COVID-19 Monoclonal Antibodies side-by-side comparison

July 26, 2021

Summary of changes since last publication (update: July 26, 2021)

- Added information about the national pause of distribution of bamlanivimab and etesevimab due to high frequencies of P.1 (Gamma) and B.1.351 (Beta) variants in the U.S. (evidence summary)

COVID-19 monoclonal antibodies side-by-side comparison

	Generic name (research name)		
	Bamlanivimab (LY-Co555) and Etesevimab (LY-CoV016)	**Casirivimab (REGN10933) and Imdevimab (REGN10987) (REGEN-COV)**	**Sotrovimab (VIR-7831)**
Manufacturer	Eli Lilly	Regeneron	GlaxoSmithKline
Indication	• **Emergency Use Authorization**: Outpatient use to treat 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, including hospitalization or death • High risk criteria in EUA: older age (for example, age ≥65 years of age), obesity or being overweight (for example, BMI >25 kg/m2 or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm), pregnancy, chronic kidney disease, diabetes, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease (including congenital heart disease) or hypertension, chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma, interstitial lung disease, cystic fibrosis and pulmonary hypertension), sickle cell disease, neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies), having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID 19))		
Dose	• 700 mg bamlanivimab and 1,400 mg etesevimab given together as a single IV infusion • No dosage adjustment is required in pregnancy or lactation; pediatrics ≥ 12 y and ≥ 40 kg; renal impairment, or mild hepatic impairment • Administer as soon as possible after positive results of SARS-CoV-2 and within 10 d of symptom onset	• 600 mg of casirivimab and 600 mg of imdevimab given together (1,200 mg) as a single IV infusion • SC injection is an alternative route of administration when IV infusion is not feasible and would lead to delay in treatment • No dosage adjustment is required in pregnancy or lactation; pediatrics ≥ 12 y and 40 kg; or renal impairment • Administer as soon as possible after positive results of SARS-CoV-2 and within 10 d of symptom onset	• 500 mg of sotrovimab given as a single IV infusion • No dosage adjustment is required in pregnancy or lactation; pediatrics ≥ 12 y and 40 kg; or renal impairment • Administer as soon as possible after positive results of SARS-CoV-2 and within 10 d of symptom onset
Preparation and administration			

	Generic name (research name)		
	Bamlanivimab (LY-Co555) and Etesevimab (LY-CoV016)	**Casirivimab (REGN10933) and Imdevimab (REGN10987) (REGEN-COV)**	**Sotrovimab (VIR-7831)**

Preparation	• Remove 1 vial of bamlanivimab and 2 vials of etesevimab from refrigerated storage and bring to room temperature for 20 mins. Do not expose to direct heat or shake the vial.
	• Withdraw 20 mL from 1 bamlanivimab vial and 40 mL from 2 etesevimab vials and inject all 60 mL into a prefilled infusion bag containing 0.9% Sodium Chloride (May use prefilled 50 mL, 100 mL, 150 mL, or 250 mL infusion bags).
	• Gently invert the bag by hand approximately 10 times to mix. Do not shake.
		• There are 2 formulations available: a co-formulated solution (1:1 ratio) or individual antibody solutions
		• Remove from refrigerated storage and bring to room temperature for 20 mins. Do not expose to direct heat or shake the vial.
		
		IV infusion:
		• Withdraw the appropriate amount of casirivimab and imdevimab from each respective vial(s) and inject into a 50 mL, 100 mL, 150 mL, or 250 mL prefilled infusion bag containing Sodium Chloride Injection.
		  ○ Using co-formulated vial: add 10 mL of co-formulated casirivimab and imdevimab
		  ○ Using individual vials: add 5 mL of casirivimab and 5 mL of imdevimab
		• Gently invert infusion bag by hand approximately 10 times to mix. Do not shake.
		
		SC injection:
		• Withdraw 2.5 mL, using a 21-gauge transfer needle, into a total of 4 syringes (3 mL or 5 mL polypropylene Luer Lock)
		  ○ Using co-formulated vial: withdraw 2.5 mL into 4 separate syringes
		  ○ Using individual vials: withdraw 2.5 mL of casirivimab into 2 syringes and 2.5 mL of imdevimab into 2 syringes
		• Replace the 21-gauge transfer needle with a 25-gauge or 27-gauge needle for SC injection
			• Remove 1 vial of sotrovimab from refrigerated storage and bring to room temperature, protected from light, for 15 mins. Gently swirl the vial several times before use without creating air bubbles. Do not shake the vial.
			• Withdraw 8 mL of sotrovimab and inject all 8 mL into a prefilled infusion bag containing 0.9% Sodium Chloride (May use prefilled 50 mL or 100 mL infusion bags).
			• Gently rock the infusion bag back and forth by hand 3 to 5 times. Do not invert the infusion bag.

