Special Assessment of Outpatient Treatments for COVID-19

Draft Evidence Report

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Prepared for

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Kai Yeung served as the lead author for the report. Molly Beinfeld led the systematic review and authorship of the comparative clinical effectiveness section of this report in collaboration with Rasheed Mohammed, Abigail Wright, and Emily Nhan. Melanie Whittington developed the cost-effectiveness model and authored the corresponding sections of the report with assistance from Noemi Fluetsch and Marina Richardson. Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Laura Cianciolo and Monica Frederick for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 29% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include GlaxoSmithKline, Merck, Pfizer, and Regeneron. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

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The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The Midwest CEPAC is an independent committee of medical evidence experts from across the Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about Midwest CEPAC is available at https://icer.org/who-we-are/people/independent-appraisal-committees/midwest-comparative-effectiveness-public-advisory-council-m-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2021/08/ICER_COVID-19-Stakeholder-List_082621.pdf.

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List of Acronyms and Abbreviations Used in this Report

AHRQ	Agency for Healthcare Research and Quality
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
EUA	Emergency Use Authorization
evLY	Equal-value life year
FDA	Food and Drug Administration
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICER	Institute for Clinical and Economic Review
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IV	Intravenous
kg	Kilogram
mg	Milligram
mL	Milliliter
N	Total number
n	Number
NIH	National Institutes of Health
PCR	Polymerase chain reaction
PICOTS	Population, Intervention, Comparators, Outcomes, Timing, Settings
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RNA	Ribonucleic acid
RR	Risk ratio
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SpO2	Oxygen saturation
SSRI	Selective serotonin reuptake inhibitor
US	United States
WAC	Wholesale acquisition cost
WHO	World Health Organization

Executive Summary

Background

COVID-19 is an infectious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of January 2022, there have been over 63 million confirmed COVID-19 cases and 840,000 COVID-19 deaths in the United States (US). The severity of the disease is classified into four levels. Most symptomatic COVID-19 patients have mild or moderate disease and do not require hospitalization. Patients who develop severe or critical disease require hospitalization with respiratory support. Many factors can increase the risk for developing severe or critical COVID-19. Some of the most common risk factors are older age, obesity, cardiovascular disease, and chronic obstructive pulmonary disease.

This draft Evidence Report is considered an Institute for Clinical and Economic Review (ICER) "Special Assessment" because the epidemiological landscape and evidence base for potential treatments for COVID-19 are both rapidly evolving and will continue to change through the remaining course of this review. This constantly shifting landscape is a dominant contextual reality. However, due to the unprecedented immediacy and scale of COVID-19, and the near-term policy decisions that will be made across multiple treatment options, ICER believes that an independent review of existing evidence on comparative clinical effectiveness and value of these treatment options will be helpful to all stakeholders.

Report Aim

In this draft Evidence Report, ICER is presenting a full evaluation of clinical and economic outcomes of four treatments for mild-to-moderate COVID-19 among outpatients at high risk of progression to severe disease: sotrovimab, molnupiravir, Paxlovid™, and fluvoxamine. The scope of the review initially included another treatment, the dual monoclonal antibody therapy REGEN-COV, but evaluation of that treatment was halted when the Food and Drug Administration (FDA) revoked its Emergency Use Authorization (EUA) due to REGEN-COV's substantially reduced activity against the Omicron variant.[1] Shortly before the posting of this Report, the FDA granted an EUA for remdesivir for our population of interest. ICER will make a determination regarding the inclusion of remdesivir in this Report at a later date.

Mechanisms of Action and FDA Regulatory Status

Sotrovimab is a recombinant human monoclonal antibody administered intravenously that works by binding to the SARS-CoV-2 viral spike protein, inhibiting either attachment or fusion to human cells. Molnupiravir is an oral ribonucleoside analog that causes viral genome replication errors.

Nirmatrelvir/ritonavir (Paxlovid) is a combination oral drug that inhibits SARS-CoV-2-3CL protease, an enzyme necessary to produce other functional SARS-CoV-2 proteins. Fluvoxamine is a generic, oral selective serotonin reuptake inhibitor (SSRI) with FDA approval for the treatment of obsessive-compulsive disorder. One hypothesized mechanism of action for fluvoxamine in the treatment of COVID-19 is through modulation of the body's inflammatory response. Sotrovimab, molnupiravir, and Paxlovid currently have EUA from the FDA. Fluvoxamine is available on the US market while university-based researchers are pursuing an EUA specifically for the treatment of COVID-19.

Comparative Clinical Effectiveness

Studies of all four therapies were conducted in overlapping timeframes but with potentially important differences in location (US vs. overseas), in the spectrum of SARS-CoV-2 variants, and their prevalence within the population. None of the clinical trials were performed at a time when the Omicron variant was present. Within this context, high-quality evidence demonstrated that if given within a limited number of days following initial symptoms of COVID-19, all four drugs of interest were superior to placebo in reducing hospitalization related to the acute infection. Sotrovimab, molnupiravir, and Paxlovid significantly reduced the relative risk of hospitalization or death from any cause compared to placebo by 79%, 30%, and 88%, respectively. Fluvoxamine reduced the relative risk of COVID-19-associated acute care (i.e., retention in a COVID-19 emergency setting or transfer to tertiary hospital due to COVID-19) compared to placebo by 32%. A per-protocol analysis of fluvoxamine limited to individuals who did not stop treatment (i.e., had greater than 80% adherence) suggested substantially greater efficacy (66% relative risk reduction) in reducing acute care use.

Sotrovimab, molnupiravir, and Paxlovid were well tolerated and had low discontinuation rates in their Phase III clinical trials. Molnupiravir has important safety considerations given laboratory evidence suggesting it may be mutagenic, teratogenic, and toxic to growing bone and cartilage. Based on a short five-day course of therapy, the FDA considers molnupiravir to have low risk for mutagenicity, but the EUA label limits usage to individuals 18 years and older who are not pregnant or breastfeeding. The FDA has also stipulated that men of reproductive potential who are sexually active with individuals of childbearing potential should abstain from sex or use a reliable method of contraception for the duration of treatment and for at least three months after the last dose of molnupiravir.

As an SSRI, fluvoxamine also carries an FDA drug class warning for increased risk of suicidal thinking for children, adolescents, and young adults taking antidepressants for major depressive disorder and other psychiatric disorders. The risk of adverse events in the fluvoxamine arm was similar to the risk in the placebo arm of the Phase III TOGETHER trial as well as to the risks in intervention arms in the Phase III trials for the other drugs of interest. However, there was a sizeable percentage

of individuals who stopped treatment due to tolerability in both the fluvoxamine and placebo arms of the TOGETHER trial (11.3% and 8.4%, respectively).

Table ES1. Number and Percentage of Hospitalizations or Deaths in Key Phase III Trials[2-9]

Intervention (Trial)	Hospitalization or Death from Any Cause, n/N (%)		Death, n/N (%)	
	Intervention	Placebo	Intervention	Placebo
Sotrovimab (COMET-ICE)	6/528 (1.1)	30/529 (5.8)	0/528 (0)	2/529 (0.3)
Molnupiravir (MOVe-OUT)	48/709 (6.8)	68/699 (9.7)	1/709 (0.1)	9/699 (1.3)
Paxlovid (EPIC-HR)	8/1039 (0.8)	66/1046 (6.3)	0/1039 (0)	12/1046 (1.1)
Fluvoxamine (TOGETHER)	79/741 (11)*	119/756 (16)*	17/741 (2.3)	25/756 (3.3)

n: number, N: total number

*Observed in a COVID-19 emergency setting (for more than six hours) or hospitalized.

While further evidence on all four treatments of interest continues to be gathered and analyzed, the COVID-19 landscape has been evolving so rapidly that currently available data cannot be expected to have evaluated the safety and effectiveness of these drugs in the real-world US population as of the date of this Report. Important uncertainties that must be considered include: 1) the rapid evolution of SARS-CoV-2 leading to variants with treatment resistance and with different morbidity and mortality impacts; 2) the enrollment of generally healthier and lower risk and predominately unvaccinated populations in the clinical trials; 3) the uncertain generalizability of data related to hospitalization rates and other health care resource utilization from studies conducted prior to the advent of the Omicron variant and based predominately or exclusively in countries outside of the US. Such issues are compounded by each treatment being supported by evidence from only one Phase III trial at this time.

