virology and disease characteristics were similar between patients randomized to the REGN-COV2 treatment groups and the placebo group across the overall population of 799 patients and the 524 patients in the phase 2 only cohort (i.e. Analysis Group 1/2 and Analysis Group 2) (Generally, these characteristics were also consistent with the first 275 patient population analysed previously (Analysis Group 1).

There was a significantly higher viral load in the seronegative patients (i.e. no prior exposure to the virus based on serological testing at study baseline) compared to those in the seropositive and other categories. This is expected. However, there were no major differences in baseline viral load between the two treatment groups within each of the seronegative and seropositive subsets.

Virologic Efficacy

Treatment with REGN-COV2 resulted in a statistically significant reduction in the time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 through day 7. This

endpoint and all other virologic endpoints tested hierarchically for Analysis Group 2 reached nominal statistical significance at the level of 5% (see Figures 1 and 2).

Figure 1. Similar reduction in Viral load with REGN-COV2 in Analysis groups 1 and 2

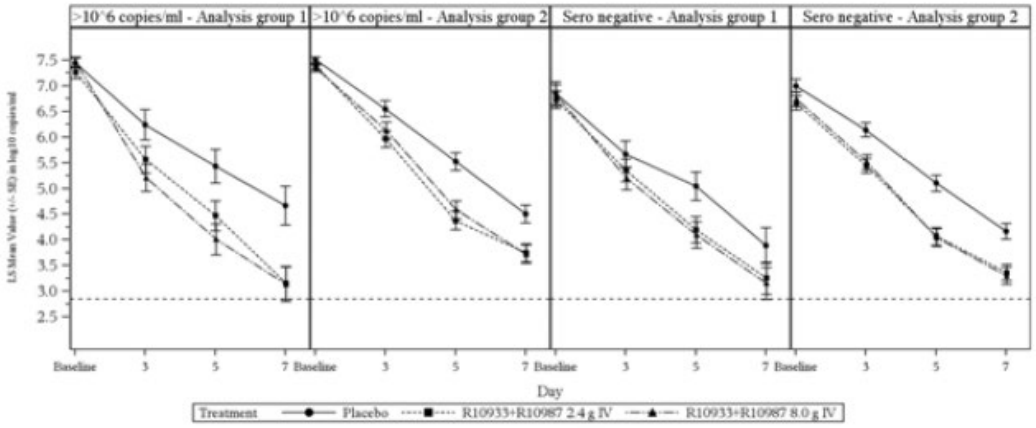
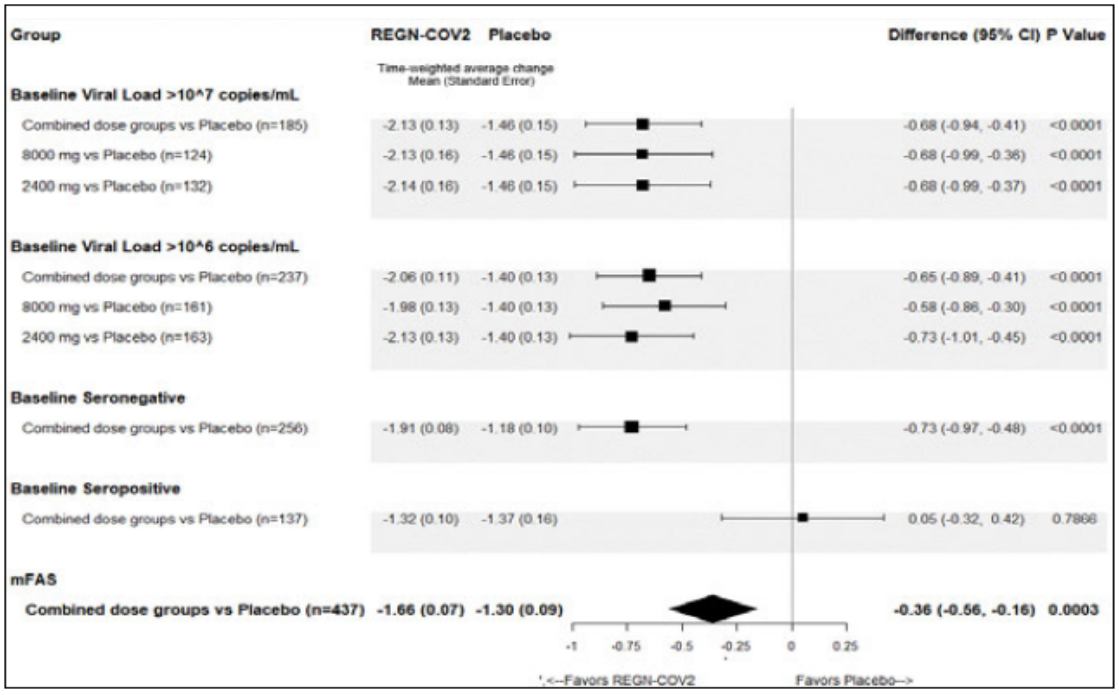


Figure 2. Reduction in average daily viral load through Day 7 (log_{10} copies/mL): Comparison of REGN-COV2 vs placebo (mFAS), Analysis group 2



Reductions were observed in various populations analysed, including in the overall mFAS of Analysis Group 2 and the subpopulations of those with higher baseline viral load (>7 log_{10} copies/mL or >6 log10 copies/mL) or who were seronegative at baseline. Consistent effects were observed for the individual doses, indicating the absence of a dose effect, and when the 2 doses were combined. Greater reductions in viral load were observed in those with higher viral load at baseline or those that were seronegative at baseline.

- REGN-COV2 significantly reduced viral load greater than placebo in all patients who were positive at baseline, on RT-qPCR, for SARS-COV-2 viral DNA. However, the magnitude of the reduction was greater in patients with greater baseline viral load.

In patients with a baseline viral load threshold of >7 log_{10} copies/mL, for each dose there was a -0.68 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 (Figure 1).

In patients with a baseline viral load threshold of >4 log_{10} copies/mL, for each dose there was a -0.47 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 for each) (Figure 2).

- With respect to serologic status, the benefit of REGN-COV2 was almost exclusively in patients who had not yet developed effective immunity to SARS-COV-2.

In patients that were seronegative at baseline, there was a -0.74 log10 copies/mL and -0.71 log_{10} copies/mL difference from placebo with the REGN-COV2 2400 mg and REGN-COV2 8000 mg treatment arms, respectively, in the least squares (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 least squares (LS) mean time-weighted-average daily change from baseline in viral load through Day 7 for patients treated with either dose of REGN-COV2 was similar to the reduction in patients treated with placebo (REGN-COV2 2400 mg, 0 log_{10} copies/mL difference from placebo, p=0.9938; REGN-COV2 8000 mg 0.1 log_{10} copies/mL difference from placebo, p=0.6539).

Although REGN-COV2 did not further enhance viral clearance in patients who already had adequate immunity to the virus, it did not reduce the rate of viral clearance. Thus, there is no apparent harm to treating patients in whom serologic status is unknown.

Medically Attended Visits (MAVs)

Data for the key secondary endpoint of medically attended visits (Analysis Group 1/2) are provided in table 3 below.

Table 3. Proportion of patients with ≥1 COVID-19 related medically-attended visits through Day 29 (mFAS), Analysis group1/2

	REGN-COV2 8000 mg (n=219)	REGN-COV2 2400 mg (n=215)	Placebo (n=213)	Treatment Effect, REGN-COV2 Combined vs Placebo	
	Number of Patients / N (%)			Difference (95% CI)	P-value
Overall	6/219 (2.7%)	6/215 (2.8%)	15/231 (6.5%)	-3.7% (-11.7%, 4.3%)	0.0240
Seronegative	4/115 (3.5%)	4/121 (3.3%)	12/124 (9.7%)	-6.3% (-17.1%, 4.6%)	0.0264
≥1 Risk Factor* for Hospitalization due to COVID-19	4/132 (3.0%)	3/134 (2.2%)	13/142 (9.2%)	-6.5% (-16.6%, 3.7%)	0.0065

* 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.

Treatment with REGN-COV2 significantly reduced the risk for COVID-19 related medically-attended visits (MAVs) compared to placebo. Overall, in the mFAS population of Analysis Group 1/2, the

proportion of patients with ≥1 MAV (hospitalization, ER visit, Urgent Care visit, physician office/telemedicine visit) was reduced by 57% in the REGN-COV2 treatment arms (2.8% combined treatment arms vs 6.5% placebo) (p=0.0240). The proportion of patients with ≥1 MAV using a narrower definition of hospitalization, ER visit, and Urgent Care visit, was also numerically lower in the REGN-COV2 treatment arms compared to placebo but did not reach statistical significance (2.3% combined treatment arms vs 4.3% placebo; p=0.1575).

These effects were similar across both REGN-COV2 dose groups, suggesting the absence of a dose response for this clinical endpoint.

Treatment benefit with REGN-COV2 seemed to start approximately 1 week after receiving treatment. This timing is consistent with the idea that clinical symptoms improve only after achieving several days of viral suppression and thus MAVs earlier in the disease course may not be modifiable with an antiviral therapy.

While in general the number of MAVs was low, natural history analysis in the placebo group showed that seronegativity, increasingly higher baseline levels of viral load and pre-existing risk factors (e.g. age >50 years old, obesity, co-morbid conditions), all assessed at baseline, correlated with higher risk for MAVs (Table 3). Treatment with REGN-COV2 in these high-risk groups showed the greatest benefit. For example, in the group of patients in the mFAS that also had pre-existing risk factors for severe COVID-19, treatment with REGN-COV2 reduced the number of patients with a MAV by 72% compared to placebo (2.6% combined vs 9.2% placebo; nominal p = 0.0065).

Similar to the analysis of the virologic data, and despite very low numbers, analysis of the MAV data suggests that MAVs in seropositive patients and patients with viral loads ≤4 log10 copies/mL are less modifiable with treatment.