<table>
<tr><th></th><th colspan="3">Generic name (research name)</th></tr>
<tr><th></th><th>Bamlanivimab (LY-Co555) and Etesevimab (LY-CoV016)</th><th>Casirivimab (REGN10933) and Imdevimab (REGN10987) (REGEN-COV)</th><th>Sotrovimab (VIR-7831)</th></tr>
<tr><td>Administration</td><td>

Use of an in-line or add-on 0.20/0.22-micron polyethersulfone (PES) filter is strongly recommended.
Attach the infusion set (polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC) to the IV bag.
The maximum infusion rate depends on the weight of the patient. The minimum infusion time depends on the size of the prefilled infusion bag selected.
For patients weighing ≥ 50 kg, the maximum infusion rate is 310 mL/h and the minimum infusion time is:

<table>
<tr><th>Size of prefilled 0.9% NaCl infusion bag</th><th>Minimum infusion time</th></tr>
<tr><td>50 mL</td><td>21 min</td></tr>
<tr><td>100 mL</td><td>31 min</td></tr>
<tr><td>150 mL</td><td>41 min</td></tr>
<tr><td>250 mL</td><td>60 min</td></tr>
</table>

For patients weighing < 50 kg, the maximum infusion rate is 310 mL/h for all bag sizes except the 250 mL bag size for which the maximum infusion rate is 266 mL/h.

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<tr><td>100 mL</td><td>31 min</td></tr>
<tr><td>150 mL</td><td>41 min</td></tr>
<tr><td>250 mL</td><td>70 min</td></tr>
</table>

Once infusion is complete, flush the tubing with 0.9% Sodium Chloride to ensure delivery of required dose.
Observe for 1 h after infusion.

</td><td>
IV infusion:

Use of an in-line or add-on 0.20-micron PES filter is recommended.
Attach the infusion set (PVC, PE-lined PVC, or polyurethane) to the IV bag.
Administer the entire infusion bag via pump or gravity over 60 mins (infusion rate: 250 mL/h).
Once infusion is complete, flush the tubing with 0.9% Sodium Chloride to ensure delivery of required dose.
Observe for 1 hour after infusion.

SC injection:

Administer the 4 syringes consecutively, each at different injection sites (thigh, back of the upper arm, or abdomen).
Do not inject into skin that is tender, damaged, bruised, or scarred.
Observe for 1 hour after injections.

</td><td>

Use of an in-line or add-on 0.20-micron PES filter is recommended.
Attach the infusion set (PVC or polyolefin) to the IV bag. Prime the infusion set with 0.9% Sodium Chloride.
Administer the entire infusion bag over 30 minutes. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
Once the infusion is complete, flush the tubing with 0.9% Sodium Chloride to ensure delivery of required dose.
Observe for 1 hour after infusion.

</td></tr>
</table>

	Generic name (research name)		
	Bamlanivimab (LY-Co555) and Etesevimab (LY-CoV016)	**Casirivimab (REGN10933) and Imdevimab (REGN10987) (REGEN-COV)**	**Sotrovimab (VIR-7831)**
Dosage forms and strengths	Single-dose vials • NDC 0002-7910-01 – single-dose vial of bamlanivimab: 700 mg/20 mL (35 mg/mL) • NDC 0002-7950-01 – single-dose vial of etesevimab: 700 mg/20 mL (35 mg/mL)	Dose Pack (may contain 2, 5, or 8 vials) provides 1 treatment dose of 2,400 mg REGEN-COV • NDC 61755-035-02 – combination of 1 vial of casirivimab (11.1 mL) and 1 vial of imdevimab (11.1 mL) • NDC 61755-037-05 – combination of 1 vial of casirivimab (11.1 mL) and 4 vials of imdevimab (2.5 mL) • NDC 61755-036-08 – combination of 4 vials of casirivimab (2.5 mL) and 4 vials of imdevimab (2.5 mL) • NDC 61755-038-08 – combination of 4 vials of casirivimab (2.5 mL) and 1 vial of imdevimab (11.1 mL) Individual packages • NDC 61755-026-01 – single-dose vial of casirivimab: 300 mg/2.5 mL (120 mg/mL) • NDC 61755-024-01 – single-dose vial of casirivimab: 1,332 mg/11.1 mL (120 mg/mL) • NDC 61755-027-01 – single-dose vial of imdevimab: 300 mg/2.5 mL (120 mg/mL) • NDC 61755-025-01 – single-dose vial of imdevimab: 1,332 mg/11.1 mL (120 mg/mL) Co-formulated casirivimab and imdevimab • NDC 61755-039-01 – single-dose vial of casirivimab/imdevimab: 600 mg/600 mg per 10 mL (60 mg/60 mg per mL)	Single-dose vial • NDC 0173-0901-86 – single dose vial of sotrovimab: 500 mg/8 mL (62.5 mg/mL)