Substantial differences in patient populations across the Phase III trials preclude us from making direct comparisons or formal quantitative indirect comparisons of safety and effectiveness across the drugs of interest. For example, sotrovimab and molnupiravir trials enrolled substantially larger proportions of individuals with obesity compared to the fluvoxamine and Paxlovid trials. The sotrovimab trial had greater proportions of individuals with diabetes than the trials of molnupiravir, fluvoxamine, and Paxlovid. Further, as noted, large variability in the countries of recruitment and the timing of trial enrollment periods reduce study comparability. The Phase III trials also defined outcomes differently. In particular, data from the fluvoxamine TOGETHER trial appears to be the least comparable to others since this trial used a distinct composite primary outcome of retention in a COVID-19 emergency setting for more than six hours or transfer to a hospital. Keeping this context of substantial uncertainty in mind, ICER Evidence Ratings shown in Table ES2 should be viewed with corresponding caution, particularly when making inferences between the comparative effectiveness of the different agents.

Table ES2. Evidence Ratings

Treatment	Comparator	Evidence Rating
Sotrovimab	Usual care	B+
Molnupiravir*	Usual care	C+
Paxlovid	Usual care	B+
Fluvoxamine	Usual care	C+

*Note: Population excludes individuals who are pregnant or who have childbearing potential.

Cost Effectiveness

To estimate the cost effectiveness of each outpatient treatment, we used estimates of relative treatment effectiveness from each intervention's pivotal trial and applied those estimates to a common "usual care" comparator arm synthesized by pooling across the usual care arms of each pivotal trial. This approach was considered optimal given how disparate the results were in the usual care arms across the pivotal trials, reflective of the differences in the background patient population, timing of study in relation to COVID-19 variants, and differences in health care practices across the different countries in which the trials were conducted. Base-case results were calculated from the health care sector perspective over a lifetime time horizon. Incremental cost-effectiveness ratios are reported below in Table ES3. All treatments had base-case results lower than $100,000 per quality-adjusted life year (QALY) gained and equal-value life year (evLY) gained. Results were particularly sensitive to assumptions regarding the relative effectiveness of the intervention and the background rate of hospitalization within the common usual care comparator arm.

Table ES3. Base-Case Incremental Cost-Effectiveness Ratios

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Hospitalization Averted
Sotrovimab	Usual care	$69,000	$58,000	$66,000	$91,000
Molnupiravir	Usual care	$55,000	$46,000	$53,000	$63,000
Paxlovid	Usual care	$18,000	$15,000	$17,000	$21,000
Fluvoxamine	Usual care	$6,000	$5,000	$6,000	$7,000

evLY: equal-value life year, QALY: quality-adjusted life year

These treatments also have important potential benefits that may not be fully captured or evaluated in the economic model, including the potential for preventing further spread of SARS-CoV-2. We have to model quantitatively the potential impact on improving hospital intensive care unit (ICU) capacity but, in addition, effective outpatient treatments may help address the disparate burden of the pandemic in disadvantaged communities and help provide psychological reassurance, allowing for broader opening of schools and workplaces. There are also important relative disadvantages of each drug when considered against other options. These disadvantages are described in Section 5.

In conclusion, assessment of the evidence on outpatient treatments for COVID-19 must be viewed as highly sensitive to the evolving landscape of COVID-19 variants and vaccination status in the US. The available data come from single pivotal trials, all conducted in settings not reflective of the health care patterns and the background risk of progression to severe disease occurring in the current Omicron wave of infections in the US. With these limitations in mind, current evidence does suggest that the drugs of interest reduce hospitalizations among patients with mild-to-moderate COVID-19 who are at high risk of progression to severe disease. Numbers of deaths in the pivotal trials are too small to draw firm conclusions. There are no short-term data suggesting serious concerns for side effects of these drugs when limited to the populations for which they are indicated. And at their current negotiated price (sotrovimab, molnupiravir, and Paxlovid) or their generic market price (fluvoxamine), these drugs appear—at this time—to have prices reasonably aligned with patient benefits. Should background risks of hospitalization from mild-moderate COVID-19 be reduced with the Omicron (or future) variant, or should these treatments be used in lower-risk populations, including patients with full vaccination, their cost effectiveness would be significantly reduced.

1. Background

COVID-19 is an infectious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of January 2022, there have been over 63 million confirmed COVID-19 cases and 840,000 COVID-19 deaths in the United States (US).[10] The direct medical costs of health care utilization from COVID-19, while substantial (>$100 billion[11] over the expected course of the pandemic), are overshadowed by the costs of reduced economic output due to the pandemic (>$7 trillion).[12] Further, COVID-19 has uneven clinical and economic impacts as older individuals, those living with comorbidities, and Black and Hispanic populations are at higher risk of infection, hospitalization, and mortality,[13] while younger individuals, women, and Hispanic populations are at higher risk of job loss as a result of the pandemic.[14]

COVID-19 is typically diagnosed using nucleic acid and antigen tests taken from the nose or throat.[15,16] The severity of disease is changing as the proportion of individuals who are vaccinated increases and the prevalence of SARS-CoV-2 variants changes. Therefore, the data presented in this paragraph may not reflect current epidemiological or clinical presentations. Prior to the Omicron variant becoming the predominant strain, and among unvaccinated individuals with COVID-19, roughly 30% are asymptomatic.[17] Among those who are symptomatic, 80% develop mild-to-moderate disease while the other 20% go on to require oxygen and/or mechanical ventilation.[18,19] Symptoms typically appear two to 14 days after infection and include fever, dry cough, fatigue, joint/muscle pains, nasal congestion, loss of smell/taste, sore throat, headache, diarrhea, nausea/vomiting, shortness of breath, cyanosis, persistent chest pain, loss of appetite, or confusion. The severity of symptomatic infections can be classified into four levels,[20,21] as illustrated below.

1. Mild disease: Individuals have symptoms but do not have shortness of breath or abnormal chest imaging.
2. Moderate disease: Individuals show evidence of lower respiratory tract disease but have oxygen saturation (SpO2) ≥94%.
3. Severe disease: Individuals have pneumonia and one of the following: SpO2 <94%, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen <300, require more than 30 breaths per minute, or have >50% lung infiltrates.
4. Critical disease: Individuals have respiratory failure, septic shock, and/or multiple organ dysfunction.

New infections with COVID-19 have risen substantially in recent months due to the higher contagiousness of the Omicron variant and failure to reach population vaccination goals. Additional options for outpatient treatment of mild-moderate disease are therefore needed, and oral options will be particularly helpful in improving access to treatment across diverse communities in the US. Multiple outpatient treatments for COVID-19 are in varying stages of development, and evaluation of the rapidly evolving evidence of the comparative clinical effectiveness and potential cost

effectiveness at different pricing levels for highly anticipated emerging outpatient treatments will be important to guide clinical practice and policy decision-making.

Report Aim

Due to the unprecedented immediacy and scale of COVID-19, ICER recognizes the need for a timely review to inform policy and practice but also that full information on all treatments and outcomes of interest may not be available at the time of review. The treatments for this Report were chosen based on the timing of expected availability of clinical evidence, expected Food and Drug Administration (FDA) approval, and clinical expert input on which treatments would be likely to have the greatest relevance for patients and clinicians. Using these criteria, we selected to evaluate the health and economic outcomes of sotrovimab, molnupiravir, nirmatrelvir/ritonavir (Paxlovid™), and fluvoxamine for the treatment of mild-to-moderate COVID-19 among patients at high risk of progression to severe disease. Our scoping document[22] had included an additional drug, casirivimab/imdevimab (REGEN-COV). However, due to its markedly lower activity against the Omicron variant, currently the most prevalent variant in the US, the FDA revoked its Emergency Use Authorization (EUA) and, thus, this Report will focus on the other drugs of interest.[21] A discussion of the clinical evidence on REGEN-COV is available in Section D2 of the Supplement. In addition, shortly before the posting of this Report, the FDA granted EUA for remdesivir for this setting. ICER will make a determination regarding the inclusion of remdesivir in this Report at a later date.