The results observed in Analysis Group 1/2 were consistent with the clinical efficacy results observed in Analysis Group 1 (2% combined treatment arms vs 7.4% placebo) and Analysis Group 2 (3.1% combined treatment arms vs 6% placebo). These data indicate the potent antiviral effects of REGN-COV2 can translate to meaningful clinical benefits for the patient by reducing the need for clinical attention that results in a MAV.

B. Treatment study COV-2066 (Supportive data)

COV-2066 is an adaptive, phase 1/2/3, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and tolerability of REGN-COV2 in hospitalized adult patients with COVID-19.

Patients were randomized in a 1:1:1 allocation ratio to receive single IV doses of 2400mg of the casirivimab and imdevimab combination, 8000 mg of the casirivimab and imdevimab combination, or placebo. Randomization was stratified by country (phase 2 only) and the type of background standard-of-care being administered for COVID-19 at randomization (phase 1 and phase 2) as follows:

- Antiviral therapies only (e.g., remdesivir, other)
- Non-antiviral therapies: Immune-based therapies, both antiviral and immune-based therapies, or no COVID-19-specific treatment

The trial population consisted of eligible adults with laboratory-confirmed SARS-COV-2 infection, symptoms consistent with COVID-19 for < 10 days, and hospitalization for ≤72 hours at the time of randomization. Patients were enrolled into 1 of 4 cohorts:

- Cohort 1A (Room Air): Patients with COVID-19 symptoms but not requiring supplemental oxygen
- Cohort 1 (Low Flow Oxygen): Patients with O2 saturation >93% on low flow oxygen via nasal cannula, simple face mask, or other similar device
- Cohort 2 (High Intensity Oxygen): Patients requiring high intensity oxygen therapy but not on mechanical ventilation
- Cohort 3 (Mechanical Ventilation): Patients on mechanical ventilation

The study is currently ongoing, enrolling adult patients requiring no supplemental oxygen support (cohort 1A) and patients requiring low flow oxygen supplementation (cohort 1); patients requiring high intensity oxygen supplementation (cohort 2) or mechanically ventilation (cohort 3) are currently on enrolment-hold since 30 Oct 2020 based on IDMC recommendations.

The study is double-blind and placebo controlled.

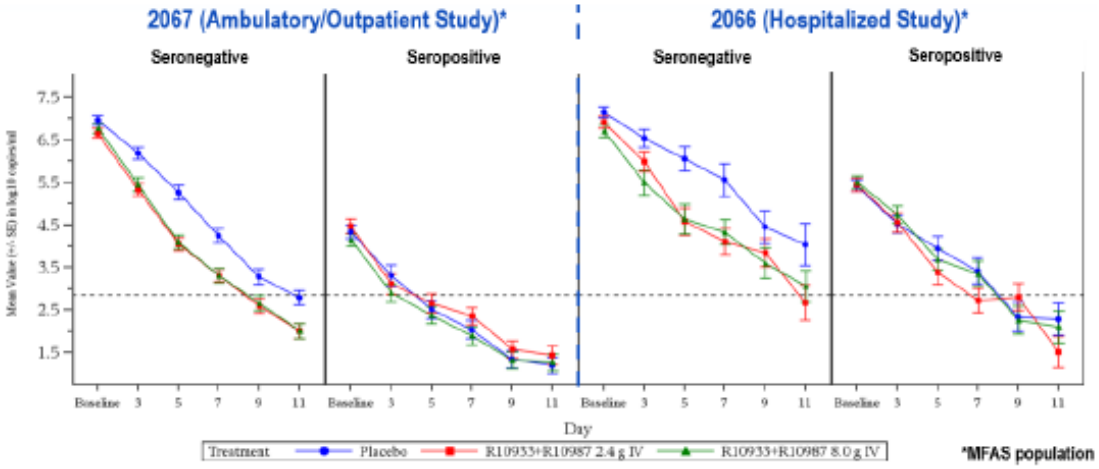
The results described here are based on the pre-specified primary analysis of the phase 1/2 portion of the study for cohort 1 and consists of the first 671 patients randomized and treated. Cohort 1A (hospitalized patients not requiring oxygen) was not included in the phase 1/2 analysis.

The primary objective of this analysis was to exclude futility in cohort 1 based on α = 0.3 (1-sided) and evaluate safety and tolerability of REGN-COV2. If futility is excluded, the composite clinical efficacy endpoint of death or mechanical ventilation would be evaluated based on α = 0.1 (1-sided).

Virologic Efficacy

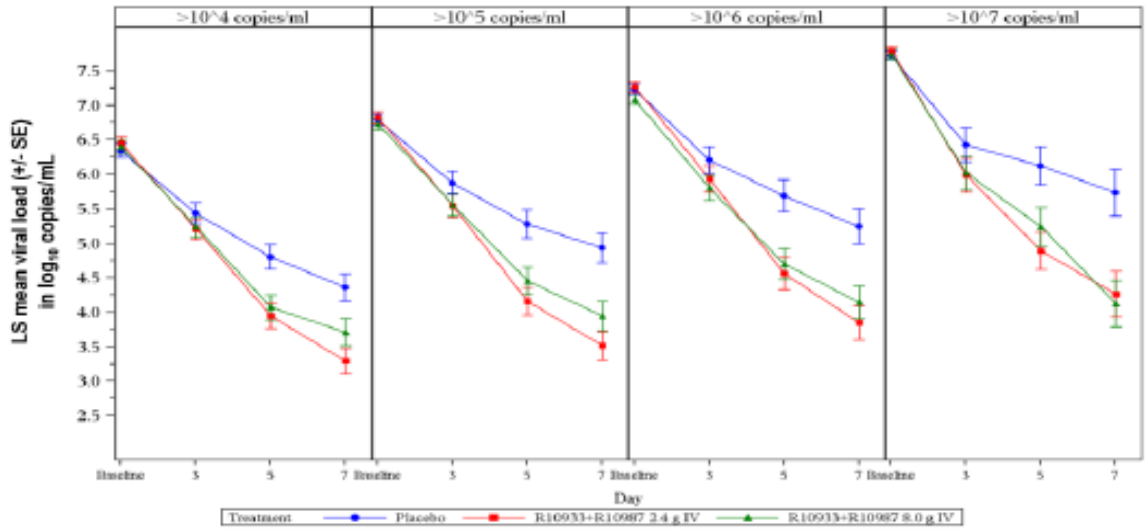
Treatment with REGN-COV2 resulted in a statistically significant reduction in the time-weighted average daily change from baseline in viral load (log_{10} copies/mL) from day 1 through day 7. Reductions were observed in the overall mFAS population and in other subpopulations, including those with higher baseline viral load (e.g. >106 copies/mL) or who were seronegative at baseline. Consistent effects were observed for the individual doses, indicating the absence of a dose effect. The antiviral benefit of REGN-COV2 was observed regardless of the background concomitant COVID-19 therapies used, such as remdesivir or dexamethasone.

Figure 3. Reduction in viral load through Day 11 (log_{10} copies/mL) by Serostatus: COV-2067 and COV-2066



The virologic efficacy results observed in COV-2066 were consistent with the virologic efficacy results observed in the outpatient study (COV-2067).

Figure 4. Reduction in average daily viral load through Day 7 (log_{10} copies/mL) by baseline viral load threshold: Comparison of REGN-COV2 vs placebo (mFAS) in cohort 1, Phase ½



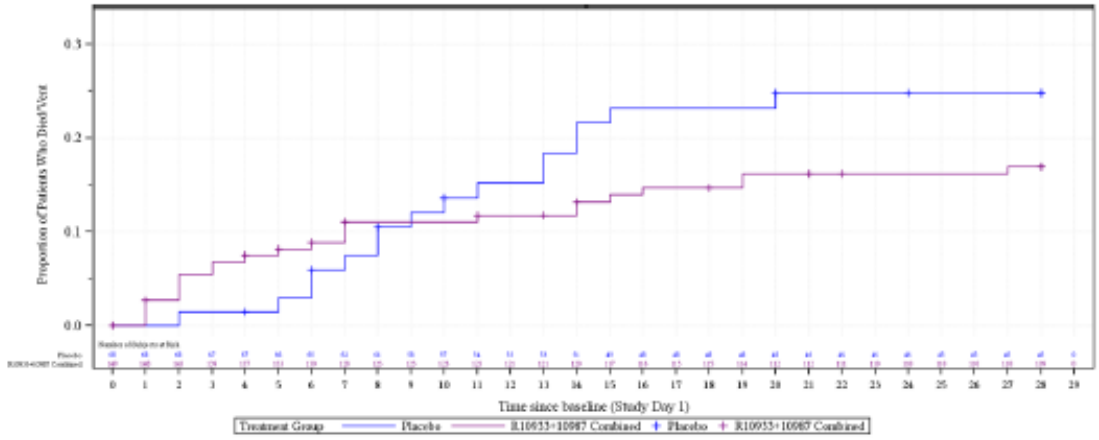
Clinical Efficacy

Futility (for clinical benefit) was excluded for REGN-COV2 (2400 mg and 8000 mg, pooled doses vs placebo) based on a 0.78 HR for risk of death or mechanical ventilation in the seronegative mFAS

population of Cohort 1 (p = 0.23, which is below the pre-specified α = 0.3 [1-sided]), with 27.5% reduction in proportion of death or ventilation. Although sample sizes were too small to definitively demonstrate clinical efficacy, there was a trend in risk reduction for death or mechanical ventilation in the pre-specified seronegative mFAS population; similar trends were also seen in patients with high viral load (which correlates with seronegativity). Trends for benefit were only apparent after approximately 1 week.