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	Bamlanivimab (LY-Co555) and Etesevimab (LY-CoV016)	**Casirivimab (REGN10933) and Imdevimab (REGN10987) (REGEN-COV)**	**Sotrovimab (VIR-7831)**
Product composition	Per mL of solution (bamlanivimab vial): • 35 mg of bamlanivimab • 0.4 mg L-histidine • 0.6 mg L-histidine hydrochloride monohydrate • 2.9 mg sodium chloride • 60 mg sucrose • 0.5 mg polysorbate 80 Per mL of solution (etesevimab vial): • 35 mg of etesevimab • 1.55 mg L-histidine • 2.10 mg L-histidinehydrochloride monohydrate • 80.4 mg sucrose • 0.5 mg polysorbate 80	Each 2.5 mL of solution contains: • 300 mg of casirivimab or imdevimab • 1.9 mg L-histidine • 2.7 mg L-histidine monohydrochloride monohydrate • 2.5 mg polysorbate 80 • 200 mg sucrose Each 11.1 mL of solution contains: • 1,332 mg of casirivimab or imdevimab • 8.3 mg L-histidine • 12.1 mg L-histidine monohydrochloride monohydrate • 11.1 mg polysorbate 80 • 888 mg sucrose	Per mL of solution (sotrovimab vial): • 62.5 mg of sotrovimab • 1.51 mg L-histidine • 2.15 mg L-histidine monohydrochloride • 0.75 mg L-methionine • 0.4 mg polysorbate 80 • 70 mg sucrose
Contraindications	None		
Warning and Precautions	• Hypersensitivity including anaphylaxis and infusion-related reactions have been observed with administration of monoclonal antibodies. If an infusion-related reaction occurs, consider slowing or stopping the infusion and administering appropriate medications. • Clinical worsening of COVID-19 after administration has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia, fatigue and altered mental status. • Benefit of treatment has not been observed in patients hospitalized due to COVID-19. None of the monoclonal antibodies are authorized for use in inpatients.		
Adverse reactions	Infusion reactions, nausea (4%), pruritus (2%), pyrexia (1%)	Infusion reactions, including pyrexia, chills, urticaria, pruritus, abdominal pain, and flushing	Infusion reactions, including pyrexia, chills, dizziness, dyspnea, pruritis, rash, and diarrhea.
Drug interactions	None		
Pharmacology	Bamlanivimab and etesevimab are IgG1 mAbs that neutralize the spike protein of SARS-CoV-2, which can block the spike protein attachment to human ACE2 receptors, thus preventing subsequent viral entry into human cells and viral replication.	Casirivimab (IgG1κ) and imdevimab (IgG1λ) are recombinant human mAbs which are unmodified in the Fc regions. Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2. The casirivimab + imdevimab combination blocked RBD binding to the human ACE2.	Sotrovimab (IgG1κ) is a recombinant human mAb which is modified in the Fc region, including M428L and N434S amino acid substitutions. Sotrovimab binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 but does not compete with human ACE2 receptor binding.

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	Bamlanivimab (LY-Co555) and Etesevimab (LY-CoV016)	**Casirivimab (REGN10933) and Imdevimab (REGN10987) (REGEN-COV)**	**Sotrovimab (VIR-7831)**
Storage/stability			
Unopened vials	Store at 2˚C-8˚C • Do not freeze or shake • Protect from light	Store at 2˚C-8˚C • Do not freeze or shake • Protect from light	Store at 2˚C-8˚C • Do not freeze or shake • Protect from light
Prepared infusion or injection	If not used immediately after dilution: • Stable at 2-8˚C for 24 h • Stable at room temperature (20- 25° C) for up to 7 h including infusion time	IV infusion – If not used immediately after dilution: • Stable at 2-8˚C for 36 h • Stable at room temperature (up to 25˚ C) for up to 4 h SC injection – If not used immediately after preparation: • Stable at 2-8˚C for 4 h • Stable at room temperature (up to 25˚ C) for up to 4 h • If refrigerated, allow syringes to equilibrate to room temperature for 20 minutes prior to administration	If not used immediately after dilution: • Stable at 2-8˚C for 24 h • Stable at room temperature (up to 25˚ C) for up to 4 h
Commercially available	Yes	Yes	GSK and Vir are working to make sotrovimab available to U.S. patients in the coming weeks
How to order	Monoclonal antibodies are direct ordered from AmerisourceBergen. For more information, please review the C19 Therapies Direct Order Request Form		Patients and healthcare professionals can access more information about eligibility, availability and financial support at gskcovidcontactcenter.com or by calling 866-GSK-COVID (866-475-2684).