Description of Interventions

Sotrovimab is a recombinant human monoclonal antibody administered as a onetime 500 mg intravenous (IV) infusion. It works by binding to the receptor-binding domain of the SARS-CoV-2 spike protein, inhibiting either attachment or fusion to human cells. Molnupiravir is ribonucleoside analog that inhibits SARS-CoV-2 viral replication by being incorporated into viral ribonucleic acid (RNA), resulting in an accumulation of errors in the viral genome. Molnupiravir is administered orally at a dose of 800 mg every 12 hours for five days. Nirmatrelvir/ritonavir (Paxlovid) is a combination treatment. Nirmatrelvir is a protease inhibitor that blocks the activity of the SARS-CoV-2-3CL protease, an enzyme necessary to produce other functional SARS-CoV-2 proteins. Ritonavir is used in this combination to slow the metabolism of nirmatrelvir, thereby increasing nirmatrelvir concentrations in the body. Ritonavir has a large number of known drug-drug interactions that pose a safety risk.[9,23] Paxlovid is administered orally at a dose of 300 mg of nirmatrelvir and 100 mg of ritonavir every 12 hours for five days. Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) and a σ-1 receptor agonist.[24] While fluvoxamine's exact mechanism of action for the treatment of COVID-19 is unknown, one theory is that by binding to the σ-1 receptor, fluvoxamine modulates cytokine production and dampens the body's excessive inflammatory response to COVID-19.[25] Fluvoxamine is administered orally at a dose of 100 mg twice daily for 10 days.

Sotrovimab, molnupiravir, and Paxlovid are available under EUA from the FDA. Sotrovimab is currently approved only for IV administration but is being tested as an intramuscular injection.[26,27] Fluvoxamine is already available as a generic medication labeled for the treatment of obsessive-compulsive disorder, but an EUA is being pursued by a university-based group for its use in COVID-19.[28]

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Route of Delivery	Dosage and Administration	EUA Population
Sotrovimab	Anti-SARS-CoV-2 spike protein	IV	One 500 mg dose	Individuals ≥12 years old, weighing ≥40 kg with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19
Molnupiravir	Promotes RNA replication error	Oral	800 mg every 12 hours for 5 days	Individuals ≥18 years old, with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19; not recommended for pregnant individuals
Paxlovid	Protease inhibitor	Oral	300 mg of nirmatrelvir and 100 mg of ritonavir, every 12 hours for 5 days	Individuals ≥12 years old, weighing ≥40 kg with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19
Fluvoxamine	Unknown, potentially σ-1 receptor agonist	Oral	100 mg twice daily for 10 days	EUA is being reviewed; but in the pivotal trial,[3] individuals were ≥18 years old, with mild-to-moderate COVID-19, at high risk for progression to severe COVID-19

EUA: Emergency Use Authorization, IV: intravenous, kg: kilogram, mg: milligram, RNA: ribonucleic acid

Other Potential Treatments

Outside of the treatments considered by this Report, there are few options for non-hospitalized outpatients with mild-to-moderate disease who are at high risk of progression to severe disease. The lack of treatment options is accentuated since the EUA for REGEN-COV and another dual monoclonal antibody therapy, bamlanivimab plus etesevimab, has been revoked due to low activity against the Omicron variant. Two other potential treatments in this setting include remdesivir and inhaled budesonide. For these patients, remdesivir 200 mg IV on day one followed by 100 mg IV on days two and three is recommended in clinical guidelines from the Infectious Diseases Society of America and the National Institutes of Health.[21,29] An open-label randomized controlled trial (RCT) of 800 µg twice daily of inhaled budesonide for 14 days administered to non-hospitalized participants who were ≥65 years old or ≥50 years with comorbidities and who had mild COVID-19, found improved self-reported time to recovery but did not statistically reduce hospital admissions or deaths. At this time, budesonide has not been recommended by the Infectious Diseases Society

of America or the National Institutes of Health for our population of interest.[21,29] See Section C of the Supplement for further details regarding clinical guidelines.

2. Patient and Caregiver Perspectives

We spoke with three patients, a physician-scientist who maintains a COVID-19 patient registry to track longitudinal quality-of-life trends, and the Chief Executive Officer of Solve ME, a non-profit organization whose goal is to promote research on chronic fatigue and long-term COVID-19. We supplemented our understanding with a published systematic review that documented the diversity of symptoms associated with COVID-19.[30]

Patients mentioned the importance of comorbid respiratory conditions (e.g., chronic obstructive pulmonary disease, asthma, and being an ex-smoker) that exacerbated their experience of COVID-19 symptoms. For instance, one patient described her difficulty in being transported to the hospital with their existing supplemental oxygen support that she uses for her chronic obstructive pulmonary disease. A patient with asthma mentioned that COVID-19 greatly exacerbated her shortness of breath causing her to feel like she was "unable to breathe" and "about to faint" while carrying out activities of daily living.

Caregivers were heavily involved with supporting activities of daily living after patients were discharged from the hospital. Caregivers supported activities such as preparing meals, bathing, and providing care for other household members who were previously cared for by the patient with COVID-19. A complicating factor for caregivers of COVID-19 patients was that they themselves may have been infected at the same time as the patient, which would greatly limit their own capacity to provide care. If the caregiver were not infected, they would need to exercise particular caution to reduce the risk of infection. Adding to this, households with members not eligible to be vaccinated or with members who were at higher risk from COVID-19 faced greater care impact and disruptions to daily life due to greater need for isolation.

Patients endorsed averting death as being the most important outcome. Patients also endorsed the restoration of their ability to carry out activities of daily living as being very important. A systematic review of quality of life and symptoms associated with COVID-19 documented a large number of symptoms associated with COVID-19, with fever, muscle pain, cough, shortness of breath, and diarrhea being the most common.[30] Additionally, the study noted that symptoms may persist for months after infection, with respiratory symptoms, fatigue, and reduced mental health being some of the most common longer-term symptoms.

In terms of their experience with treatment, a patient reported appreciating the near immediate restoration of their ability to taste and to smell. At the time that the interviews were conducted, only monoclonal antibodies were available for the drugs of interest. However, patients expressed a preference for oral agents, and intramuscular and subcutaneous injections over IV infusions. Patients ultimately expressed willingness to use whichever treatment was most effective, regardless of mode of administration.

Patients with employer-sponsored health insurance (in contrast to patients dually eligible for Medicare and Medicaid) mentioned the substantial financial burden of COVID-19 hospitalization. Whereas COVID-19 testing and vaccines are covered without out-of-pocket costs, there is no federal requirement that plans fully cover the costs of COVID-19 treatment. Earlier in the pandemic, many individual health plans have waived cost-sharing for treatment either voluntarily or due to state requirement.[31] However, the majority of the voluntarily cost-sharing waivers have now expired. Research supports the potentially large financial burden of COVID-19 hospitalizations. Even early in the pandemic, when cost-sharing waivers were likely more common, out-of-pocket costs for hospitalizations for COVID-19 for privately insured and Medicare beneficiaries were $788 and $277.[32] Among those who did not have hospital facility cost-sharing waived in that study, out-of-pocket costs for hospitalizations for COVID-19 for privately insured and Medicare beneficiaries were $3,840 and $1,536, respectively.

Stakeholders also discussed the need for easy access to rapid diagnostic tests so that patients could be treated early. Currently, treatment is constrained in part by lack of availability of rapid testing, leading to a potential undercounting of COVID-19 cases. Inequities in diagnostic access could amplify inequities in treatment. Further, with constrained diagnostic capacity, patients need to rely on self-assessment of symptoms. Indeed, several patients indicated that difficulty breathing was a key reason for initially seeking treatment.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Details on our systematic literature review methodology may be found in Section D1 of the Supplement.

Scope of Review

In January 2022, the FDA revoked the EUA for REGEN-COV due to greatly reduced activity of the agent against the Omicron variant. This review focuses on assessing the evidence of the clinical effectiveness of sotrovimab, molnupiravir, Paxlovid, and fluvoxamine for non-hospitalized patients with mild-to-moderate COVID-19. These four agents either have demonstrated activity against the Omicron variant or have presumed activity due to mechanism of action. The full scope of the review is in Section D1 of the Supplement. A discussion of the clinical effectiveness of REGEN-COV is also available in Section D2 of the Supplement.

Evidence Base

Key information about the pivotal trials for each agent, including information on study size, duration, patient characteristics, and outcome measures is shown in Table 3.1.