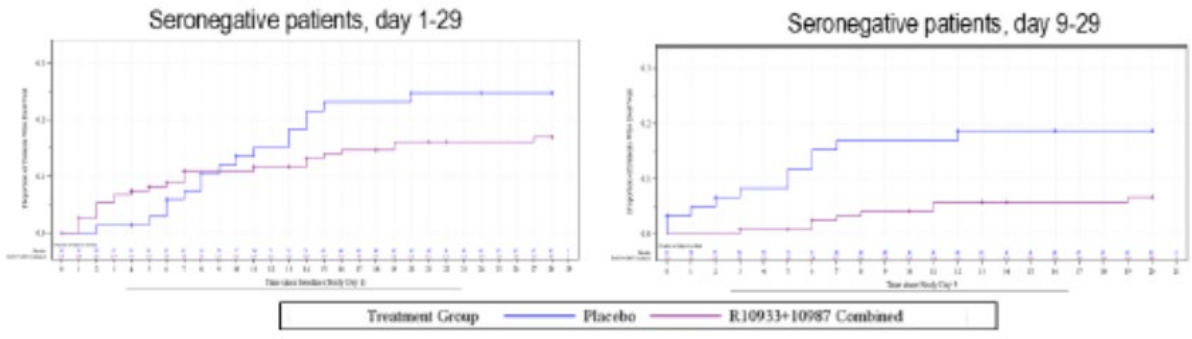
Minimum follow-up for this futility analysis was 1 week after treatment initiation. A follow up analysis with complete 28-day follow-up on all patients shows incremental improvement in clinical benefit (as expected due to non-proportional hazard ratio), with 0.71 HR for risk of death or mechanical ventilation. A post-hoc analysis showed a 31.5% relative risk reduction in the proportion of patients who died or went on mechanical ventilation in the seronegative mFAS population (P = 0.095, [one-sided]).

Figure 5. Kaplan Meier curve for cumulative incidence of death or mechanical ventilation in Seronegative patients: Comparison of REGN-COV2 vs placebo (mFAS) in cohort 1, Phase 1/2



Patients randomized through 01 Dec 2020, data cut-off date 19 Jan 2021.

Figure 6. Kaplan Meier curve for cumulative incidence of death or mechanical ventilation in seronegative patients for Day 1-29 and Day 9-29 (Landmark analysis): Comparison REGN-COV2 vs placebo (mFAS) in cohort 1, Phase 1/2



Patients randomized through 01 Dec 2020, data cut-off date 19 Jan 2021.

Treatment benefit (on clinical endpoints) with REGN-COV2 seemed to start approximately 8 days after receiving treatment (Figure 4). This timing is consistent with the idea that clinical impact would occur only after achieving several days of viral suppression and thus death or mechanical ventilation events earlier in the disease course may not be modifiable with an antiviral therapy.

A review of the Kaplan Meier curve indicates non-proportional hazard is observed in the data. As such, additional landmark analyses were done to evaluate the impact of REGN-COV2 from day 9 to 29, which showed a risk reduction of 69% (p = 0.006) in death or mechanical ventilation for seronegative patients on low flow oxygen (Figure 5).

In seropositive patients, there is no clear clinical benefit of the antibody cocktail (clinical endpoint HR: 0.99 for combined doses).

Table 4. Patients that died or went on mechanical ventilation: Comparison of REGN-COV2 vs placebo in Cohort 1 (Seropositive mFAS), Phase 1/2

	Placebo (N=96)	Combined REGN-COV (N=174)
Event #	8	15
Cum. Incid. (%) (80% CI)	8.9% (5.7%, 13.6%)	9.1% (6.6%, 12.4%)
HR (80%CI)		0.99 (0.56, 1.74)
P-value		0.4912

Patients randomized through 01 Dec 2020, data cut-off date 19 Jan 2021.

While cohort 1A of study COV-2066 would be relevant to the indication of this procedure, these data were considered supportive.

REGN-COV2 (nominal significance) reduced viral load greater than placebo in patients who were SARS-COV-2 RT-qPCR positive by NP swab at baseline (mFAS). The magnitude of the reduction was greater in patients with greater baseline viral load.

With respect to serologic status, the benefit of REGN-COV2 was almost exclusively in patients who had not yet developed effective immunity to SARS-COV-2 (seronegative patients). These data were consistent with the observation in study COV-2067.

A trend for treatment benefit was observed (relative risk reduction in proportion of patients who died or were mechanically ventilated through day 29 was 31.5%). No treatment benefit was apparent during the first 8 days of treatment. The delayed treatment effect is not unexpected and consistent with the proposed mode of action i.e. viral control translates in clinical benefit. Given the time needed to achieve viral control it might be possible that early events are not modifiable by the antibody therapy.

Further, results do not allow any firm conclusion. Results are not significant at the specified one-sided significance level of α=0.1, which is far more uncertain than would usually be required to conclude any benefit. It is agreed that there appears to be a positive trend, but this is highly uncertain given the limitations that can be observed (statistical significance, uncertainty in the estimates, analysis model and assumptions, etc.)

Table 5. Overview of key efficacy data

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
Therapeutic indication: *Treatment of confirmed COVID-19 in patients that do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.*					
COV-2067: OUTPATIENT STUDY, a phase 1/2/3 randomized, double-blind, placebo-controlled trial in ambulatory adults with mild to moderate COVID-19 symptoms	The average daily change in viral load through day 7 Medically-Attended Visits (MAVs) for COVID-19 were defined as hospitalizations, emergency room (ER) or urgent care visits, or physician office or telemedicine visits with the primary reason for the visit being COVID-19.	Outpatients who are at high risk of severe coronavirus disease 2019 (COVID-19)	not described	REGN10933+REGN10987 (low dose): REGN10933+REGN10987 (high dose) Placebo: 130 patients	Viral load reduction of greater than placebo in all patients who were positive at baseline (RT-qPCR, for SARS-COV-2 viral DNA). Reduction of COVID-19-related medically-attended visits (MAVs) compared to placebo
COV-2066: adaptive, phase 1/2/3, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, and tolerability of REGN-COV2 in hospitalized adult patients with COVID-19.	Investigate the effect of REGN-COV2 on the composite endpoint of death or mechanical ventilation (whichever occurs first) in hospitalised patients with covid-19	Hospitalized patients with covid-19			Trend towards a reduction of death or mechanical ventilation in the subset of Patients with O2 saturation >93% on low flow oxygen via nasal cannula, simple face mask, or other similar device.

Populations

The Study COV-2067 was done in adults. There are no data currently available from this study in paediatrics. An amendment to add this age group to the study was introduced in January 2021. However, paediatric patients ≥12 years have been included in the REGN-COV2 study COV-2069.

Nevertheless, the existing PK data from adult patients with COVID-19 indicate the PK of casirivimab and imdevimab can be described by linear and concentration-independent clearance. Typically, linear clearance for IgG monoclonal antibodies is similar between adults and adolescents, after adjusting for body weight, and is independent of age. As the lower end of the proposed body weight range for paediatric patients ≥12 years of age (40 kg) falls within the range of expected body weights for adult patients, similar exposures are expected between these 2 populations for a single IV dose of REGN-COV2. Exposures are therefore expected to be similar to those in adults as their weights overlap with those of the adult patients, and weigh is the only baseline covariate that would be anticipated to affect exposure. Further, the mAbs in the REGN-COV2 cocktail are directed against an exogenous target, and therefore based on this mechanism of action, a difference in safety and efficacy between paediatric patients ≥12 years and adults, is not expected.

The CHMP accepted this extrapolation of data to adolescents (children aged 12 and over).

2.2.2. Conclusions on efficacy

The efficacy of REGN-COV2 in 799 outpatient adults with COVID-19 was evaluated in a randomized, double-blinded, placebo-controlled clinical trial, study COV-2067. Patients were randomised in a 1:1:1 manner to receive a single intravenous (IV) infusion of 2400 mg of the combination of casirivimab and imdevimab (1200 mg of each), 8000 mg of the combination of casirivimab and imdevimab (4000 mg of each), or placebo (n=266, n=267, n=266, respectively). To be eligible for enrolment, subjects had to have laboratory-confirmed SARS-CoV-2 infection, COVID-19 symptom onset ≤ 7 days from randomization, maintain O2 saturation ≥93% breathing room air, not have prior or current use of putative COVID-19 treatments (e.g. convalescent plasma, systemic corticosteroids or remdesivir) and not have been previously or currently hospitalised for treatment of COVID-19.

The study duration was 28 days for each patient. Throughout the study nasopharyngeal (NP) swab samples were collected; information about any medically attended visits related to COVID-19 was also collected.

An initial descriptive analysis on virologic endpoints was conducted on the first 275 patients (Analysis Group 1). To independently replicate the descriptive analyses conducted in the first 275 patients, the primary virologic analyses were conducted in the next 524 patients (Analysis Group 2). The primary clinical analyses were conducted in the entire 799 patient population. (Analysis Group 1/2).

For all efficacy endpoints, analyses were conducted in a modified full analysis set (mFAS) defined as subjects who had a positive reverse transcription quantitative polymerase chain reaction (RT-qPCR) test at baseline. In Analysis Group 2, the primary virologic endpoint was the reduction in daily viral load (log_{10} copies/mL) from baseline through day 7 (measured as a mean time-weighted-average daily change). The key clinical endpoint (Analysis Group 1/2) was the proportion of patients who tested RT-qPCR positive at baseline requiring 1 or more medically attended visits (MAVs) for progression of COVID-19.

The virologic endpoints in Analysis Group 1 were hierarchically tested and confirmed in Analysis Group 2. There was significant reduction in viral load among all patients treated with REGN-COV2. The

largest reduction in viral load were seen among patients with high viral load at baseline (> 106 or > 107 copies/mL) and among patients who were seronegative at baseline.

Overall, demonstrated benefits seen were the reduction of COVID-19-related medically-attended visits (MAVs) compared to placebo, and reported in the overall mFAS, in seronegatives and in subjects with ⩾1 risk factor for severe disease.

In addition, the viral load reduction of greater than placebo in all patients who were positive at baseline (RT-qPCR, for SARS-COV-2 viral DNA), for the magnitude of the effects was greater in patients with higher baseline viral load and the

benefit of REGN-COV2 was almost exclusively in patients who had not yet developed effective immunity to SARS-COV-2.

