

**Office of Pharmaceutical Quality  
Chemistry, Manufacturing, and Controls  
EUA Amendment Review**

<b>EUA Number:</b>	000091
<b>eCTD Sequence Number:</b>	0235 (Supporting Document Number (SDN) 236), 0237 (SDN 238)
<b>Product Name:</b>	REGEN-COV (casirivimab (REGN10933) with imdevimab (REGN10987))
<b>Action item:</b>	Authorization of changes to the Fact Sheet for Healthcare Providers on the storage conditions of prepared syringes of casirivimab and imdevimab
<b>OBP Name:</b>	REGN10933: MAB HUMAN (IGG1) ANTI P0DTC2 (SPIKE_SARS2) [REGN10933] REGN10987: MAB HUMAN (IGG1) ANTI P0DTC2 (SPIKE_SARS2) [REGN10987]
<b>Indications:</b>	<ul style="list-style-type: none"> <li>For treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization</li> <li>For post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death</li> </ul>
<b>Sponsor:</b>	Regeneron, Inc
<b>Clinical Division:</b>	CDER/OND/OID/DAV
<b>Submission Date</b>	November 9, 2021 (eCTD 0235), November 12, 2021 (eCTD 0237)
<b>Primary Reviewers:</b>	Lei Zhang, Ph.D. Reyes Candau-Chacon, Ph.D. (Microbiology and Facilities) Vicky Borders-Hemphill, Pharm.D. (Product Quality Labeling)
<b>Secondary Reviewers:</b>	Patrick Lynch, Ph.D. Candace Gomez-Broughton, Ph.D. (Microbiology and Facilities)
<b>Tertiary Reviewer</b>	Emily Jing, Ph.D.

**A. EXECUTIVE SUMMARY**

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of revisions to the permitted syringe storage times in the following sections of the Fact Sheet for Healthcare Providers:

- Recent Major Changes, Preparation and Administration, Dosage And Administration (Section 2.4), and How Supplied/Storage And Handling (Section 19) – updated storage temperature range and duration

Authorization of this change request will allow for lengthening the storage condition of the prepared casirivimab and imdevimab syringes from no more than 4 hours in a refrigerator or room temperature to no more than 24 hours in a refrigerator or 8 hours at room temperature. Relevant sections of the Fact Sheet for Healthcare Providers are updated to include the following storage condition instructions for prepared syringes under EUA use:

*If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 24 hours, or at room temperature up to 25°C (77°F) for no more than 8 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.*

Microbial information supports the update to the storage condition of prepared syringes of casirivimab and imdevimab under emergency use. Additional details are provided in the primary technical reviews submitted to IND 148069.

## **B. REVIEW**

Data and information to support the proposed change controls were submitted to IND 148069 (eCTD 0623, SDN 659). Refer to the quality microbiology review memo dated September 16, 2021 in DARRTS for technical microbiology assessments by the Office of Pharmaceutical Manufacturing Assessment.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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11/15/2021 06:03:52 PM

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)  
CLINICAL VIROLOGY REVIEW**

**EUA-000091**

**DATE REVIEW COMPLETED: 11/15/2021**

**Reviewer:** Michael Thomson, Ph.D.  
**Sponsor:** Regeneron Pharmaceuticals, Inc.  
777 Old Saw Mill River Road  
Tarrytown, NY 10591-6707  
914.847.7400

**Regulatory History (Virology-Related Submissions Reviewed):**

Submission	Received	Assigned	Content
<a href="#">SDN 236</a>	11/09/2021	11/08/2021	Updated Fact Sheet for HCPs
<a href="#">SDN 238</a>	11/12/2021	11/12/2021	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**

