Monoclonal Antibodies

A Review of Pertinent Drug Information for SARS-CoV-2

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Data as of November 17, 2021

Adaptive Immunity

- **Active immunity:** seroconversion occurs within 1-3 weeks of COVID-19 symptom onset

- **Passive immunity:** direct administration of monoclonal antibodies (mAb) or convalescent plasma
  - Benefit of mAb: target specific viral epitopes and domains, mass produced, administered in a specified quantity, no reliance on donors

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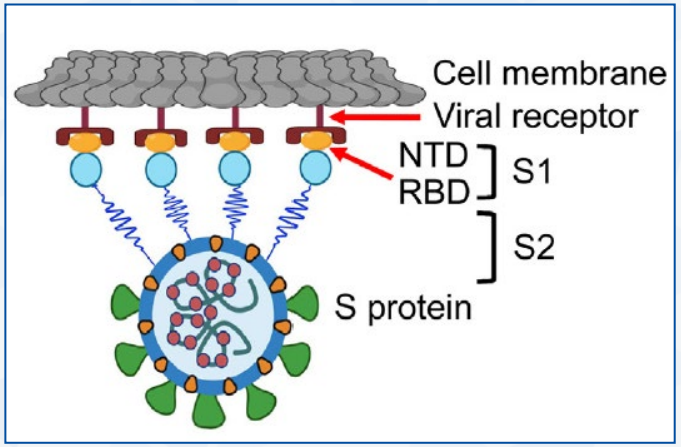
Zhao J, et al. Clin Infect Dis. 2020;71:2027-34. https://doi.org/10.1093/cid/ciaa344

Mechanism of Action

- Spike (S) protein essential for:
  - Viral attachment to host receptor (S1)
  - Virus-cell fusion (S2)
- Monoclonal antibodies (mAbs) bind to receptor binding domain (RBD) of S protein
  - Block viral entry into host cells



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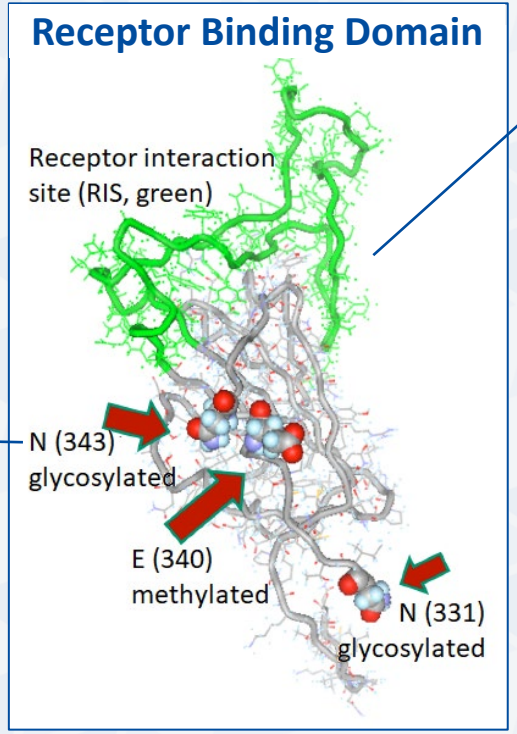
Jiang S, et al. Trends Immunol. 2020;41:355-9. https://doi.org/10.1016/j.it.2020.03.00

mAb Binding Sites

Sotrovimab binds to an epitope distinct from the RBM

- Exact mechanism of action unknown
- Prevents membrane fusion after virus binds ACE2



Receptor-binding motif (in green)

- Portion of RBD that interacts with ACE2
- Binding site for:
  - Bamlanivimab + Etesevimab
  - Casirivimab + Imdevimab
- mAb binding prevents virus-host interaction

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Speiser DE, et al. Vaccines (Basel). 2020;8(3):404. https://doi.org/10.3390/vaccines8030404

Mechanism of Action

- Post-exposure monoclonal antibody neutralization of COVID-19 is assisted by multiple effector functions:
  - Antibody-mediated neutralization of pathogen
  - Antibody-dependent cellular cytotoxicity
  - Antibody-dependent cellular phagocytosis
  - Complement-dependent cytotoxicity

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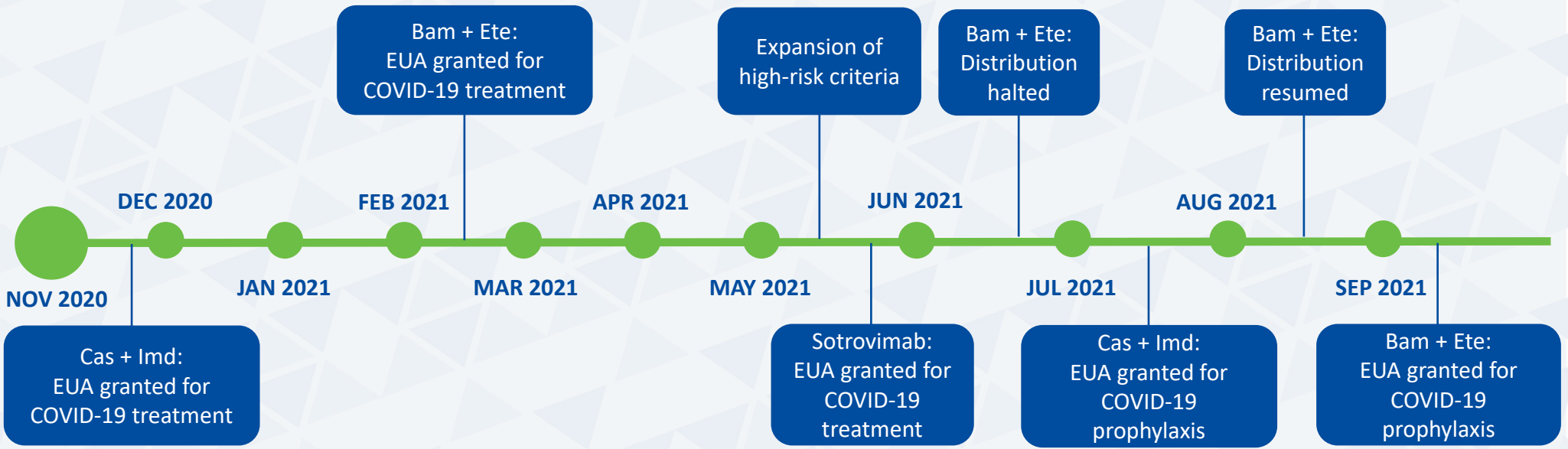
Lu LL, et al. Nat Rev Immunol. 2018;18:46-61. https://doi.org/10.1038/nri.2017.106
Winkler ES, et al. Cell. 2021;184(7):1804-20. http://doi.org/10.1016/j.cell.2021.02.026

Timeline of EUA Updates



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Eli Lilly: Bamlanivimab + Etesevimab

Alternate Names: LY3819253 + LY3832479

LY-CoV555 + LY-CoV016

JS016, CB6 (Etesevimab)

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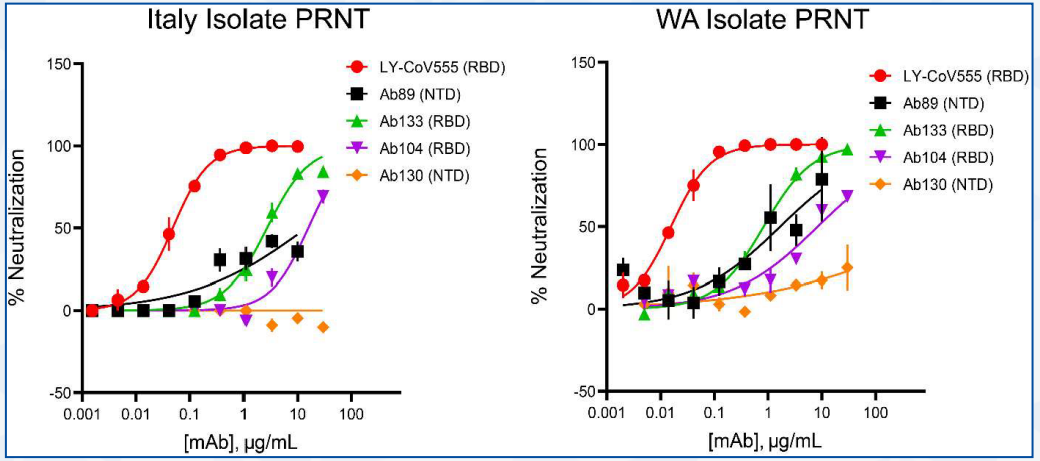
Bamlanivimab – *In vitro* Activity

- Greater neutralization potency than other RBD-binding, ACE2-blocking antibody finalists, despite similar binding affinities

- Ability to bind to RBD in both "up" and "down" conformations may account for increased neutralization activity

Neutralization Potency



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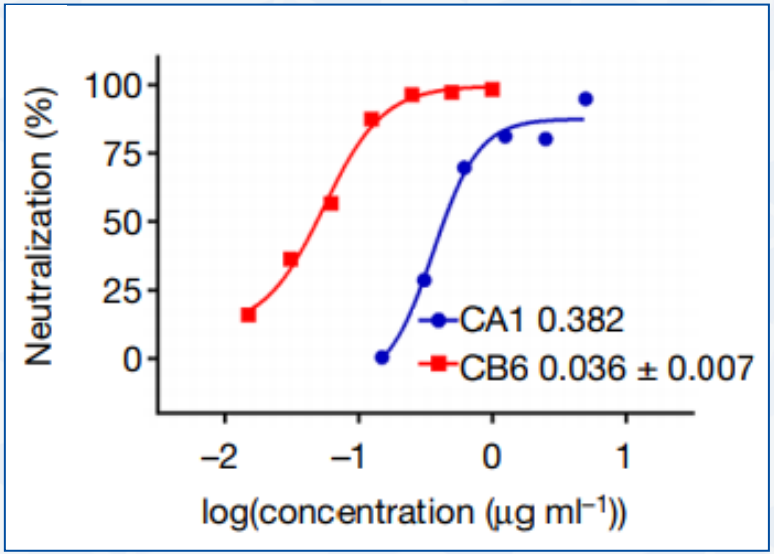
Jones BE, et al. Sci Transl Med. 2021;13(593):eabf1906. https://doi.org/10.1126/scitranslmed.abf1906

Etesevimab – *In vitro* Activity

- Two potential monoclonal antibodies initially identified from convalescing patient
  - Similar ability to block binding of SARS-CoV-2 RBD to ACE2 receptor
  - Bind to overlapping epitopes
- Lower 50% neutralization dose against infected cells for CB6



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Shi R, et al. Nature. 2020;584:120-4. https://doi.org/10.1038/s41586-020-2381-y

In vivo Animal Data

Bamlanivimab in Rhesus Macaques

	Prophylaxis
Methods	Antibody administered intravenously 1 day prior to viral challenge
Viral Inoculum	1.1×10^5 PFU
Antibody Doses	1 mg/kg (N=4) 2.5 mg/kg (N=4) 15 mg/kg (N=3) 50 mg/kg (N=3) Control (N=4)
Sample Types	Lower respiratory tract (LRT): Nasal swab, throat swab Upper respiratory tract (URT): BAL, lung tissue
Outcomes	Change in viral load (gRNA and sgRNA)

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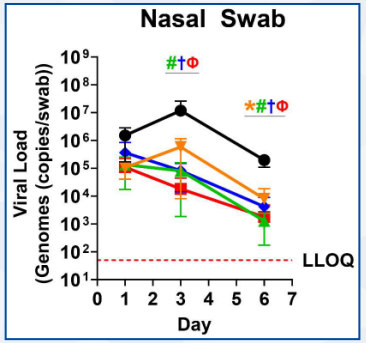
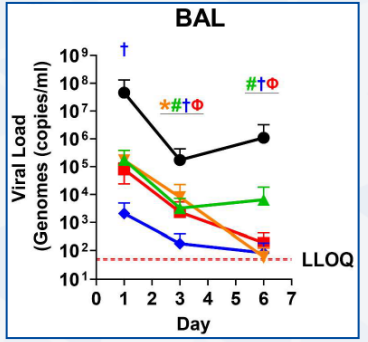
In vivo Animal Data

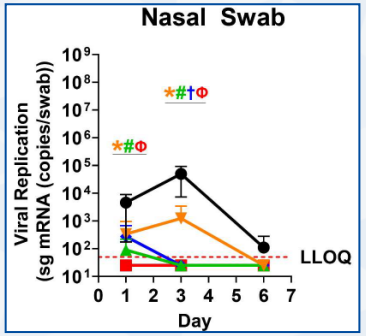
Bamlanivimab in Rhesus Macaques

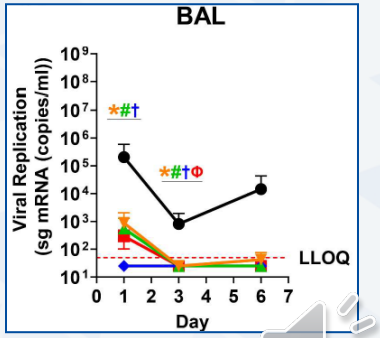
Key Findings

- Reduced viral concentrations and replication on day 1 in all BAL and most LRT samples
- Viral replication undetectable in all locations by day 3 at most doses









- 50 mg/kg IgG1 Control
- 1 mg/kg LY-CoV555
- 2.5 mg/kg LY-CoV555
- 15 mg/kg LY-CoV555
- 50 mg/kg LY-CoV555

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Jones BE, et al. Sci Transl Med. 2021;13(593):eabf1906. https://doi.org/10.1126/scitranslmed.abf190

In vivo Animal Data

Etesevimab in Rhesus Macaques

	Prophylaxis	Treatment
Methods	Antibody administered 1 day prior to viral challenge	Antibody administered on day 1 and day 3 post-viral challenge
Viral Inoculum	1.0×10^5 $TCID_{50}$	
Antibody Dose	50 mg/kg (N=3/group) Placebo (N=3)	
Sample Type	Throat swabs	
Outcomes	Change in viral load (RNA) Pathological lung damage	

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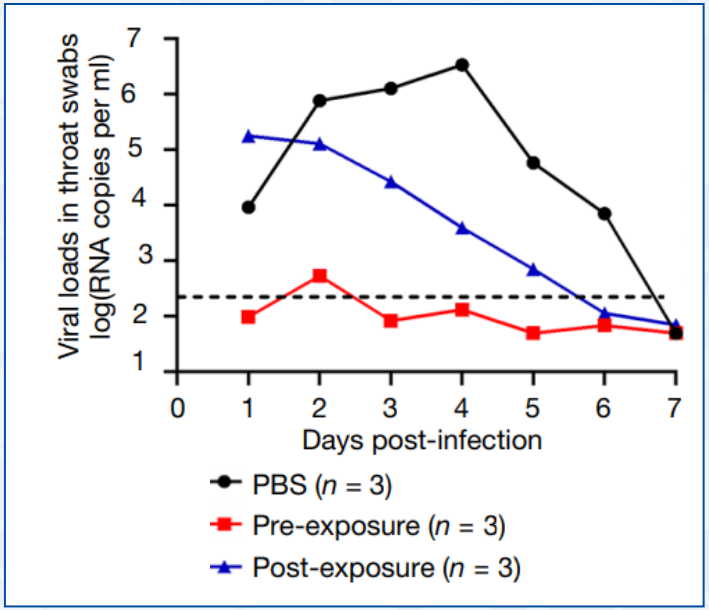
In vivo Animal Data

Etesevimab in Rhesus Macaques

Key Findings

- Low levels of virus detectable among animals receiving prophylactic doses
- Treatment doses resulted in reduced viral loads by day 2 compared to placebo
- Reduced infection-related lung damage in both prophylaxed and treated animals