Sotrovimab

We identified two RCTs that met our inclusion criteria for sotrovimab. COMET-ICE is a Phase III trial that randomized 1,057 patients to 500 mg IV single infusion administration of sotrovimab or placebo.[33] At the time of this Report, only a pre-specified interim data analysis has been published. Evidence for COMET-ICE was acquired from a conference poster and a non-peer-reviewed pre-print.[2,4] We also examined a non-peer-reviewed pre-print of a real-world study that assessed the effectiveness of sotrovimab in non-hospitalized patients diagnosed with mild-to-moderate severity of COVID-19 (Delta variant) compared to a propensity-matched cohort.[34] This observational real-world study included patients from an integrated health system of 40 hospitals located in Pennsylvania.[34] We included this study in our review as it may be more generalizable than the pivotal trials in our review. More details on the design and outcomes for this real-world study are in Section D2 and Tables D23 and D29-D30 of the Supplement.

COMET-TAIL is a non-inferiority trial that randomized 983 patients to 500 mg intramuscular or 500 mg IV single infusion of sotrovimab.[27] At the time of this Report, data for COMET-TAIL only exists in the form of a press release; as such, this Report will mainly focus on the data for the IV version of sotrovimab from the COMET-ICE trial.

COMET-ICE

COMET-ICE was a Phase III randomized, placebo-controlled multi-center trial with 57 clinical sites: 45 in the US, six in Brazil, three in Spain, two in Canada, and one in Peru.[4] Patients included in the study were unvaccinated adults with a high risk of progression to severe COVID-19 that had COVID-19 symptom onset as well as a polymerase chain reaction (PCR) or antigen test within five days of randomization.[33] Obesity was the most common qualifying risk factor in the COMET-ICE trial population (63%),[2] which is consistent with some of the other trials in our review.

A total of 1,057 adult participants were randomly assigned to either of the two treatment arms with 528 participants receiving sotrovimab and 527 participants receiving placebo. The median age of participants in COMET-ICE at baseline was 53 years, and 54% were female.[2] Most participants were White (87%) and 8% were Black; 65% of participants identified as Hispanic or Latino.

The primary efficacy outcome of COMET-ICE was the proportion of patients with COVID-19 progression that resulted in hospitalization for more than 24 hours or death through day 29.[4] The main secondary outcome of the trial was a composite of emergency department visit, hospitalization of any duration, or death due to any cause by day 29.[4] The trial was stopped early due to positive results.

COMET-TAIL

COMET-TAIL is a Phase III randomized, open-label, multi-center, non-inferiority trial designed to evaluate the efficacy, safety, and tolerability of the intramuscular administration of sotrovimab.[27] The trial included adults and adolescents (12 years and up) with (n=376) participants receiving the 500 mg dose of intramuscular sotrovimab and (n=378) participants receiving the 500 mg dose of IV sotrovimab.[35] For the primary endpoint, a 3.5% non-inferiority margin for the upper-bound of the 95% confidence interval (CI) was established for the trial in conjunction with input from the FDA.[27]

Molnupiravir

We identified a Phase IIa and a Phase II/III randomized, double-blind, placebo-controlled trial of molnupiravir. The Phase IIa study evaluated the effect of molnupiravir on viral load, safety, and tolerability.[36] The pivotal trial for molnupiravir, MOVe-OUT, included a Phase II portion and a Phase III portion. The Phase II portion served as a dose-finding study and was followed by the Phase III portion of the study, which evaluated the 800 mg dose of molnupiravir (the authorized dose in the EUA).[37] In this review, we focus on the Phase III portion of the trial and refer to this Phase III portion as "MOVe-OUT." We obtained results from this Phase III portion from an interim data analysis and a final data analysis from an FDA Advisory Committee Meeting and from a peer-reviewed publication.[5,7,38,8] Information on the Phase IIa trial is included in Section D2 and Tables D5, D10, D15, and D22 of the Supplement.

MOVe-OUT

MOVe-OUT was a randomized, double-blind, placebo-controlled Phase III trial of molnupiravir. Patient enrollment took place globally with 46% of the participants being recruited from Latin America, 33% from Europe, 12% from Africa, and 3% from Asia.[8] Patients were included in this trial if they were unvaccinated, at high risk for progression to severe COVID-19 and had a laboratory-confirmed diagnosis of COVID-19 as well as symptom onset within five days of randomization. Obesity was the most common qualifying risk factor for progression of disease (74%).[8]

A total of 1,433 patients were enrolled, short of the 1,500-enrollment goal, after a decision was made to stop recruiting patients based on positive interim results. Participants were randomized to 800 mg of molnupiravir or placebo twice daily for five days. The median age of participants in the full-population analysis of the MOVe-OUT trial at baseline was 43 years, and 51% were female.[8] Most of the participants in the trial were White (57%), 5% were Black, and 50% of the participants identified as Hispanic or Latino.[8] The primary outcome assessed in MOVe-OUT was the percentage of patients that became hospitalized and/or died from the time of randomization through day 29 and incidence of adverse events. The secondary outcome for the study is a patient-reported outcome of improvement or progression of COVID-19 signs and symptoms through day 29, which was reported by measuring the severity of disease at different timepoints using the World Health Organization (WHO) 11-point scale.[8]

Paxlovid

Evidence to inform our review of Paxlovid in non-hospitalized patients came from one Phase II/III randomized clinical trial, EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients).[39] At the time of this Report, information on the EPIC-HR trial was limited to a press release from the manufacturer and the EUA fact sheet. An additional Phase II/III trial, EPIC-SR (Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients) is described in Section D2 and Tables D5, D12, and D19 of the Supplement.

The EPIC-HR trial was a multi-center Phase III trial that randomized 2,246 patients to 400 mg oral tablets of Paxlovid or placebo twice daily for five days (Table 3.1).[6] Non-hospitalized adults were eligible to participate if they had a positive SARS-CoV-2 test with symptom onset no more than five days prior to randomization and had at least one risk factor for high risk of progression to severe disease. Patients were excluded if they had been admitted to a hospital or had received any treatments for COVID-19 prior to randomization, had received a vaccination for SARS-CoV-2, had a known human immunodeficiency virus (HIV) infection with a viral load greater than 400 copies/mL or taking certain medications for HIV treatment, or were pregnant, breastfeeding, or could become pregnant. The mean age of the participants in the EPIC-HR trial at baseline was 46 years, and 49% were female. The majority (72%) of participants were White and a small minority (5%) were Black. The most common risk factor for severe COVID-19 was obesity (36%) (Table 3.1).[9] The primary

outcome of EPIC-HR was COVID-19-related hospitalization or death for any cause through day 28. Secondary outcomes included adverse events, COVID-19 symptom severity and time to resolution, pharmacokinetics, viral load, and hospital and intensive care unit (ICU) length of stay.

Fluvoxamine

Our review of fluvoxamine was informed primarily by one randomized placebo-controlled Phase III trial conducted at 11 sites in Brazil (TOGETHER). Two additional small US-based trials of fluvoxamine, STOP-COVID and STOP-COVID 2, were also identified and are reviewed in Section D2 and Tables D5, D8, D13, and D20 of the Supplement.

The TOGETHER trial was an adaptive platform-based trial focused on evaluating repurposed drugs (i.e., drugs already marketed for other indications) with anti-inflammatory properties for mild COVID-19 symptoms.[40] In the TOGETHER trial, 1,497 patients were randomized to receive 100 mg fluvoxamine or placebo twice daily for 10 days (Table 3.1).[3] Patients 18 years and older were eligible to participate if they presented to a participating outpatient care site with symptoms consistent with COVID-19 that began within seven days, had a positive rapid antigen test for SARS-CoV-2, and had at least one risk factor for high risk of progression to severe disease. Patients were excluded if they had been hospitalized previously for COVID-19, had been vaccinated for SARS-CoV-2, had any other concomitant infections, were currently using SSRIs, or had uncontrolled psychiatric disorders or suicidal ideation consistent with the FDA black box warning for fluvoxamine.[41]

Mean age of the participants in the TOGETHER trial at baseline was 50 years, and 58% were female. The vast majority (96%) of participants were mixed race. The most common risk factor for severe COVID-19 was age ≥50 years (44%) (Table 3.1). The primary outcome of the trial was a composite endpoint of COVID-19-related admission to an emergency setting (defined as observation for more than six hours) or referral to tertiary hospital due to COVID-19 progression within 28 days. Retention in a hospital-like setting was described as an adequate proxy for conventional hospitalization given that the wave of COVID-19 infection in Brazil during the study period (June 2020 to August 2021) exceeded conventional hospital capacity. At that time, Brazil implemented hospital-like services in emergency settings that provided care including oxygen support and mechanical ventilation.[3] Secondary endpoints of the TOGETHER trial included viral clearance, time to symptom resolution, hospital length of stay, and adverse events.