<p>REGN10933 Heavy Chain</p> <p>QVQLVESGEGG LVKPGGSLRL <b>SCAASGFTFS</b> DYIYMSWIRQA PGKGLEWVSY <b>ITYSGSTIYY</b><sup>60</sup></p> <p>ADSVKGRFTI SRDIAKSSLY LQMNSLRRAED TAVYYC<b>ARDR</b> <b>GTTMVPFDYW</b> GQGTLVTVSS<sup>120</sup></p> <p>ASTKGPSVFP LAPSSKSTSG <b>GTAALGCLVK</b> DYFPEPVTVS WNSGALTSGV HTPFAVLQSS<sup>180</sup></p> <p>GLYSLSSVVT VPSSSLGTQT <b>YICNVNHKPS</b> NTKVDKVKVEP <b>KSCDKHTHCP</b> <b>PCPAPPELLGG</b><sup>240</sup></p> <p style="text-align: center;">           HC: CP PC            LC: GEC<sup>214</sup> </p> <p>PSVFLFPPKP KDTLMISRTP <b>EVT</b>CVVVDVSD HEDPEVKFNW YVDGVEVHNA KTKPREEQY<sup>300</sup></p> <p>STYRVVSVLT VLHQDWLNGK <b>EYKCKVSNKA</b> LPAPIEKTIK KAKGQPREPQ VYTLPPSRDE<sup>360</sup></p> <p>LTKNQVSL<b>TC</b> LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSGGSFFLY SKLTVDKSRW<sup>420</sup></p> <p>QQGNVFS<b>CSV</b> MHEALHNHYT QKSLSLSPGK<sup>450</sup></p> <p>REGN10933 Light Chain</p> <p>DIQMTQSPSS LSASVGRVIT <b>ITCQASQDIT</b> NYLNWYQKPK GKAPKLLIYA <b>ASNLETGVPS</b><sup>60</sup></p> <p>RFSGSGSGTD FTFTISGLQP EDIATY<b>CQQ</b> YDNLPLTFPG GTKVEIKRTV AAPSVFIFPP<sup>120</sup></p> <p>SDEQLKSGTA SVV<b>CLLN</b>NFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYLSLSTLT<sup>180</sup></p> <p>LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGE<b>C</b><sup>214</sup></p> <p style="text-align: center;">           HC: KSC<sup>223</sup> </p>	<p>REGN10987 Heavy Chain</p> <p>QVQLVESGEGG VVQPGRSRLR <b>SCAASGFTFS</b> NYAMYWVRQA PGKGLEWVAV <b>ISYDGSNKYY</b><sup>60</sup></p> <p>ADSVKGRFTI SRDIAKSSLY LQMNSLRRAED TAVYYC<b>ASGS</b> <b>DYGDYLLVYV</b> GQGTLVTVSS<sup>120</sup></p> <p>ASTKGPSVFP LAPSSKSTSG <b>GTAALGCLVK</b> DYFPEPVTVS WNSGALTSGV HTPFAVLQSS<sup>180</sup></p> <p>GLYSLSSVVT VPSSSLGTQT <b>YICNVNHKPS</b> NTKVDKVKVEP <b>KSCDKHTHCP</b> <b>PCPAPPELLGG</b><sup>240</sup></p> <p style="text-align: center;">           HC: CP PC            LC: TEC<sup>215</sup> </p> <p>PSVFLFPPKP KDTLMISRTP <b>EVT</b>CVVVDVSD HEDPEVKFNW YVDGVEVHNA KTKPREEQY<sup>300</sup></p> <p>STYRVVSVLT VLHQDWLNGK <b>EYKCKVSNKA</b> LPAPIEKTIK KAKGQPREPQ VYTLPPSRDE<sup>360</sup></p> <p>LTKNQVSL<b>TC</b> LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSGGSFFLY SKLTVDKSRW<sup>420</sup></p> <p>QQGNVFS<b>CSV</b> MHEALHNHYT QKSLSLSPGK<sup>450</sup></p> <p>REGN10987 Light Chain</p> <p>QSALTQPASV SGSPGQSITI <b>SC</b>TGTSSDVG GYNYVSWYQQ HPGKAPKLMY <b>YDVKRFP</b>SGV<sup>60</sup></p> <p>SNRFSGSKSG NTASLTISGL <b>QSEDEADYIC</b> <b>N</b>SLTSISTWV FGGGKTLTVL <b>GQPKAAPSV</b>TV<sup>120</sup></p> <p>LFPSSSEELQ ANKATLV<b>CL</b>I SDFYPGAVTV AWKADSSPVK AGVETTTPSK <b>QSN</b>NKYAAS<sup>180</sup></p> <p>YLSLTPEQWK SHRSY<b>SC</b>QVT HEGSTVEKTV APT<b>CS</b><sup>216</sup></p> <p style="text-align: center;">           HC: KSC<sup>223</sup> </p>
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**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<sup>300</sup> is shown in green. The heavy chain C-terminal Lys<sup>450</sup>, predominantly removed during the manufacturing process, is shown in pink.