Evidence summary	**Bamlanivimab ± etesevimab – Treatment trials** **Summary: Limited evidence suggests that the combination of bamlanivimab plus etesevimab reduces COVID-19 related hospitalizations or death in ambulatory patients recently diagnosed with symptomatic COVID-19 who are at high risk for progressing to severe COVID-19. Data from the ACTIV-3 study suggest bamlanivimab is not effective in hospitalized patients.** • The clinical trial program of bamlanivimab (alone or in combination with etesevimab) consists of a phase 1 study of bamlanivimab in hospitalized patients (NCT04411628), a phase 2/3 study in patients recently diagnosed with symptomatic COVID-19 in the ambulatory setting (BLAZE-1, NCT04427501), and a phase 3 study in residents and long-term care facilities (BLAZE-2, NCT04497987). Additionally, bamlanivimab has been evaluated in the National Institute of Health (NIH) ACTIV-3 trial (NCT04501978) and is currently being evaluated in the NIH ACTIV-2 trial (NCT04518410). • The bamlanivimab treatment arm of the ACTIV-3 trial was stopped early based on interim data demonstrating that bamlanivimab was unlikely to be effective in hospitalized patients who are in the late stage of their illness, suggesting that the timing of initiation of mAb therapy is critical to efficacy. • Interim and final analysis of the phase 2 results from the phase 2/3 BLAZE-1 trial are published and summarized in Appendix 1. • Interim data from the BLAZE-1 trial suggested that bamlanivimab was associated with a reduction in COVID-19 related hospitalization (including ED visits) in ambulatory patients with mild to moderate COVID-19 illness given a mAb infusion within a median of 4 days of symptom onset. A post-hoc analysis suggested the magnitude of benefit was larger among patients ≥ 65 years old or among those with a BMI ≥ 35 kg/m^2. In this subgroup, the absolute difference between bamlanivimab-treated and placebo-treated patients was 11%. At the interim analysis, clinical endpoints were evaluated descriptively, and confidence intervals were not calculated. • In the final analysis of phase 2 data from the BLAZE-1 trial, which included data from bamlanivimab only arms and data from the bamlanivimab plus etesevimab treatment arm, all bamlanivimab treatment arms reduced COVID-19 related hospitalizations compared with placebo; however, the difference was only statistically significant between the combination treatment arm and placebo. This is likely due to the trial being underpowered due to a low frequency of clinical events in each treatment arm and a small number of participants in each arm. In a post-hoc analysis (descriptively analyzed only), there were no COVID-19 related hospitalizations in the combination treatment arm (vs. 7 in the placebo arm) in patients ≥ 65 years old or in patients with a BMI ≥ 35 kg/m^2. • In January, Lilly announced results from the phase 3 component of the BLAZE-1 trial, which confirmed results from the phase 2 component. According to the press release, among 1,035 high-risk patients, events - COVID-19 related hospitalizations or death – were significantly reduced in patients treated with the combination of bamlanivimab plus etesevimab compared with placebo (11 events (2.1%) vs. 36 events (7.0%), respectively; *P* = .0004). Ten COVID-19 related deaths occurred, all in the placebo group. Combination treatment also significantly reduced viral load and accelerated symptom improvement compared with placebo. • In March, Lilly announced results of a new cohort of the BLAZE-1 trial evaluating bamlanivimab 700 mg plus etesevimab 1400 mg, which is the dosing now authorized in the EUA. According to the press release, among 769 high-risk patients, events - COVID-19 related hospitalizations or death – were reduced by 87% in patients treated with the combination of bamlanivimab 700 mg plus etesevimab 1400 mg compared with placebo (4 events (< 1%) vs. 15 events (6%), respectively; *P* < .0001). Four COVID-related deaths occurred, all in the placebo group. The safety profile of bamlanivimab plus etesevimab was consistent with prior data.

Casirivimab plus imdevimab (REGEN-COV) – Treatment trials

Summary: Limited evidence suggests that REGEN-COV reduces COVID-19 related hospitalization or death in ambulatory patients recently diagnosed with symptomatic COVID-19, particularly in those who are serum antibody negative at baseline. Preliminary data suggest that REGEN-COV may be beneficial in reducing death or mechanical ventilation in hospitalized patients on low-flow oxygen who are serum antibody negative at baseline; however, the trial is ongoing and the effect of treatment in hospitalized patients remains uncertain.

