REGN-COV2 Use in Ambulatory Patients with COVID-19

This letter responds to your request for clinical information on the use of REGN-COV2 (casirivimab and imdevimab) in ambulatory patients with coronavirus disease 2019 (COVID-19) pharmacokinetics.

In Brief

- REGN-COV2 is an investigational medication that consists of two monoclonal antibodies (casirivimab and imdevimab). This investigational medication is being studied as a treatment for patients with COVID-19. The safety and efficacy of REGN-COV2 has not been evaluated by regulatory authorities, and it has not received market approval in any country.

- An ongoing, randomized, double-blind, placebo-controlled, seamless Phase 1/2/3 study assessed the safety, tolerability and efficacy of REGN-COV2 in ambulatory patients with COVID-19.

    - Patients were randomized 1:1:1 to intravenous REGN-COV2 8.0g (high dose), REGN-COV2 2.4g (low dose) or placebo in addition to standard of care.

    - An interim descriptive analysis of data from Phase 1/2 of the study included 275 patients enrolled in the trial and was conducted to assess the safety and efficacy of REGN-COV2 and refine the endpoints for subsequent confirmation in the second cohort. A second interim analysis of data from Phase 2 included the next 524 patients enrolled in the trial and was conducted to prospectively confirm the Cohort 1 analysis. Results of the same key prespecified endpoints from the Cohort 1 analysis are reported.

    - In a preliminary readout of data from Phase 3 (N=4,567), REGN-COV2 1.2g and 2.4g significant reduced the risk of COVID-19-related hospitalization or death by 70% and 71%, respectively compared with placebo ($p=0.0024$ and $p<0.0001$). Serious adverse events occurred in 1.1% of patients in the REGN-COV2 1.2g group, 1.3% of patients in the REGN-COV2 2.4g group and 4% of patients in the placebo group. There was 1 death in each of the REGN-COV2 1.2g and 2.4g groups, and 5 deaths in the placebo group.

- REGN-COV2 is currently being studied in 5 ongoing clinical studies.

Abbreviations

ACE=angiotensin-converting enzyme 2
AE=adverse event
COVID-19=Coronavirus Disease 2019
EUA=emergency use authorization
IVIG=intravenous immunoglobulin
mAb=monoclonal antibody
NP=nasopharyngeal
PK=pharmacokinetics
RT-qPCR=reverse transcription quantitative polymerase chain reaction
SAE= serious adverse event
SQ=subcutaneous
TWA=time-weighted average

Background

REGN-COV2 is an investigational medication that consists of two highly potent, non-competing, neutralizing human antibodies (casirivimab and imdevimab) that bind to regions on the external spike proteins on the SARS-CoV-2 envelope. The two antibodies are designed to target separate entities on the receptor-binding domain of the spike protein's S1 subunit. Binding to the spike proteins blocks the virus binding to the ACE receptor, thereby blocking viral entry into cells and allowing the complex of the virus and the antibody to be cleared by the immune system. Pre-clinical data support that the REGN-COV2 antibodies blocks infection when administered prior to exposure in animals and results in faster viral clearance in animals already infected with SARS-CoV-2.[1]

Clinical Experience

Phase 1/2/3 Trial in Non-Hospitalized Patients with COVID-19 (Study 2067)[2-4]

Study Design

The ongoing, randomized, double-blind, placebo-controlled, seamless Phase 1/2/3 study (NCT04425629) assessed the safety, tolerability and efficacy of REGN-COV2 in ambulatory patients with COVID-19.

Key inclusion criteria in the first portion of the study were adult, non-hospitalized COVID-19 patients with confirmed SARS-CoV-2 (by antigen or molecular diagnostic test ≤72 hours prior to randomization) and with onset of symptoms ≤7 days from randomization. Key exclusion criteria included admission to a hospital prior to randomization or hospitalization at randomization due to COVID-19, participation in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or IVIG within 3 months or less than 5 half-lives of the investigational product, and prior (defined as 30 days or less than 5 half-lives), current, or future use of convalescent plasma, mAbs, IVIG, systemic corticosteroids, or COVID-19 EUA approved treatments.