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Clinical Trials

NCT Number	Patient Population	Treatment Groups	Status
NCT04427501 BLAZE-1	Treatment of outpatients with mild to moderate COVID-19 illness	Bamlanivimab Bamlanivimab + Etesevimab Placebo	Active, Not Recruiting – some results available
NCT04497987 BLAZE-2	Prevention (and treatment) of COVID-19 illness in skilled nursing and assisted living facility residents and staff	Bamlanivimab Bamlanivimab + Etesevimab Placebo	Completed – some results available
NCT04634409 BLAZE-4	Treatment of outpatients with mild to moderate COVID-19 illness	Bamlanivimab Bamlanivimab + Etesevimab Bamlanivimab + Sotrovimab Bamlanivimab + Etesevimab + LY-CoV1404 Placebo	Completed – press release & EUA data available

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Source: https://clinicaltrials.gov

Ambulatory Treatment

BLAZE-1 (Phase 2)

Study Design

- Non-hospitalized adults
- ≥ 1 mild/moderate COVID-19 symptom
- 1st positive SARS-CoV-2 test ≤ 72 hours from start of infusion

Treatment Groups

- Part A:
  - Bamlanivimab
    - 700 mg IV x 1
    - 2800 mg IV x 1
    - 7000 mg IV x 1
  - Placebo
- Part B:
  - Bamlanivimab + Etesevimab
    - 2800 mg/2800 mg IV x 1
  - Placebo

Outcomes

- Primary:
  - Change from baseline viral load at day 11 (± 4 days) from positive results
- Secondary:
  - Viral clearance
  - Symptom burden
  - COVID-19 related hospitalization, ED visit, or death by day 29
  - Safety

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Chen P, et al. N Engl J Med. 2021;384(3):229-37. https://doi.org/10.1056/NEJMoa2029849
Gottlieb RL, et al. JAMA. 2021;325(7):632-44 https://doi.org/10.1001/jama.2021.0202

Ambulatory Treatment

Bamlanivimab + Etesevimab (Phase 2)

Characteristic	Bamlanivimab Monotherapy (N=309)	Bamlanivimab 2800 mg + Etesevimab 2800 mg (N=112)	Placebo (N=156)
Age (years), median (IQR) ≥ 65, n (%)	45 (18-86) 33 (11)	44 (30-60) 13 (12)	46 (35-57) 23 (15)
Body-mass index (kg/m^2), median (IQR) ≥ 30 to < 40, n/total (%) ≥ 40, no/total (%)	29.4 (NA) 112/304 (37) 24/304 (8)	27.2 (22.9-33.0) 33/109 (30) 7/109 (6)	29.2 (25.9-34.2) 63/152 (41) 9/152 (6)
Risk factors for severe COVID-19, n(%)*	215 (70)	67 (60)	105 (67)
Mild disease, n(%) Moderate disease, n(%)	232 (75) 77 (25)	92 (82) 20 (18)	125 (80) 31 (20)
Duration of symptoms, median (IQR)	4 (NA)	4 (3-5)	4 (3-6)
Viral load (cycle threshold), mean (SD)	23.9 (NA)	22.7 (8.0)	23.8 (7.8)

*Age ≥ 55, BMI ≥ 30 kg/m^2, diabetes, chronic kidney disease, cardiovascular disease, chronic respiratory disease, immunosuppressive disease/treatment
NA: not available

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Ambulatory Treatment

Bamlanivimab + Etesevimab (Phase 2)

Primary Outcome: Viral load change at day 11

Treatment Group	n	Viral Load Change, mean	Difference (95% CI)
Placebo	146	-3.80	
Bamlanivimab, 700 mg	100	-3.72	0.09 (-0.35 to 0.52)
Bamlanivimab, 2800 mg	103	-4.08	-0.27 (-0.71 to 0.16)
Bamlanivimab, 7000 mg	95	-3.49	0.31 (-0.13 to 0.76)
Bamlanivimab + Etesevimab	102	-4.37	-0.57 (-1.00 to -0.14)

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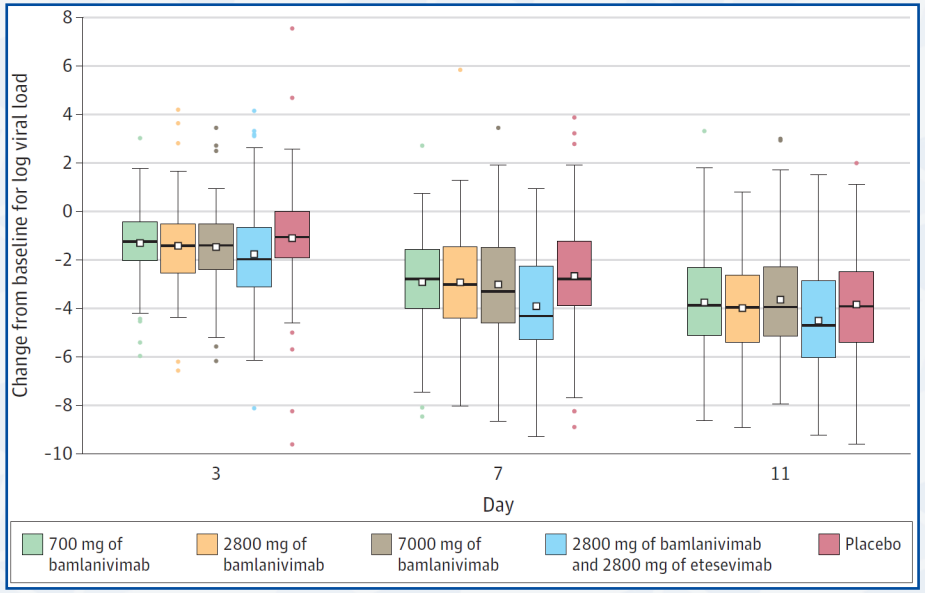
Ambulatory Treatment

Bamlanivimab + Etesevimab (Phase 2)

Secondary Outcomes: Viral Clearance and Symptom Burden



- No significant differences between combination therapy group vs. placebo in any of the following on days 7, 11, 15 or 22:
  - Viral clearance (2 consecutive negative SARS-CoV-2 tests)
  - Symptom improvement
  - Symptom resolution (excluding loss of appetite & changes in taste/smell)
- Symptom scores improved vs. placebo on day 11 only

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Ambulatory Treatment

Bamlanivimab + Etesevimab (Phase 2)

Secondary Outcomes: Viral Clearance and Symptom Burden

	Bamlanivimab Monotherapy			Bamlanivimab + Etesevimab (N=109)	Placebo (N=152)
	700 mg (N=101)	2800 mg (N=107)	7000 mg (N=101)		
Time to SARS-CoV-2 Clearance (days), median	25	23	25	21	24
Time to symptom improvement (days), median	6	6	6	6	8
Time to symptom resolution (days), median	8	8	9	8	9

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Ambulatory Treatment

Bamlanivimab + Etesevimab (Phase 2)

Secondary Outcomes: Hospitalizations, ED Visits and Death

	Bamlanivimab Monotherapy			Bamlanivimab + Etesevimab (N=112)	Placebo (N=156)
	700 mg (N=101)	2800 mg (N=107)	7000 mg (N=101)		
Hospitalization or ED visit by day 29, n (%)*	1 (1.0)	2 (1.9)	2 (2.0)	1 (0.9)	9 (5.8)
P value (vs. placebo)	0.09	0.21	0.21	0.049	
Hospitalization or ED visit by day 29 for patients ≥ 65 years or BMI ≥ 35 kg/m^2, n (%)	1/37 (2.7)	1/30 (3.3)	2/34 (5.9)	0/31	7/52 (13.5)

*12 hospitalizations, 3 ED visits

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Ambulatory Treatment

Bamlanivimab + Etesevimab (Phase 2)

Secondary Outcomes: Safety

	Bamlanivimab			Bamlanivimab + Etesevimab (N=112)	Placebo (N=156)
	700 mg (N=101)	2800 mg (N=107)	7000 mg (N=101)		
Serious adverse events, n(%)	0	0	0	1 (0.9)	1 (0.6)
Adverse events, n(%)					
Mild	17 (16.8)	18 (16.8)	10 (9.9)	15 (13.4)	21 (13.5)
Moderate	7 (6.9)	5 (4.7)	7 (6.9)	3 (2.7)	18 (11.5)
Severe	2 (2.0)	3 (2.8)	5 (5.0)	1 (0.9)	3 (1.9)
Infusion-related reactions, n(%)	6 (2.0)			2 (1.8)	1 (0.6)

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Ambulatory Treatment

Bamlanivimab + Etesevimab (Phase 2)

Adverse Event	Bamlanivimab Monotherapy (N=309)	Bamlanivimab + Etesevimab (N=112)	Placebo (N=143)
Nausea	12 (3.9)	4 (3.6)	6 (3.8)
Diarrhea	9 (2.9)	1 (0.9)	7 (4.5)
Dizziness	9 (2.9)	1 (0.9)	3 (1.9)
Vomiting	5 (1.6)	1 (0.9)	4 (2.6)
Pruritis	5 (1.6)	2 (1.8)	1 (0.6)
Headache	5 (1.6)	0	3 (1.9)
Rash	2 (0.6)	1 (0.9)	1 (0.6)
Pyrexia	4 (1.3)	1 (0.9)	0
Syncope	2 (0.6)	0	2 (1.3)
Chest Discomfort	3 (1.0)	0	1 (0.6)
Nasal Congestion	3 (1.0)	0	1 (0.6)
Chills	4 (1.3)	0	0

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Ambulatory Treatment

BLAZE-1 (Phase 3)

Study Design

- Non-hospitalized adults and adolescents ≥ 12 years
- ≥ 1 mild/moderate COVID-19 symptom
- 1st positive SARS-CoV-2 test ≤ 72 hours from start of infusion
- ≥ 1 risk factor for severe COVID-19 disease

Treatment Groups

- Bamlanivimab + Etesevimab
  - 2800 mg/2800 mg IV x 1
  - 700 mg/1400 mg IV x 1
- Placebo

Outcomes

- Primary:
  - COVID-19-related hospitalization or death from any cause by day 29
- Secondary:
  - Viral load change from baseline to day 7
  - Persistently high viral load on day 7
  - Hospitalization, ED visit, or death from any cause by day 29
  - Symptom resolution
  - Safety

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Dougan M, et al. N Engl J Med. 2021;385(15):1382-92. https://doi.org/10.1056/NEJMoa2102685

Ambulatory Treatment

BLAZE-1 (Phase 3)

- Patients at high risk for progression to severe COVID-19 disease

Any Adult with

- BMI ≥ 35 kg/m2
- CKD
- Diabetes
- Immunosuppressive disease
- Receiving immunosuppressive treatment
- ≥ 65 years of age

≥ 55 Years of Age and

- Cardiovascular disease
- Hypertension
- COPD/other chronic respiratory disease

12-17 Years of Age and

- BMI ≥ 85th percentile for age and sex
- Sickle cell disease
- Congenital or acquired heart disease
- Neurodevelopmental disorders
- Dependence on a medical-related device or procedure
- Asthma, reactive airway or other chronic respiratory disease
- Diabetes
- CKD
- Immunosuppressive disease
- Receiving immunosuppressive treatment

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Ambulatory Treatment

Bamlanivimab + Etesevimab (Phase 3)

Characteristic	Bam 2800 mg + Ete 2800 mg (N=518)	Placebo (N=517)	Bam 700 mg + Ete 1400 mg (N=511)	Placebo (N=258)
Age (years) < 18, n (%) ≥ 65, n (%)	54.3 ± 17.1* 4 (0.8) 168 (32.4)	53.3 ± 16.4* 7 (1.4) 155 (30.0)	57 (12, 93)† 10 (2.0) 158 (30.9)	55 (13, 89)† 6 (2.3) 75 (29.1)
Body-mass index (kg/m^2), median	34.14	33.90	32.50	34.40
≥ 55 years + Hypertension Diabetes ≥ 55 years + COPD	183/514 (35.6) 151 (29.2) 54/514 (10.5)	164/510 (32.2) 134 (25.9) 30/510 (5.9)	191 (38.1) 139 (27.2) 41 (8.2)	85 (33.7) 59 (22.9) 15 (6.0)
Mild disease, n(%)	397 (76.6)	403 (77.9)	380 (74.4)	202 (78.3)
Duration of symptoms	4 (0-29)‡	4 (0-13) ‡	4 (0, 19)†	3 (1, 15)†
Viral load (cycle threshold), mean	23.98	23.97	24.20	24.70

*mean ± standard deviation; †median (min, max); ‡median (IQR)

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Dougan M, et al. Clin Infect Dis. 2021. [Epub ahead of print]. https://doi.org/10.1093/cid/ciab912

Ambulatory Treatment

Bamlanivimab + Etesevimab (Phase 3)

Primary Outcome: Hospitalizations and Death

High Dose

	Bam 2800 mg + Ete 2800 mg (N=518)	Placebo (N=517)	*P* value
Hospitalization or death from any cause by day 29, n (%)	11 (2.1)	36 (7.0)	< 0.001
Hospitalization by day 29, n (%)	11 (2.1)	33 (6.4)	
Death by day 29, n (%)	0	10 (1.9)	

Low Dose

	Bam 700 mg + Ete 1400 mg (N=511)	Placebo (N=258)	*P* value
Hospitalization or death from any cause by day 29, n (%)	4 (0.8)	15 (5.8)	< 0.001
Hospitalization by day 29, n (%)	4 (0.8)	11 (4.3)	
Death by day 29, n (%)	0	4 (1.6)	

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Ambulatory Treatment

Bamlanivimab + Etesevimab (Phase 3)

Clinical Secondary & Exploratory Outcomes

High Dose

	Bam 2800 mg + Ete 2800 mg (N=518)	Placebo (N=517)	*P* value
Hospitalization, ED visit or death from any cause by day 29, n (%)	12 (2.3)	37 (7.2)	< 0.001
Time to sustained symptom resolution (days), median	8	9	0.007
Duration of hospitalization (days), mean ± SD	7.3 ± 6.4	11.2 ± 10.1	

Low Dose

	Bam 700 mg + Ete 1400 mg (N=511)	Placebo (N=258)	*P* value
Hospitalization, ED visit or death from any cause by day 29, n (%)	6 (1.2)	15 (5.8)	< 0.001
Time to sustained symptom resolution (days), median	8	10	< 0.01

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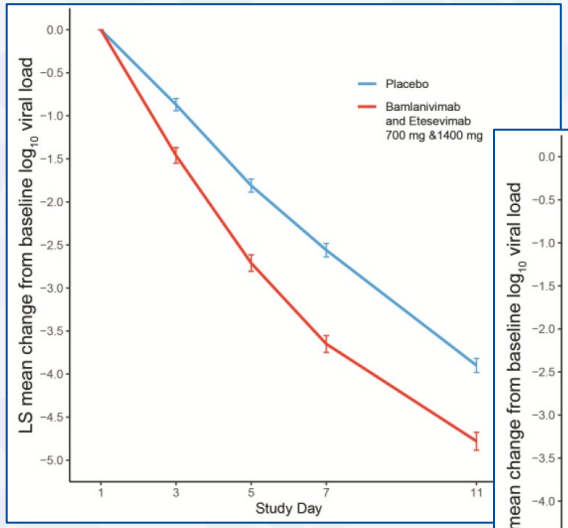
Ambulatory Treatment

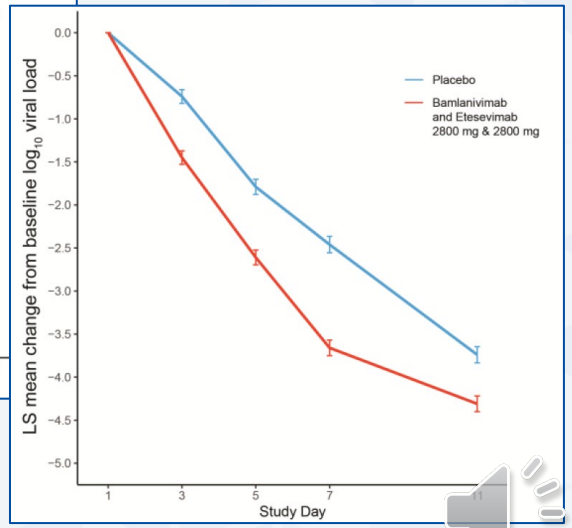
Bamlanivimab + Etesevimab (Phase 3)