Table 3.1. Overview of Key RCTs in Non-Hospitalized Adults with Mild-to-Moderate COVID-19 at High Risk for Severe Disease[2-6,8,9,26,39,40,42]

Intervention/Trial	Inclusion/Exclusion Criteria	Outcomes	Baseline Characteristics	Trial Status
Sotrovimab COMET-ICE Phase III N=1,057 Enrollment: 8/27/20-3/21	Inclusion: -Symptom onset within 5 days Exclusion: -Prior COVID-19 vaccination -Pregnancy, breastfeeding, or could become pregnant -Signs and symptoms of severe/critical disease	Primary: -COVID-19 progression and hospitalization (>24 hours) or death through day 29 Secondary: -ED visit, hospitalization of any duration, or death due to any cause by day 29 -Progression to severe/critical disease	-Age (median): 53 -Gender (female): 54% -Race/ethnicity: 87% White, 8% Black, 4% Asian, <1% American Indian or Alaska Native, 65% Hispanic -92% US enrollment -Risk factors: BMI ≥30 60%; age ≥55 years 47%; diabetes 22%	Complete Main source(s): Gupta 2021 Pre-Print
Molnupiravir MOVe-OUT Phase III N=1,433 Enrollment: 5/6/21-10/2/21	Inclusion: -Symptom onset within 5 days Exclusion: -Unwillingness to use contraception at least 4 days after treatment -Prior COVID-19 vaccination -Pregnancy, breastfeeding, or could become pregnant -HBV or HCV infection with complications	Primary: -COVID-19-related hospitalization or death from any cause through day 29 -Incidence of adverse events Secondary: -WHO 11-point clinical progression scale	-Age (median): 43 -Gender (female): 51% -Race/ethnicity: 57% White, 7% American Indian or Alaska Native 7%, 5% Black, 3% Asian, 50% Hispanic -6% US enrollment -Risk factors: BMI ≥30 74%; age >60 years 17%; diabetes 16%	Complete Main source(s): Bernal NEJM 2021
Paxlovid EPIC-HR Phase II/III N=2,246 Enrollment: 7/21-11/4/21	Inclusion: -Symptom onset within 5 days Exclusion: -Prior COVID-19 infection or vaccination -Pregnancy, breastfeeding, or could become pregnant -HIV infection	Primary: -COVID-19-related hospitalization or death from any cause through day 28 Secondary: -Adverse events -Symptom severity and time to resolution -Viral load -Hospital or intensive care LOS	-Age (mean): 46 -Gender (female): 49% -Race/ethnicity: 72% White, 5% Black, 14% Asian, 45% Hispanic -41% US enrollment -Risk factors: BMI ≥30 36%; age >60 years 20%; diabetes 12%	Complete Main source(s): -Paxlovid EUA document -Pfizer press release 12/14/21
Fluvoxamine TOGETHER Phase III Adaptive Trial N=1,497 Enrollment: 1/20/21-9/9/21	Inclusion: -Symptom onset within 7 days Exclusion: -Prior COVID-19 vaccination or hospitalization -Current use of SSRIs; uncontrolled psychiatric disorders or suicidal ideation	Primary: -COVID-19-related admission to an emergency setting or referral to tertiary hospital within 28 days Secondary: -Viral clearance -Time to symptom resolution -Hospital LOS -Adverse events	-Age (median): 50 -Gender (female): 58% -Race/ethnicity: 96% mixed, 1% White, 1% Black, 3% unknown -0% US enrollment -Risk factors: BMI ≥30 31%; age ≥50 years 44%; Type 2 diabetes 13%	Ongoing (interim data)* Main source(s): Reis Lancet 2021

BMI: body mass index, ED: emergency department, EUA: Emergency Use Authorization, HBV/HCV: hepatitis B/C virus, HIV: human immunodeficiency virus, LOS: length of stay, N: total number, SSRI: selective serotonin reuptake inhibitor, WHO: World Health Organization

*Our data represents the results from the entire population, after the trial's data safety monitoring committee recommended that recruitment be stopped after the study met prespecified superiority criterion for the primary endpoint trial. However, the study investigators informed us that they are continuing the study to evaluate secondary outcomes.

3.2. Results

Clinical Benefits and Harms

Table 3.2 summarizes key clinical benefits from the Phase III trials of the drugs of interest.

Table 3.2. Key Trial Results[2-9]

Intervention (Trial)	Hospitalization or Death from Any Cause, n/N (%)		Mortality, n/N (%)		Change in Viral Load from Baseline, log10 Copies/mL (95% CI)	
	Intervention	Placebo	Intervention	Placebo	Intervention	Placebo
Sotrovimab (COMET-ICE)	6/528 (1.1)	30/529 (5.8)	0/528 (0)	2/529 (0.3)	Difference from placebo: -0.232‡	
Molnupiravir (MOVe-OUT)	48/709 (6.8)	68/699 (9.7)	1/709 (0.1)	9/699 (1.3)	Difference from placebo: -0.33 (-0.5, -0.16)§	
Paxlovid (EPIC-HR)	8/1,039 (0.8)	66/1,046 (6.3)	0/1,039 (0)	12/1,046 (1.1)	Difference from placebo: -0.93§	
Fluvoxamine (TOGETHER)	79/741 (11)*	119/756 (16)*	17/741 (2.3)	25/756 (3.3)	NR	NR

CI: confidence interval, mL: milliliter, n: number, N: total number, NR: not reported
*Observed in a COVID-19 emergency setting (for more than six hours) or hospitalized.
†Least squares mean (standard error).
‡Mean difference from placebo reported on day eight.
§Reported on day five.

Sotrovimab

In COMET-ICE, 6/528 (1%) of participants who received sotrovimab and 30/529 (6%) of participants who received placebo progressed to hospitalization or death by day 29, a 79% (95% CI: 50% to 91%) relative risk reduction in favor of sotrovimab (Table 3.2).[4]

Mortality by day 29 did not differ between the two groups.[4] No deaths occurred in the treatment arm while two deaths were reported in the placebo arm; of the two deaths that occurred in the placebo arm, one of the patients died without being hospitalized.[4] Sotrovimab was associated with a 66% reduction in the composite outcome of emergency department visit, hospitalization, or death. Among patients hospitalized, none of the participants in the sotrovimab group required high-flow oxygen or mechanical ventilation while 10 patients in the placebo group required high-flow oxygen and four patients were placed on mechanical ventilation. Overall, in the safety population, the incidence of any adverse or infusion-related reactions was similar in the treatment and placebo group. Adverse events occurred in 11/523 (2%) of participants in the sotrovimab arm and in 32/526 (6%) of participants in the placebo arm. The most notable disease-specific adverse event was COVID-19 pneumonia, which occurred in 5/523 (<1%) of patients in the sotrovimab arm and in 22/526 (4%) of patients in the placebo arm.[4]

A recent real-world study by Huang 2021 corroborates the evidence in COMET-ICE and supports the effectiveness of sotrovimab against the Delta variant.[34] The primary outcome for the real-world study was hospitalization or death by day 28. Sixteen out of 311 (5.1%) patients who received sotrovimab experienced the primary outcome compared to 174/2,046 (8.5%) patients in the placebo arm by day 28 (RR: 0.60, 95% CI: 0.37 to 1.00, p=0.05). This difference in the primary outcome was mostly driven by higher mortality in the placebo arm (60/2,046 [2.9%] in the placebo arm compared to zero deaths in the treatment arm).[34] Additional details from this real-world study are included in Section D2 and Tables D23 and D29-D30 of the Supplement.

In COMET-TAIL, 2.7% of patients in the intramuscular administration arm of sotrovimab progressed to hospitalization (greater than 24 hours) or death compared to 1.3% of patients in the IV administration arm.[27] The 500 mg intramuscular administration of sotrovimab was determined to be equivalent (non-inferior) to the 500 mg IV administration based on an adjusted difference of 1.07% (95% CI: -1.25% to 3.39%), which is below the pre-specified 3.5% non-inferiority margin.[27] The risk of hospitalization or death in the IV arm was consistent with the risk in the IV arm in COMET-ICE. Of note, the evidence from COMET-TAIL only exists in the form of a press release.