Patients were randomized 1:1:1 to intravenous (IV) REGN-COV2 8.0g (high dose) or 2.4g (low dose) or placebo in addition to standard of care. The REGN-COV2 investigational medication included equal amounts of both antibodies (casirivimab and imdevimab). Biomarkers were collected in all phases of this study on days 1, 7, and 29 and NP swabs were collected on days 1, 3, 5, 7, 9, 11, 13, 15, 18, 22, 25, and 29. In the phase 1 portion of the study, serum was collected for PK endpoints on days 1, 3, 5, 7 and 15.

Cohort 1: Phase 1/2 Descriptive Analysis[2]

An interim descriptive analysis of data from Phase 1/2 of the study included 275 patients enrolled in the trial and was conducted to assess the safety and efficacy of REGN-COV2 and refine the endpoints for subsequent confirmation in the second cohort.

Several pre-specified endpoints were designated for Phase 1/2 of the study, however, no formal hypothesis testing was performed. The key pre-specified efficacy endpoints are described below:

- Virologic: TWA change in the viral load (log_{10} copies/mL) from baseline through Day 7, measured by RT-qPCR
- Clinical: Proportion of patients with at least 1 COVID-19 related medically attended visit through Day 29

Safety assessments included Grade 3/4 AEs (Phase 1 only), SAEs that occurred or worsened through Day 29 (Phase 1 and 2), and AEs of special interest (Phase 1 and 2): Grade ≥2 hypersensitivity or infusion-related reactions.

At baseline patients were tested for antibodies to SARS-CoV-2 specific proteins (IgG Spike, IgA Spike, and IgG nucleocapsid) and considered seropositive if at least one or more was detected, otherwise they were considered seronegative. In patients with borderline serostatus or missing data, they were categorized as Other.

Baseline Demographics

Mean age of patients was 44 years, 49% were male, 56% were Hispanic, 13% were African American, 42% were obese, and 64% had at least 1 risk factor for severe COVID-19 (Table 1). None of the 275 patients in this analysis received remdesivir. The median number of days of COVID-19 symptoms before randomization was 3 days.

Table 1. Patient Demographics at Baseline

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Parameters	**Placebo (n=93)**	**REGN-COV2 2.4g IV (n=92)**	**REGN-COV2 8.0g IV (n=90)**	**REGN-COV2 Both Doses (n=182)**	**All Patients (N=275)**
Age, median (IQR)*	45 (34-54)	43 (33.5-51)	44.0 (36-53)	43 (35-52)	44 (35-52)
Sex, n (%)					
Male	50 (54)	46 (50)	38 (42)	84 (46)	134 (49)
Ethnicity, n (%)†					
Hispanic of Latino	46 (49)	52 (57)	55 (61)	107 (59)	153 (56)
Race, n (%)†					
White	72 (77)	74 (80)	78 (87)	152 (84)	224 (81)
Black or African-American	14 (15)	15 (16)	6 (7)	21 (12)	35 (13)
Asian	2 (2)	0	1 (1)	1 (1)	3 (1)
American Indian or Alaska Native	2 (2)	0	0	0	2 (1)
Unknown	2 (2)	0	1 (1)	1 (1)	3 (1)
Not reported	1 (1)	3 (3)	4 (4.4)	7 (3.8)	8 (3)
BMI‡	29.7±7.1	30.4±6.6	30.6±7.2	30.5±6.9	30.3±7.0
Obesity, n (%)§	34 (37)	39 (42)	42 (47)	81 (45)	115 (42)
Median time from symptom onset to randomization, days (range)	3.0 (0-8)	3.5 (0-7)	3.0 (0-8)	3.0 (0-8)	3.0 (0-8)
At least 1 risk factor for hospitalization, n (%)¶	58 (62)	57 (62)	61 (68)	118 (65)	176 (64)

Notes: *Interquartile range (IQR) defined as quartile 1 to quartile 3.
† Race and ethnicity reported by the patients.
‡ BMI is the weight in kilograms divided by the square of the height in meters.
§ Obesity is defined as BMI>30
¶ Risk factors for hospitalization include age >50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised status (immunosuppression or receipt of immunosuppressants).