Secondary Outcomes: Viral Load and Symptom Resolution

- Significantly greater decrease in viral load compared to placebo on day 7
  - High dose: -1.20 $\log_{10}$; $P < 0.001$
  - Low dose: -0.99 $\log_{10}$; $P < 0.0001$

- Significantly greater proportion of patients with persistently high viral load on day 7 received placebo
  - High dose: 29.5% vs. 9.8%; $P < 0.001$
  - Low dose: 41.1% vs. 14.9%; $P < 0.0001$





SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Dougan M, et al. N Engl J Med. 2021;385(15):1382-92. https://doi.org/10.1056/NEJMoa2102685
Dougan M, et al. Clin Infect Dis. 2021. [Epub ahead of print]. https://doi.org/10.1093/cid/ciab912

Ambulatory Treatment

Bamlanivimab + Etesevimab (Phase 3)

Secondary Outcomes: Safety

		Bam 2800 mg + Ete 2800 mg (N=518)	Placebo (N=517)		Bam 700 mg + Ete 1400 mg (N=511)	Placebo (N=258)
Serious adverse events, n (%)		7 (1.4)	5 (1.0)		6 (1.2)	2 (0.8)
Adverse events, n (%) Mild Moderate Severe		69 (13.3) 37 (7.1) 24 (4.6) 7 (1.4)	60 (11.6) 35 (6.8) 20 (3.9) 5 (1.0)		46 (9.0) 26 (5.1) 16 (3.1) 4 (0.8)	25 (9.7) 15 (5.8) 8 (3.1) 1 (0.4)
Top 4 adverse events, n (%)	Nausea Rash Dizziness Diarrhea	5 (1.0) 6 (1.2) 4 (0.8) 2 (0.4)	4 (0.8) 3 (0.6) 3 (0.6) 2 (0.4)	Increased LFTs Increased CRP Dizziness Anemia	5 (1.0) 3 (0.6) 4 (0.8) 3 (0.6)	3 (1.2) 1 (0.4) 0 0

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Dougan M, et al. N Engl J Med. 2021;385(15):1382-92. https://doi.org/10.1056/NEJMoa2102685
Dougan M, et al. Clin Infect Dis. 2021. [Epub ahead of print]. https://doi.org/10.1093/cid/ciab912

Ambulatory Treatment

BLAZE-4 (Phase 2)

Study Design

- Non-hospitalized adults
- ≥ 1 mild/moderate COVID-19 symptom
- 1st positive SARS-CoV-2 test ≤ 72 hours from start of infusion
- Key exclusions:
  - Age ≥ 65 years
  - BMI ≥ 35 kg/m^2

Treatment Groups

- Bamlanivimab
  - 700 mg IV x 1
- Bamlanivimab + Etesevimab
  - 700 mg/1400 mg IV x 1
  - 2800 mg/2800 mg IV x 1
- Bamlanivimab + Sotrovimab
  - 700 mg/500 mg IV x 1
- Placebo

Outcomes

- Primary:
  - Viral load > 5.27 $\log_{10}$ on Day 7 (+2 days)
- Secondary:
  - Change in viral load from baseline to Day 7
  - COVID-19 related hospitalization, ED visit, or death at day 29
  - Symptom burden
  - Safety

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CDER Review: Emergency Use Authorization for Bamlanivimab and Etesevimab
Available at: https://www.fda.gov/media/146255/download

Ambulatory Treatment

Bamlanivimab + Etesevimab (Low Risk – Prelim Data)

Baseline Characteristics

Characteristic	Total Population (N=515)
Age (years), median ≥ 65 years	39 1%
Hispanic/Latino	29%
African American	6%
High risk for severe disease, n (%)	8%
Disease severity Mild Moderate	 84% 16%
Viral load (CT), mean	25

- Bamlanivimab 700 mg + Etesevimab 1400 mg (N=158)
- Bamlanivimab 2800 mg + Etesevimab 2800 mg (N=101)
- Bamlanivimab 700 mg (N=103)
- Placebo (N=153)

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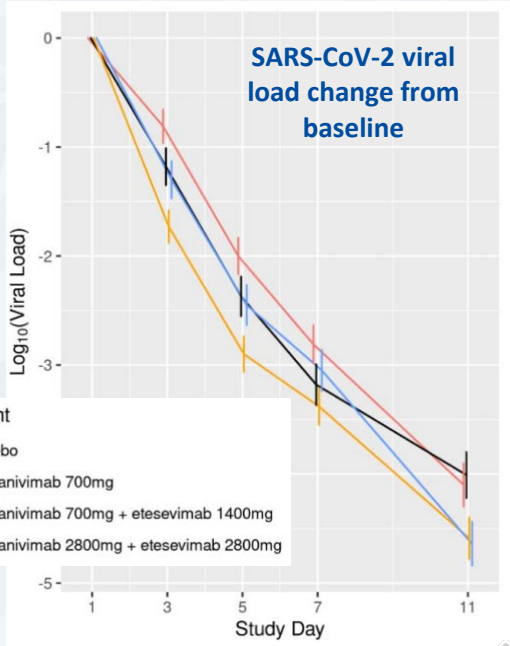
CDER Review: Emergency Use Authorization for Bamlanivimab and Etesevimab
Available at: https://www.fda.gov/media/146255/download

Ambulatory Treatment

Bamlanivimab + Etesevimab (Low Risk – Prelim Data)

Preliminary Results:

	Bamlanivimab 700 mg + Etesevimab 1400 mg (N=147)	Bamlanivimab 2800 mg + Etesevimab 2800 mg (N=99)	Placebo (N=135)
Viral load > 5.27 on Day 7	21 (14)	10 (10)	42 (31)
P value (vs. placebo)	<0.001	<0.001	



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CDER Review: Emergency Use Authorization for Bamlanivimab and Etesevimab
Available at: https://www.fda.gov/media/146255/download

Ambulatory Prophylaxis

BLAZE-2

Study Design

- Adults ≥ 18 years
- Resident/staff at skilled nursing or assisted living facility with ≥ 1 confirmed case of SARS-CoV-2
- ≤ 7 days from index case's positive test
- SARS-CoV-2 PCR negative

Treatment Groups

- Bamlanivimab
  - 4200 mg IV x 1
- Placebo

Outcomes

- Primary
  - Symptomatic, PCR-confirmed SARS-CoV-2 infection by day 57
- Secondary
  - Moderate or worse SARS-CoV-2 infection by day 57
  - Any SARS-CoV-2 infection by day 29
  - Safety

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Cohen MS, et al. JAMA. 2021;326(1):46-55. http://doi.org/10.1001/jama.2021.882

Ambulatory Prophylaxis

Bamlanivimab

Baseline Demographics

Characteristic	Residents		Staff	
	Bam 4.2 g (N=161)	Placebo (N=139)	Bam 4.2 g (N=323)	Placebo (N=343)
Age (years), median (range) ≥ 65, n (%)	76 (31-104) 126 (78.3)	75 (41-96) 109 (78.4)	43 (18-82) 19 (5.9)	42 (18-74) 28 (8.2)
Body-mass index (kg/m^2), median (range)	28.2 (15.4-64.7)	29.1 (14.1-77.4)	29.9 (16.4-62.0)	30.3 (16.5-65.7)
High risk for severe COVID-19*, n (%)	161 (100)	139 (100)	132 (40.9)	143 (41.7)

*All residents were high risk; Staff were high risk if ≥ 65 years, BMI ≥ 35, CKD, DM, immunosuppressive disease, or receiving immunosuppressive treatment or ≥ 55 years with cardiovascular disease, HTN, COPD, or other chronic respiratory disease

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

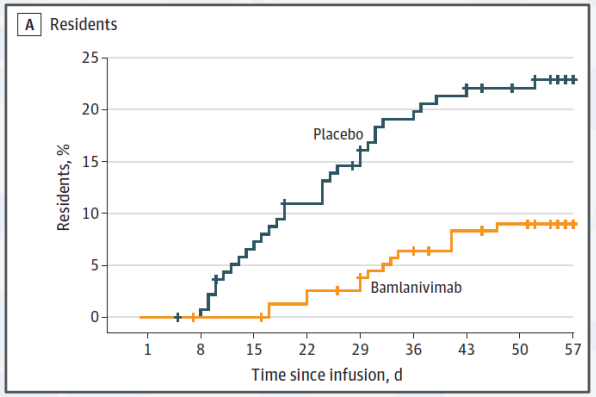
Cohen MS, et al. JAMA. 2021;326(1):46-55. http://doi.org/10.1001/jama.2021.8828

Ambulatory Prophylaxis

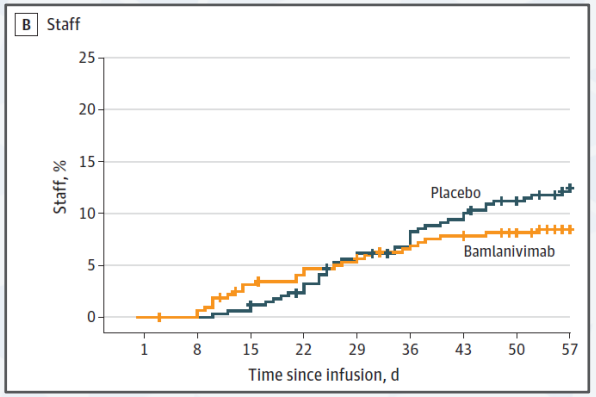
Bamlanivimab

Primary Outcome: Symptomatic infection

	Bamlanivimab 4.2 g (N=484)	Placebo (N=482)	*P* value
Symptomatic SARS-CoV-2 infection, n (%)	41 (8.5)	73 (15.2)	< 0.001



Bam: 8.8%
Placebo: 22.5%
P < 0.001



Bam: 8.4%
Placebo: 12.2%
P < 0.06

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Cohen MS, et al. JAMA. 2021;326(1):46-55. http://doi.org/10.1001/jama.2021.8828

Ambulatory Prophylaxis

Bamlanivimab

Secondary Outcomes: Positive PCR, Moderate or Worse Infection

	Bam 4.2 g (N=484)	Placebo (N=482)	*P* value
PCR-confirmed SARS-CoV-2 infection (regardless of symptoms) by day 29, n (%)	86 (17.9)	112 (23.3)	0.02
Moderate or worse SARS-CoV-2 infection by day 57	40 (8.3)	68 (14.1)	< 0.001

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Cohen MS, et al. JAMA. 2021;326(1):46-55. http://doi.org/10.1001/jama.2021.8828

Ambulatory Prophylaxis

Bamlanivimab

Secondary Outcomes: Safety

	Bam 4.2 g (N=588)	Placebo (N=587)
Serious adverse event, n (%)	22 (3.7)	19 (3.2)
Event leading to death, n/N (%)	5/484 (0.9)	6/482 (1.0)
COVID-19-related death, n/N (%)	0	4/482 (0.8)
Adverse events occurring in ≥ 1% of participants, n (%)		
UTI	12 (2.0)	14 (2.4)
HTN	7 (1.2)	10 (1.7)
Fall	2 (0.3)	6 (1.0)
Dizziness	4 (0.7)	6 (1.0)
Arthralgia	6 (1.0)	4 (0.7)

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Cohen MS, et al. JAMA. 2021;326(1):46-55. http://doi.org/10.1001/jama.2021.8828

Emergency Use Authorization

- **February 9, 2021:** EUA granted for treatment of patients ≥ 12 years of age and ≥ 40 kg with mild/moderate COVID-19 at high risk of progressing to severe disease, including hospitalization or death
- **June 25, 2021:** National distribution halted due to increasing rates of Gamma and Beta variants expected to have decreased susceptibility to Bamlanivimab + Etesevimab
- **August 27, 2021:** Resumption of use and distribution in areas with < 5% combined frequency of variants resistant to Bamlanivimab + Etesevimab
- **September 16, 2021:** EUA granted for post-exposure prophylaxis of COVID-19 in patients ≥ 12 years of age and ≥ 40 kg at high risk for progression to severe COVID-19, including hospitalization or death

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Emergency Use Authorization

- Dosing
  - Bamlanivimab 700 mg + Etesevimab 1400 mg IV x 1
    - Must combine 1 vial Bamlanivimab + 2 vials Etesevimab
  - No dosage adjustments for any specific populations

- Administration
  - Administer within 10 days of symptom onset
  - Infusion duration 21-70 minutes depending on patient weight and diluent volume
  - Observe patients for at least 1 hour after infusion is complete

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US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. Available at: http://pi.lilly.com/eua/bam-and-ete-eua-factsheet-hcp.pdf

Summary

Bamlanivimab + Etesevimab

- Significantly reduced viral load from baseline compared to placebo in ambulatory patients with mild-moderate symptoms
- Administration within 3 days of positive SARS-CoV-2 test result led to 70% reduction in hospitalizations/death among high-risk ambulatory patients
- Time to sustained symptom resolution reduced by 1-2 days
- Significantly reduces development of symptomatic infection, especially among high-risk patients, when administered post-exposure

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Regeneron: Casirivimab + Imdevimab

Alternate Names: REGN10933 + REGN10987

REGN-COV2

REGEN-COV

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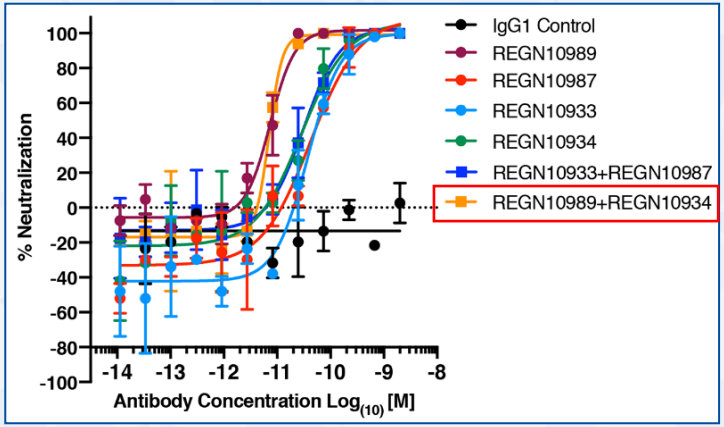
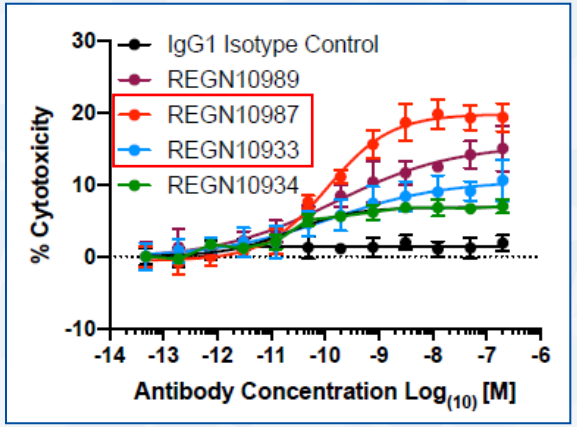
REGEN-COV – *In vitro* Activity

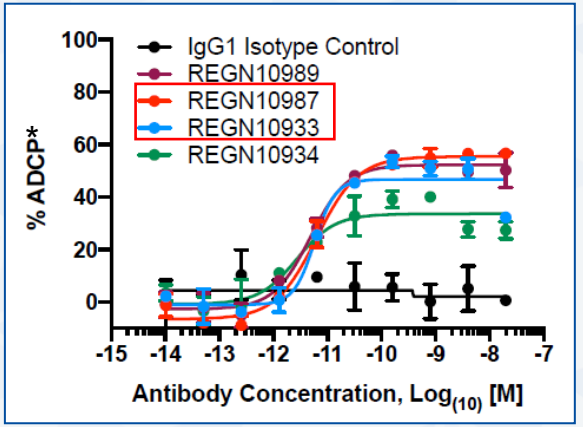
- 200 neutralizing mAbs identified → 4 finalists selected

Neutralization Potency



Antibody Effector Functions





*Antibody-dependent cellular phagocytosis

REGN10989: Imdevimab; REGN10933: Casirivimab

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Hansen J, et al. Science. 2020;369:1010-4. https://doi.org/10.1126/science.abd082