Molnupiravir

In the full-population analysis of the MOVe-Out trial (N=1,433), 48/709 (6.8%) of participants in the molnupiravir group and 68/699 (9.7%) of participants in the placebo group had been hospitalized or were dead by day 29 following randomization, a 30% (no 95% CI reported) relative risk reduction in favor of molnupiravir (Table 3.2).[8] One death occurred in the treatment arm and nine deaths occurred in the placebo arm; the patient who died in the treatment arm had metastatic cancer and died due to multiorgan failure from COVID-19. No formal statistical testing was performed for this relatively rare outcome of death, other than as part of the composite outcome with hospitalization described above.

At the time of the interim analysis (N=775), the primary outcome was more favorable; 28/385 (7.3%) of participants in the molnupiravir group and 53/377 (14.1%) of participants in the placebo group were hospitalized or dead by day 29 following randomization, a relative risk reduction of 48%.[8] This represents a decrease in the reported efficacy for the primary endpoint from the interim analysis to the full population analysis of 18 percentage points in relative risk reduction. Similarly, the absolute risk difference dropped from 6.8% (95% CI: -11.3 to -2.4) in the interim analysis to 3% (95% CI: -5.9 to -0.1) in the full population analysis (Table 3.1).[8]

The incidence of adverse events was higher in the placebo group due to the higher incidence of COVID-19 complications. A total of 216 patients (30.4%) in the molnupiravir arm had one or more adverse events compared to 231 patients (33%) in the placebo arm. Participants in the treatment arm were also less likely to discontinue their treatment regimen due to an adverse event, an

outcome that occurred in 10 patients (1.4%) in the treatment arm and in 20 patients (2.9%) in the placebo arm (Table 3.3).[8]

Molnupiravir is also suspected to cause embryo-fetal toxicity and bone and cartilage toxicity. It is not recommended for use during pregnancy and is not authorized for use for patients under 18 years of age.[43] While molnupiravir's mechanism of action (causing viral mutagenesis) raised concerns with mutagenicity in initial in-vitro assays,[44] subsequent in-vivo animals assays and the short course of therapy has caused the FDA to classify molnupiravir as "low risk" for genotoxicity.[45]

Paxlovid

At the time of this Report, full results from the EPIC-HR trial were not available. The primary endpoint of the EPIC-HR trial was calculated in the modified intention-to-treat analysis population, which was defined as the participants dosed within five days of symptom onset who did not receive previous monoclonal antibody treatment (n=2,085). In this analysis, the proportion of patients with a COVID-19-related hospitalization or death through day 28 was 8/1,039 (0.8%) in the Paxlovid group and 66/1,046 (6.3%) in the placebo group, an 88% relative risk reduction (no CI provided) and an absolute reduction of 5.62% (95% CI: -7.21, -4.03, Kaplan-Meier estimated) (Table 3.2).

In the EPIC-HR trial, adverse events that occurred more frequently in the Paxlovid group than the placebo group included distorted sense of smell (6%), diarrhea (3%), hypertension (1%), and muscle pain (1%). Discontinuation due to adverse events occurred in 2% of participants in the Paxlovid group and 4% in the placebo group.[9]

Fluvoxamine

In the TOGETHER trial, 79/741 (11%) of participants in the fluvoxamine group (intention-to-treat analysis) were observed in a COVID-19 emergency setting (for more than six hours) or transferred to a hospital compared to 119/756 (16%) of participants in the placebo group (relative risk reduction 32%, 95% CI: 12% to 48%) (Table 3.2).[3] The observed difference in the primary endpoint between fluvoxamine and placebo was driven largely by the proportion of patients observed in an emergency setting (1% in the fluvoxamine vs. 5% in the placebo group, p=0.0001), while rates of hospitalization (all cause or COVID-19-related) did not differ between groups. There were also no statistically significant differences in viral clearance, time to hospitalization, hospital length of stay, death, or mechanical ventilation between the two groups.

Adherence to both fluvoxamine and placebo treatment regimens (defined as adhering more than 80% of the time) was relatively low in the TOGETHER trial. See the "Uncertainty and Controversies Specific to Fluvoxamine" section for further discussion of potential reasons for non-adherence in this trial. Among patients taking fluvoxamine, 548/741 (74%) were adherent, compared to 619/758 (82%) for patients taking placebo.[3] In the per-protocol population, the relative risk reduction of the

primary endpoint was more favorable (relative risk reduction 66%, 95% CI: 46% to 79%) than in the intention-to-treat population. Furthermore, in the per-protocol analysis, there was one death (<1%) in the fluvoxamine group and 12 deaths (2%) in the placebo group (p=0.022). The exclusion of the relatively large number of non-adherent individuals can introduce bias in the per-protocol analysis. Therefore, we suggest that the intention-to-treat analysis be given greater consideration than the per-protocol analysis for informing clinical and policy decision-making.

In a recent systematic review with meta-analysis, the researchers judged that the primary composite outcome in the TOGETHER trial (observation in a COVID-19 emergency setting for more than six hours or hospitalization) was not comparable to the hospitalization outcome in the STOP-COVID 1 or STOP-COVID 2 trials and instead pooled data on emergency room visits or hospitalizations lasting >24 hours across the three trials.[46] In this pooled estimate, 88/1,093 (8.1%) in the fluvoxamine group had an emergency department visit or hospitalization lasting >24 hours compared to 121/1,103 (11%) in the control group (RR: 0.75; 95% CI: 0.58 to 0.97).

As noted earlier, in the TOGETHER trial, 84 (26%) participants in the fluvoxamine group and 64 (18%) participants in the placebo group discontinued due to treatment intolerability.[3] However, the risk for having any adverse event or a serious adverse event in the fluvoxamine arm is similar to the risk in the placebo arm of the TOGETHER trial as well as to the intervention arms in the Phase III trials for the other drugs of interest (Table 3.3).

Table 3.3. Key Adverse Events[2-6,8]

Intervention (Trial)	Any Adverse Event, n/N (%)		Serious Adverse Events, n/N (%)		Discontinuation Due to Adverse Event, n/N (%)	
	Intervention	Placebo	Intervention	Placebo	Intervention	Placebo
Sotrovimab (COMET-ICE)	114/523 (22)	123/526 (23)	11/523 (2)	32/526 (6)	0	0
Molnupiravir (MOVe-OUT)	216/710 (30)	231/701 (33)	49/710 (7)	67/701 (10)	10/710 (1)	20/701 (3)
Paxlovid (EPIC-HR)	255/1,109 (23)*	268/1,115 (24)*	18/1,109 (2)	74/1,115 (7)	23/1,109 (2)	47/1,115 (4)
Fluvoxamine (TOGETHER)	169/741 (23)†	188/756 (25)†	59/741 (8)	70/756 (9)	84/741 (26)	64/756 (18)‡

n: number, N: total number

*Treatment-emergent adverse event.

†Summed treatment-emergent adverse events of various severities.

‡Discontinuation due to side effects.

Subgroup Analyses and Heterogeneity

In the pivotal trials of the agents in this review, treatment effects across most subgroups were generally indistinguishable from the average treatment effect. In patients with diabetes in the MOVe-Out trial (full analysis set) of molnupiravir, patients treated with molnupiravir had slightly greater risk of being hospitalized or dying compared to the placebo arm (15.9% vs. 14.5%).[5]

We sought subpopulation data from manufacturers on the effectiveness of the interventions in subgroups of interest such as race, vaccination status, variant of concern, time since randomization, serum antibody status, and individual risk factors for progression to severe disease. Data was either not available or insufficient to assess differential effectiveness in these populations. In particular, we highlight the low representation of Black patients in the Phase III trials for molnupiravir and Paxlovid. This is problematic because Black populations are at higher risk of infection, hospitalization, and mortality due to COVID-19.[13]

Uncertainty and Controversies

While the clinical trials of all four agents demonstrate statistically significant benefits of treatment, there remains substantial uncertainty regarding the comparative effectiveness of each drug in the current US landscape. Some of this uncertainty is due to the preliminary nature of the evidence base, which for several drugs includes only data that has not yet progressed through peer review. In attempts to compare these drugs to each other, there are some differences in the composite outcome measures used, and differences in the spectrum of risk factors for progression to severe COVID-19 among different trial populations.

But perhaps the most notable foundation of the uncertainty in the evidence is the difficulty in interpreting the relevance of results of studies done in ex-US settings, during time periods with different COVID-19 variants dominating the clinical environment. This is not to criticize the design of the clinical trials of these drugs, nor should anyone expect studies done during a fast-moving pandemic to be able to provide high certainty in all areas. Clinical and policy decisions will need to be made given the best evidence available, yet it will be equally important for decision-makers to be aware of the limitations of the evidence and the key remaining questions that future studies should address. We expand on these issues further below.