These data are consistent in Study COV-2066 and Study COV-2067. The trend in risk reduction for death or mechanical ventilation in the pre-specified seronegative mFAS population. Similar trends were also seen in patients with high viral load (Cohort 1 (Low Flow Oxygen): Patients with O_2 saturation >93% on low flow oxygen via nasal cannula, simple face mask, or similar device. (Study COV-2067).

The CHMP also considered that the observed benefits are preliminary and would require further confirmation within the appropriate framework.

2.2.3. Safety

Data on safety were collected in the studies performed.

A. Study COV-2067 (main study)

Only targeted adverse events were collected during the study COV-2067, consisting of 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, and in phase 1 only, all grade 3 and grade 4 treatment-emergent adverse events (TEAEs)

A summary of the targeted AEs is provided in the table 6 below for all patients in the study (FAS of Analysis Group 1/2, n=799 patients).

Table 6. Overview of Adverse Events

	Placebo (N=262)	REGN-COV2	
		2400 mg IV (N=258)	8000 mg IV (N=260)
Patients with any AESI	2 (0.8%)	0	4 (1.5%)
Infusion-related reactions grade ≥2 through day 4	1 (0.4%)	0	4 (1.5%)
Patients with hypersensitivity reactions grade ≥2 through day 29	2 (0.8%)	0	0
AESI leading to study infusion interruption	1 (0.4%)	0	1 (0.4%)
Patients with any SAE	6 (2.3%)	4 (1.6%)	2 (0.8%)
Patients with any grade 3 or 4 TEAE	4 (1.5%)	3 (1.2%)	2 (0.8%)
Deaths	0	0	0
Patients with any TEAE Leading to study withdrawal	0	0	1 (0.4%)

Serious Adverse Events

Serious Adverse Events (SAEs) were experienced by 4 (1.6%) patients in the REGN-COV2 2400 mg group, 2 (0.8%) patients in REGN-COV2 8000 mg group and 6 (2.3%) patients in the placebo group (Table 6). None of the events were considered to be related to the studied drug. The SAEs reported were evaluated and considered to be due to advanced and progressive COVID-19 disease and/or associated concomitant clinical conditions.

None of the SAEs reported by more than one patient. There were no grade 4 SAE events reported. Grade 3 events were reported in 3 (1.2%) in REGN-COV2 2400 mg group, 2 (0.8%) in REGN-COV2 8000 mg group, and 4 (1.5%) in the placebo group.

Adverse Events of Special Interest

Adverse Events of Special Interest (AESIs) were experienced by 4 (1.5%) patients in the REGN-COV2 8000 mg group and 2 (0.8%) patients in the placebo group. No patient experienced an AESI in the REGN-COV2 2400 mg group. One (0.4%) patient in the REGN-COV2 8000 mg dose group discontinued study treatment due to infusion-related reactions. One (0.4%) patient each in REGN-COV2 8000 mg dose group and the placebo group experienced treatment interruption due to AESIs: treatment in the patient in the REGN-COV2 8000 mg group was terminated and the patient only received a partial dose; treatment in the patient in the placebo group was tolerated at a lower infusion rate and the patient was able to receive the full dose (Table 6). The adverse events reported as AESIs were all moderate in intensity and no severe or serious AESIs were reported. All AESIs were reported on the day of study drug infusion except for one event of hypersensitivity reaction (preferred term: Rash) reported on day 20 in the placebo group.

Deaths

No patients experienced an event leading to death.

B. Study COV-2066 (hospitalised patients)

Specifically, in COV-2066 cohort 1 (09 Dec 2020 data cut), similar numbers of deaths and SAEs across treatment arms were observed.

Deaths: 10.8% in placebo group, 9.4% in 2400 mg low dose group, 8.9% in 8000 mg high dose group

SAEs: 24.3% in placebo group, 20.1% in 2400 mg low dose group, 20.9% in 8000 mg high dose group

AESIs were reported in 1.8% in the placebo group, 1.8% in the 2400 mg low dose group, 3.1% in the 8000 mg high dose group.

There was a numerically higher number of patients with infusion-related reactions Grade ≥2 through day 4 in the 8000 mg high dose group (n=6, 2.7%) compared to placebo (n=3, 1.4%), and the 2400 mg low dose group (n=2, 0.9%).

Hypersensitivity reactions through day 29 were reported in 0.5% in the placebo group, 1.3% in the 2400 mg low dose group, and 0.9% in the 8000 mg high dose group.

C. Study COV-2069 (prevention study)

The study COV-2069 provides additional safety data but it cannot support the treatment indication.

AEs occurred in a numerically lower proportion of patients who received REGN-COV2 with the difference driven by the increased rate of SARS-CoV-2 infections in the placebo group.

Seronegative patients: 20.3% (n=45) in placebo group and 10.2% (n=19) in REGNCOV2 group.

Seropositive patients: 23.9% (n=11) in placebo group and 8.3% (n=5) in REGN-COV2 group.

Other: 11.1% (n=2) in placebo group and 28.6% (n=6) in REGN-COV2 group.

Small numbers of patients experienced SAEs:

Seronegative patients: 1.4% (n=3) in placebo group and 0.5% (n=1) in REGN-COV2 group.

Seropositive patients: 2.3% (n=1) in placebo group and 1.7% (n=1) in REGN-COV2 group.

Other: 0% (n=0) in placebo group and 4.8% (n=1) in REGN-COV2 group. This one patient had 3 SAEs which were all related to 3 fractures sustained during a traumatic accident.

There was only one COVID-19 related hospitalisation and that was in the placebo group.

There was only 1 death in the study, in a seropositive patient in the placebo group, occurring approximately 6 weeks after study drug administration (preferred term: cardiac arrest). Review of the case does not suggest a relationship between this death and SARS-CoV-2 infection.

No patients experienced AESIs of Grade ≥3 injection site reactions or hypersensitivity reactions.

The overall number of patients with injection site reactions was low: 1.4% (4/286) in the placebo group, 2.6% (7/267) in the REGN-COV2 group.

D. Post-marketing data

Cumulatively, there have been 503 events reported in 160 cases, in the USA following the emergency use authorisation granted for REGN-COV2.

Overall, the events observed and reported were consistent with those observed in clinical trials. No new safety signals were identified from safety reports received under the emergency use. The events reported were consistent with infusion related reactions or underlying COVID-19 disease in these patients.

Of the 57 medication error cases reported cumulatively, 46 of these describe an incident. No adverse events were reported to be associated with these medication errors.

Cumulatively, 79 cases reported 171 serious adverse events excluding medication errors. The most commonly reported events cumulatively, occurring ≥ 10 patients, were headache, dyspnoea, nausea, chills, chest pain, fatigue, injection site pain, and pyrexia. These events are consistent with infusion related reactions or symptoms of COVID-19, similar to adverse events observed in the clinical trials and also included the medication error cases. The onset of the events was most commonly within 24 hours of the infusion, 117 events (38 patients) occurred within 24 hours of study drug infusion. There were no fatal events reported.

In the analysis of complete safety dataset no new safety signals were identified. Safety data reported are consistent with clinical trials experience. After cumulative review of data, no safety issue has been identified that would impact the condition for use.

2.2.4. Conclusions on safety

Overall, no SAEs reported were considered to be related to the study medicinal product. No patients experienced an event leading to death. The AESIs events reported were all moderate in intensity and

no severe or serious AESIs were reported. All AESIs were reported on the day of study drug infusion including hypersensitivity reactions. The frequency was low.

From the US post-marketing data, the most commonly reported events cumulatively, occurring ≥ 10 patients, were headache, dyspnoea, nausea, chills, chest pain, fatigue, injection site pain, and pyrexia. These events are consistent with infusion related reactions or symptoms of COVID-19. No new signals were detected.

From the currently available safety information there are no major safety concerns. The reported safety data indicated that REG-COV2 has a favourable safety profile. The Committee considered that once it is authorised for use, this medicine should be subject to additional monitoring. This enables to stimulate ADR reporting in order for new safety information to be identified quickly. Healthcare Professionals will be asked to report any suspected adverse reactions.

2.3. Non-clinical aspects

SARS-CoV-2 spike glycoprotein (S protein) is a class I transmembrane envelope protein that forms a homo-trimer and mediates binding, fusion, and viral entry into host cells. The S protein is essential for virus infectivity and is the main target of the humoral immune response, as demonstrated by serology analysis of recovered COVID-19 patients. The S protein mediates binding to the host receptor angiotensin converting enzyme 2 (ACE2), resulting in membrane fusion and entry of the virus into susceptible cells. The S protein is composed of 2 functional subunits: the S1 subunit that contains the receptor binding domain (RBD), which binds to ACE2 on host cells, and the S2 subunit, which mediates fusion of the viral and cellular membranes. Structural studies have mapped the interface between human ACE2 and SARS-CoV-2 RBD, and results suggest simultaneous binding of 2 individual S protein trimers to a single ACE2 dimer.

As the S protein is required for viral entry, blockade of its interaction with the ACE2 receptor may offer a powerful way to block viral infectivity and spread. Indeed, a vaccine study utilizing the S protein as an immunogen has shown prophylactic efficacy in the rhesus macaque model of COVID-19, with a several log-fold decrease in viral load versus naïve animals.

REGN10933 and REGN10987 are high-affinity human IgG1 anti-SARS-CoV-2 mAbs that bind specifically to the RBD of the S protein of SARS-CoV-2 and neutralize virus activity by blocking binding to ACE2. REGN10933 and REGN10987 were developed for co-administration (referred to as REGN-COV2) to minimize the likelihood of virus escape. REGN10933 was isolated from Regeneron's VelocImmune® human antibody mouse platform. REGN10987 was isolated from B cells of human donor previously infected with SARS-CoV-2.