REGEN-COV – *In vitro* Activity

	Position in genome	3299	3312	3853	4326	4407	4411	4425	4435	4442	4527	4531	4533	4545	4546	4554	5040	5122	5130	5137	5383	5412	6460
	Position in spike gene	222	235	776	1249	1330	1334	1348	1358	1365	1450	1454	1456	1468	1469	1477	1963	2045	2053	2060	2306	2335	3383
	Reference nucleotide	T	T	C	A	A	T	A	A	G	G	G	T	T	T	C	C	G	C	T	G	C	T
	Variant nucleotide	A	A	A	G	C	C	G	T	T	A	A	G	C	C	A	T	A	A	G	A	A	C
	Position in protein	**74**	**79**	**259**	**417**	**444**	**445**	**450**	**453**	**455**	**484**	**485**	**486**	**490**	**490**	**493**	**655**	**682**	**685**	**687**	**769**	**779**	**1128**
	Ref Residue	**N**	**F**	**T**	**K**	**K**	**V**	**N**	**Y**	**L**	**E**	**G**	**F**	**F**	**F**	**Q**	**H**	**R**	**R**	**V**	**G**	**Q**	**V**
	Variant Residue	**K**	**I**	**K**	**E**	**Q**	**A**	**D**	**F**	**F**	**K**	**D**	**V**	**P**	**P**	**K**	**Y**	**Q**	**S**	**G**	**E**	**K**	**A**
PASSAGE 2	**10933 50ug/ml**	0%	0%	0%	0%	0%	0%	0%	10%	0%	0%	0%	88%	0%	0%	0%	1%	90%	0%	15%	87%	0%	0%
	10934 50ug/ml	0%	0%	0%	0%	0%	0%	95%	0%	0%	6%	0%	0%	0%	1%	0%	10%	93%	0%	0%	0%	0%	0%
	10987 10ug/ml	0%	0%	0%	0%	45%	41%	0%	0%	0%	0%	0%	0%	0%	0%	0%	50%	6%	47%	0%	0%	0%	0%
	10989 50ug/ml	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	0%	0%	0%	100%	0%	0%	0%	0%	20%	0%
	10987/33 10ug/ml	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	10989/34 50ug/ml	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	0%	0%	0%	93%	11%	0%	0%	0%	0%	0%
	10989/87 10ug/ml	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Isotype control 50ug/ml	16%	13%	10%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	54%	50%	0%	8%	0%	0%	4%
	Virus Only	8%	8%	22%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	28%	83%	0%	7%	0%	0%	8%

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Baum A, et al. Science. 2020;369:1014-8. https://doi.org/10.1126/science.abd083

In vivo Animal Data

Rhesus Macaque

	Prophylaxis		Treatment
	Study 1	Study 2	
Methods	Antibody administered 3 days prior to viral challenge		Antibody administered 1 day after viral challenge
Viral Inoculum	1.0×10^5 PFU	1.05×10^6 PFU	1.05×10^6 PFU
Antibody Doses	50 mg/kg (N=6) Placebo (N=6)	0.3 mg/kg (N=4) 50 mg/kg (N=4) Placebo (N=4)	25 mg/kg (N=4) 150 mg/kg (N=4) Placebo (N=4)
Sample Types	Nasopharyngeal swab BAL	Nasopharyngeal swab Oral swab	Nasopharyngeal swab Oral swab
Outcomes	Change in viral load (gRNA and sgRNA)		

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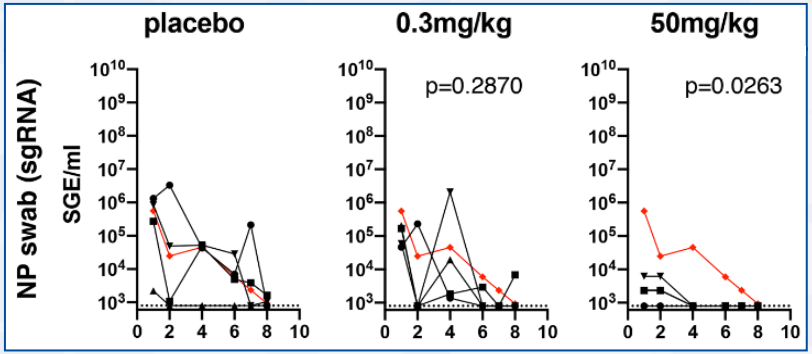
Baum A, et al. Science. 2020;369:1014-8. https://doi.org/10.1126/science.abd0831

In vivo Animal Data

Rhesus Macaque

Key Findings - Prophylaxis

- Increased rates of gRNA clearance, near complete ablation of sgRNA among animals receiving 50 mg/kg
- Viral clearance rates similar between NP swab and BAL fluid samples; more rapid clearance noted on oral swab samples



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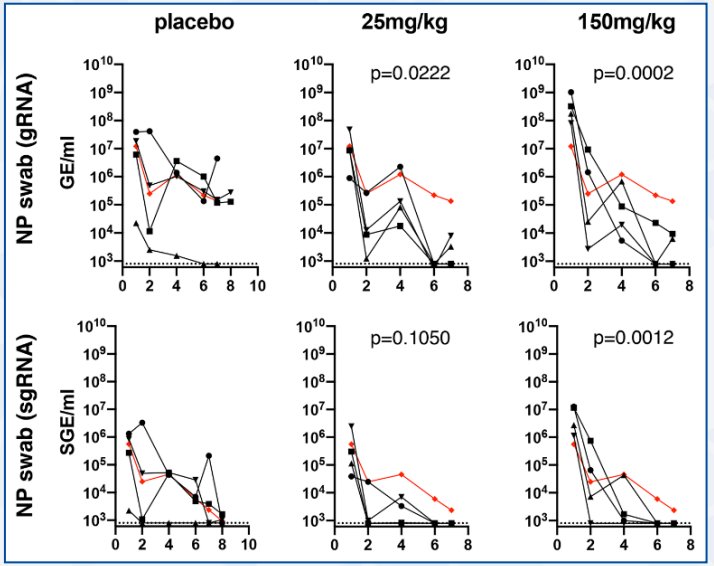
Key Findings - Treatment

- Similarly increased viral clearance (gRNA and sgRNA) among animals receiving either 25 mg/kg or 150 mg/kg



Baum A, et al. Science. 2020;eabe2402. https://doi.org/10.1126/science.abe240

In vivo Animal Data

Golden Hamster

	Prophylaxis	Treatment
Methods	Antibody administered 2 days prior to viral challenge	Antibody administered 1 day after viral challenge
Viral Inoculum	2.3×10^4 PFU	
Antibody Doses	50 mg/kg (N=5) 5 mg/kg (N=5) 0.5 mg/kg (N=5) Placebo (N=5)	
Sample Types	Lung tissue	N/A
Outcomes	Body weight change Change in viral load (gRNA and sgRNA) Area of lung exhibiting pathology typical of pneumonia	Body weight change

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Baum A, et al. Science. 2020;369:1014-8. https://doi.org/10.1126/science.abd0831

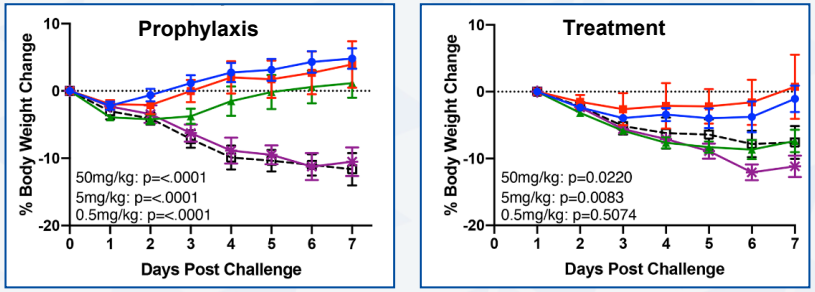
In vivo Animal Data

Golden Hamster

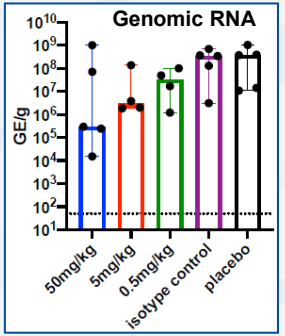
Key Findings

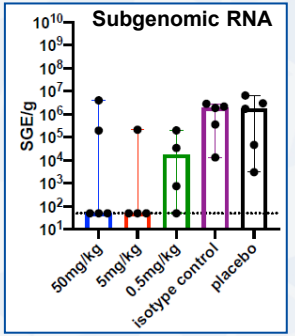
- Decreased weight loss among all groups receiving prophylaxis
- Treatment with higher doses prevented weight loss
- Viral load not significantly impacted by prophylaxis
- Significantly less lung affected in animals receiving prophylactic antibodies

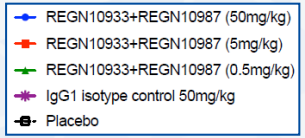
Weight Loss



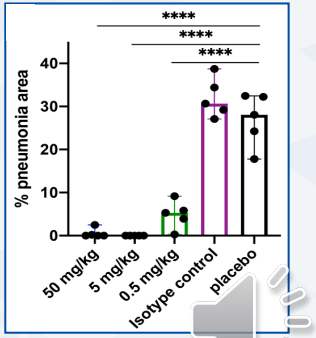
Viral Load on Day 7 (Prophylaxis)







Affected Lung



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Baum A, et al. Science. 2020;eabe2402. https://doi.org/10.1126/science.abe240

Clinical Trials

NCT Number	Patient Population	Treatment Groups	Status
NCT04425629 COV-2067	Treatment of outpatients with mild to moderate COVID-19 illness	REGEN-COV IV Placebo	Recruiting – some data available
NCT04426695 COV-2066	Treatment of hospitalized patients with COVID-19 illness	REGEN-COV IV Placebo	Completed – press release data available
NCT04381936 RECOVERY	Treatment of hospitalized patients with COVID-19 illness	REGEN-COV IV Standard of care	Recruiting – some data available
NCT04452318 COV-2069	Prevention of COVID-19 illness in household contacts of individuals infected with SARS-CoV-2	REGEN-COV SubQ REGEN-COV IM Placebo	Completed – some data available
NCT04518410 ACTIV-2	Treatment of outpatients with mild to moderate COVID-19 illness	REGEN-COV IV Placebo	Recruiting
NCT05074433 COV-2176	Prevention of symptomatic COVID-19 illness in immunocompromised patients	REGEN-COV SubQ Placebo	Recruiting

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Source: https://clinicaltrials.gov

Ambulatory Treatment

COV-2067 (Phase 2)

Patient Population

- Non-hospitalized adults
- Symptom onset ≤ 7 days from randomization
- SARS-CoV-2 confirmed by molecular testing ≤ 72 hours from randomization

Treatment Groups

- Casirivimab + Imdevimab
  - 1200 mg/1200 mg IV x 1
  - 4000 mg/4000 mg IV x 1
- Placebo

Outcomes

- Virologic:
  - Time-weighted average change from baseline in viral load through day 7
- Clinical:
  - Proportion of patients with ≥ 1 COVID-19-related medically-attended visit through day 29
  - Safety

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Weinreich DM, et al. N Engl J Med. 2021;384(3):238-51. https://doi.org/10.1056/NEJMoa2035002
Weinreich DM, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.06.09.21257915

Ambulatory Treatment

Casirivimab + Imdevimab (Phase 2)

Baseline Demographics

	REGEN-COV2 2.4 g (N=266)	REGEN-COV2 8.0 g (N=267)	Placebo (N=266)
Age (years), median (IQR)	42 (31-52)	42 (30-52)	42 (32-53)
Male sex, n (%)	122 (45.9)	120 (44.9)	134 (50.4)
BMI > 30 kg/m^2, n (%)	101 (38.0)	104 (39.0)	93 (35.0)
≥ 1 Risk factor for hospitalization*, n (%)	165 (62.0)	160 (59.9)	158 (59.4)
Baseline serum antibody negative, n (%)	140 (52.6)	134 (50.2)	134 (50.4)
Duration of symptoms, median (IQR)	3 (2-5)	3 (2-5)	3 (2-5)

*Age > 50 years, obesity, cardiovascular disease, chronic lung disease, chronic metabolic disease, chronic kidney disease, chronic liver disease, immunocompromised

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Weinreich DM, et al. N Engl J Med. 2021;384(3):238-51. https://doi.org/10.1056/NEJMoa2035002
Weinreich DM, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.06.09.21257915

Ambulatory Treatment

Casirivimab + Imdevimab (Phase 2)

Baseline Viral Load

	Group 1 (N = 275)	Group 2 (N = 524)
Baseline serology status: **negative** Viral load (million copies/mL), median (IQR)	113 (41.1) 15.00 (0.77, 71.00)	292 (55.7) 53.20 (1.91, 71.00)
Baseline serology status: **positive** Viral load (million copies/mL), median (IQR)	123 (44.7) 0.003 (0.00, 0.03)	176 (33.6) 0.01 (0.00, 0.35)

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Weinreich DM, et al. N Engl J Med. 2021;384(3):238-51. https://doi.org/10.1056/NEJMoa2035002
Weinreich DM, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.06.09.21257915

Ambulatory Treatment

Casirivimab + Imdevimab (Phase 2)

Virologic Outcome: Viral load change at day 7 (Group 1)

	Placebo			REGEN-COV2 2.4 g			REGEN-COV2 8.0 g		
	mFAS (N=78)	Sero(-) (N=28)	Sero(+) (N=37)	mFAS (N=70)	Sero(-) (N=34)	Sero(+) (N=27)	mFAS (N=73)	Sero(-) (N=35)	Sero(+) (N=29)
Time-weighted average change in viral load through day 7 (log_{10} copies/mL), least-squares mean ± SE	-1.34±0.13	-1.37±0.20	-1.24±0.16	-1.60±0.14	-1.89±0.18	-1.24±0.19	-1.90±0.14	-1.96±0.18	-1.63±0.20
Difference vs. placebo (log_{10} copies/mL)				-0.25±0.18	-0.52±0.26	0.00±0.24	-0.56±0.18	-0.60±0.26	-0.39±0.25

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Weinreich DM, et al. N Engl J Med. 2021;384(3):238-51. https://doi.org/10.1056/NEJMoa2035002

Ambulatory Treatment

Casirivimab + Imdevimab (Phase 2)

Virologic Outcome: Viral load change at day 7 (Group 2)

	Placebo			REGEN-COV2 2.4 g			REGEN-COV2 8.0 g		
	mFAS (N=146)	Sero(-) (N=93)	Viral Load > 10^7 (N=70)	mFAS (N=137)	Sero(-) (N=80)	Viral Load > 10^7 (N=58)	mFAS (N=141)	Sero(-) (N=77)	Viral Load > 10^7 (N=52)
Time-weighted average change in viral load through day 7 (log_{10} copies/mL), least-squares mean ± SE	-1.30±0.09	-1.18±0.10	-1.46±0.15	-1.69±0.09	-1.92±0.11	-2.14±0.16	-1.64±0.09	-1.90±0.11	-2.13±0.16
Difference vs. placebo (log_{10} copies/mL)				-0.38±0.12	-0.74±0.14	-0.68±0.16	-0.34±0.12	-0.71±0.14	-0.68±0.16