Abbreviations: BMI=body mass index; IV=intravenous; SD=standard deviation.

At baseline, 113 (41%) patients were seronegative, 123 (45%) patients were seropositive, and 39 (14%) patients were categorized as Other.

In seronegative patients (n=113), the median viral load base on NP swabs was 7.18 log10 copies/mL compared with 3.49 log10 copies/mL in seropositive patients (n=123). Patients categorized as Other for serology status (n=39) had a median viral load of 5.15 log10 copies/mL.

Virologic Endpoints

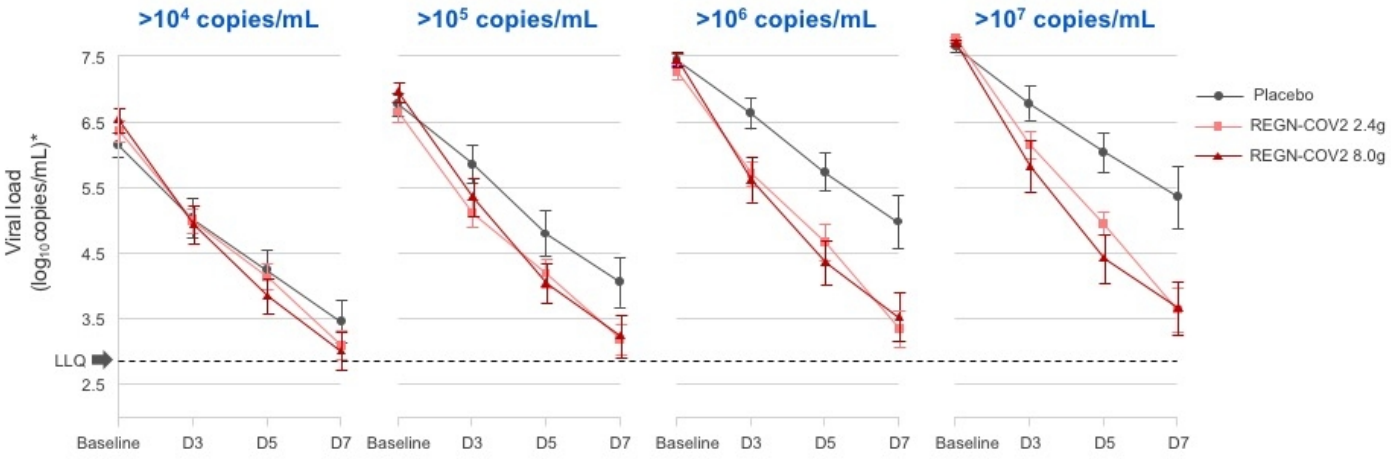
In the overall population, the high dose group had a 0.56 log reduction in viral load through Day 7 compared with placebo and the low dose group had a 0.25 log reduction (Table 2). In the seronegative patients, the high dose group had a 0.6 log reduction in viral load through Day 7 compared with placebo and the low dose group had a 0.52 log reduction.

Table 2. Change from Baseline in Viral Load in Nasopharyngeal Samples (mFAS)				
	Placebo	**REGN-COV2 2.4g IV**	**REGN-COV2 8.0g IV**	**REGN-COV2 Both Doses**

Table 2. Change from Baseline in Viral Load in Nasopharyngeal Samples (mFAS)				
All patients (n)	78	70	73	143
TWA change at Day 7 in viral load, log10 copies/mL, LSM±SE	-1.34±0.13	-1.60±0.14	-1.90±0.14	-1.74±0.11
Difference vs placebo, log10 copies/mL, LSM±SE		-0.25±0.18	-0.56±0.18	-0.41±0.15
Seronegative patients (n)	28	34	35	69
TWA change at Day 7 in viral load, log10 copies/mL, LSM±SE	-1.37±0.20	-1.89±0.18	-1.98±0.18	-1.94±0.13
Difference vs placebo, log10 copies/mL, LSM±SE		-0.52±0.26	-0.60±0.26	-0.56±0.23
Seropositive patients (n)	37	27	29	56
TWA change at Day 7 in viral load, log10 copies/mL, LSM±SE	-1.24±0.16	-1.24±0.19	-1.63±0.20	-1.45±0.13
Difference vs placebo, log10 copies/mL, LSM±SE		0.00±0.24	-0.39±0.25	-0.21±0.20
Abbreviations: IV=intravenous; LSM=least squares mean; mFAS=modified full analysis set; SE=standard error; TWA=time-weighted average.				