**Molecular formula:** REGN10933: C<sub>6454</sub>H<sub>9976</sub>N<sub>1704</sub>O<sub>2024</sub>S<sub>44</sub>; REGN10987: C<sub>6396</sub>H<sub>9882</sub>N<sub>1694</sub>O<sub>2018</sub>S<sub>42</sub>

**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 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous (IV) infusion or subcutaneous injection

**Abbreviations:** ACE2, angiotensin-converting enzyme 2; CoV, coronavirus; COVID-19, coronavirus disease 2019; EC<sub>50, 90</sub>, 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

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**  
**CLINICAL VIROLOGY REVIEW**  
**EUA-000091      DATE REVIEW COMPLETED: 11/15/2021**

**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 was granted EUA on November 21, 2020 for the treatment of mild to moderate COVID-19 in non-hospitalized adult and pediatric subjects (12 years and older, weighing ≥40 kg), based on clinical data from trial COV-2067. The EUA was amended on July 30, 2021 to include an indication of post-exposure prophylaxis in adults and pediatric subjects (12 years and older, weighing ≥40 kg), based on clinical data from trial COV-2069.

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 final OND memo](#)).

The submission under **SDN 236** is an updated Fact Sheet for Healthcare Providers (HCPs); the submission under **SDN 238** includes the revised Fact Sheet with changes accepted by the sponsor. The sponsor made changes to Section 15, Antiviral Resistance, to include updated pseudotyped virus-like particle (VLP) data; additional minor changes to this section were subsequently proposed by the Division.

**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 **yellow** highlight, and the changes proposed by the Division in **red** font. The final accepted version is shown in the section following.

**15 MICROBIOLOGY/RESISTANCE INFORMATION**

Antiviral Resistance

[To Applicant: We've accepted all but one of the proposed changes, and made some minor changes for clarity.]  
[Applicant response: Regeneron accepts]

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.

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**  
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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 (**77-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. Substitutions tested concurrently which had reduced susceptibility to casirivimab and imdevimab together included N440K+E484K (21-fold), found in the B.1.619/B.1.625 lineages, and N439K+E484K (23-fold), found in the AV.1 lineage; variants harboring these concurrent substitutions have been detected rarely in the US.

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 9). 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 (**7-fold**) or E484K (**25-fold**), ~~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 (**9-fold**), ~~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 **L452R+E484Q (7-fold)**, ~~as indicated above~~. 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 activity against pseudotyped VLP expressing **individual substitutions R346K+, E484K+ and N501Y**, found in the B.1.621/B.1.621.1 (Mu; Colombia origin) lineage **although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing R346K+E484K+N501Y (23-fold)**.

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

<b>Lineage with Spike Protein Substitution</b>	<b>Country First Identified</b>	<b>WHO Nomenclature</b>	<b>Key Substitutions tested</b>	<b>Fold Reduction in Susceptibility</b>
B.1.1.7	UK	Alpha	N501Y <sup>a</sup>	no change <sup>e</sup>

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)  
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B.1.351	South Africa	Beta	K417N+E484K+N501Y <sup>b</sup>	no change <sup>e</sup>
P.1	Brazil	Gamma	K417T+E484K+N501Y <sup>c</sup>	no change <sup>e</sup>
B.1.617.2/AY.3	India	Delta	L452R+T478K	no change <sup>e</sup>
AY.1/AY.2 <sup>f</sup>	India	Delta [+K417N]	K417N+L452R+T478K <sup>d</sup>	no change <sup>e</sup>
B.1.427/B.1.429	USA (California)	Epsilon	L452R	no change <sup>e</sup>
B.1.526 <sup>g</sup>	USA (New York)	Iota	E484K	no change <sup>e</sup>
B.1.617.1/B.1.617.3	India	Kappa/no designation	L452R+E484Q	no change <sup>e</sup>
C.37	Peru	Lambda	L452Q+F490S	no change <sup>e</sup>
B.1.621/B.1.621.1 <sup>h</sup>	Colombia	Mu	R346K <sup>+</sup> , E484K <sup>+</sup> , N501Y	no change <sup>e</sup>

<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup> 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.