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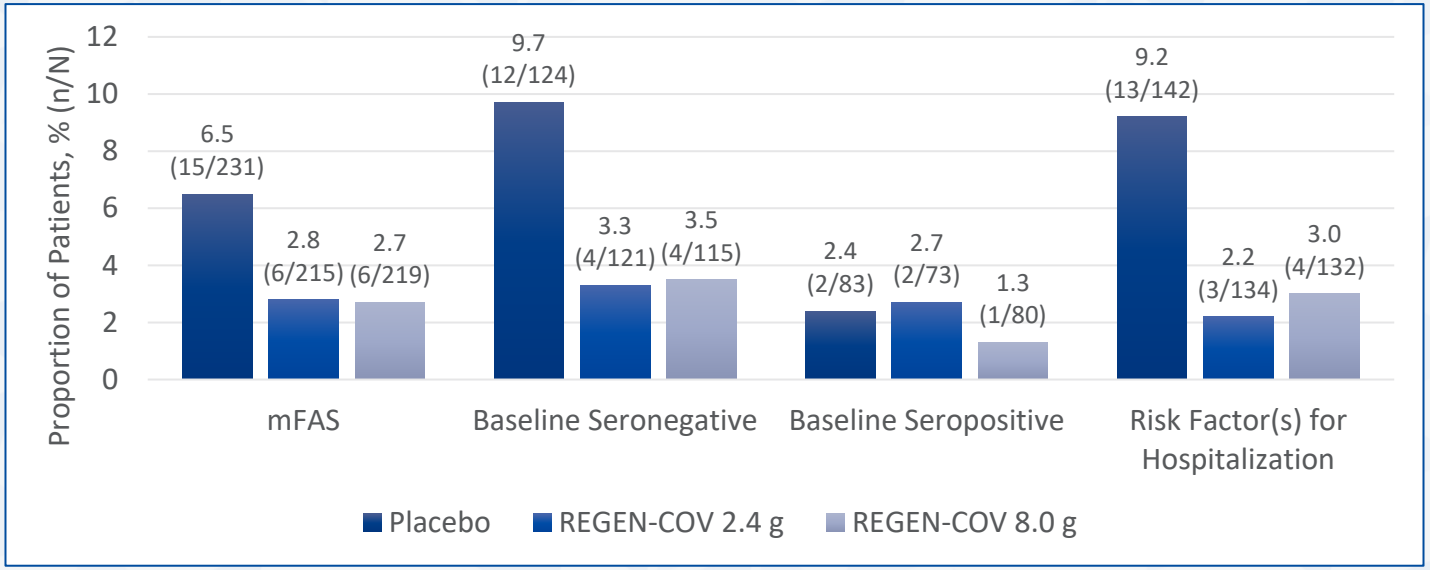
Weinreich DM, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.06.09.21257913

Ambulatory Treatment

Casirivimab + Imdevimab (Phase 2)

Clinical Outcome: ≥ 1 medically attended visit at day 29 (Groups 1 + 2)



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Weinreich DM, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.06.09.21257913

Ambulatory Treatment

Casirivimab + Imdevimab (Phase 2)

Additional Outcomes: Safety (Groups 1 + 2)

	Placebo (N=262)	REGEN-COV2 2.4 g (N=258)	REGEN-COV2 8.0 g (N=260)
Serious adverse event	6 (2.3)	4 (1.6)	2 (0.8)
Infusion-related reactions Grade ≥ 2 thru Day 4	1 (0.4)	0	4 (1.5)
Hypersensitivity reactions Grade ≥ 2 thru Day 29	2 (0.8	0	0
Event leading to death	0	0	0
Event leading to infusion interruption	1 (0.4)	0	1 (0.4)

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Weinreich DM, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.06.09.21257913

Ambulatory Treatment

COV-2067 (Phase 3)

Patient Population

- Non-hospitalized adults
- Symptom onset ≤ 7 days from randomization
- SARS-CoV-2 confirmed by molecular testing ≤ 72 hours from randomization
- ≥ 1 risk factor for severe COVID-19 disease

Age > 50 years	Obesity
Cardiovascular disease	Chronic lung disease
Chronic metabolic disease	Chronic kidney disease
Chronic liver disease	Immunocompromised

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Treatment Groups

- Casirivimab + Imdevimab
  - 600 mg/600 mg IV x 1
  - 1200 mg/1200 mg IV x 1
  - ~~4000 mg/4000 mg IV x 1~~
- Placebo

Outcomes

- Primary:
  - COVID-19 related hospitalization or death from any cause by day 29
- Secondary:
  - COVID-19-related hospitalization or death from any cause from day 4 through 29
  - Time to symptom resolution
  - Safety

Weinreich DM, et al. N Engl J Med. 2021. [Epub ahead of print]. https://doi.org/10.1056/NEJMoa2108163

Ambulatory Treatment

Casirivimab + Imdevimab (Phase 3)

Baseline Demographics

Characteristic	REGEN-COV 1.2 g (N=736)	Placebo (1.2 g – concurrent) (N=748)	REGEN-COV 2.4 g (N=1355)	Placebo (2.4 g – concurrent) (N=1341)
Age (years), median (IQR) ≥ 65, n (%)	49 (37-58) 93 (12.6)	48 (35-57) 88 (11.8)	50 (39-60) 214 (15.8)	50 (37-58) 144 (10.7)
Body-mass index (kg/m^2), mean ± SD	31.5 ± 7.3	31.1 ± 6.5	31.1 ± 6.3	31.2 ± 6.6
Age ≥ 50, n (%) BMI ≥ 30 kg/m^2, n (%) Cardiovascular disease, n (%)	357 (48.5) 410 (55.7) 282 (38.3)	--	715 (52.8) 787 (58.1) 520 (38.4)	678 (50.6) 772 (57.6) 473 (35.3)
Baseline serum antibody negative, n (%)	500 (67.9)	519 (69.4)	940 (69.4)	930 (69.4)
Duration of symptoms, median (IQR)	3 (2-5)	3 (2-4)	3 (2-5)	3 (2-5)
Viral load (log_{10} copies/mL), mean ± SD	6.73 ± 1.86	6.63 ± 1.82	6.72 ± 1.71	6.66 ± 1.75

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Weinreich DM, et al. N Engl J Med. 2021. [Epub ahead of print]. https://doi.org/10.1056/NEJMoa2108163

Ambulatory Treatment

Casirivimab + Imdevimab (Phase 3)

Primary Outcome: Hospitalizations and Death

	REGEN-COV 1.2 mg (N=736)	Placebo (N=748)	*P* value	REGEN-COV 2.4 mg (N=1355)	Placebo (N=1341)	*P* value
Hospitalization or all-cause death by day 29, n (%)	7 (1)	24 (3.2)	0.0024	18 (1.3)	62 (4.6)	<0.0001
Hospitalization by day 29, n (%)	6 (0.8)	23 (3.1)		17 (1.3)	59 (4.4)	
Death by day 29, n (%)	1 (0.1)	1 (0.1)		1 (<0.1)	3 (0.2)	

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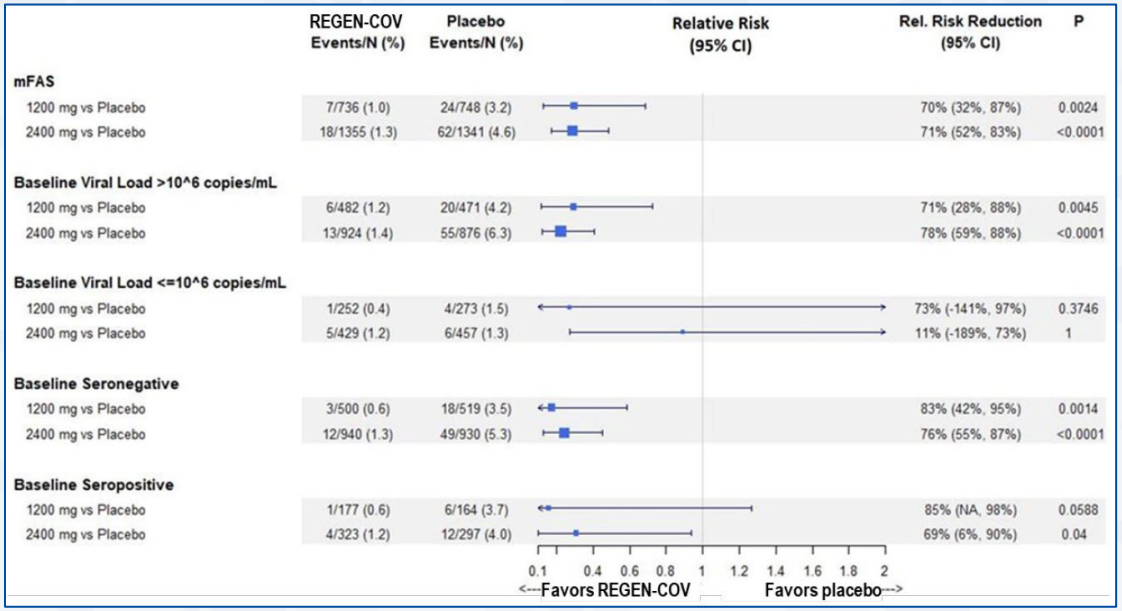
Weinreich DM, et al. N Engl J Med. 2021. [Epub ahead of print]. https://doi.org/10.1056/NEJMoa2108163

Ambulatory Treatment

Casirivimab + Imdevimab (Phase 3)

Subgroup Analyses: Hospitalizations and Death



	REGEN-COV Events/N (%)	Placebo Events/N (%)	Relative Risk (95% CI)	Rel. Risk Reduction (95% CI)	P
mFAS					
1200 mg vs Placebo	7/736 (1.0)	24/748 (3.2)		70% (32%, 87%)	0.0024
2400 mg vs Placebo	18/1355 (1.3)	62/1341 (4.6)		71% (52%, 83%)	<0.0001
Baseline Viral Load >10^6 copies/mL					
1200 mg vs Placebo	6/482 (1.2)	20/471 (4.2)		71% (28%, 88%)	0.0045
2400 mg vs Placebo	13/924 (1.4)	55/876 (6.3)		78% (59%, 88%)	<0.0001
Baseline Viral Load <=10^6 copies/mL					
1200 mg vs Placebo	1/252 (0.4)	4/273 (1.5)		73% (-141%, 97%)	0.3746
2400 mg vs Placebo	5/429 (1.2)	6/457 (1.3)		11% (-189%, 73%)	1
Baseline Seronegative					
1200 mg vs Placebo	3/500 (0.6)	18/519 (3.5)		83% (42%, 95%)	0.0014
2400 mg vs Placebo	12/940 (1.3)	49/930 (5.3)		76% (55%, 87%)	<0.0001
Baseline Seropositive					
1200 mg vs Placebo	1/177 (0.6)	6/164 (3.7)		85% (NA, 98%)	0.0588
2400 mg vs Placebo	4/323 (1.2)	12/297 (4.0)		69% (6%, 90%)	0.04

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Weinreich DM, et al. N Engl J Med. 2021. [Epub ahead of print]. https://doi.org/10.1056/NEJMoa2108163

Ambulatory Treatment

Casirivimab + Imdevimab (Phase 3)

Secondary Outcomes: Hospitalization/Death (Day 4-29), Symptom Resolution

	REGEN-COV 1.2 g (N=736)	Placebo (N=748)	*P* value	REGEN-COV 2.4 g (N=1355)	Placebo (N=1341)	*P* value
Hospitalization or all-cause death between day 4 and 29, n (%)	5/735 (0.7)	18/748 (2.4)	0.0101	5/1351 (0.4)	46/1340 (3.4)	< 0.0001
Time to symptom resolution (days), median	10	14	< 0.0001	10	14	< 0.0001

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Weinreich DM, et al. N Engl J Med. 2021. [Epub ahead of print]. https://doi.org/10.1056/NEJMoa2108163

Ambulatory Treatment

Casirivimab + Imdevimab (Phase 3)

Secondary Outcomes: Safety

	REGEN-COV 1.2 g (N=827)	REGEN-COV 2.4 g (N=1849)	Placebo (N=1843)
Serious adverse event	9 (1.1)	24 (1.3)	74 (4.0)
Infusion-related reactions Grade ≥ 2 thru Day 4	2 (0.2)	1 (<0.1)	0
Hypersensitivity reactions Grade ≥ 2 thru Day 29	0	1 (<0.1)	1 (<0.1)
Event leading to death	1 (0.1)	1 (<0.1)	5 (0.3)
Event leading to infusion interruption	1 (0.1)	0	0

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Weinreich DM, et al. N Engl J Med. 2021. [Epub ahead of print]. https://doi.org/10.1056/NEJMoa2108163

Ambulatory Prophylaxis

COV-2069 (Cohort A)

Patient Population

- Adults and adolescents ≥ 12 years
- Household exposure to SARS-CoV-2 positive individual within 96h of positive test
- SARS-CoV-2 PCR negative
- Resides in same household as index case until study day 29

Treatment Groups

- Casirivimab + Imdevimab
  - 600 mg/600 mg SubQ x 1
- Placebo

Outcomes

- Primary:
  - Symptomatic, PCR-confirmed SARS-CoV-2 infection through day 29
- Secondary:
  - SARS-CoV-2 PCR positivity & duration
  - High viral load frequency & duration
  - Symptom duration
  - Safety

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

O'Brien MP, et al. N Engl J Med. 2021;385(13):1184-95. https://doi.org/10.1056/NEJMoa2109682

Ambulatory Prophylaxis

Casirivimab + Imdevimab (Cohort A)

Baseline Demographics

Characteristic	REGEN-COV 1.2 g (N=753)	Placebo (N=752)
Age (years), mean (range) < 18, n (%) ≥ 50, n (%)	43 (12-87) 34 (4.5) 294 (39.0)	43 (12-92) 34 (4.5) 280 (37.2)
Body-mass index (kg/m^2), mean ± SD BMI ≥ 30 kg/m^2, n (%)	28.9 ± 12.4 261 (34.7)	28.5 ± 6.3 250 (33.2)
≥ 1 risk factor for severe COVID-19*, n (%)	570 (75.7)	567 (75.4)

*Based on EUA Fact Sheet definitions updated 5/14/21

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

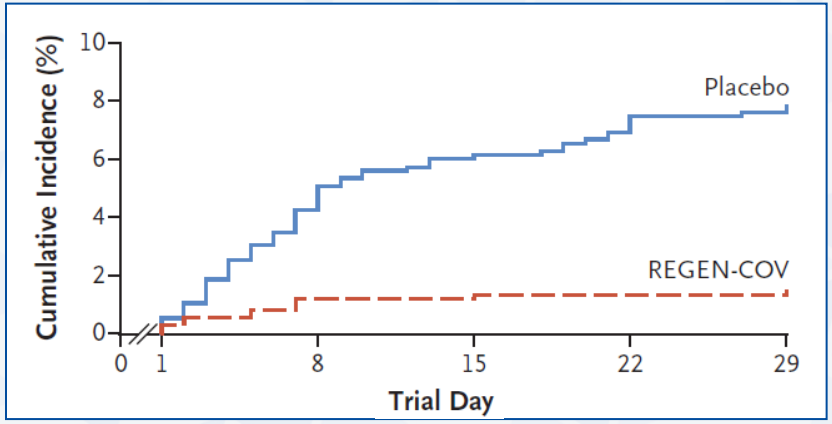
O'Brien MP, et al. N Engl J Med. 2021;385(13):1184-95. https://doi.org/10.1056/NEJMoa2109682

Ambulatory Prophylaxis

Casirivimab + Imdevimab (Cohort A)

Primary Outcome: Symptomatic infection in seronegative patients

	REGEN-COV 1.2 g (N=753)	Placebo (N=752)	*P* value
Symptomatic SARS-CoV-2 infection among patients seronegative at baseline, n (%)	11 (1.5)	59 (7.8)	< 0.001



9 and 32 of symptomatic infections occurred within 1st week after administration of REGEN-COV and placebo, respectively

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SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

O'Brien MP, et al. N Engl J Med. 2021;385(13):1184-95. https://doi.org/10.1056/NEJMoa2109682

Ambulatory Prophylaxis

Casirivimab + Imdevimab (Cohort A)

Subgroup Analyses: High-risk seronegative, Seropositive, and Various Age Groups

	Development of symptomatic SARS-CoV-2 infection		
	REGEN-COV 1.2 g	Placebo	*P* value
High-risk patients* seronegative at baseline, n (%)	10/570 (1.8)	42/567 (7.4)	--†
Patients seropositive at baseline, n (%)	1/235 (0.4)	5/222 (2.3)	0.14
Age groups, n (%)			
≥ 12 to < 18 years	0/34	4/34 (11.8)	0.11
≥ 18 to < 50 years	5/424 (1.2)	29/438 (6.6)	< 0.001
≥ 50 years	6/295 (2.0)	26/280 (9.3)	< 0.001

*Based on EUA Fact Sheet definitions updated 5/14/21

†*P* value not specified; odds ratio (95% CI): 0.22 (0.10, 0.46)