2.3.1. Pharmacology

2.3.1.1. In vitro

Binding to target

The structural basis for REGN10933 and REGN10987 binding to the target SARS-CoV-2 receptor binding domain (RBD) was assessed using cryogenic electron microscopy (cryo-EM). Single-particle cryo-EM of the complex of SARS-CoV-2 spike RBD bound to Fab fragments of REGN10933 and REGN10987 shows that the two antibodies in this cocktail can simultaneously bind to distinct regions of the RBD. REGN10933 binds at the top of the RBD, extensively overlapping the binding site for ACE2. The epitope for REGN10987 is located on the side of the RBD, away from the REGN10933 epitope, and

has little to no overlap with the ACE2 binding site. Analysis of the binding interface between the RBD and the 2 antibody Fab fragments indicated that REGN10933 and REGN10987 almost exclusively contact the RBD via their heavy chains. Results from cross-competition studies using SPR technology, further demonstrated that REGN10933 and REGN10987 bind non-overlapping epitopes on SARS-CoV-2 RBD.

Moreover, sequence analysis using of 79,677 publicly available SARS-CoV-2 genomes identified through mid-August 2020 revealed that the RBD residues bound by REGN10933 and REGN10987 are highly conserved regions (i.e.≥99.96% and ≥99.98%, respectively, at each position across 58,728 SARS-CoV-2 S protein variants that were of sufficient quality for the analysis).

The kinetic binding parameters for the interaction of anti-SARS-CoV-2 S protein mAbs with monomeric and dimeric SARS-CoV-2 RBD as well as with stabilised, trimerized SARS-CoV-2 S protein were determined using surface plasmon resonance (SPR) technology. SPR experiments demonstrate that REGN10933 and REGN10987 each bind monomeric and dimeric recombinant SARS-CoV-2 RBD and stabilized, trimerized SARS-CoV-2 S protein with high affinities.

In addition, binding of the individual mAbs and REGN-COV2 to immobilised monomeric SARS-CoV-2 RBD protein was shown in a concentration-dependent manner with EC50 values in the subnanomolar range via ELISA. Furthermore, the ability of REGN10933, REGN10987, and REGN-COV2 to block binding of dimeric SARS-CoV-2 RBD to human ACE2 was analysed using sandwich ELISA. Results provided show that dimeric SARS-CoV-2 RBD binds human ACE2 with an EC50 value of 150pM, and that REGN10933, REGN10987 and REGN-COV2 mediate concentration-dependent blocking of 100pM RBD binding to ACE2 with IC50 values in the picomolar range.

Overall, binding to target was appropriately evaluated using different methods to analyse binding sites, structural analysis of the REGN-COV2-target-complex, binding affinities and concentration-dependent blocking of SARS-CoV-2 RBD to human ACE2. REGN10933 and REGN10987 bind to non-overlapping epitopes of the SARS-CoV-2 RBD. As no RBD residues are shared by REGN10933 and REGN10987, a single point mutation is unlikely to affect both epitopes. Furthermore, sequence analysis revealed that the epitopes bound by REGN-COV2 were conserved in circulating SARS-CoV-2 viruses (as of August 2020).

2.3.2. Pharmacology

Primary pharmacology

Binding affinity and primary mode of action

REGN10933 (casirivimab) and REGN10987 (imdevimab) each bind monomeric and dimeric recombinant SARS-CoV-2 RBD (receptor binding domain) with nanomolar and picomolar affinities, respectively, and stabilized, trimerized SARS-CoV-2 S protein with picomolar affinities. The epitopes for the two different antibodies are not overlapping (no competition of binding), providing support to the scientific rationale of combining the two antibodies in REGN-COV2. The binding of REGN10933, REGN10987, and REGN-COV2 to SARS-CoV-2 RBD is concentration-dependent, with EC50 values in the subnanomolar range. Furthermore, concentration-dependent inhibition of RBD binding to its receptor ACE2 (angiotensin converting enzyme 2) by REGN10933, REGN10987, or REGN-COV2 was demonstrated with IC50s in the picomolar range.

***In vitro* antibody effector function activity**

IgG antibodies bound to target cells can activate effector functions via their constant (Fc) region by interacting with specific Fcγ receptors (FcγR) expressed on different cells (like phagocytes and NK cells), or by binding to complement proteins in serum. Antibody effector functions are an important part of the humoral immune response and can contribute to increased clearance of infective agents.

The effector function potential of REGN10933, REGN10987 and REGN-COV2 was assessed to determine:

1) the ability to mediate ADCP (antibody-dependent cellular phagocytosis) of target cells using monocyte-derived macrophages as effector cells

2) the ability to mediate ADCC (antibody-dependent cellular cytotoxicity) of target cells using primary NK cells as effector cells

3) the ability to activate FcγR3A receptor signalling in an ADCC-surrogate reporter assay

4) the ability to mediate CDC (complement-dependent cytotoxicity) of target cells in presence of normal human serum (NHS)

In summary, studies demonstrate that REGN10933, REGN10987 and REGN-COV2 mediate ADCP and ADCC of target cells expressing SARS-CoV-2S protein (EC50 values in pico- to low nanomolar range), but do not mediate CDC. Based on these *in vitro* investigations, it can be concluded that antibody effector functions ADCP and ADCC are a part of mode of action for REGN-COV2.

***In vitro* neutralisation of different SARS-CoV-2 variants and escape mutants**

Reduced binding affinity and/or neutralization activity for antibodies targeting viruses may occur because of development of escape mutants under drug pressure, or due to change of balance between naturally circulating virus populations. Genetic analyses performed by the Company indicate that RBD residues bound by REGN10933 and REGN10987 are conserved in circulating SARS-CoV-2 viruses (as of August 2020) and confirm that epitopes are non-overlapping. Hence, the use of a combination is likely to reduce the likelihood of loss of antiviral activity on different variants and escape mutants. Furthermore, the Company has investigated the ability of REGN10933, REGN10987, and REGN-COV2 to neutralize SARS-CoV-2 spike protein in pseudoparticles expressing the predominant circulating SARS-COV2 virus (D614G with variant D614N), and 37 other different RBD variants (aa319-541) that were in circulation as of March 2020. Of the 39 virus variants tested, REGN10987 demonstrated a >5-fold reduction in neutralization potency in the presence of only one variant: N439K, compared with reference virus. The REGN-COV2 combination did not demonstrate reduction in neutralization potency >5-fold with any of the variants tested.

Europe is at the moment (February 2021) experiencing an increase in spread of the SARS-CoV-2 variants 20I/501Y.V1 (first detected in UK), 20H/501Y.V2 (first detected in South Africa) and 20J/501Y.V3 (first detected Brazil/Japan). Transmissibility is increased for these variants, and there is a concern for increased morbidity and mortality. Key mutations are partly overlapping and presented in Table 7 (WHO Weekly Update 9 February 2021).

Table 7. Summary of emerging information on key variants of concern, as of 8 February 2021 (Source: WHO Weekly Epidemiological Update 9 February 2021)[2]

Nextstrain clade	20I/501Y.V1	20H/501Y.V2†	20J/501Y.V3
Pango lineage	B.1.1.7	B.1.351	B.1.1.28
GISAID clade	GR	GH	GR
Alternate names	VOC202012/01†	VOC202012/02	P.1†
First detected by	United Kingdom	South Africa	Brazil / Japan
First appearance	20 September 2020	Early August 2020	December 2020
Key mutations	• N501Y • D614G • 69/70 deletion • 144Y deletion • A570D • *E484K (detected only in 11 sequences)*[1]	• N501Y • D614G • E484K • K417N	• N501Y • D614G • E484K • K417N

It is noted that the panel of RBD variants and circulating SARS-COV2 virus included in the study above were selected based on the predominant SARS-COV2 virus and variants circulating in March 2020. However, in the response to the initial list of questions by CHMP, the Company confirmed that it is monitoring all variants identified via surveillance in an ongoing manner. The Company has so far evaluated the impact of individual mutations identified in either the United Kingdom (UK) or South African (SA) variants and the full UK B.1.1.7 variant on neutralization potency of REGN10933, REGN10987 and REGN-COV2 combination in the Vesicular Stomatitis Virus (VSV) based pseudovirus neutralization assay (Table 8). Neither of the individual mAbs nor the combination demonstrated loss of neutralization potency against the N501Y, D614G, or UK B.1.1.7 variant. K417N and E484K variants both reduced neutralization potency of REGN10933 but had no impact on the neutralization potency of REGN10987 or the REGNCOV2 combination. Independent external assessment of REGN10933, REGN10987 and the combination REGN-COV2 confirmed that the combination retains neutralization activity against both the B.1.1.7 and the B.1.1351 variants. Therefore, the Company concluded that the antibody combination remains active against both the UK B.1.1.7 variant and the individual mutations identified in the SA variant.

Table 8. Neutralisation Potency of REGN10933, REGN10987 and REGEN-COV Combination

Variant	REGN10933		REGN10987		REGEN-COV	
	IC_{50} (M)	fold decrease from reference	IC_{50} (M)	fold decrease from reference	IC_{50} (M)	fold decrease from reference
K417N [a]	4.78E-10	7.15	3.50E-11	0.86	5.24E-11	1.04
E484K [b]	1.13E-09	24.79	6.25E-11	1.71	3.28E-11	2.15
N501Y [c]	1.75E-10	0.93	1.65E-10	0.83	1.90E-10	0.96
D614G [d]	4.34E-11	0.90	4.57E-11	0.79	3.28E-11	0.68
UK B.1.1.7 [e,f]	1.52E-10	0.98	8.01E-11	0.70	1.40E-10	1.04

[2] https://www.who.int/publications/m/item/weekly-epidemiological-update---9-february-2021

Reference (D614G) [a]	6.69E-11	N/A	4.06E-11	N/A	5.03E-11	N/A
Reference (D614G) [b]	4.57E-11	N/A	3.65E-11	N/A	3.28E-11	N/A
Reference (D614G) [c]	1.88E-10	N/A	1.98E-10	N/A	1.98E-10	N/A
Reference (D614) [d]	4.81E-11	N/A	5.76E-11	N/A	4.82E-11	N/A
Reference (D614G) [e]	1.55E-10	N/A	1.15E-10	N/A	1.35E-10	N/A

[a,b,c,d,e] Specific reference sequence assessed in the same assay as each variant is identified in the table.

