DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
CLINICAL VIROLOGY REVIEW
EUA-000091 **DATE REVIEW COMPLETED:** 08/16/2021

Reviewer: Michael Thomson, Ph.D.
Sponsor: Regeneron Pharmaceuticals, Inc.
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Regulatory History (Virology-Related Submissions Reviewed):

Submission	Received	Assigned	Content
SDN 158	08/03/2021	08/04/2021	Updated Fact Sheet for HCPs
SDN 161	08/09/2021	08/10/2021	Updated Fact Sheet for HCPs

Product Names: Casirivimab (REGN10933) and imdevimab (REGN10987); combination = REGEN-COV: two neutralizing, non-competing recombinant human anti-SARS-CoV-2 spike protein IgG1 monoclonal antibodies.

Structures

REGN10933 (IgG1κ) **REGN10987 (IgG1λ)**

Blue sequences: complementarity determining regions. The cysteine residues (red) confirmed to form predicted disulfide bonds are connected by solid red lines. The Fc N-linked glycosylation site at Asn^{300} is shown in green. The heavy chain C-terminal Lys^{450}, predominantly removed during the manufacturing process, is shown in pink.

Molecular formula: REGN10933: $C_{6454}H_{9976}N_{1704}O_{2024}S_{44}$; REGN10987: $C_{6396}H_{9882}N_{1694}O_{2018}S_{42}$
Molecular weight: REGN10933: 145.23 kDa; REGN10987: 144.14 kDa
Drug category: Antiviral
Indication: Adult patients with COVID-19 at high risk for clinical complications.
Dosage Form/Route of administration: A combination of 1,200 mg of REGN10933 and 1,200 mg of REGN10987 administered as a single intravenous (IV) infusion.

Abbreviations: ACE2, angiotensin-converting enzyme 2; CoV, coronavirus; COVID-19, coronavirus disease 2019; $EC_{50, 90}$, 50% or 90% effective concentration; mAb, monoclonal antibody; NP, nasopharyngeal; RBD, receptor binding domain; RT-PCR, reverse transcription-polymerase chain reaction; S, spike protein; SARS, severe acute respiratory syndrome; VSV, vesicular stomatitis virus

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SUMMARY and BACKGROUND

The sponsor is developing two recombinant, neutralizing, non-competing human IgG1 monoclonal antibodies (mAbs) for co-administration, casirivimab and imdevimab (combination product = REGEN-COV), targeting the spike (S) protein of SARS-CoV-2 for treatment and prevention of COVID-19. Neither of these mAbs contain modifications to the Fc domain. The sponsor is evaluating casirivimab (REGN10933) and imdevimab (REGN10987) in ongoing treatment trial COV-2067, a prevention trial (COV-2069) and a healthy volunteer study evaluating subcutaneous dosing (COV-2093). Casirivimab and imdevimab were also studied in treatment trial COV-20145 (closed) and in two treatment trials of hospitalized patients with COVID-19, COV-2066 (closed) and the ongoing RECOVERY trial being conducted in the UK. The sponsor was granted EUA on November 21, 2020 for the treatment of mild to moderate COVID-19 in non-hospitalized adult and pediatric, based on clinical data from trial COV-2067.

Casirivimab and imdevimab target non-overlapping epitopes on the SARS-CoV-2 spike protein, and block spike protein attachment through the receptor binding domain (RBD) to the human ACE2 receptor. For an overview of the non-clinical Virology data submitted for casirivimab and imdevimab see the Non-Clinical Data to Support Efficacy section XIII of the EUA multidisciplinary review (EUA91 PEP team review).

The submission under **SDN 158** is a response to a Virology information request and an updated Fact Sheet for Healthcare Providers (HCPs); the submission under **SDN 161** includes the revised Fact Sheet with changes accepted by the sponsor. The sponsor incorporated changes to Section 15, Antiviral Resistance, to include additional pseudotyped virus-like particle (VLP) and authentic virus data, as requested (BBI148069.549). (b) (4) [redacted]

Sponsor's response to Virology IR sent 08/02/2021

Virology comment: Please indicate whether the authentic viruses tested in the submission to seq. 0526 (B.1.617.2 [Delta] and P.1 [Gamma]) were sequence confirmed following propagation prior to testing. Please incorporate the authentic virus data for Delta and Gamma variants into the Fact Sheet for Healthcare providers (HCP), Section 15. Please also incorporate the pseudotyped VLP data for AY.1/AY.2 and C.37 (Lambda) into the HCP Fact Sheet.

Sponsor's response: Authentic viruses were all sequenced by BEI (beiresources.org). All sequences are confirmed except the B1.617.2 (delta), which is still in process.

We agree with the Agency's request to update the Fact Sheet for HCP. The additional data on variants were incorporated in the Fact Sheet included in this submission i.e., on the Fact Sheet updated to incorporate the new authorization for post-exposure prophylaxis.