- The clinical trial program of REGEN-COV consists of a phase 1/2/3 study in patients recently diagnosed with COVID-19 in the ambulatory setting (NCT04425629), a phase 2/3 study in certain hospitalized patients with COVID-19 (NCT04426695), and a phase 3 trial in healthy adults and adolescents who are household contacts of infected individuals (NCT04452318). A UK-only trial (RECOVERY) is evaluating REGEN-COV in hospitalized patients.
- Interim results from the phase 1/2 component of the phase 1/2/3 trial in ambulatory patients are published and summarized in Appendix 1.
- Interim data from 275 patients from the phase 1/2 component of the phase 1/2/3 trial suggested that REGEN-COV enhanced viral clearance (thereby reducing viral load) in the overall cohort of ambulatory patients recently diagnosed with symptomatic COVID-19. The magnitude of effect was greatest in patients who were serum antibody-negative at baseline. REGEN-COV was associated with an absolute 3% difference vs. placebo in the incidence of medically attended visits in the overall cohort of patients, but the confidence interval was wide and included 0. In the subgroup of patients who was serum antibody-negative at baseline, REGEN-COV was associated with an absolute 9% difference vs. placebo in the incidence of medically attended visits, but again, the confidence interval was wide and included 0. No formal hypothesis testing was performed on any endpoint.
- On February 25, the Independent Data Monitoring Committee announced that REGEN-COV reduces hospitalization or death in ambulatory patients recently diagnosed with symptomatic COVID-19 and recommended that patients no longer be enrolled in the placebo arm in the phase 3 component of the phase 1/2/3 trial.
- Regeneron announced that the phase 2/3 trial evaluating REGEN-COV in hospitalized COVID-19 patients requiring low-flow oxygen who are seronegative for antibodies at baseline passed the futility analysis and will continue. In the futility analysis, seronegative patients treated with REGEN-COV had a lower risk of death or progressing to mechanical ventilation than patients treated with placebo (hazard ratio: 0.78; 95% CI, 0.51-1.2). Previously, the arm evaluating REGEN-COV in hospitalized COVID-19 patients requiring high-flow oxygen was stopped due to futility.
- In March, Regeneron announced the results from the phase 3 component of the Outpatient trial. According to the press release, the 1,200 mg and 2,400 mg dosage regimens of REGEN-COV compared to placebo significantly reduced COVID-19 related hospitalization or death (7 events (1.0%) vs. 24 events (3.2%) and 18 events (1.3%) vs. 62 events (4.6%), respectively). Among the high-risk patients receiving the 1,200 mg dosage regimen (n = 736) vs. placebo (n = 748) there was 70% risk reduction in COVID-19 related hospitalization or death (P = .0024). There was a 71% risk reduction (P < .0001) among the high-risk patients receiving the 2,400 mg dosage regimen (n = 1,355) vs. placebo (n = 1,341). For both regimens compared to placebo, the median reduction of time to COVID-19 symptom resolution was 4 days (P < .0001). Regeneron will submit this new data to regulatory authorities to request the lower 1,200 mg dosage regimen be added to the EUA.

- In April, Regeneron announced separate results from the Multi-part phase 3 trial. The trial enrolled participants without COVID-19 symptoms (asymptomatic) who lived in the same household as an individual who tested positive for SARS-CoV-2 within the 4 days prior and evaluated subcutaneous administration of REGEN-COV. Participants were tested for SARS-CoV-2 at baseline. Participants who tested negative were placed in the prevention trial (2069A) and those who tested positive were put in the treatment trial (2069B). According to the 2069A press release, the 1,200 mg dosage regimen of REGEN-COV (n = 753) compared to placebo (n = 752) reduced the risk of symptomatic COVID-19 infection by 81% (*P* < .0001; 11 events (1.5%) vs. 59 events (7.8%), respectively) through day 29 in participants who tested negative for SARS-CoV-2 at baseline. For those who developed symptomatic COVID-19 infection, resolution of symptoms, on average, occurred after 1 week in the REGEN-COV group vs. 3 weeks in the placebo group. There was a 93% reduction in cumulative weeks with symptoms in the REGEN-COV group compared to placebo (13 weeks vs. 188 weeks, respectively; *P* < .0001). According to the 2069B press release, the 1,200 mg dosage regimen of REGEN-COV (n = 100) compared to placebo (n = 104) reduced the risk of symptomatic COVID-19 by 31% (29 events (29%) vs. 44 events (42%), respectively; *P* = .038) through day 29 and by 76% (5 events (5%) vs. 22 events (21%), respectively; *P* = .0007) from day 3 to 29 in asymptomatic participants who tested positive for SARS-CoV-2 at baseline. There was a 45% reduction in cumulative weeks with symptoms in the REGEN-COV group compared to placebo (13 weeks vs. 188 weeks, respectively; *P* = .0273).
- In May, Regeneron presented further results, initially released in March, from the phase 3 component of the Outpatient trial at the 2021 American Thoracic Society International conference. According to the press release, a safety assessment was conducted in 5,531 patients up to day 169. Serious adverse events occurred in 1.1% of participants in the 1,200 dosage regimen, 1.3% in the 2,400 mg dosage regimen, and 4.0% in the placebo groups. The serious adverse events were noted to be largely related to COVID-19. There was 1 death in the 1,200 dosage regimen group (n = 827), 1 death in the 2,400 mg dosage regimen group (n = 1,849), and 5 deaths in the placebo groups (n = 1,843).
- In June, Regeneron announced results from the UK phase 3 RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial in hospitalized patients. According to the press release, 9,785 participants hospitalized with COVID-19 were randomized to receive usual care plus 8,000 mg REGEN-COV or usual care alone. Usual care was determined by the individual facilities and clinicians. The primary outcome was all-cause mortality at day 28. In seronegative participants (n = 3,153), 24% of participants in the REGEN-COV-treated group died vs. 30% in the usual care alone group (rate ratio: 0.80; 95% CI, 0.70-0.91; ***P*** = .001). The results were not statistically significant including the larger seropositive group.

Sotrovimab (VIR-7831) – Treatment Trials

Summary: Limited evidence suggests that sotrovimab reduces COVID-19 related hospitalizations or death in ambulatory patients recently diagnosed with symptomatic COVID-19 who are at high risk for progressing to severe COVID-19.