[f] UK B.1.1.7 variant contains the following mutations in the spike protein: H69del, V70del, Y145del, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

[g] SA 501Y.V2 variant contains the following mutations in the spike protein: D80Y, D215Y, K417N, E484K, N501Y, D614G, A701V

[h] CA variant contains the following mutations in the spike protein: L452R, D614G

Although data are reassuring, the situation with respect to predominant virus and key variants of concern is changing over time. Indeed, Starr et al. recently published a mapping of how all mutations to SARS-CoV-2's receptor-binding domain (RBD) affect binding by the antibodies in the REGN-COV2 cocktail and the antibody LY-CoV016 from another manufacturer. Reassuringly, their maps confirm that the N501Y mutation detected in several commonly circulating variants has no effect on the neutralizing capacity of REGN-COV2.

The potential effect of drug pressure on selection of escape mutants was investigated in vitro in VSV encoding SARS-CoV-2 S protein in the presence of REGN10933, REGN10987 and the combination REGN-COV2. In addition, SARS-CoV-2 spike RNA sequencing analysis of virus isolated from rhesus monkeys following prophylactic or therapeutic administration of REGN-COV2 was performed. Taken together, results from these pre-clinical studies indicate that in contrast to monotherapy with individual anti-S protein mAbs, treatment with the combination REGN-COV2 is less likely to lead to selection of viral escape mutants or decline in capacity of REGN-COV2 to neutralize SARS-CoV-2. More compelling clinical reports on virus population shifts emerging in patients treated with neutralizing antibodies are however accumulating.

Overall, available data suggest that the combination REGN-COV2 retains neutralization activity also against the important circulating B.1.1.7 and B.1.1351 variants. Importantly, the Company confirmed that they are continuously monitoring publicly available viral isolate sequences, published literature, sequencing data from internal *in vitro* and *in vivo* pre-clinical studies, as well as from patient sequencing data from clinical studies for spike protein variants and selecting those of potential concern for functional follow-up analysis.

Antibody-dependent enhancement (ADE)

One potential problem for antibody-based anti-viral therapeutics is the risk of exacerbating severity of the viral infection via antibody-dependent enhancement (ADE). ADE can occur through two distinct mechanisms in viral infections: by enhanced antibody-mediated virus uptake into Fc gamma receptor IIa (FcγRIIa)-expressing phagocytic cells leading to increased viral infection and replication, or by excessive antibody Fc-mediated effector functions or immune complex formation causing enhanced inflammation and immunopathology. Lack of, or insufficient, neutralising capacity of the antibody is considered to be an important driver in both mechanisms.

The Company used a cellular assay to determine the ADE potential for REGN-COV2, but notes the following caveats: 1) a Vesicular Stomatitis Virus (VSV)-SARS-CoV-2 S protein pseudoparticle system (pVSV-SARS-CoV-2-S pseudoparticles) is an artificial surrogate for SARS-CoV-2 virus, and 2) FcγR-positive immortalized cell lines are artificial surrogates for FCGR-positive primary cells. Results

demonstrated that REGN10987 alone or REGN-COV2 mediates entry of pVSV-SARS-CoV-2-S pseudoparticles into FcγRII+ Raji and FcγRI+/FcγRII+ THP1 cells, but not any of the other tested cell lines, despite expression of FcγRI or FcγRII. REGN10933 alone did not mediate entry of pVSV-SARS-CoV-2-S pseudoparticles into any of the tested cell lines. The assessment of these results is hampered by the equivocal results across different cell lines, and the obvious caveats pointed out by the Company. At potential insufficient neutralisation ADE in patients is a cause for concern, and further data is needed prior to extended clinical use. Thus, no firm conclusion can be drawn from non-clinical point of view at this stage.

In conclusion, while waiting for further non-clinical data, available clinical safety data should be scrutinized for occurrence of ADE in order to support safety.

Proof of Concept in *in vivo* models

Thus far, the *in vivo* efficacy of single doses of REGN-COV2 has been assessed for the treatment and prevention of SARS-CoV-2 infection in two NHP studies and one Syrian golden hamster study. Monkey and hamster are recognised models for pathogenic COVID-19 studies and have also been used for non-clinical evaluation of SARS-CoV-2 vaccines. Both species develop mild to moderate COVID19-like disease upon inoculation of upper airways with SARS-CoV-2. However, development of clinical symptoms of infection like loss of body weight and pulmonary pathology are more pronounced in hamster compared to monkeys, possibly making hamster a more suitable model to evaluate the effect of REGN-COV2.

Two to three days after REGN-COV2 administration in prophylactic studies, or one day prior to treatment in therapeutic setting, animals were challenged with an inoculum of SARS-CoV-2 virus via intranasal (IN) route (hamsters) or both IN and intratracheal (IT) route (monkeys). In all three studies, REGN-COV2 at doses from 5 mg/kg (hamster) clearly reduced viral load and replication in airways and reduced lung pathology compared with placebo or isotype control antibody. In hamster, body weight loss was reversed. It is noted that the therapeutic effect was modest compared to results in the prophylactic setting. No evidence of ADE, as assessed by increased viral load, more severe lung pathology, or enhanced weight loss, was observed in any treated animal.

Animal studies are not considered useful to address duration of effect of REGN-COV2. This is best predicted by clearance and half-life in patients. Complete ablation of viral genomic RNA (inoculate and newly replicating virus) was not observed in airways of animals in any study groups, indicating that there is a risk of transmissibility even in the prophylactic setting.

The preliminary conclusion is that REGN-COV2 reduces viral load and replication of SARS-COV2 in airways of animals, and thereby reduce infection mediated lung pathology in these models. In April 2021, results from two more vivo studies in hamster will be available, including both prophylactic and therapeutic setting. Considering that hamster appear to be a useful and relevant model, these results are likely to add useful information. Provided that clinical data can support efficacy, the results from the additional ongoing studies in hamster are however not considered pivotal for the progress of the current Art. 5(3) procedure.

Secondary pharmacology

Adequately covered by discussions of effector functions and cross-reactivity in human and non-human primate tissues under Primary pharmacology and Other toxicology studies, respectively.

Safety pharmacology

The lack of dedicated studies on safety pharmacology is acceptable since safety pharmacology parameters were included as part of the GLP-compliant repeat-dose toxicity study in cynomolgus monkeys.

Pharmacodynamic interactions

Not applicable for selective monoclonal antibodies.

2.3.3. Pharmacokinetics

The pharmacokinetic properties of REGN10933 and REGN10987 when given alone and in combination (as REGN-COV2) were evaluated following IV and SC administration in two non-GLP PK studies in uninfected male Cynomolgus monkeys. Repeat-dose PK studies have not been conducted, but TK data from a GLP-compliant 4-week repeat-dose toxicity study in monkeys were presented. Females were not included in the PK studies, but TK data from both males and females do not indicate sex differences.

Pharmacokinetic data

The nonclinical PK data obtained for REGN-COV2 were as predicted for mAbs directed against an exogenous target, with linear kinetics demonstrated for both REGN10933 and REGN10987 when administered alone as well as in combination, and no impact on the PK and TK of the individual REGN10933 and REGN10987 mAbs was observed when given in combination.

The mean terminal $t_{1/2}$ calculated during the elimination phase ranged from approximately 13 to 18 days across the various dose groups for REGN10933, REGN10987, and REGN-COV2. Following SC administration of 10 mg/kg/antibody (total dose of 20 mg/kg REGN-COV2), mean t_{max} was approximately 4 days post-dose, and the estimated bioavailability was 81.6%.

Toxicokinetic data

In the 4-week repeat-dose toxicity study, continuous exposure to total REGN10933, total REGN10987, or total REGN-COV2 was maintained in all drug-treated animals throughout the treatment period and an 8-week recovery period. Dose-proportional increases in exposures were observed, indicating that linearity in PK was maintained throughout the study and there was no impact on the TK of the individual REGN10933 or REGN10987 mAbs when given in combination. Accumulation was observed following repeated dosing (accumulation ratios 1.8- to 2.7-fold), with steady state by fourth dose. Serum samples were not analysed for potential anti-drug antibodies (ADAs). No apparent impacts were, however, seen on individual concentration-time profiles from the definitive PK study or the toxicity study, indicating lack of neutralising ADAs.

Distribution, metabolism and excretion

Studies have not been conducted. This is acceptable, and in line with ICH S6(R1). Limited distribution beyond the blood compartment is expected for antibodies against foreign antigens. This is supported by negative cross-reactivity studies, and low volumes of distribution observed in the single dose PK studies in non-infected animals. The expected metabolic pathway is degradation to smaller peptides and individual amino acids that will enter the endogenous pool of amino acids.

2.3.4. Toxicology

A limited toxicological programme was conducted for REGN-COV2, comprising a 4-week repeat-dose toxicity study in cynomolgus monkeys, and tissue cross-reactivity studies with normal human and monkey tissues, and human foetal tissues. For monoclonal antibodies directed at foreign targets (i.e., bacterial, viral targets etc.), a short-term safety study in one species can be considered; no additional toxicity studies, including reproductive toxicity studies, are required (ICH S6(R1)). Considering that REGN-COV2 is directed at the epitopes on the receptor binding domain of the SARS-CoV-2 spike protein, and no cross reactivity has been observed towards human tissues, the limited toxicity programme is acceptable.

Although the batches use in the toxicity studies were produced by an early process not intended for the clinical product, they are considered clinically relevant based on similar quality attributes for material produced by all processes.

Repeat-dose toxicity in cynomolgus monkeys

In a 4-week study in male and female cynomolgus monkeys (aged 2.2-4 years), weekly IV injections of 50 mg/kg REGN10933 alone or REGN10987 alone, or weekly IV or SC injections of up to 150 mg/kg/antibody REGN-COV2 were well tolerated. Incidences of increased ALT, lens opacity and injection site abrasions were considered unlikely related to treatment, due to slight severity, single incidences, and (except for skin abrasion) similar findings in non-treated animals.