Patients with increasingly higher baseline viral levels had correspondingly greater reductions from placebo in viral load at Day 7 with REGN-COV2 treatment (Figure 1).

Figure 1. Mean Viral Load over Time According to Baseline Viral Load Category



Mean Difference in Change from Baseline at Day 7				
2.4g vs placebo	-0.64	-0.83	-1.46	-1.84
8.0g vs placebo	-0.90	-1.12	-1.54	-1.75

Overall population. *Bars represent +/- standard error values.

Clinical Endpoints

Patients treated with either dose of REGN-COV2 had numerically lower medically attended visits compared with placebo (Table 3). The majority of patients with medically attended visits were seronegative at baseline. Most visits occurred in the emergency room or physician's office.

Table 3. Patients with ≥1 COVID-19 Medically Attended Visit through Day 29 (FAS)				
(%)	Placebo	REGN-COV2 2.4g IV	REGN-COV2 8.0g IV	REGN-COV2 Both Doses
All patients (n)	93	92	90	182

Table 3. Patients with ≥1 COVID-19 Medically Attended Visit through Day 29 (FAS)				
Patients with ≥1 medically attended visit, n (%)	6 (6)	3 (3)	3 (3)	6 (3)
Proportion difference vs placebo, % (95% CI)		-3 (-18, 11)	-3 (-18, 11)	-3 (-16, 9)
Seronegative patients (n)	33	41	39	80
Patients with ≥1 medically attended visit, n (%)	5 (15)	2 (5)	3 (8)	5 (6)
Proportion difference vs placebo, % (95% CI)		-10 (-32, 13)	-8 (-30, 16)	-9 (-29, 11)
Seropositive patients (n)	47	37	39	76
Patients with ≥1 medically attended visit, n (%)	1 (2)	1 (3)	0	1 (1)
Proportion difference vs placebo, % (95% CI)		1 (-21, 22)	-2 (-23, 19)	-1 (-19, 17)
Abbreviations: FAS=full analysis set.				

Safety Data

Both REGN-COV2 doses had similar safety results (Table 4). Serious adverse events (SAEs), infusion-related reactions, and hypersensitivity reactions were balanced across treatment groups. There were no deaths reported.

Table 4. SAEs and AESI in the Safety Population (N=269)			
n (%)	Placebo (n=93)	REGN-COV2 2.4g IV (n=88)	REGN-COV2 8.0g IV (n=88)
SAE	2 (2)	1 (1)	0
AESI	2 (2)	0	2 (2)
Serious AESI	0	0	0
Infusion-related reactions Grade ≥2 through Day 4	1 (1)	0	2 (2)
Hypersensitivity reactions Grade ≥2 through Day 29	2 (2)	0	1 (1)
Adverse events that occurred or worsened during the observation period*			
Grade 3 or 4 event	1 (1)	1 (1)	0
Event that led to death	0	0	0
Event that led to withdrawal from trial	0	0	0
Event that led to infusion interruption	1 (1)	0	1 (1)
Notes: * Events were not present a baseline or were an exacerbation of a preexisting condition that occurred during the time from administration of REGN-COV2 or placebo to the last study visit. Abbreviations: AESI=Adverse event of special interest that included Grade ≥2 infusion related reactions or hypersensitivity reactions; SAE=Serious adverse event; TEAE=Treatment emergent adverse event which included SAEs or AESIs.			

Pharmacokinetic Data

After single IV doses of 2.4g and 8.0g, median concentrations of the individual components (casirivimab and imdevimab) increased in serum over time in a dose-proportional manner and demonstrated a linear PK. The mean estimated half-life for the REGN-COV2 antibodies ranged from 25 to 37 days for both antibodies.