- The clinical trial program of sotrovimab consists of the ongoing phase 1/2/3 COMET-ICE trial (NCT04545060), the ongoing phase 2 COMET-PEAK trial (NCT04779879), the phase 3 COMET-TAIL trial, and the phase 3 COMET-STAR trial. Emergency use of sotrovimab was authorized based on the interim analysis of the phase 3 COMET-ICE trial, a randomized, double-blind, placebo-controlled trial, in which outpatient (non-hospitalized) adults with mild-to-moderate COVID-19 infection (onset within 5 days of enrollment) were administered sotrovimab 500 mg IV (n = 291) or placebo (n = 292). The primary endpoint was progression of COVID-19 at day 29, defined as hospitalization for > 24 hours for acute management of any illness or death from any cause. At day 29, 1% of participants in the sotrovimab-treated group and 7% in the placebo group had progression of COVID-19 (adjusted relative

risk reduction: 85%; 97.24% CI, 44-96; *P* = .002). At day 29, all-cause mortality was not seen in the sotrovimab-treated group vs. 1 participant in the placebo group. Analysis of change from baseline in viral load is not available as data are not yet available in the majority of the trial participants.

- In June, **GSK and Vir announced the final results of the phase 3 COMET-ICE trial. According to the press release**, analysis of final day 29 data con**firms** sotrovimab significantly reduces hospitalization and risk of death in adults with mild-to-moderate COVID-19 at high risk for progression to severe disease. The primary endpoint was progression of COVID-19 at day 29, defined as hospitalization for > 24 hours for acute management of any illness or death from any cause. Of the 1,057 participants evaluated, at day 29, 6 participants (1%) in the sotrovimab-treated group and 30 (6%) in the placebo group had progression of COVID-19 (adjusted relative risk reduction: 79%; *P* < .001). In the safety analysis of 1,0.37 participants, the most common adverse events in the sotrovimab-treated group were rash (1%) and diarrhea (2%).

Passive Vaccination/Prevention trials

Summary: Preliminary results from Eli Lilly and Regeneron suggest that mAbs may be effective at providing passive immunity to patients who need immediate protection or who respond poorly to vaccination. Full study results need to be published to verify magnitude of effect.

- Preliminary results shared by Eli Lilly from the unpublished BLAZE-2 trial suggest that bamlanivimab reduces the risk of contracting symptomatic COVID-19 among residents and staff of long-term care facilities. Briefly, in the BLAZE-2 trial, 965 participants (n = 299 residents and n = 666 staff) who were SARS-CoV-2 negative at baseline were randomized to receive 4,200 mg of bamlanivimab or placebo. At 8 weeks, there were significantly fewer bamlanivimab-treated patients who developed symptomatic COVID-19 compared with placebo-treated patients (odds ratio: 0.43; *P* = .00021). In the subgroup of nursing home residents, the risk of symptomatic COVID-19 was also significantly decreased (odds ratio: 0.8; *P* = .00026). There were 4 COVID-19-related deaths in the placebo arm; none occurred in the bamlanivimab arm.
- Interim results shared by Regeneron from its phase 3 prevention trial suggest that REGEN-COV reduces the risk of symptomatic COVID-19 among patients at high risk of infection due to household exposure to a COVID-19 patient. Among the first 400 evaluable patients randomized to receive REGEN-COV (1,200 mg via subcutaneous injection) or placebo, there were no cases of symptomatic COVID-19 in the REGEN-COV arm compared with 8 cases in the placebo arm. REGEN-COV was associated with a 50% risk reduction for development of symptomatic or asymptomatic infection (10 in REGEN-COV arm – all asymptomatic vs. 23 in the placebo arm). Asymptomatic infections in the REGEN-COV arm were associated with decreased peak virus levels and a short duration of viral shedding.

Resistance

Summary: See the table below for summary of *in vitro* pseudotyped virus-like particle neutralization data for SARS-CoV-2. The EUA for bamlanivimab alone has been revoked due to impaired efficacy with sustained prevalence of variants; however, bamlanivimab plus etesevimab is available via the EUA pathway. Local prevalence of variants may play a role in selection of a mAb.

- In May/June, the CDC identified that the P.1 (Gamma) and the B.1.351 (Beta) variants are circulating with a high frequency in several states. According to the update, based on in vitro assays demonstrating bamlanivimab and etesevimab are not active against the P.1 variant or the B.1.351 variant, the Assistant Secretary for Preparedness and Response paused distribution of bamlanivimab and etesevimab nationally until further notice. The FDA recommends using casirivimab and imdevimab as alternative monoclonal antibody therapy in these states.