Cytokine levels measured for 5 days following first dose were either below LLOQ (IL-2, IL-4, IL-5, and IFN-γ), or not considered treatment-related (IL-6, IL-10, TNF-α, and IL-8) due to low magnitude (within predose or control ranges) and sporadic findings. In addition, sporadic increases in plasma MCP-1 concentrations above control levels were observed in 4 animals on Day 1, considered of uncertain relation to REGN10933 and/or REGN10987 administration. Based on viral targets, and lack of other findings in non-infected animals, an immunotoxic potential of REGN-COV2 is not expected.

Based on the lack of adverse effects, the NOAELs are considered to be at the highest dose levels administered, i.e. 50 mg/kg REGN10933 and 50 mg/kg REGN10987 when administered alone and 150 mg/kg/antibody (total dose of 300 mg/kg REGN-COV2) when administered in combination. Estimated human exposure margins at NOAEL are ≥4.7 for the treatment setting, and ≥7.4 for the prophylaxis setting (Investigator's Brochure ed 4). These margins were based on cumulative AUC from initiation of dosing to recovery necropsy in monkeys, predicted AUC_{inf} in patients in a treatment setting (up to 8 g REGN-COV2 as single IV dose) and predicted AUC_{inf} in healthy subjects in a prophylactic setting (SC, up to 1200 mg REGN-COV2 per week for 4 weeks).

Reproductive toxicity

No studies were conducted. IgG1 antibodies do cross the placenta and may be transferred via milk. In the repeat-dose toxicology study in young cynomolgus monkeys (2.2 to 4.0 years old), there were no drug-related macroscopic or microscopic changes in the testes, epididymides, ovaries, uterus, or vagina. In view of exogenous targets, and lack of cross reactivity with reproductive or foetal tissues in the tissue cross reactivity studies, effects of REGN-COV2 on developing foetus or breast-fed infants are not expected. Lack of studies is acceptable.

Local tolerance

In the repeat-dose toxicity study there were no macroscopic or microscopic findings at the IV or SC administration sites considered related to REGN10933 or REGN10987.

Other toxicity studies

Tissue cross-reactivity

In tissue cross-reactivity studies on normal human and monkey tissues, and on human foetal tissues, there was no off-target binding of REGN10933 or REGN10987.

Antigenicity

Serum samples have not been analysed for potential ADA formation, but an immunogenic response against human antibodies may be expected in animals. In a pilot PK study (study R10933-PK-20074), a sudden drop in exposure levels were observed in one monkey from post-dose day 22, possibly related to ADA formation. TK parameters from repeat-dose toxicity study do however indicate that, if present, the potential ADAs had non-significant effects due to continuous exposure in all animals throughout 4 weeks of dosing and 8 weeks of recovery.

Immunotoxicity

Sporadic increase in plasma MCP-1 concentrations in the repeat-dose toxicity study, considered as outliers, were considered of uncertain relation to REGN10933 and/or REGN10987 administration. Based on lack of other findings in non-infected animals, and due to viral targets, an immunotoxic potential of REGN-COV2 is not expected.

Impurities

No studies have been provided. At present, the lack of studies on impurities is acceptable. Following assessment of quality data, studies may be needed.

2.4. Quality aspects

2.4.1. Introduction

REGN-COV2 is a combination pack containing two monoclonal antibodies as active substances, Casirivimab (REGN10933) and Imdevimab (REGN10987).

Casirivimab 120 mg/mL and Imdevimab 120 mg/mL are presented as concentrates for solution for infusion in separate vials (1332 mg in 11.1 mL each or 300 mg in 2.5 mL each). Casirivimab and Imdevimab are formulated with a L-histidine buffer, sucrose, polysorbate 80 and water for injection. The formulations do not contain preservatives.

Casirivimab and Imdevimab must be administered together as a single intravenous infusion immediately after dilution with 0.9% sodium chloride.

2.4.2. Active Substance

General Information

Casirivimab (REGN10933) and Imdevimab (REGN10987) are IgG1 kappa anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) recombinant monoclonal antibodies targeting non-overlapping epitopes of the receptor binding domain (RBD) of the spike (S) protein. REGN-COV2 exhibits neutralisation activity. The blockage of the S protein interaction with angiotensin-converting enzyme 2 (ACE2) leads to inhibition of infection of host cells.

Casirivimab and Imdevimab both contain a single N-linked glycosylation site on each heavy chain.

The biological and physico-chemical properties have been extensively described.

Manufacture, process controls and characterisation

Manufacture

Information regarding the manufacturing and testing sites and their EU GMP status was provided.

Casirivimab and Imdevimab are produced in CHO cells. A two-tiered cell banking system of master cell bank (MCB) and working cell bank (WCB) is in place. After thawing of a WCB vial, the cells are grown in suspension culture in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. Purification is performed with a series of chromatography steps, ultra-/diafiltration steps and viral inactivation and filtration steps. The active substances are subsequently formulated with the excipients.

The manufacturing processes are considered standard for the production of monoclonal antibodies.

Control of materials

Raw materials used in the manufacture of Casirivimab and Imdevimab are provided and are in accordance with pharmacopoeial standard. Control of materials is adequately described.

Control of critical steps and intermediates

Control of critical steps and intermediates is adequately described. At this stage of development, the preliminary in-process controls (IPCs) defined as those that directly control or eliminate potential adventitious agent contamination or that contribute to critical quality attributes (CQAs) are considered sufficient.

Process validation

No formal validation of the active substance manufacturing processes has been performed yet. This is acceptable in the context of this procedure. Formal process validation studies will be expected at the time of marketing authorisation application (MAA).

Manufacturing process development

Information to support various changes introduced during development was provided. An extensive comparability exercise, in accordance with ICH Q5E, is expected at the time of MAA, including detailed comparison of process performance, head-to-head comparisons, extended characterisation and stability (for example forced degradation studies).

Characterisation

Extensive analytical characterisation was performed to provide a detailed understanding of the physicochemical properties of Casirivimab and Imdevimab. Quality attributes including identity, secondary and tertiary structure, molar mass, molecular weight, size heterogeneity, purity, charge heterogeneity, and chemical heterogeneity, were all assessed. Post-translational modifications were also examined.

The Company provided, as requested during the procedure, information on biological characterisation including RBD binding, neutralisation activity and Fc effector functions (antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), FcGammaR3A).

Process- and product-related impurities are sufficiently characterised and adequately controlled. Justification is provided based on prior knowledge from other monoclonal antibodies. This is acceptable in the context of this procedure.

Specification

Specifications and acceptance criteria are set in accordance with ICH Q6B and include control of identity, purity and impurities, potency and other general tests. The justification provided for the specifications is acceptable in the context of this procedure. It is noted that the test panel and acceptance criteria will be revised at the time of MAA as additional experience is gained with the manufacturing process and additional analytical data are obtained.

Analytical procedures

The suitability of the methods commensurate with stage of development has been demonstrated and a summary of validation results is provided.

Batch analyses

Representative batch analyses data is provided for the manufacturing process of casirivimab and imdevimab. Batch release data indicate robust and reproducible manufacturing processes. All pre-defined acceptance criteria are met.

Reference standard

Casirivimab and Imdevimab reference materials are derived from formulated active substance lots, which were manufactured for clinical studies.

The certificates of analysis for the reference materials are provided.

Container closure

The container closure systems for casirivimab and imdevimab were described.

Stability

Based on available data, the Company proposed a preliminary shelf life for casirivimab and imdevimab, which is considered acceptable for the time being, taking into account prior experience of other monoclonal antibodies manufactured using the same platform.

It is noted that the Company proposes to extend the shelf life in the future, provided that no significant trends or out-of-specification results (OOS) are detected in ongoing, long-term stability studies. This is

in line with the CHMP Guideline on "Requirements for quality documentation concerning biological investigational medicinal products in clinical trials" and accepted in the context of this procedure.

At the time of MAA, shelf life determination should be based on ICH Q5C principles and additional stability data will be expected. A justification based on prior knowledge and other accumulated data could be considered.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

REGN-COV2 concentrate for solution for infusion is a combination pack consisting of two borosilicate glass vials containing formulated Casirivimab and formulated Imdevimab: 1332 mg in 11.1 mL withdrawable volume or 300 mg in 2.5 mL withdrawable volume for each monoclonal antibody.

REGN10933 and REGN10987 finished products contain no novel excipient or excipients of human or animal origin. The excipients - L-histidine and L-histidine monohydrochloride monohydrate (buffer with

target pH 6.0), sucrose (stabilising agent), polysorbate 80 (stabilising agent) and water for injection – are compendial and commonly used for the formulation of biopharmaceuticals. The two formulations do not contain preservatives. The solution for each vial is clear to slightly opalescent, colourless to pale yellow.

The qualitative and quantitative composition for REGN-COV2 was provided and is considered adequate.

Pharmaceutical development

Information on formulation development was provided together with comparability data to support various changes introduced during manufacturing process development.

The vials and stoppers for REGN-COV2 are commonly used for other medicinal products. The materials are compendial.

Finished product impurity information was provided and is acceptable.

Potential impurities derived from the container closure system were evaluated. The data indicate no to very low potential of impurities. This is acceptable.

A compatibility study was conducted to study was to establish the in-use stability of the REGN10933/REGN10987 mixture intended for infusion.

Manufacture of the product and process controls

Manufacture

The manufacturing and testing sites and their EU GMP status were provided.

During finished product manufacturing, REGN10933 and REGN10987 are processed separately. The finished product manufacturing processes represent a standard fill-finish process consisting of thawing of the formulated active substances, pooling and mixing, sterile filtration and aseptic filling, stoppering, and capping/crimping. The individual processing steps are adequately described, and process controls are indicated. Each monoclonal antibody is independently filled into separate vials.