Follow-up response. Adequate response. The changes to Antiviral Resistance portion of Section15 of the Fact Sheet for HCPs are shown in the following section.

MODIFICATIONS TO THE FACT SHEET FOR HEALTH CARE PROVIDERS

The sponsor's proposed changes to the Antiviral Resistance portion of Section 15 of the Fact Sheet for HCPs are shown below in purple, and the changes proposed by the Division in red in the following section. The final accepted version is shown in the section following.

15 MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to casirivimab and imdevimab administered together. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

Escape variants were identified following two passages in cell culture of recombinant VSV encoding SARS-CoV-2 spike protein in the presence of casirivimab or imdevimab individually, but not following two passages in the presence of casirivimab and imdevimab together. Variants which showed reduced susceptibility to casirivimab alone included those with spike protein amino acid substitutions K417E (182-fold), K417N (7-fold), K417R (61-fold), Y453F (>438-fold), L455F (80-fold), E484K (25-fold), F486V (>438-fold) and Q493K (>438-fold). Variants which showed reduced susceptibility to imdevimab alone included substitutions K444N (>755-fold), K444Q (>548-fold), K444T (>1,033-fold), and V445A (548-fold). Casirivimab and imdevimab together showed reduced susceptibility to variants with K444T (6-fold) and V445A (5-fold) substitutions.

In neutralization assays using VSV VLP pseudotyped with spike protein variants identified in circulating SARS-CoV-2, variants with reduced susceptibility to casirivimab alone included those with E406D (51-fold), V445T (107-fold), G476S (5-fold), E484Q (19-fold), G485D (5-fold), ~~G476S (5-fold),~~ F486L (61-fold), F486S (>715-fold), Q493E (446-fold), Q493R (70-fold), and S494P (5-fold) substitutions, and variants with reduced susceptibility to imdevimab alone included those with P337L (5-fold), N439K (463-fold), N439V (4-fold), N440K (28-fold), K444L (153-fold), K444M (1,577-fold), G446V (135-fold), N450D (9-fold), Q493R (5-fold), Q498H (17-fold), P499S (206-fold) substitutions. The G476D substitution had an impact (4-fold) on casirivimab and imdevimab together.

Casirivimab and imdevimab individually and together retained neutralization activity against pseudotyped VLP expressing all spike protein substitutions found in the B.1.1.7 lineage (Alpha; UK origin) and against pseudotyped VLP expressing only N501Y found in B.1.1.7 and other circulating lineages (Table 3). Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing all spike protein substitutions, or individual substitutions K417N, E484K or N501Y, found in the B.1.351 lineage (Beta; South Africa origin), and all spike protein substitutions or key substitutions K417T, E484K, or N501Y, found in the P.1 lineage (Gamma; Brazil origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing K417N or E484K, as indicated above. The E484K substitution is also found in the B.1.526 lineage (Iota; USA [New York] origin). Casirivimab and imdevimab, individually and together, retained neutralization activity against the L452R substitution found in the B.1.427/B.1.429 lineages (Epsilon; USA [California] origin).

Casirivimab and imdevimab, individually and together, retained neutralization activity against pseudotyped VLP expressing L452R+T478K substitutions found in the B.1.617.2 and AY.3 lineages (Delta; India origin). Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing K417N+L452R+T478K substitutions found in the B.1.617.2 sublineages AY.1/AY.2 ~~lineages~~ (commonly known as "Delta plus"; ~~/~~India origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing K417N+L452R+T478K substitutions, as indicated above. Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing L452R+E484Q substitutions, found in the B.1.617.1/B.1.617.3 lineages (Kappa/no designation; India origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing E484Q, as indicated above. Casirivimab and imdevimab together retained activity against pseudotyped VLP expressing individual substitutions R346K, E484K and N501Y, found in the B.1.621/B.1.621.1 (no designation; Colombia origin) lineage. Casirivimab and imdevimab, individually and together, retained neutralization activity against pseudotyped VLP expressing L452Q+F490S substitutions found in the C.37 lineage (Lambda; Peru origin). ~~Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing L452R+T478K+K417N substitutions found in the AY.1/AY.2 lineages (Delta/India origin), although casirivimab alone,~~

~~but not imdevimab, had reduced activity against pseudotyped VLP expressing L452R+T478K+K417N substitutions, as indicated above.~~