Variant	Bamlanivimab and Etesevimab	Casirivimab and Imdevimab	Sotrovimab[c]
B.1.1.7 or Alpha (UK origin)	No change[a]	No change[b]	No change[a]
B.1.351 or Beta (South Africa origin)	215-fold reduction in susceptibility	No change[b]	No change[a]
P.1 or Gamma (Brazil origin)	> 46-fold reduction in susceptibility	No change[b]	No change[a]
B.1.427/B.1.429 (California origin)	9-fold reduction in susceptibility	No change[b]	No change[a]
B.1.526 (New York origin)	31-fold reduction in susceptibility	No change[b]	No change[a]
B.1.617 or Delta (India origin)	NR	No change[b]	No change[a]

[a] < 5-fold reduction in susceptibility
[b] ≤ 2-fold reduction in susceptibility
[c] No change in susceptibility using authentic virus for B.1.1.7, B.1.351, and P.1 variants; data not available for other variants

Abbreviations: BMI = body mass index; ED = emergency department; mAb = monoclonal antibody; NTD = N-terminal domain; NR = not reported; RBD = receptor binding domain

Appendix 1: Select clinical trial data

	Bamlanivimab		Bamlanivimab and Etesevimab	Casirivimab and Imdevimab
Reference and study design	Kumar R, et al. *Clin Infect Dis* 2021; Epub ahead of print. • Retrospective, SC, case-control	**BLAZE 1 trial** Chen P, et.al. *N Engl J Med* 2021; 384:229-237. (NCT04427501) • Phase 2/3, MC, R, DB, PC • Interim analysis (Sept. 5, 2020) of phase 2	Gottlieb R, et.al. *JAMA* 2021; 325:632-644. (NCT04427501) • Phase 2/3, MC, R, DB, PC • Final analysis (Oct. 6, 2020) of phase 2	Weinreich D, et.al. *N Engl J Med* 2021; 384:238-251. (NCT04425629) • Phase 1-3, MC, DB, PC, RT • Interim analysis (Sept. 4, 2020) of phase 1-2
Number of patients enrolled	403	452	577	275
Inclusion criteria and baseline demographics	**Inclusion criteria** • Age ≥18 years • Not hospitalized • Positive SARS-CoV-2 viral infection • Risk factors of severe COVID-19 or healthcare workers • Referral for bamlanivimab **Baseline characteristics (bamlanivimab therapy, n = 218)** • Median age: 66 (range: 57-74 y) • White: 173/403 (79.4%) • English speaking: 207/403 (95.0%) • Mild-moderate disease severity: 198/218 (90.8%)	**Inclusion criteria** • Age ≥18 years • Not hospitalized • ≥1 mild or moderate COVID-19 symptom • First positive SARS-CoV-2 viral infection determination ≤ 3 d prior to infusion **Baseline characteristics (combined LY-Co555 arms, n = 309)** • Median age: 45 y (range: 18-86 y) • White: 269/305 (88.2%) • Risk factors for severe COVID-19: 215/309 (69.6%) • Mild disease at entry: 232/309 (75.1%) • Median duration of symptoms: 4 d • Aged ≥65 y: 10.7%	**Baseline characteristic (LY-Co555 plus LY-CoV016)** • Median age: 44 y (range: 30-60 y) • White: 105/111 (94.6%) • Risk factors for severe COVID-19: 67/112 (59.8%) • Mild disease at entry: 92/112 (82.1%) • Median duration of symptoms: 4 d	**Inclusion criteria** • Age ≥18 years • Not hospitalized • First positive SARS-CoV-2 viral infection determination ≤ 3 d prior to infusion start; onset of symptoms ≤ 7 d before randomization • Symptoms consistent with COVID-19 • SpO2 ≥93% on room air **Baseline characteristics (combined REGEN-COV arms, n = 182)** • Median age: 43 y (35-52 y) • White: 152/182 (84%) • Median time from symptom onset: 3 d (range, 0-8 d) • ≥ 1 risk factor for hospitalization: 118/182 (65%) • Baseline serum antibody negative status: 80/182 (44%)