Process validation

Process validation of the finished product manufacturing processes are adequately described.

Product specification

Specifications and acceptance criteria are set in accordance with ICH Q6B and include control of identity, purity and impurities, potency and other general tests. The justification provided is acceptable in the context of this procedure. It is noted that the test panel and acceptance criteria will be revised at the time of MAA as additional experience is gained with the manufacturing process and additional analytical data are obtained.

Analytical procedures

The majority of test methods is provided in the active substance section of the application. Methods specific to the finished product are sufficiently described.

The suitability of the methods commensurate with stage of development has been demonstrated and a summary of validation results is provided.

Batch analysis

Batch analysis data for finished product batches are provided and the data indicate that the pre-defined acceptance criteria were met.

Reference standard

The same reference standards as for REGN10933 and REGN10987 active substances are used.

Stability of the product

A preliminary shelf life for the finished products of 12 months when stored at 2°C to 8°C in the original carton and protected from light is proposed. It takes into consideration predictive modelling and prior knowledge, which is considered acceptable in the context of this procedure and the COVID-19 pandemic. Reference is made to the Draft toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications (EMA/CHMP/BWP/QWP/IWG/694114/2019). At the time of MAA, shelf life determination should be based on ICH Q5C principles and additional stability data will be expected.

In the absence of preservative, REGN-COV2 should be diluted and administered immediately after opening of the vials. If immediate administration is not possible, the diluted infusion solution may be stored for up to 4 hours at room temperature (up to 25°C) or refrigerated between 2°C to 8°C for up to 36 hours. If refrigerated, the infusion solution should be allowed to equilibrate to room temperature for approximately 30 minutes prior to administration.

Adventitious agents

No animal- or human-derived raw materials with a risk for virus or TSE contamination are used in the manufacture and no risk materials were used for the generation of the antibody-producing cell line and cell banks.

Cell banks were characterised according to ICH Q5A guideline and routine screening of adventitious viruses has been implemented.

A sufficient viral clearance capacity has been demonstrated for the downstream manufacturing processes. Validation studies indicated efficient virus inactivation/removal.

The submitted information indicate adequate adventitious agents evaluation safety.

2.4.4. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of REGN-COV2 is considered acceptable in the context of this procedure and the COVID-19 pandemic, when used in accordance with the conditions for use.

3. Overall conclusions

To date there are limited treatment options available for COVID-19. There is only one antiviral treatment for COVID-19, VEKLURY (remdesivir), which is approved in the EU only for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) or other non-invasive ventilation at start of treatment. There are no authorised treatments for individuals with mild to moderate COVID-19 early in the disease course.

Regeneron Pharmaceuticals, Inc. and F. Hoffman-La Roche, Ltd (Roche) are co-developing two non-competing, high-affinity human IgG1 anti-SARS-CoV-2 monoclonal antibodies (mAbs), REGN10933 and REGN10987, that bind specifically to the receptor binding domain (RBD) of the spike (S) glycoprotein of SARS-CoV-2, blocking viral entry into host cells.

These two fully human, neutralising monoclonal antibodies were investigated in a double-blind, phase 1–3 trial involving non-hospitalised patients with COVID-19. A summary of the quality, non-clinical and clinical data that support this CHMP Opinion are summarised below.

Quality aspects

Considering the data provided by the Company on the manufacture, characterisation, pharmaceutical development, control and stability of the active substance and finished product, the overall quality of REGN-COV2 is acceptable in the context of this procedure and the COVID-19 pandemic, when used in accordance with the conditions for use.

Non-clinical aspects

Non-clinical pharmacology, pharmacokinetics and toxicology studies were submitted.

Results from these studies demonstrated that REGN10933 and REGN10987 bind monomeric and dimeric recombinant SARS-CoV-2 RBD with nanomolar and picomolar affinities, respectively, and stabilized, trimerized SARS-CoV-2 S protein with picomolar affinities. Multiple *in vitro* experiments were performed to assess effector function of REGN10933, REGN10987, and REGN-COV2 demonstrating that dependent cellular phagocytosis (ADCP) and antibody-dependent cellular cytotoxicity (ADCC) with EC50 values in the low nanomolar to picomolar range. Of note, REGN10933, REGN10987, and REGN-COV2 mediated a concentration-dependent increase in activation of reporter cells expressing Fc gamma receptor IIIA (FCGR3A) in the presence of target cells. Including this assay as an additional release assay is considered. REGN10933, REGN10987, and REGN-COV2 did not mediate complement-dependent cytotoxicity (CDC) against target cells in the presence of normal human serum.

Binding to target was appropriately evaluated using different methods to analyse binding sites, structural analysis of the REGN-COV2-target-complex, binding affinities and concentration-dependent blocking of SARS-CoV-2 RBD to human ACE2. REGN10933, REGN10987 and REGN-COV2 neutralization activity against SARS-CoV2 virus and Vesicular Stomatitis Virus (VSV) pseudotyped with SARS-CoV-2-Spike Protein was evaluated using cell-based assay formats. The ability of REGN10933 and REGN10987 to neutralize entry of non-replicating VSV pseudoparticles pseudotyped with 37 different receptor binding domain (aa R319-F541) variants of SARS-CoV-2 S protein in circulation, was assessed. *In vitro* viral escape mutant studies were performed to evaluate the selection of SARS-CoV-2 S protein escape mutant due to presence of a range of concentrations (0.0016 to 50 μg/mL) of anti-S protein mAbs (REGN10933, REGN10987 and REGN-COV2). Loss of potency was assessed by observable Cytopathic effect (CPE) assay in the presence of increasing concentrations of antibodies indicating potential selection of escape mutants. REGN10933 and REGN10987 individually and together retained neutralization activity against pseudovirus expressing all spike protein substitutions found in the B.1.1.7 variant (UK origin) and against pseudovirus expressing only N501Y found in B.1.1.7 and other circulating variants

In vitro binding and cell-based functional studies were complemented by *in vivo* studies conducted in NHP rhesus macaque monkeys and Syrian Golden hamsters. Overall there are no concerns from non-clinical point of view.

Clinical aspects

In study COV-2067, out-patients were treated with a single dose (either low or high dose) of REGN-COV2, the combination of two monoclonal antibodies, no dose dependency of the effects was observed.

The data indicate that treatment with REGN-COV2 resulted in a greater viral load reduction compared to placebo in all patients who were positive at baseline, on RT-qPCR, for SARS-COV-2 viral DNA. The magnitude of the effect was greater in patients with higher baseline viral load. With respect to serologic status, the suggested benefit of REGN-COV2 seems to be limited to patients who were seronegative at baseline. These might include patients who not yet developed effective immunity to SARS-COV-2. In contrast, patients who had already developed adequate immunity to the virus, before treatment with REGN-COV2, did not benefit from enhanced viral clearance.

The data indicate that REGN-COV2 might reduce medically attended visits (a composite of emergency room visits, hospitalisations, telemedicine consultation etc.) due to COVID-19. This effect is driven by the subgroups of seronegative subjects and subjects with risk factors for the progression to severe COVID-19 at baseline. Currently it is not possible to determine if this effect is driven by a specific component of the composite endpoint.

At this stage, these findings have not yet been confirmed in a confirmatory clinical study.

Supportive evidence is provided by the treatment study COV-2066 (in hospitalized adult patients with COVID-19). Results in patients with O2 saturation >93% on low flow oxygen via nasal cannula, simple face mask, or other similar device were reported (cohort 1).

In this population, REGN-COV2 reduced viral load compared to placebo in patients who were SARS-COV-2 RT-qPCR positive by NP swab at baseline (mFAS). The magnitude of the reduction was greater in patients with greater baseline viral load. With respect to serologic status, the benefit of REGN-COV2 was almost exclusively observed in patients who had not yet developed effective immunity to SARS-COV-2 (seronegative patients). These data are consistent with the observation in study COV-2067. However, the critically relevant data to the indication claimed from Cohort 1A are currently not available.

Dose

Two different doses, either low (1200 and1200 mg) or high dose (4000 and4000 mg) of REGN-COV2 were evaluated; no dose dependency of the effects was observed.

The data suggested that a single intravenous application of 1200 mg of casirivimab and 1200 mg of imdevimab combination has an impact on prevention of symptomatic SARS-CoV-2 infection and reduction of potential for virus transmission.

Safety aspects

No SAEs reported were considered to be related to study medicinal product. No patients experienced an event leading to death. The AESIs events reported were all moderate in intensity and no severe or serious AESIs were reported. All AESIs were reported on the day of study drug infusion including hypersensitivity reactions.

From the currently available safety information there were no major safety concerns. The reported safety data indicated that REG-COV2 has a favourable safety profile. The Committee considered that this medicine once it is authorised for use, it should be subject to additional monitoring. This enables to stimulate the ADR reporting in order for new safety information to be identified quickly. Healthcare Professionals will be asked to report any suspected adverse reactions.

Overall Conclusions

The data suggest that a single intravenous application of 1200 mg of the casirivimab and 1200 mg imdevimab combination has an impact on viral titres and clinical progression of symptomatic SARS-CoV-2 infection as determined by an effect on medically attended visits in patients with risk factors for severe disease. The effect seems to be limited to patients who are seronegative at baseline. However, testing of anti-viral immunity is not expected to be feasible prior to treatment therefore the target population for the use of REGN-COV2 for the treatment of confirmed COVID-19 that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19. An extrapolation of the effect to adolescents at high risk of severe COVID-19 is accepted.

The reported safety data indicate that REGNCOV2 has a favourable safety profile. The most salient unfavourable effects were infusion reactions including hypersensitivity reactions. The frequency was low.

The Committee, as a consequence considered that the preliminary results of the trial assessed within this procedure lend support for the treatment of COVID-19 patients, aged 12 years and older, that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19, and based on an individual appraisal of benefits and risks by healthcare professionals, taking into account the unmet medical need for therapies in this patient population and in the current COVID-19 pandemic.