Cohort 2: Phase 2 Prospective Confirmatory Analysis[3]

A second interim analysis of data from Phase 2 included the next 524 patients enrolled in the trial and was conducted to prospectively confirm the Cohort 1 analysis. Results of the same key prespecified endpoints from the Cohort 1 analysis was reported below.

Baseline Demographics of Cohort 1 and Cohort 2 Combined (N=799)

At baseline, approximately 51% of patients were seronegative, 38% of patients were seropositive, and 11% of patients were categorized as Other.

Mean age of patients was 42 years, 47% were male, 50% were Hispanic, 9% were African American and 61% had at least 1 risk factor for severe COVID-19.

Virologic Endpoints in Cohort 2 (n=524)

In Cohort 2, the TWA change in viral load from baseline at Day 7 was a 0.36 $\log_{10}$ copies/mL greater reduction in the REGN-COV2 combined dose group compared with the placebo group (p=0.0003). In patients with high viral load (defined as $>10^7$ copies/mL), the TWA change in viral load reduction from baseline at Day 7 in the REGN-COV2 combined dose group compared with the placebo group was 0.68 $\log_{10}$ copies/mL (p<0.0001).

Clinical Endpoints in Cohort 1 and Cohort 2 Combined (N=799)

Treatment with REGN-COV2 reduced COVID-19-related medical visits through Day 29 by 57% (2.8% in the REGN-COV2 combined dose group vs 6.5% in the placebo group; p=0.024). In patients with ≥1 risk factor (included age >50 years, obesity, cardiovascular disease, chronic lung disease, chronic metabolic disease, chronic kidney disease, chronic liver disease, and immunocompromised status), treatment with REGN-COV2 reduced medical visits by 72% compared with placebo (nominal p=0.0065).

A descriptive analysis of a larger data set indicated that time to alleviation of symptoms was not strongly associated with treatment, baseline viral load or baseline serum antibody status.

Safety

Serious adverse events were numerically greater in the placebo group compared with the REGN-COV2 treatment arms (0.8% high dose, 1.6% low dose, 2.3% placebo). Numerically greater infusion reactions occurred with the REGN-COV2 treatment arms compared with placebo (1.5% high dose, 0% low dose, 0.4% placebo).

Phase 3 Analysis[4]

Results from the Phase 3 study in 4,567 patients were reported. Based on Phase 1/2 analyses showing no significant differences between the REGN-COV2 8.0g and 2.4g doses, the Phase 3 protocol was amended to compare the REGN-COV2 1.2g and 2.4g doses versus placebo, and the REGN-COV2 8.0g data were converted to a descriptive analysis. The protocol was also amended to include only patients with ≥1 risk factor for severe COVID-19.

The primary endpoint was COVID-19-related hospitalizations or all-cause deaths through Day 29.

Baseline Demographics

Approximately 35% of patients were Latino/Hispanic, 5% were Black/African American and the median age was 50 years old (range: 18-96 years).

All patients had at least 1 risk factor, including obesity (58%), age ≥50 years (51%) and cardiovascular disease, including hypertension (36%).

Clinical Endpoints

Key results were reported in the modified Full Analysis Set population, which includes all randomized patients with a positive SARS-CoV-2 RT-qPCR test from nasopharyngeal swabs at randomization and ≥1 risk factor for severe COVID-19 (Table 5). REGN-COV2 1.2g and 2.4g significant reduced the risk of COVID-19-related hospitalization or death by 70% and 71% compared with placebo (p=0.0024 and p<0.0001, respectively).

Table 5. Key Results from Phase 3 Outpatient Trial (mFAS)*				
	Placebo (n=748)	REGN-COV2 1.2g IV (n=736)	Placebo (n=1,341)	REGN-COV2 2.4g IV (n=1,355)
Patients with ≥1 COVID-19-related hospitalization or death through Day 29				
No. of patients with events (%)	24 (3.2)	7 (1.0)	62 (4.6)	18 (1.3)
Risk reduction	70% (p=0.0024)		71% (p<0.0001)	
Time to COVID-19 symptom resolution				
Median (days)	14	10	14	10
Median reduction (days)	4 (p<0.0001)		4 (p<0.0001)	
Notes: *The formal hierarchical analysis first evaluated the 2.4g dose vs concurrent placebo and then evaluated the 1.2g dose vs concurrent placebo.				