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O'Brien MP, et al. N Engl J Med. 2021;385(13):1184-95. https://doi.org/10.1056/NEJMoa2109682

Ambulatory Prophylaxis

Casirivimab + Imdevimab (Cohort A)

Secondary Outcomes: Positive PCR, High Viral Load, and Symptom Duration

	REGEN-COV 1.2 g (N=753)	Placebo (N=752)	*P* value
PCR-confirmed SARS-CoV-2 infection (regardless of symptoms) during EAP, n (%)	36 (4.8)	107 (14.2)	< 0.001
Duration of PCR-confirmed SARS-CoV-2 infection (weeks), combined total Duration per patient (weeks), mean ± SD	41.0 1.1 ± 0.4	231.0 2.2 ± 1.1	< 0.001
Viral load > 4 $\log_{10}$ copies/mL during EAP, n (%)	12/745 (1.6)	85/749 (11.3)	< 0.001
Duration of high-viral load > 4 $\log_{10}$ copies/mL (weeks), combined total Duration per patient (weeks), mean ± SD	14.0 0.4 ± 0.6	136.0 1.3 ± 0.9	< 0.001
Duration of symptomatic PCR-confirmed SARS-CoV-2 (weeks), combined total Duration per patient (weeks), mean ± SD	12.7 1.2 ± 1.0	187.7 3.2 ± 2.7	< 0.001

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O'Brien MP, et al. N Engl J Med. 2021;385(13):1184-95. https://doi.org/10.1056/NEJMoa2109682

Ambulatory Prophylaxis

Casirivimab + Imdevimab (Cohort A)

Secondary Outcomes: Safety

	REGEN-COV 1.2 g (N=1311)	Placebo (N=1306)
Serious adverse event, n (%)	10 (0.8)	15 (1.1)
ED visit or hospitalization due to COVID-19, n (%)	0	4 (0.3)
Event leading to death, n (%)	2 (0.2)	2 (0.2)
Adverse events occurring in ≥ 2% of participants, n (%)		
Symptomatic COVID-19	15 (1.1)	112 (8.6)
Asymptomatic COVID-19	54 (4.1)	108 (8.3)
Headache	24 (1.8)	46 (3.5)
Injection-site reaction	55 (4.2)	19 (1.5)

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O'Brien MP, et al. N Engl J Med. 2021;385(13):1184-95. https://doi.org/10.1056/NEJMoa2109682

Ambulatory Prophylaxis

Casirivimab + Imdevimab (Cohort A)

Primary Outcome at 8 Months: Symptomatic infection seronegative patients

- No additional mAb doses administered
- ~35% of patients in each arm received at least 1 COVID-19 vaccine by end of month 8

	REGEN-COV 1.2 g (N=841)	Placebo (N=842)	*P* value
Symptomatic SARS-CoV-2 infection during months 2-8, n (%)	7 (0.8)	38 (4.5)	< 0.001

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Regeneron. 2020 Nov 8. [Press release]. Available at: https://newsroom.regeneron.com/news-releases/news-release-details/new-phase-3-analyses-show-single-dose-regen-covr-casirivimab-and

Ambulatory Prophylaxis

COV-2069 (Cohort B)

Patient Population

- Non-hospitalized adults and adolescents ≥ 12 years
- Household exposure to SARS-CoV-2 positive individual within 96h of positive test
- Asymptomatic
- SARS-CoV-2 PCR positive

Treatment Groups

- Casirivimab + Imdevimab
  - 600 mg/600 mg SubQ x 1
- Placebo

Outcomes

- Primary:
  - Signs and symptoms of infection within 14 days of positive PCR or during efficacy assessment period
- Secondary:
  - Duration of high viral load
  - Duration of symptoms
  - Safety

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O'Brien MP, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.06.14.2125856

Ambulatory Prophylaxis

Casirivimab + Imdevimab (Cohort B)

Baseline Demographics

Characteristic	REGEN-COV 1.2 g (N=101)	Placebo (N=106)
Age (years), mean ± SD ≥ 50, n (%)	39.2 ± 17.7 31 (30.7)	42.5 ± 18.3 39 (36.8)
Body-mass index (kg/m^2), mean ± SD BMI ≥ 30 kg/m^2, n (%)	28.3 ± 6.7 37 (36.6)	27.8 ± 6.5 30 (28.3)
≥ 1 risk factor for severe COVID-19, n (%)	31 (31.0)	34 (32.7)

*Based on initial EUA Fact Sheet definitions from 11/21/20

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O'Brien MP, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.06.14.21258563

Ambulatory Prophylaxis

Casirivimab + Imdevimab (Cohort B)

Primary Outcome: Symptomatic infection in seronegative patients

	REGEN-COV 1.2 mg (N=100)	Placebo (N=104)	*P* value
Development of signs/symptoms of COVID-19 within 14 days from positive PCR at baseline or during EAP, n (%)	29 (29.0)	44 (42.3)	0.038
Hospitalizations or ED visits, n (%)	0	6 (5.8)	--

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O'Brien MP, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.06.14.21258563

Ambulatory Treatment

Casirivimab + Imdevimab (Cohort B)

Secondary Outcomes: Duration of high viral load and symptoms in seronegative patients

	REGEN-COV 1.2 g (N=100)	Placebo (N=104)	*P* value
Duration of symptomatic SARS-CoV-2 infection within 14 days of positive PCR at baseline or during the EAP (weeks), combined total	89.6	170.3	0.0273
Duration per symptomatic patient (weeks), mean ± SD	3.1 ± 4.1	3.9 ± 4.5	
Duration of high viral load (> 4 log10 copies/mL) during the EAP (weeks), combined total	48	82	0.0010
Duration per participant (weeks), mean ± SD	0.5 ± 0.7	0.8 ± 0.8	

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O'Brien MP, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.06.14.2125856

Ambulatory Treatment

Casirivimab + Imdevimab (Cohort B)

Secondary Outcomes: Safety

	REGEN-COV 1.2 g (N=155)	Placebo (N=156)
Serious adverse event, n(%)	0	4 (2.6)
Injection site reactions, n (%) Grades 1-2 Grade ≥ 3	 6 (3.9) 0	 1 (0.6) 0
Hypersensitivity reactions Grade ≥ 3	0	0
Event leading to death	0	0

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O'Brien MP, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.06.14.21258563

IV versus SubQ

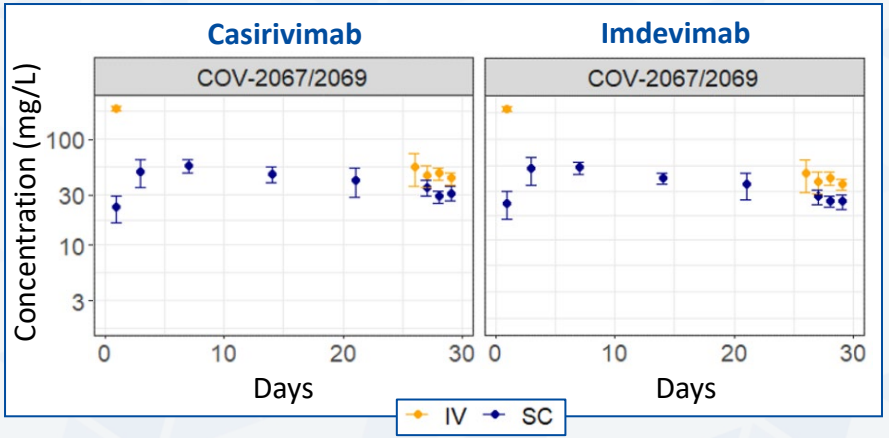
Casirivimab + Imdevimab

- **IV versus SubQ Comparison:** Pharmacokinetics

	Casirivimab 600 mg	Imdevimab 600 mg
Intravenous Dosing*		
C_{eoi} (mg/L)	185 ± 74.5	192 ± 78.9
C_{28} (mg/L)	46.4 ± 22.5	38.3 ± 19.6
Subcutaneous Dosing		
C_{max} (mg/L)	47.5 ± 12.9	46.1 ± 13.8
t_{max} (days), median (range)	7.5 (4-9)	7.5 (4-9)
AUC_{0-28} (mg*day/L)	953 ± 213	1609 ± 419
C_{28} (mg/L)	33.5 ± 12.3	26.9 ± 9.1

*Mean ± SD unless otherwise specified

Concentration-Time Curves After 1200 mg Dose



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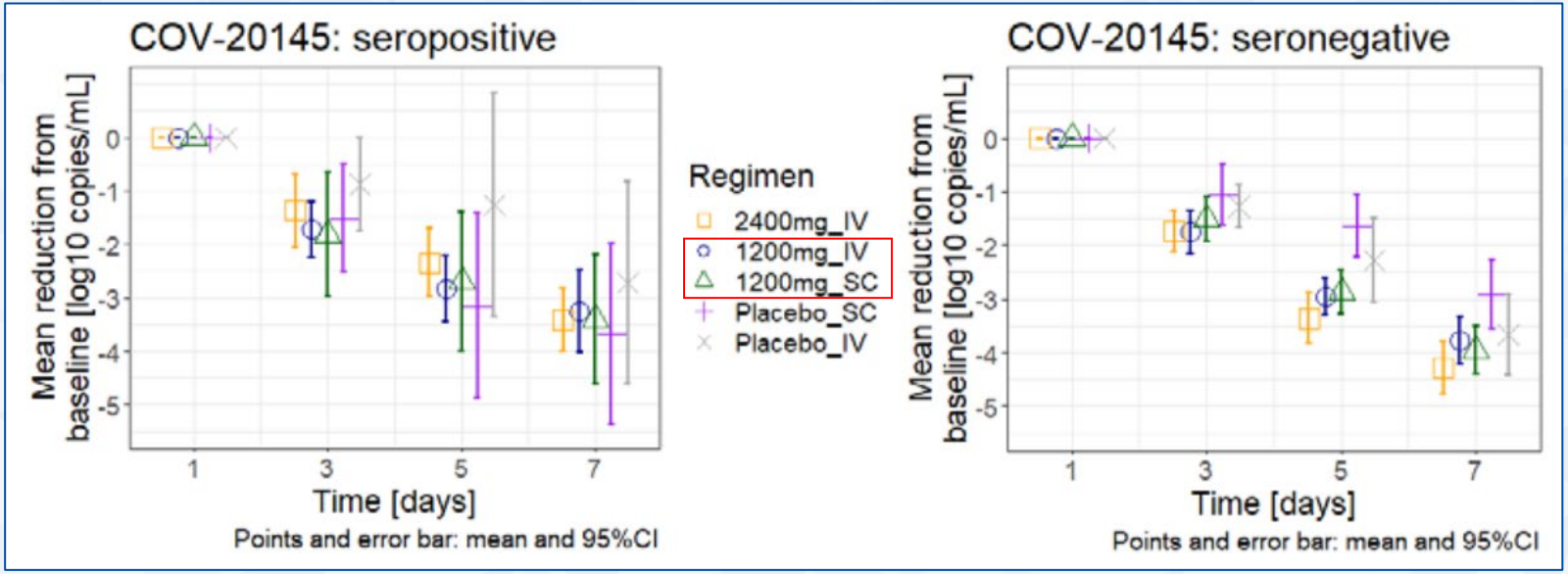
Weinreich DM, et al. N Engl J Med. 2021. [Epub ahead of print]. https://doi.org/10.1056/NEJMoa2108163
O'Brien MP, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.06.14.21258563
CDER Review: Emergency Use Authorization for Casirivimab and Imdevimab. Available at: fda.gov/media/150165/download

Ambulatory Treatment

Casirivimab + Imdevimab (IV vs. SubQ)

- **IV versus SubQ Comparison:** Viral Load Reduction



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CDER Review: Emergency Use Authorization for Casirivimab and Imdevimab
Available at: fda.gov/media/150165/download

Emergency Use Authorization

- **November 21, 2020:** EUA granted for treatment of patients ≥ 12 years of age and ≥ 40 kg with mild/moderate COVID-19 at high risk of progressing to severe disease, including hospitalization or death

- **July 30, 2021:** EUA granted for post-exposure prophylaxis of COVID-19 in patients ≥ 12 years of age and ≥ 40 kg at high risk for progression to severe COVID-19, including hospitalization or death

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Emergency Use Authorization

- Dosing
  - Treatment and Prophylaxis: 1200 mg IV or SubQ x 1
  - For ongoing exposures, repeat prophylaxis with 600 mg IV or SubQ every 4 weeks for duration of exposure
  - No dosage adjustments for any specific populations

- Administration
  - Treatment: Administer within 10 days of symptom onset
  - Administer intravenous infusion over 20-50 minutes, depending on diluent volume
  - Administer subQ injections as a set of 4 injections with each at a different injection site
  - Observe patients for at least 1 hour after administration is complete

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US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Casirivimab and Imdevimab. Available at: https://www.regeneron.com/downloads/treatment-covid19-eua-fact-sheet-for-hcp.pdf
Isa F, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.11.10.21265889

Inpatient Treatment

COV-2066

Patient Population

- Hospitalized adults
- Symptom onset ≤ 10 days from randomization
- SARS-CoV-2 confirmed by molecular testing ≤ 72 hours from randomization

Treatment Groups

- Casirivimab + Imdevimab
  - 1200 mg/1200 mg IV x 1
  - 4000 mg/4000 mg IV x 1
- Placebo

Outcomes

- Virologic:
  - Time-weighted average change from baseline in viral load through day 7
- Clinical:
  - Mechanical ventilation or death from day 6-29 and day 1-29

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Somersan-Karakaya S, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.11.05.21265653

Inpatient Treatment

Casirivimab + Imdevimab

Baseline Demographics

Characteristic	REGEN-COV 2.4 g (N=406)	REGEN-COV 8.0 g (N=398)	Placebo (N=393)
Age (years), median (IQR)	60 (20-97)	62 (20-98)	64 (20-97)
Length of COVID-19 illness prior to baseline (days), median (IQR)	6 (4-8)	6 (4-8)	5 (4-8)
Baseline serum antibody negative, n (%)	191 (47.0)	178 (44.7)	201 (51.1)
Concomitant medications, n (%)			
Remdesivir	212 (52.2)	225 (56.5)	220 (56.0)
Systemic corticosteroids	294 (72.4)	307 (77.1)	294 (74.8)
Use of supplemental oxygen, n (%)	223 (54.9)	223 (56.0)	226 (57.5)

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Somersan-Karakaya S, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.11.05.21265653

Inpatient Treatment

Casirivimab + Imdevimab

Virologic Outcome: Viral load change at day 7 among seronegative patients

	REGEN-COV2 2.4 g (N=150)	REGEN-COV2 8.0 g (N=160)	REGEN-COV Combined (N=310)	Placebo (N=131)
Time-weighted average change in viral load through day 7 (log_{10} copies/mL), least-squares mean ± SE	-1.28 ± 0.09	-1.34 ± 0.09	-1.31 ± 0.06	-1.03 ± 0.10
Difference vs. placebo (log_{10} copies/mL)	-0.25 ± 0.13	-0.31 ± 0.13	-0.28 ± 0.12	--
P value	0.066	0.020	0.017	--

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Somersan-Karakaya S, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.11.05.21265653

Inpatient Treatment

Casirivimab + Imdevimab

Clinical Outcomes: Mechanical ventilation or death among patients with high viral load

	REGEN-COV Combined (N=445)	Placebo (N=211)
Mechanical ventilation or death during days 6-29, n (%)	44 (9.9)	28 (13.3)
P value	0.205	--