<sup>d</sup> 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).

<sup>e</sup> No change:  $\leq 2$ -fold reduction in susceptibility.

<sup>f</sup> Commonly known as "Delta plus".

<sup>g</sup> Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

<sup>h</sup> Key substitutions in this variant were tested individually for susceptibility to casirivimab and imdevimab, alone and in combination.

In a plaque reduction assay, eCasirivimab 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) lineages (Table 2), although casirivimab alone, but not imdevimab, had reduced activity against B.1.351 (5-fold), P.1 (>371-54-fold) and B.1.617.1 (6-fold) variants.

[To Applicant: Please confirm whether this should be >371-fold. According to study report R10933-PH-20091 v5, an EC<sub>50</sub> value could not be accurately calculated]

[Applicant response: Regeneron accepts]

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 <sup>a</sup>	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	no change <sup>b</sup>
B.1.351	South Africa	Beta	K417N <sup>+</sup> , E484K <sup>+</sup> , N501Y	no change <sup>b</sup>
P.1	Brazil	Gamma	K417T <sup>+</sup> , E484K <sup>+</sup> , N501Y	no change <sup>b</sup>

## DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

### CLINICAL VIROLOGY REVIEW

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B.1.617.2	India	Delta	L452R <del>+</del> T478K	no change <sup>b</sup>
B.1.617.1	India	Kappa	L452R <del>+</del> E484Q	no change <sup>b</sup>

<sup>a</sup> Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage

<sup>b</sup> No change:  $\leq 2$ -fold reduction in susceptibility.

In clinical trial COV-2067, interim data indicated only one variant (G446V) occurring at an allele fraction  $\geq 15\%$ , 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.

## ACCEPTED VERSION OF THE FACT SHEET FOR HEALTH CARE PROVIDERS (SDN 238)

### 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), G476S (5-fold), E484Q (19-fold), G485D (5-fold), F486L (61-fold), F486S (>715-fold), Q493E (446-fold), Q493R (77-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), Q498H (17-fold), P499S (206-fold) substitutions. The G476D substitution had an impact (4-fold) on casirivimab and imdevimab together. Substitutions tested concurrently which had reduced susceptibility to casirivimab and imdevimab together included N440K+E484K (21-fold), found in the B.1.619/B.1.625 lineages, and N439K+E484K (23-fold), found in the AV.1 lineage; variants harboring these concurrent substitutions have been detected rarely in the US.



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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 1).

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 (7-fold) or E484K (25-fold). 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 (9-fold). 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 L452R+E484Q (7-fold). 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 activity against pseudotyped VLP expressing R346K+E484K+ N501Y found in the B.1.621/B.1.621.1 (Mu; Colombia origin) lineage although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing R346K+E484K+N501Y (23-fold).

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

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

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C.37	Peru	Lambda	L452Q+F490S	no change <sup>e</sup>
B.1.621/B.1.621.1	Colombia	Mu	R346K+E484K+N501Y	no change <sup>e</sup>

- <sup>a</sup> 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.
- <sup>b</sup> 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.
- <sup>c</sup> 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.
- <sup>d</sup> 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).
- <sup>e</sup> No change:  $\leq 2$ -fold reduction in susceptibility.
- <sup>f</sup> Commonly known as “Delta plus”.
- <sup>g</sup> Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

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) lineages (Table 2), although casirivimab alone, but not imdevimab, had reduced activity against B.1.351 (5-fold), P.1 (>371-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 4: Authentic SARS-CoV-2 Neutralization Data for Casirivimab and Imdevimab Together**

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

- <sup>a</sup> Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage
- <sup>b</sup> No change:  $\leq 2$ -fold reduction in susceptibility.

In clinical trial COV-2067, interim data indicated only one variant (G446V) occurring at an allele fraction  $\geq 15\%$ , 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.

**CONCLUSIONS**

The sponsor updated the Antiviral Resistance portion of Section 15 of the Fact Sheet for HCPs with minor editorial changes and to revise some of the pseudotyped virus-like particle (VLP) data. Additional minor edits for clarification were made to this section by the Division.

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Clinical Virology Reviewer

**CONCURRENCES**

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