Early Status of the Evidence Base

The evidence base for all four drugs remains at an early stage of maturity. As of January 2022, the Phase III RCT evidence for sotrovimab is only available as a pre-print (i.e., without peer review) and the evidence for Paxlovid is based on the manufacturer's press release and the EUA factsheet for health care providers.[6,9] This lack of data makes it difficult to fully evaluate these drugs. Illustrating the evolution of our understanding of treatment efficacy, in the molnupiravir Phase III trial, the

interim analysis reported a relative risk reduction of 48% in all-cause hospitalization or death while the full analysis reported a relative risk reduction of 30% (Table 3.2).[8] Such issues are compounded by each treatment being supported by only one Phase III RCT.

Lack of Comparability Across Trials for the Drugs of Interest

Substantial differences in patient populations across the Phase III trials preclude us from making direct comparisons across these trials. Sotrovimab and molnupiravir trials enrolled substantially larger proportions of individuals with obesity compared to the fluvoxamine and Paxlovid trials. The sotrovimab trial had greater proportions of individuals with diabetes than the molnupiravir, fluvoxamine, and Paxlovid trials. Clinical experts have advised that the current broad definition of "high-risk" outpatients contains groups that are at much higher risk, such as older individuals, than others, such as individuals with hypertension only. Further, as will be emphasized below, the large variability in the countries of recruitment and the timing of trial enrollment reduces study comparability.

Another factor in the uncertainty across trials is that they defined outcomes differently. The trials of sotrovimab, molnupiravir, and Paxlovid have very similar composite outcomes, but experienced clinical trial experts know that even identical composite outcomes in different trials are prone to differences in clinical record-keeping and other factors that can create unknown biases. In this review, the most obvious difference lies in the composite outcome measure for fluvoxamine compared to the other agents. The fluvoxamine TOGETHER trial appears to be the least comparable in this regard. The primary outcome in the fluvoxamine TOGETHER trial was retention in a COVID-19 emergency setting for more than six hours or transferred to a hospital. In contrast, the primary outcome for the Phase III trials for sotrovimab, molnupiravir, and Paxlovid was hospitalization or death. The authors of the TOGETHER trial, which was performed in Brazil, point out that the way they defined their composite outcome was driven by the limits on hospital capacity in that country during peak COVID-19 waves.[3] These limits meant that very ill patients were required to be held for long periods of time in emergency department settings rather than be admitted to hospital. This broader definition was described therefore as an adequate proxy for conventional hospitalization, but the comparability of these outcomes remains unclear. Further, while sotrovimab, molnupiravir, and Paxlovid reduced hospitalizations or death, fluvoxamine did not have a statistically significant effect on hospitalizations alone or death alone as secondary outcomes.

Generalizability of Results

The SARS-CoV-2 virus is rapidly evolving, with different variants appearing and gaining dominance in different parts of the world at different points in time. None of the Phase III trials reported inclusion of patients infected with the Omicron variant. Only the Phase III trial for molnupiravir (MOVe-OUT) reported inclusion of patients infected with the Delta variant. This rapid evolution

reduces the certainty with which we can apply results from trials conducted even as recently as one year ago to the current population of patients who will become infected with COVID-19 in the US now and in the future. As a result of these shifts, the relative effectiveness of treatments may vary. As an extreme example, as noted earlier, while REGEN-COV demonstrated high efficacy in its Phase III RCT and was the dominant outpatient treatment used for many months,[47] when the Omicron variant emerged, laboratory data indicated that REGEN-COV had limited activity against it, and distribution of the treatment was curtailed markedly and its EUA was revoked.[48,49] The clinical consequences of COVID-19 infection appear to be changing as well, with the Omicron variant leading to less severe disease compared to prior variants.[50] All else being equal, less severe disease will reduce the clinical and economic value of treatment, whereas if a more lethal variant were to emerge and become dominant, the relative effectiveness of outpatient treatments might lead to significantly greater absolute benefit across the population.

In addition to rapid evolution of SARS-CoV-2 affecting the generalizability of prior study findings, the population being treated in the studies we reviewed also differs from the full population of patients likely to be treated today. First, key trials for the drugs of interest either explicitly excluded individuals vaccinated against SARS-CoV-2 or were conducted at a time when few to no individuals were vaccinated. Compared to trial results among unvaccinated groups with comorbid risk factors, clinical experts have advised that it is likely that vaccinated groups with comorbid risk factors would have lower risks of serious infection progressing to a requirement for hospitalization, thereby reducing to some extent the relative and absolute benefit of treatment.

Second, individuals enrolled in the Phase III trials may be healthier than treated individuals in the real world. We identified nine real-world studies of populations treated with the drugs of interest or REGEN-COV.[34,51-58] See Section D2 and Tables D23-D32 of the Supplement for more details regarding these studies. When comparing the characteristics of the trial populations to the real-world study populations, we find that the trial populations were younger than those reported in real-world study populations, with ages ranging between 43 and 53 in the Phase III trials (Table 3.1), and 53 and 65 in the real-world studies we identified. Similarly, the trial populations were less likely to have chronic obstructive pulmonary disease, diabetes, chronic kidney disease, or liver disease than the treated populations in the real-world studies. These factors may be associated with the highest risks for severe COVID-19 disease.[59-62] Perhaps reflecting the lower-risk population in the clinical trials, the rates of hospitalization for the untreated COVID-19 population (i.e., placebo arm) in the Phase III trials—with the exception of fluvoxamine—were lower than in most of the control arms in these real-world studies (Table 3.2).

Lastly, study participants in the molnupiravir and fluvoxamine trials were primarily or exclusively outside of the US. This reduces the generalizability of results to the US population since countries may vary in prevalent SARS-CoV-2 variants, health care practices and infrastructure, and risk factors for developing COVID-19. Recent information from the Centers for Disease Control and Prevention

(CDC) suggests that in the current Omicron wave, the risk for hospitalization among known-infected individuals has been dropping well below the rates seen in the usual care arms of each of these agents.[50] Even among the trials of the agents themselves, there exist important differences in the background rate of hospitalization and death in the usual care arms. For example, the primary outcome rates for the usual care arm in the TOGETHER trial of fluvoxamine were substantially higher (16%) than in the Phase III trials for sotrovimab, molnupiravir, and Paxlovid (5.8 to 9.7%).

Uncertainty and Controversies Specific to Sotrovimab

As stated previously, the generalizability of trial data to real-world populations is limited. For sotrovimab, we had identified one real-world study, which evaluated the effectiveness of sotrovimab in a single academic center among patients infected with the Delta variant.[34] This study found lower effectiveness of sotrovimab in preventing hospitalization or death (relative risk reduction of 40%) compared to the key Phase III trial (COMET-ICE, relative risk reduction of 79%).

A press release reporting on the COMET-TAIL trial suggested that sotrovimab administered intramuscularly is not inferior to sotrovimab administered intravenously.[27] It is possible that intramuscular sotrovimab would displace IV sotrovimab due to ease of administration and could partially displace oral therapies due to the ease of one-time administration. However, there is currently a lack of data to fully evaluate the efficacy and safety of intramuscular sotrovimab.

Uncertainty and Controversies Specific to Molnupiravir

Aside from uncertainty illustrated by the change in estimated efficacy between the interim and final data from the Phase III trial, molnupiravir's mechanism of action also raises concerns that use of this drug could lead to new, viable viral variants. A briefing document prepared by FDA staff for the Antimicrobial Drugs Advisory Committee Meeting to judge molnupiravir's efficacy and safety contained additional data on the potential for molnupiravir to cause mutations that result in reduced viral susceptibility to host antibodies or other COVID-19 antiviral or antibody treatments.[63] In the Phase III MOVe-OUT trial, among the 12% of patients with full genome sequence data, there was a statistically significant increase in the viral mutation rate after the five day course of therapy, as compared to placebo. The briefing document also reported on findings from the Phase I and II studies suggesting that molnupiravir could cause mutations in the SARS-CoV-2 spike protein, a key determinant of host antibody and targeted monoclonal activity. Clinicians and policymakers will need to balance the concrete needs of an individual patient for treatment against the theoretical concerns that such treatment has for entire populations.