Table 1: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y[a]	no change[e]
B.1.351	South Africa	Beta	K417N, E484K, N501Y[b]	no change[e]
P.1	Brazil	Gamma	K417T, E484K, N501Y[c]	no change[e]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	no change[e]
B.1.526[f]	USA (New York)	Iota	E484K	no change[e]
B.1.617.1/B.1.617.3	India	Kappa/no designation	L452R+E484Q	no change[e]
B.1.617.2/AY.3	India	Delta	L452R+T478K	no change[e]
AY.1/AY.2[g]	India	Delta [+K417N]	K417N, L452R, T478K[d]	no change[e]
B.1.621/B.1.621.1	Colombia	No designation	R346K, E484K, N501Y	no change[e]
C.37	Peru	Lambda	L452Q+F490S	no change[e]
~~AY.1[d]~~	~~India~~	~~Delta~~	~~L452R+T478K+K417N~~	~~no change[e]~~
~~AY.2~~	~~India~~	~~Delta~~	~~L452R+T478K+K417N~~	~~no change[e]~~

[a] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

[b] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.

[c] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F

[d] For AY.1: Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: (T19R, G142D, E156G, F157-, F158-, K417N, L452R, T478K, D614G, P681R, D950N).

[e] No change: ≤2-fold reduction in susceptibility.

[f] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

[g] Commonly known as "Delta plus"

[**8/6/2021 Comment To Applicant (regarding B.1.621 lineage):** Please assess casirivimab and imdevimab against the spike protein and/or R346K+E484K+N501Y substitutions from this lineage.]

[**8/9/2021 Applicant Comment to FDA**: Accepted. The Sponsor will assess casirivimab and imdevimab against the spike protein and/or R346K+E484K+N501Y substitutions from this lineage.]

In a plaque reduction assay, casirivimab and imdevimab together retained activity against authentic SARS-CoV-2 variants of B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.1 (Kappa) and B.1.617.2 (Delta) lineages (Table 10), although casirivimab alone, but not imdevimab, had reduced activity against B.1.351 (5-fold), P.1 (154-fold) and B.1.617.1 (6-fold) variants.

It is not known how pseudotyped VLP or authentic SARS-CoV-2 data correlate with clinical outcomes.

Table 2: Authentic SARS-CoV-2 Neutralization Data for Casirivimab and Imdevimab Together using a Plaque Reduction Assay

SARS-CoV-2 Lineage	Country First Identified	WHO Nomenclature	Key Substitutions[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	no change[b]
B.1.351	South Africa	Beta	K417N, E484K, N501Y	no change[b]
P.1	Brazil	Gamma	K417T, E484K, N501Yc	no change[b]
B.1.617.1	India	Kappa	L452R, E484Q	no change[b]
B.1.617.2	India	Delta	L452R+T478K	no change[b]

[a] Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage
[b] No change: ≤2-fold reduction in susceptibility.

~~In a plaque reduction assay, casirivimab and imdevimab together retained activity against authentic SARS-CoV-2 variants of B.1.1.7 (Alpha), B.1.351 (Beta) and B.1.617.1 (Kappa), P.1 (Gamma), and B.617.2 (Delta) lineages (Table 2), although casirivimab alone, but not imdevimab, had reduced activity against B.1.351 (5-fold), and B.1.617.1 (6-fold) and P.1 (154-fold) variants. Note that confirmatory sequencing of each of the tested isolates has not yet been completed.~~

~~It is not known how pseudotyped VLP or authentic SARS-CoV-2 data correlate with clinical outcomes.~~

In clinical trial COV-2067, interim data indicated only one variant (G446V) occurring at an allele fraction ≥15%, which was detected in 3/66 subjects who had nucleotide sequencing data, each at a single time point (two at baseline in subjects from placebo and 2,400 mg casirivimab and imdevimab groups, and one at Day 25 in a subject from the 8,000 mg casirivimab and imdevimab group). The G446V variant had reduced susceptibility to imdevimab of 135-fold compared to wild-type in a pseudotyped VSV VLP neutralization assay but retained susceptibility to casirivimab alone and casirivimab and imdevimab together.

It is possible that resistance-associated variants to casirivimab and imdevimab together could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

ACCEPTED VERSION OF THE FACT SHEET FOR HEALTH CARE PROVIDERS (SDN 161)

15 MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to casirivimab and imdevimab administered together. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

Escape variants were identified following two passages in cell culture of recombinant VSV encoding SARS-CoV-2 spike protein in the presence of casirivimab or imdevimab individually, but not following two passages in the presence of casirivimab and imdevimab together. Variants which showed reduced susceptibility to casirivimab alone included those with spike protein amino acid substitutions K417E (182-fold), K417N (7-fold), K417R (61-fold), Y453F (>438-fold),

L455F (80-fold), E484K (25-fold), F486V (>438-fold) and Q493K (>438-fold). Variants which showed reduced susceptibility to imdevimab alone included substitutions K444N (>755-fold), K444Q (>548-fold), K444T (>1,033-fold), and V445A (548-fold). Casirivimab and imdevimab together showed reduced susceptibility to variants with K444T (6-fold) and V445A (5-fold) substitutions.