Safety

A safety assessment was conducted on all available patient data up to Day 169, and identified no new safety signals. Serious adverse events occurred in 1.1% (9/827) of patients in the REGN-COV2 1.2g group, 1.3% (24/1,849) of patients in the REGN-COV2 2.4g group and 4% (74/1,843) of patients in the placebo group. There was 1 death in each of the REGN-COV2 1.2g and 2.4g groups, and 5 deaths in the placebo group.

Ongoing Clinical Trial Information - Recruiting or Active

REGN-COV2 is currently being studied in the following studies:

- Study 2066 (NCT04426695): Seamless phase 1/2/3 study in hospitalized COVID-19 patients[5]
- Study 2067 (NCT04425629): Seamless phase 1/2/3 study in ambulatory COVID-19 patients[6]
- Study 2069 (NCT04452318): Phase 3 prophylaxis study of SQ formulation in healthy adults with a household contact to a COVID-19 patient[7]
- Study 2093 (NCT04519437): Multidose PK/safety study of SQ formulation in normal human volunteers[8]
- RECOVERY: Phase 3 UK/NHS study in hospitalized COVID-19 patients[9]

Clinicians interested in information regarding ongoing clinical research may find the following websites useful:

- www.clinicaltrials.gov (National Institutes of Health)

REGN-COV2 Use in Ambulatory Patients with COVID-19 References

1. Regeneron's REGN-COV2 Antibody Cocktail Reduced Viral Levels and Improved Symptoms in Non-hospitalized COVID-19 Patients. [press release]. Tarrytown, NY, Regeneron; September 29, 2020. Accessed October 15, 2020, from https://investor.regeneron.com/news-releases/news-release-details/regenerons-regn-cov2-antibody-cocktail-reduced-viral-levels-and.
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4. Phase 3 trial shows REGEN-COV (casirivimab with imdevimab) antibody cocktail reduced hospitalization or death by 70% in non-hospitalized COVID-19 patients. [press release]. Tarrytown, NY, Regeneron; March 26, 2021. Accessed March 26, 2021, from https://investor.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody

5. Safety, tolerability, and efficacy of anti-spike (S) SARS-CoV-2 monoclonal antibodies for hospitalized adult patients with COVID-19. Available at https://clinicaltrials.gov/ct2/show/NCT04426695. Accessed on October 15, 2020.

6. Safety, tolerability, and efficacy of anti-spike (S) SARS-CoV-2 monoclonal antibodies for the treatment of ambulatory adult patients with COVID-19. Available at https://clinicaltrials.gov/ct2/show/NCT04425629. Accessed on October 15, 2020.

7. Study assessing the efficacy and safety of anti-spike SARS CoV-2 monoclonal antibodies for prevention of SARS CoV-2 infection asymptomatic in healthy adults who are household contacts to an individual with a positive SARS-CoV-2 RT-PCR Assay. Available at https://clinicaltrials.gov/ct2/show/NCT04452318. Accessed on October 15, 2020.

8. Study assessing the safety, tolerability, pharmacokinetics, and immunogenicity of repeated subcutaneous doses of anti-spike (S) monoclonal antibodies (REGN10933+REGN10987) in adult volunteers as related to COVID-19. Available at https://clinicaltrials.gov/ct2/show/NCT04519437. Accessed on October 15, 2020.

9. RECOVERY COVID-19 Phase 3 Trial to Evaluate Regeneron's REGN-COV2 Invesigational Antibody Cocktail in the UK. [press release]. Tarrytown, NY, Regeneron; September 14, 2020. Accessed October 15, 2020, from https://newsroom.regeneron.com/news-releases/news-release-details/recovery-covid-19-phase-3-trial-evaluate-regenerons-regn-cov2