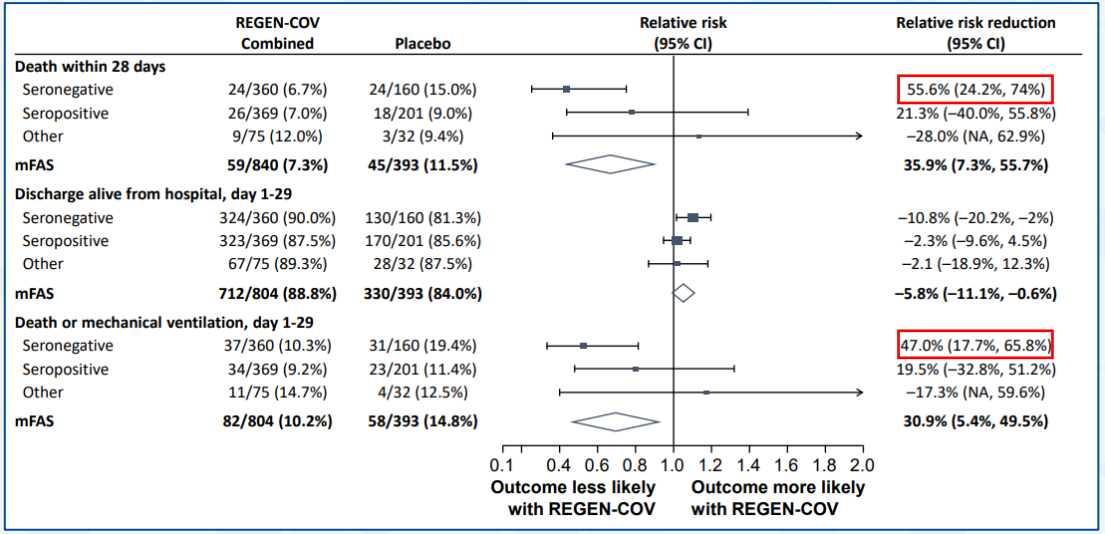
SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Somersan-Karakaya S, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.11.05.21265653

Inpatient Treatment

Casirivimab + Imdevimab

Subgroup Analyses: Mortality, Discharge alive, Mechanical ventilation or death on days 1-29



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Somersan-Karakaya S, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.11.05.2126565

Inpatient Treatment

Casirivimab + Imdevimab

Secondary Outcomes: Safety

	REGEN-COV Combined (N=1340)	Placebo (N=667)
Serious adverse events, n (%)	14 (1)	3 (0.4)
Infusion-related reactions (Grade ≥ 2) through day 4, n (%)	26 (1.9)	6 (0.9)
Hypersensitivity reactions (Grade ≥ 2) through day 29	9 (0.7)	2 (0.3)

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Somersan-Karakaya S, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.11.05.21265653

Inpatient Treatment

RECOVERY

Patient Population

- Hospitalized adults and adolescents ≥ 12 years and ≥ 40 kg
- Clinically suspected or laboratory confirmed SARS-CoV-2

Treatment Groups

- Casirivimab + Imdevimab
  - 4000 mg/4000 mg IV x 1
- Usual care

Outcomes

- Primary:
  - 28-day all-cause mortality
- Secondary:
  - Time to hospital discharge
  - In patients not ventilated at baseline, composite of progression to mechanical ventilation or ECMO or death

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Horby PW, et al. medRxiv. [Preprint]. https://doi.org/10.1101/2021.06.15.21258542

Inpatient Treatment

Casirivimab + Imdevimab

Baseline Demographics

Characteristic	REGEN-COV 8 g (N=4839)	Usual Care (N=4946)
Age (years), mean ± SD	61.9 ± 14.6	61.9 ± 14.4
Duration of symptoms (days), median (IQR)	9 (6-12)	9 (6-12)
Time from hospital admission (days), median (IQR)	2 (1-3)	2 (1-3)
Respiratory support received, n (%)		
No oxygen	332 (7)	309 (6)
Simple oxygen	2980 (62)	3016 (61)
Non-invasive oxygen	1244 (26)	1317 (27)
Invasive mechanical ventilation	283 (6)	304 (6)
Received corticosteroids, n (%)	4530 (94)	4639 (94)

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Horby PW, et al. medRxiv. [Preprint]. https://doi.org/10.1101/2021.06.15.21258542

Inpatient Treatment

Casirivimab + Imdevimab

Primary Outcome: 28-day mortality among seronegative patients

	REGEN-COV 8 g (N=1633)	Usual Care (N=1520)	*P* value
28-day mortality, n (%)	396 (24)	451 (30)	0.001

28-Day Mortality Among All Patients

	REGEN-COV 8 g (N=4839)	Usual Care (N=4946)	*P* value
28-day mortality, n (%)	944 (20)	1026 (21)	0.17

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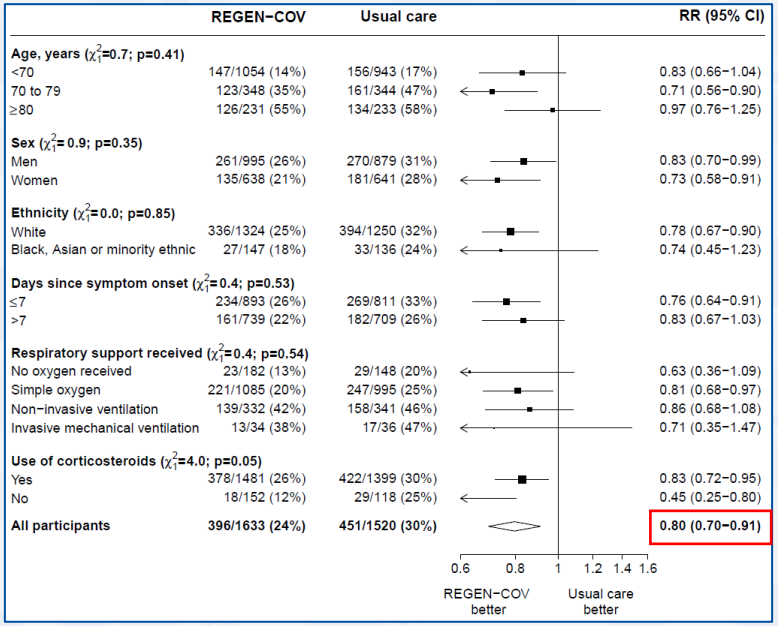
Horby PW, et al. medRxiv. [Preprint]. https://doi.org/10.1101/2021.06.15.21258542

Inpatient Treatment

Casirivimab + Imdevimab

Subgroup Analyses: 28-day mortality among seronegative patients



	REGEN-COV	Usual care	RR (95% CI)
Age, years (χ^2_1=0.7; p=0.41)			
<70	147/1054 (14%)	156/943 (17%)	0.83 (0.66–1.04)
70 to 79	123/348 (35%)	161/344 (47%)	0.71 (0.56–0.90)
≥80	126/231 (55%)	134/233 (58%)	0.97 (0.76–1.25)
Sex (χ^2_1= 0.9; p=0.35)			
Men	261/995 (26%)	270/879 (31%)	0.83 (0.70–0.99)
Women	135/638 (21%)	181/641 (28%)	0.73 (0.58–0.91)
Ethnicity (χ^2_1=0.0; p=0.85)			
White	336/1324 (25%)	394/1250 (32%)	0.78 (0.67–0.90)
Black, Asian or minority ethnic	27/147 (18%)	33/136 (24%)	0.74 (0.45–1.23)
Days since symptom onset (χ^2_1=0.4; p=0.53)			
≤7	234/893 (26%)	269/811 (33%)	0.76 (0.64–0.91)
>7	161/739 (22%)	182/709 (26%)	0.83 (0.67–1.03)
Respiratory support received (χ^2_1=0.4; p=0.54)			
No oxygen received	23/182 (13%)	29/148 (20%)	0.63 (0.36–1.09)
Simple oxygen	221/1085 (20%)	247/995 (25%)	0.81 (0.68–0.97)
Non-invasive ventilation	139/332 (42%)	158/341 (46%)	0.86 (0.68–1.08)
Invasive mechanical ventilation	13/34 (38%)	17/36 (47%)	0.71 (0.35–1.47)
Use of corticosteroids (χ^2_1=4.0; p=0.05)			
Yes	378/1481 (26%)	422/1399 (30%)	0.83 (0.72–0.95)
No	18/152 (12%)	29/118 (25%)	0.45 (0.25–0.80)
All participants	**396/1633 (24%)**	**451/1520 (30%)**	**0.80 (0.70–0.91)**

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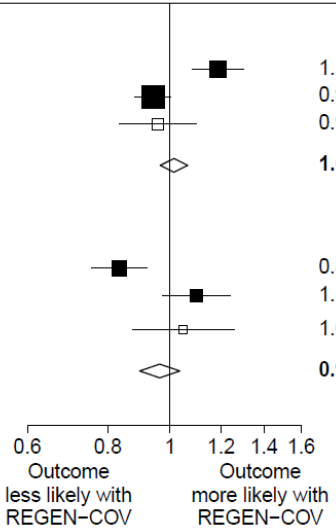
Horby PW, et al. medRxiv. [Preprint]. https://doi.org/10.1101/2021.06.15.21258542

Inpatient Treatment

Casirivimab + Imdevimab

Secondary Outcomes: Discharge alive, Mechanical ventilation or death

Outcome, subgroup	REGEN-COV	Usual care	RR (95% CI)
Discharge alive from hospital (χ^2_1=16.6; p<0.001)			
Seronegative	1046/1633 (64%)	878/1520 (58%)	1.19 (1.08–1.30)
Seropositive	1970/2636 (75%)	2031/2636 (77%)	0.94 (0.88–1.00)
Unknown	359/570 (63%)	504/790 (64%)	0.96 (0.83–1.10)
All participants	**3375/4839 (70%)**	**3413/4946 (69%)**	**1.01 (0.97–1.07)**
Invasive mechanical ventilation or death (χ^2_1=12.0; p<0.001)			
Seronegative	487/1599 (30%)	542/1484 (37%)	0.83 (0.75–0.92)
Seropositive	456/2449 (19%)	415/2450 (17%)	1.10 (0.97–1.24)
Unknown	146/508 (29%)	194/708 (27%)	1.05 (0.87–1.26)
All not on invasive mechanical ventilation at randomisation	**1089/4556 (24%)**	**1151/4642 (25%)**	**0.96 (0.90–1.04)**



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Horby PW, et al. medRxiv. [Preprint]. https://doi.org/10.1101/2021.06.15.21258542

Inpatient Treatment

Casirivimab + Imdevimab

Secondary Outcomes: Safety

	REGEN-COV 8 g (N=1792)	Usual Care (N=1714)
Serious adverse events, n (%)	7 (0.4)	NR
Potential infusion reactions within 72h after randomization, n (%)		
Sudden worsening in respiratory status	359 (21)	372 (22)
Fever	79 (4)	52 (3)
Sudden hypotension	66 (4)	39 (2)
Clinical haemolysis	26 (1)	31 (2)
Any thrombotic event	31 (2)	24 (1)

NR, not reported

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Horby PW, et al. medRxiv. [Preprint]. https://doi.org/10.1101/2021.06.15.21258542

Summary

Casirivimab + Imdevimab

- Greatest viral load changes observed in patients seronegative or with high viral load at baseline
- Decreased risk of hospitalizations and all-cause mortality by ~70% among high-risk, seronegative outpatients ≤ 7 days from symptom onset
- Decreased risk of symptomatic infection by ~80% in SARS-CoV-2 PCR-negative household contacts of persons infected with COVID-19
- Decreased progression to mechanical ventilation or death in seronegative patients hospitalized with COVID-19
- Pending FDA decision on EUA expansion for pre-exposure prophylaxis and inpatient treatment

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GlaxoSmithKline: Sotrovimab

Alternate Names: GSK-4182136

VIR-7831

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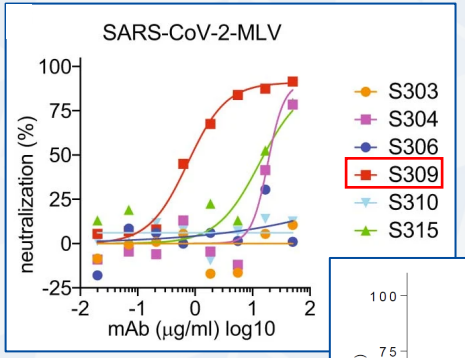
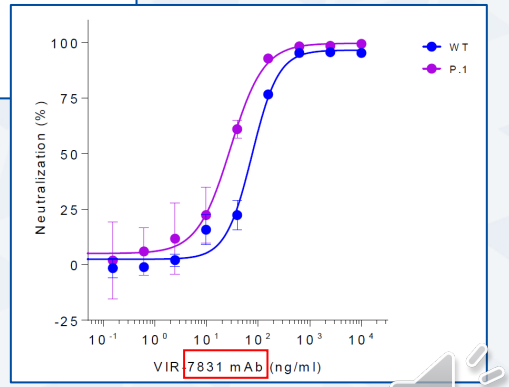
Sotrovimab – *In vitro* Activity

- 25 neutralizing mAbs identified from a **SARS-CoV** survivor
  - S309 observed to have greatest **SARS-CoV-2** neutralization
  - VIR-7831 derived from S309
    - Extended half-life
    - Potentially enhanced distribution to respiratory mucosa

Neutralization Potency





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Pinto D, et al. Nature. 2020;583(7815):290-5. https://doi.org/10.1038/s41586-020-2349-y
Cathcart AL, et al. bioRxiv. [Preprint]. https://doi.org/10.1101/2021.03.09.434607

In vivo Animal Data

Golden Hamster

	Prophylaxis	
Methods	Antibody administered 1 or 2 days prior to viral challenge	
Viral Inoculum	7.4 x 10^4 $TCID_{50}$	
Antibody Doses	<u>Day -1</u> 30 mg/kg (N=6) 5 mg/kg (N=6) 0.5 mg/kg (N=6) 0.05 mg/kg (N=6) Placebo (N=6)	<u>Day -2</u> 15 mg/kg (N=6) 5 mg/kg (N=6) 0.5 mg/kg (N=6) 0.05 mg/kg (N=6) Placebo (N=6)
Sample Types	Lung tissue	
Outcomes	Body weight change Viral load on day 4	

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Cathcart AL, et al. bioRxiv. [Preprint]. https://doi.org/10.1101/2021.03.09.434607

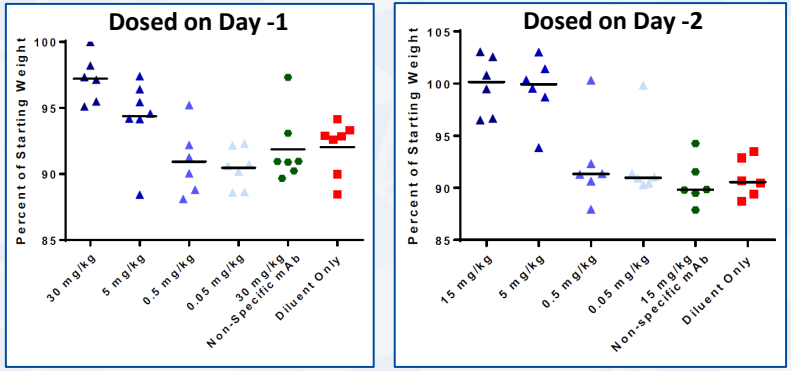
In vivo Animal Data

Golden Hamster

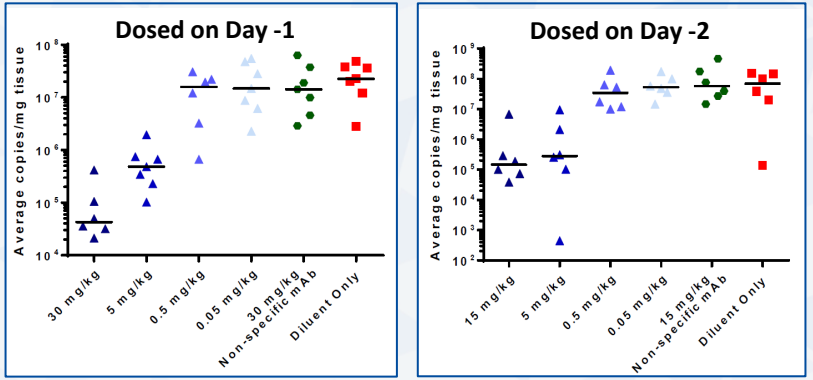
Key Findings

- Significant reduction in weight loss with doses ≥ 5 mg/kg
- Significant decreases in lung viral load with doses ≥ 5 mg/kg

Weight Loss



Viral Load on Day 4



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Cathcart AL, et al. bioRxiv. [Preprint]. https://doi.org/10.1101/2021.03.09.434600