	Bamlanivimab		Bamlanivimab and Etesevimab	Casirivimab and Imdevimab
	• Median duration of symptoms: 2 d			
Interventions	• Bamlanivimab therapy: single IV infusion of 700 mg (n = 218) • No bamlanivimab (n = 185)	Single IV infusion of: • LY-Co555 700 mg (n = 101) • LY-Co555 2,800 mg (n = 107) • LY-Co555 7,000 mg (n = 101) • LY-Co555 2,800 mg plus LY-CoV016 2,800 mg (n = 112) • Placebo (n = 143 at interim; n = 156 at final)		Single IV infusion of REGEN-COV (casirivimab plus imdevimab): • REGEN-COV 2.4 g, low-dose (n = 92) • REGEN-COV 8 g, high-dose (n = 90) • Placebo (n = 93)
Virologic endpoints	NR	**Primary endpoint: Mean change in log SARS-CoV-2 VL from baseline to day 11 ± 4 d** • Placebo: -3.80 • LY-Co555 700 mg: -3.72 (*P* = .69 vs. placebo) • LY-Co555 2800 mg: -4.08 (*P* = .21 vs. placebo) • LY-Co555 7000 mg: -3.49 (*P* = .16 vs. placebo) • Combination group: -4.37 (difference vs. placebo: -0.57; 95% CI, -1.00 to -0.14; *P* = .01)		**Time-weighted average change VL from baseline to day 7 (log_{10} scale) with negative serum antibody status** • LSM difference from placebo: -0.52 log_{10} copies/mL (95% CI, -1.04 to 0.00) in low-dose group • LSM difference from placebo: -0.60 log_{10} copies/mL (95% CI, -1.12 to -0.08) in high-dose group
Clinical endpoints	**30-day hospitalization** • Bamlanivimab therapy: 16/218 (7.3%) • No bamlanivimab: 37/185 (20%) • Relative risk (RR): 0.37 (95% CI, 0.21-0.64; *P* < .001) **No statistical difference in secondary outcomes**	**Interim analysis:** **COVID-19 related hospitalization (including ED visit) within 28 d of treatment** • Placebo: 9/143 (6.3%) • Pooled doses: 5/309 (1.6%) **(Post-hoc) COVID-19 related hospitalization among patients**	**Final analysis:** **COVID-19 related hospitalization (including ED visit) within 28 d of treatment** • Placebo: 9/156 (5.8%) • LY-Co555 700 mg: 1/101 (1%) ○ Difference vs. placebo: -4.8% (95% CI, -8.9% to -0.6%; *P* = .09) • LY-Co555 2800 mg: 2/107 (1.9%)	**COVID-19-related medical visits including hospitalization or ED, urgent care, or physician office/telemedicine visits within 28 d of treatment in full analysis set** • Placebo: 6/93 (6%) • Pooled doses: 6/182 (3%) • Difference: -3% (95% CI, -16 to 9) **In serum-antibody negative subgroup**

	Bamlanivimab		Bamlanivimab and Etesevimab	Casirivimab and Imdevimab
	• ICU admission • Mechanical ventilation requirement • Mortality • Duration of hospitalization	**≥ 65 y or among those with BMI ≥ 35 kg/m^2** • Placebo: 7/48 (15%) • Pooled doses: 4/95 (4%)	○ Difference vs. placebo: -3.9% (95% CI, -8.4% to 0.6%; *P* = .21) • LY-Co555 7000 mg: 2/101 (2%) ○ Difference vs. placebo: -3.8% (95% CI, -8.3% to -0.8%; *P* = .21) • Combination: 1/112 (0.9%) ○ Difference vs. placebo: -4.9% (95% CI, -8.9% to -0.8%; *P* =.049) **(Post-hoc): COVID-19 related hospitalization among patients ≥ 65 y or among those with BMI ≥ 35** • Placebo: 7/52 (13.5%) • LY-Co555 700 mg:1/37 (2.7%) • LY-Co555 2800 mg: 1/30 (3.3%) • LY-Co555 7000 mg: 2/34 (5.9%) • Combination: 0/31 (0%)	• Placebo: 5/33 (15%) • Pooled doses: 5/80 (6%) • Difference: -9% (95% CI, -29 to 11)
Variants	NR	NR	**Putative treatment-emergent bamlanivimab-resistant variants:** • Placebo: 7/145 (4.8%) • LY-Co555 700 mg:7/98 (7.1%) • LY-Co555 2800 mg: 10/102 (9.8%) • LY-Co555 7000 mg: 11/97 (11.3%) • Combination: 1/102 (1%)	NR
Safety	SAEs not formally assessed; 3 reports of infusion-associated headaches	• No SAEs reported in LY-Co555 arms • AEs reported in 22.3% in LY-Co555 groups; 24.5% for placebo	• No SAEs reported in LY-Co555 monotherapy arms; 1 SAE reported with combination and with placebo	2 infusion-related reactions of grade 2 severity or higher were reported in the high-dose REGEN-COV arm

	Bamlanivimab		Bamlanivimab and Etesevimab	Casirivimab and Imdevimab
		• Infusion-rated reactions: 2.3% in LY-Co555 groups; 1.4% for placebo	• Probable infusion-related, immediate hypersensitivity reactions reported in 9 patients (6 LY-Co555 monotherapy, 2 combination, and 1 placebo) • Most frequently reported AEs: nausea and diarrhea • No deaths were reported	
Comments	• Small number of participants in each arm and overall sample size • Inclusion of healthcare workers without risk factors for severe COVID-19 • Unable to capture hospitalizations or ED visits at other institutions	• Small number of participants in each arm and overall sample size • Small number of clinical events so true benefit is not fully conclusive	• Small number of participants in each arm and overall sample size • Small number of clinical events so true benefit is not fully conclusive	• Small number of participants in each arm and overall sample size • Small number of clinical events so true benefit is not fully conclusive

Abbreviations: AE= adverse effects; BMI = body mass index; CI = confidence interval; DB = double-blind; ED= emergency department; MC = multi-center; NR = not reported; PC = placebo-controlled; R = randomized; SAE = serious adverse event; SC = single center; VL=viral load