In neutralization assays using VSV VLP pseudotyped with spike protein variants identified in circulating SARS-CoV-2, variants with reduced susceptibility to casirivimab alone included those with E406D (51-fold), V445T (107-fold), G476S (5-fold), E484Q (19-fold), G485D (5-fold), F486L (61-fold), F486S (>715-fold), Q493E (446-fold), Q493R (70-fold), and S494P (5-fold) substitutions, and variants with reduced susceptibility to imdevimab alone included those with P337L (5-fold), N439K (463-fold), N439V (4-fold), N440K (28-fold), K444L (153-fold), K444M (1,577-fold), G446V (135-fold), N450D (9-fold), Q493R (5-fold), Q498H (17-fold), P499S (206-fold) substitutions. The G476D substitution had an impact (4-fold) on casirivimab and imdevimab together.

Casirivimab and imdevimab individually and together retained neutralization activity against pseudotyped VLP expressing all spike protein substitutions found in the B.1.1.7 lineage (Alpha; UK origin) and against pseudotyped VLP expressing only N501Y found in B.1.1.7 and other circulating lineages (Table 3). Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing all spike protein substitutions, or individual substitutions K417N, E484K or N501Y, found in the B.1.351 lineage (Beta; South Africa origin), and all spike protein substitutions or key substitutions K417T, E484K, or N501Y, found in the P.1 lineage (Gamma; Brazil origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing K417N or E484K, as indicated above. The E484K substitution is also found in the B.1.526 lineage (Iota; USA [New York] origin). Casirivimab and imdevimab, individually and together, retained neutralization activity against the L452R substitution found in the B.1.427/B.1.429 lineages (Epsilon; USA [California] origin). Casirivimab and imdevimab, individually and together, retained neutralization activity against pseudotyped VLP expressing L452R+T478K substitutions found in the B.1.617.2 and AY.3 lineages (Delta; India origin). Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing K417N+L452R+T478K substitutions found in the B.1.617.2 sublineages AY.1/AY.2 (commonly known as “Delta plus”; India origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing K417N+L452R+T478K substitutions, as indicated above. Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing L452R+E484Q substitutions, found in the B.1.617.1/B.1.617.3 lineages (Kappa/no designation; India origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing E484Q, as indicated above. Casirivimab and imdevimab together retained activity against pseudotyped VLP expressing individual substitutions R346K, E484K and N501Y, found in the B.1.621/B.1.621.1 (no designation; Colombia origin) lineage. Casirivimab and imdevimab, individually and together, retained neutralization activity against pseudotyped VLP expressing L452Q+F490S substitutions found in the C.37 lineage (Lambda; Peru origin).

Table 3: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

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B.1.427/B.1.429	USA (California)	Epsilon	L452R	no change[e]

B.1.526[f]	USA (New York)	Iota	E484K	no change[e]
B.1.617.1/B.1.617.3	India	Kappa/no designation	L452R+E484Q	no change[e]
B.1.617.2/AY.3	India	Delta	L452R+T478K	no change[e]
AY.1/AY.2[g]	India	Delta [+K417N]	K417N, L452R, T478K[d]	no change[e]
B.1.621/B.1.621.1	Colombia	No designation	R346K, E484K, N501Y	no change[e]
C.37	Peru	Lambda	L452Q+F490S	no change[e]

[a] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.
[b] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.
[c] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F
[d] For AY.1: Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: (T19R, G142D, E156G, F157-, F158-, K417N, L452R, T478K, D614G, P681R, D950N).
[e] No change: ≤2-fold reduction in susceptibility.
[f] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).
[g] Commonly known as "Delta plus".

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It is not known how pseudotyped VLP or authentic SARS-CoV-2 data correlate with clinical outcomes.

Table 4: Authentic SARS-CoV-2 Neutralization Data for Casirivimab and Imdevimab Together using a Plaque Reduction Assay

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B.1.617.1	India	Kappa	L452R, E484Q	no change[b]
B.1.617.2	India	Delta	L452R, T478K	no change[b]

[a] Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage
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It is possible that resistance-associated variants to casirivimab and imdevimab together could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

CONCLUSIONS

The sponsor updated the Antiviral Resistance portion of Section 15 of the Fact Sheet for HCPs to include additional pseudotyped virus-like particle (VLP) and authentic virus data, as requested. Additional minor edits were also made by the Division to this section. The sponsor agreed to assess the spike protein and/or R346K+E484K+N501Y substitutions found in the B.1.621 lineage for susceptibility to casirivimab and imdevimab, although casirivimab and imdevimab together retained activity against the individual substitutions, as indicated in the updated Fact Sheet.

Michael Thomson, Ph.D.
Clinical Virology Reviewer

CONCURRENCES

_____Date: _____
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