Clinical Trials

NCT Number	Patient Population	Treatment Groups	Status
NCT04545060 COMET-ICE	Treatment of outpatients with mild to moderate COVID-19 illness	Sotrovimab Placebo	Completed – data available
NCT04913675	Treatment of high-risk outpatients with mild to moderate COVID-19 illness	Sotrovimab IV Sotrovimab IM	Active, Not Recruiting
NCT04501978 ACTIV-3	Treatment of hospitalized patients with COVID-19 illness	Placebo	Sotrovimab arm closed
NCT04634409 BLAZE-4	Treatment of outpatients with mild to moderate COVID-19 illness	Bamlanivimab + Sotrovimab Placebo	Completed – press release data available

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Source: https://clinicaltrials.gov

Ambulatory Treatment

COMET-ICE

Patient Population

- Non-hospitalized adults
- Symptom onset ≤ 5 days from randomization
- SARS-CoV-2 confirmed by molecular testing ≤ 5 days from randomization
- ≥ 1 risk factor for severe COVID-19 disease

Age > 55 years
Diabetes requiring medication
Congestive heart failure
Moderate to severe asthma
BMI > 30 kg/m^2
Chronic kidney disease
COPD

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Treatment Groups

- Sotrovimab
  - 500 mg IV x 1
- Placebo

Outcomes

- Primary:
  - COVID-19 related hospitalization or death from any cause by day 29
- Secondary:
  - COVID-19-related ED visit, hospitalization or death from any cause
  - Mortality
  - Patient-reported outcomes
  - Viral load
  - Progression of disease
  - Safety

Gupta A, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.11.03.21265533

Ambulatory Treatment

Sotrovimab

Baseline Demographics

Characteristic	Sotrovimab (N=528)	Placebo (N=529)
Age (years), median (range) ≥ 65, n (%)	53.0 (18-96) 105 (20)	52.5 (17-88) 108 (20)
Body-mass index (kg/m^2), mean ± SD	32.3 ± 6.7	32.2 ± 6.6
BMI > 30 kg/m^2, n (%) Age ≥ 55, n (%) Diabetes requiring medication, n (%)	330 (63) 243 (46) 119 (23)	341 (64) 256 (48) 109 (21)
Duration of symptoms, n (%) ≤ 3 days 4-5 days	 314 (59) 213 (40)	 310 (59) 219 (41)

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Gupta A, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.11.03.21265533

Ambulatory Treatment | Sotrovimab

Primary Outcome: Hospitalizations and Death

	Sotrovimab (N=528)	Placebo (N=529)	*P* value
Hospitalization > 24 hours or all-cause death by day 29, n (%)	6 (1)	30 (6)	< 0.001
Hospitalization > 24 hours by day 29, n (%)	6 (1)	29 (5)	
Death by day 29, n (%)	0	2 (< 1)	

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Gupta A, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.11.03.21265533

Ambulatory Treatment

Sotrovimab

Secondary Outcomes: ED visits, hospitalizations and death, disease progression

	Sotrovimab (N=528)	Placebo (N=529)
ED visit, hospitalization, or all-cause death	13 (2)	39 (7)
Severe or critical progression*	7 (1)	28 (5)
ICU admission for any cause	0	10 (2)

*Development of any need for supplemental oxygen

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Gupta A, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.11.03.21265533

Ambulatory Treatment | Sotrovimab

Secondary Outcomes: Safety

	Sotrovimab (N=523)	Placebo (N=526)
Serious adverse events, n (%) Related to study treatment	11 (2) 0	32 (6) 2 (< 1)
Adverse events occurring in > 1% of patients, n (%) Diarrhea	 8 (2)	 4 (< 1)
Any infusion-related reaction, n (%)	6 (1)	6 (1)

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Gupta A, et al. MedRxiv [Preprint]. https://doi.org/10.1101/2021.11.03.21265533

Emergency Use Authorization

- **May 26, 2021:** EUA granted for treatment of patients ≥ 12 years of age and ≥ 40 kg with mild/moderate COVID-19 at high risk of progressing to severe disease, including hospitalization or death

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Emergency Use Authorization

- Dosing
  - Treatment: 500 mg IV x 1
  - No dosage adjustments for any specific populations

- Administration
  - Treatment: Administer within 10 days of symptom onset
  - Administer intravenous infusion over 30 minutes
  - Observe patients for at least 1 hour after administration is complete

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US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Sotrovimab
Available at: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Sotrovimab/pdf/SOTROVIMAB-EUA.PDF#nameddest=HCPFS

Ambulatory Treatment

BLAZE-4 (Phase 2)

Study Design

- Non-hospitalized adults
- ≥ 1 mild/moderate COVID-19 symptom
- 1st positive SARS-CoV-2 test ≤ 72 hours from start of infusion
- Key exclusions:
  - Age ≥ 65 years
  - BMI ≥ 35 kg/m^2

Treatment Groups

- Bamlanivimab + Sotrovimab
  - 700 mg/500 mg IV x 1
- Placebo

Outcomes

- Primary:
  - Viral load > 5.27 $\log_{10}$ on Day 7 (+2 days)
- Secondary:
  - Change in viral load from baseline to Day 7
  - COVID-19 related hospitalization, ED visit, or death at day 29
  - Symptom burden
  - Safety

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CDER Review: Emergency Use Authorization for Sotrovimab
Available at: https://www.fda.gov/media/146255/download

Ambulatory Treatment

Bamlanivimab + Sotrovimab (Phase 2)

Lilly, Vir Biotechnology and GSK Announce Positive Topline Data from the Phase 2 BLAZE-4 Trial Evaluating Bamlanivimab with VIR-7831 in Low-Risk Adults with COVID-19

March 29, 2021

PDF

- In combination, the two monoclonal antibodies demonstrated a 70% relative reduction in persistently high viral load at day 7 compared to placebo -

INDIANAPOLIS and SAN FRANCISCO and LONDON, March 29, 2021 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY), Vir Biotechnology, Inc. (NASDAQ: VIR) and GlaxoSmithKline plc (LSE/NYSE: GSK) today announced topline data from the expanded Phase 2 BLAZE-4 trial studying low-risk adult patients with mild to moderate COVID-19. Results showed that investigational bamlanivimab (LY-CoV555) 700 mg co-administered with VIR-7831 (also known as GSK4182136) 500 mg demonstrated a 70 percent ($p<0.001$) relative reduction in persistently high viral load (> 5.27; cycle threshold value < 27.5) at day 7 compared to placebo, meeting the primary endpoint.

In addition, bamlanivimab administered with VIR-7831 demonstrated a statistically significant reduction compared to placebo in the key virologic secondary endpoints of mean change from baseline to days 3, 5 and 7 in SARS-CoV-2 viral load. There were no events for the secondary endpoint of COVID-19 related hospitalization or death by day 29 in either study arm. One patient (in the treatment arm) visited the emergency room for COVID-19 related symptoms. No serious adverse events were seen with co-administration of bamlanivimab and VIR-7831.

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Eli Lilly, Vir Biotechnology, GSK. 2021 Mar 29. [Press Release]. Available at: https://www.gsk.com/en-gb/media/press-releases/lilly-vir-biotechnology-and-gsk-announce-positive-topline-data-from-the-phase-2-blaze-4-trial-evaluating-bamlanivimab-with-vir-7831-in-low-risk-adults-with-covid-19/

Summary

Sotrovimab

- Low risk for development of resistance due to highly conserved epitope
- Decreased risk of hospitalizations and all-cause mortality by 79% among high-risk outpatients ≤ 5 days from symptom onset

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Emergency Use Authorization

- **[Bamlanivimab + Etesevimab, Casirivimab + Imdevimab, and Sotrovimab]**
  - are authorized for the treatment of mild to moderate COVID-19 in adults and pediatric patients (≥ 12 years and ≥ 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death
  - are not authorized for use in patients:
    - who are hospitalized **due to COVID-19**, OR
    - who require oxygen therapy due to COVID-19, OR
    - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity

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US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Casirivimab and Imdevimab
US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab
US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Sotrovimab

Emergency Use Authorization Criteria

High Risk Criteria

- Older age (ex. ≥ 65 years)
- Adults with BMI ≥ 25 kg/m^2
- Age 12-17 with BMI ≥ 85th percentile for age and gender
- Pregnancy
- CKD
- Diabetes
- Immunosuppressive disease or treatment
- Cardiovascular disease
- Hypertension
- Chronic lung diseases
- Sickle cell disease
- Neurodevelopmental disorders
- Other conditions that confer medical complexity
- Medical-related technological dependence

Other medical conditions or factors (ex. race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of [monoclonal antibody therapy] under the EUA is not limited to the medical conditions or factors listed above

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US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Casirivimab and Imdevimab
US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab
US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Sotrovimab

Emergency Use Authorization

- **[Bamlanivimab + Etesevimab and Casirivimab + Imdevimab]**
  - are authorized to be administered in adults and pediatric individuals (≥ 12 years and ≥ 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk of progression to severe COVID-19, including hospitalization or death, and are:
    - not fully vaccinated **or** not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination **and**
      - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC **or**
      - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (ex. SNF, prison)
  - are not a substitute for vaccination against COVID-19
  - are not authorized for pre-exposure prophylaxis for prevention of COVID-19

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Monoclonal Antibody Efficacy Against Select SARS-CoV-2 Variants

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SARS-CoV-2 Variants

- Variants of Concern:
  - Previously included Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Epsilon (B.1.427/429)
  - Only current variant of concern is Delta (B.1.617.2 and AY lineages)
    - Increased transmissibility
    - Potential reduction in neutralization by some EUA mAb treatments
    - Potential reduction in neutralization by post-vaccination sera

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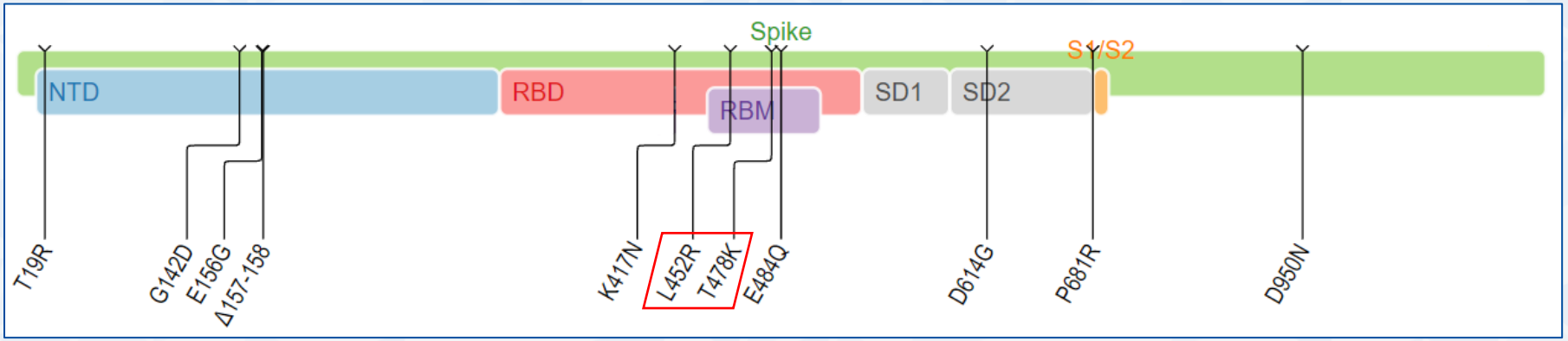
CDC - SARS-CoV-2 Variants. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html. November 2, 2021

Delta Variant Mutations

- RBD spans amino acids 330-531
  - Mutations in this range have the potential to affect mAb binding
  - L452R and T478K present in all Delta variants
  - K417N and E484Q mutations present in < 0.5% of Delta variants



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Coronavirus Antiviral & Resistance Database. covdb.stanford.edu/page/mutation-viewer. November 2, 202

Delta Variant Impact on mAb Activity

	Fold Change in IC_{50} from Wild Type						
	Bam	Ete	Bam + Ete	Cas	Imd	Cas + Imd	Sot
Overall Change*	**> 100**	**0.6**	**1**	**0.8**	**1.4**	**1**	**1**
L452R	> 100	1	5	1	2	2.5	0.6
T478K	-	-	-	2.9	1.4	2.6	-
K417N	0.3	> 100	-	10	0.6	1.3	0.6
E484Q	100	1.3	-	26.5	1.1	1.5	-

*For Delta variants expressing L452R and T478K only

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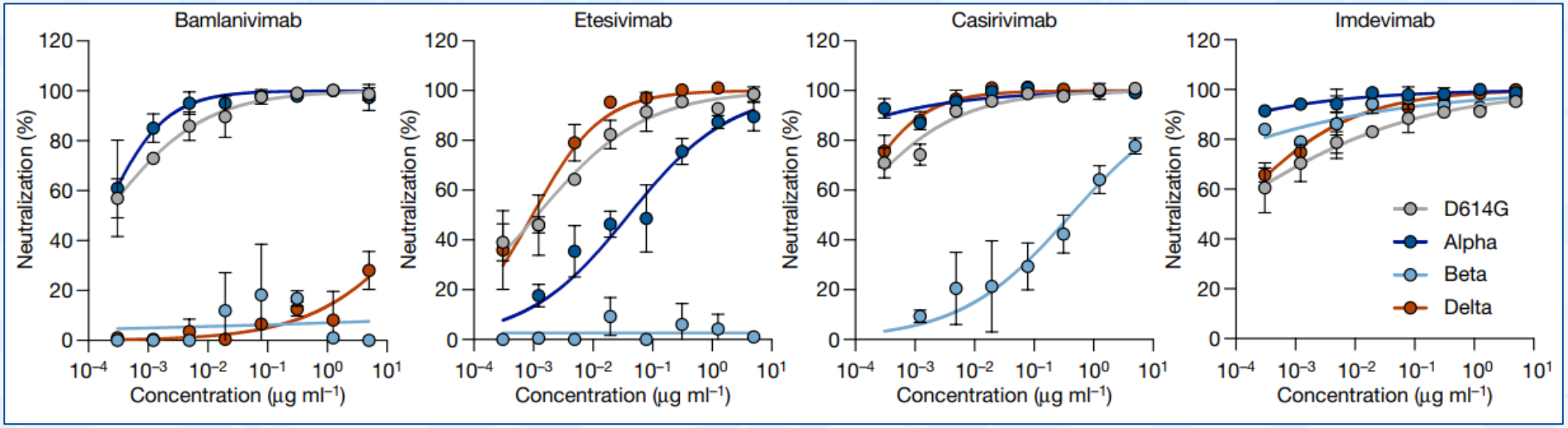
Coronavirus Antiviral & Resistance Database. covdb.stanford.edu/page/mutation-viewer. November 2, 202

Changes in Neutralization Activity



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Planas D, et al. Nature. 2021;596(7871):276-80. https://doi.org/10.1038/s41586-021-03777-9

Delta Variant

Summary

Variant	Key Mutations	Efficacy Retained?		
		Bamlanivimab + Etesevimab	Casirivimab + Imdevimab	Sotrovimab
Delta	L452R, T478K	Y	Y	Y
Delta + K417N	L452R, T478K, K417N	N	Y	Y
Delta + E484Q	L452R, T478K, E484Q	Y	Y	Y

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Additional mAb Under Investigation

Name	Developer	Study Design
Regdanvimab (CT-P59)	Celltrion	Phase 2/3 – outpatient treatment
Tixagevimab + Cilgavimab (AZD8895 + AZD1061)	AstraZeneca/Vanderbilt University Medical Center/DARPA/BARDA	Phase 3 – pre/post-exposure prophylaxis Phase 3 – inpatient treatment Phase 3 – outpatient treatment
TY027	Tychan	Phase 3 – inpatient treatment
BRII-196 + BRII-198	Brii Biosciences/NIAID	Phase 3 – inpatient treatment

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Yang L, et al. Antibody Therapeutics. 2020;3:205-12. https://doi.org/10.1093/abt/tbaa02

Monoclonal Antibodies

A Review of Pertinent Drug Information for SARS-CoV-2

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Data as of November 17, 2021