Uncertainty and Controversies Specific to Paxlovid

A key source of uncertainty with Paxlovid is the early status of the evidence base. At the time of this Report, the efficacy and safety of Paxlovid is principally supported by one study, the Phase III

EPIC-HR trial. Information from this study was pulled from a press release from the manufacturer and the EUA fact sheet. This limits our ability to fully evaluate the quality of the study, understand the generalizability of the results, and assess potential subgroup effects. Another potential, albeit theoretical, concern is that viral resistance to Paxlovid, a protease inhibitor, is possible as HIV has developed resistance to certain protease inhibitors.[64]

Uncertainty and Controversies Specific to Fluvoxamine

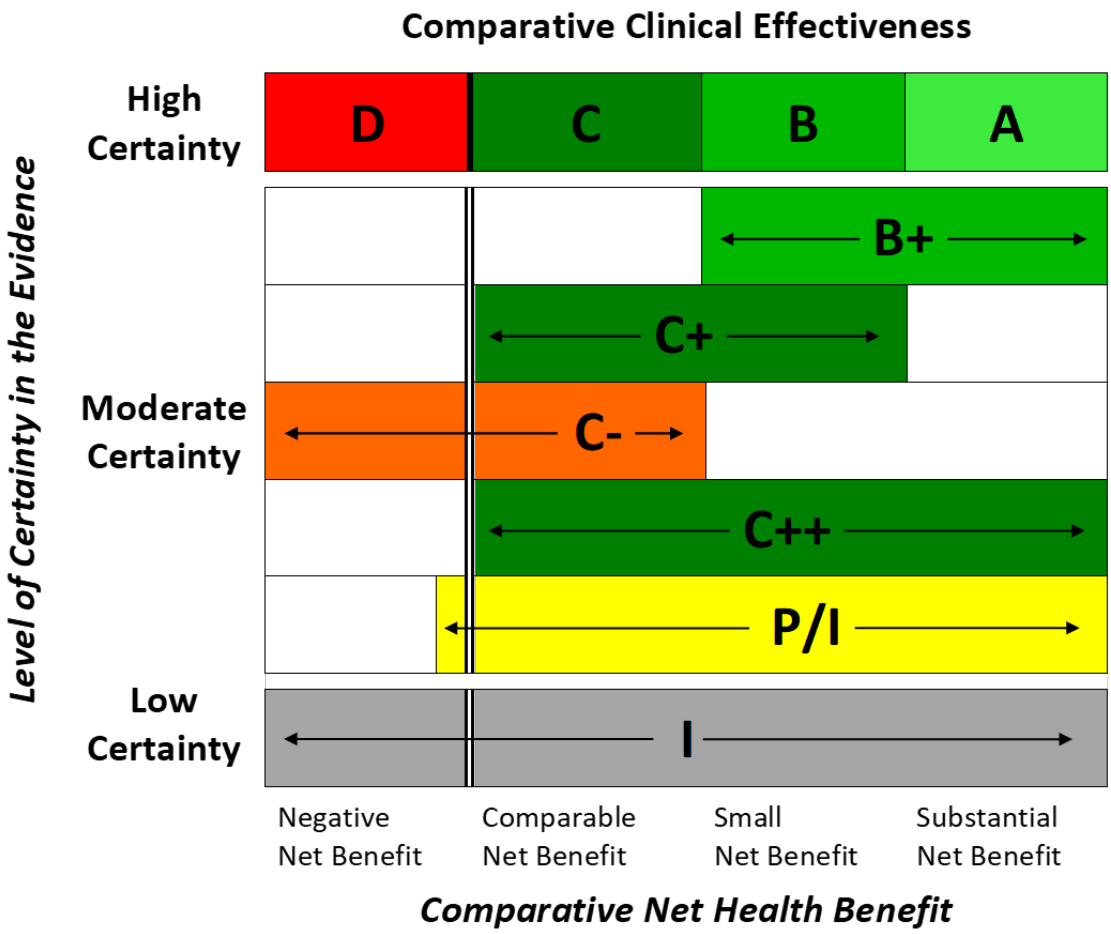
Aside from the issues that reduce comparability, it is possible that fluvoxamine may not help contain the population-level spread of COVID-19 as much as other treatment options. In contrast to the other drugs of interest, fluvoxamine treatment did not reduce patient viral load, so it is possible that treated patients could spread the disease for a longer time. This hypothesis was not tested in any of the trials.

An additional source of uncertainty specific to fluvoxamine is the large number of study participants who did not adhere to treatment in both the fluvoxamine (26%) and usual care (18%) arms. As noted earlier, there was a much higher relative risk reduction in the primary outcome in the per-protocol analysis (66%) as compared to the intention-to-treat analysis (32%). While the reasons for this lack of adherence are unknown, it is possible that the longer duration of treatment (10 days compared to five days for Paxlovid and molnupiravir) combined with many individuals' symptoms resolving before day 10,[65] contributes to lower reported adherence. Fluvoxamine is generally well-tolerated and similar numbers of participants stopped fluvoxamine (n=84) and placebo (n=64) owing to issues of tolerability. None of the Phase III trials for the other drugs of interest reported on adherence, so clinicians and policymakers will need to weigh the degree to which the per-protocol results for fluvoxamine should be considered in decision-making.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Sotrovimab

Sotrovimab significantly reduced the risk of hospitalization or death from any cause (relative risk reduction of 79%; 95% CI: 50% to 91%), with a 95% CI in favor of a larger benefit. The number of hospitalizations and deaths was low in the intervention and placebo arms, therefore a small change in these numbers would greatly affect the estimated relative risk. The treatment was generally well-tolerated and had low discontinuation rates. However, sotrovimab's efficacy and safety are supported by a limited and somewhat conflicting evidence base of one Phase III RCT and one observational study (which suggested lower efficacy of sotrovimab than in the RCT).[34] For these reasons, we judge that there is adequate evidence to demonstrate that sotrovimab provides at least an incremental net health benefit compared to usual care, but the true magnitude of that benefit cannot be determined given the current status of the evidence and the rapidly evolving COVID-19 landscape. The draft ICER Evidence Rating for sotrovimab is therefore "*Incremental or Better*" (B+).

Molnupiravir

Molnupiravir significantly reduced the risk of hospitalization or death from any cause (relative risk reduction of 30%; no 95% CI reported).[8] Determining the clinical relevance of this relatively small absolute benefit is further complicated by the likelihood of lower baseline risks for progression to serious illness with the Omicron variant, and by lower hospitalization rates in general in the US compared to overseas health systems. Theoretical concerns about an increased risk of evolution of new viral variants and potential side effects due to the mechanism of action also cloud the precision with which the overall net health benefit can be determined. We believe that when molnupiravir use is restricted to the FDA label (e.g., individuals 18 years and older, who are not pregnant, or breastfeeding and to a course of therapy of five days), much of this risk can be mitigated, but it does not seem unreasonable to assume that these risks may, on a population basis, negate the relatively small clinical benefits. For these reasons, we have assigned a draft ICER Evidence Rating for the overall net health benefits of molnupiravir of "*Comparable or Incremental*" (C+).

Paxlovid

Paxlovid significantly reduced the risk of hospitalization or death from any cause (relative risk reduction of 88%; no 95% CI reported). The treatment was generally well-tolerated and had low discontinuation rates. There are a large number of known drug interactions with ritonavir that presents a safety risk (due to its mechanism of action of inhibiting the cytochrome P450, family III, subfamily A [CYP3A] enzyme).[9] There was only one Phase III RCT to support Paxlovid's efficacy and safety. For these reasons, as with sotrovimab, we believe the evidence is adequate to demonstrate at least incremental net health benefit compared to usual care, but the true magnitude of that benefit cannot be determined given the current status of the evidence and the rapidly evolving

COVID-19 landscape. We have assigned a draft ICER Evidence Rating for the comparative clinical effectiveness of Paxlovid of "*Incremental or Better*" (B+).

Fluvoxamine

Fluvoxamine significantly reduced the risk of COVID-19-related emergency observation (more than six hours) or tertiary hospital stay (RR of 32%; 95% CI, 12% to 48%) in the TOGETHER trial.[3] However, there is uncertainty regarding fluvoxamine's efficacy in the US given the relatively wide CIs, differences in health care management and outcomes in Brazil versus the US, the lack of effect on hospitalizations alone, and the potential implications of a smaller US-based trial that was stopped early due to slowing recruitment and lack of efficacy.[66] Further, the relatively long duration of treatment (10 days in the largest trial) may lead to lower real-world adherence and effectiveness. There was a lower percentage of serious adverse events in the intervention arm compared to the placebo arm but there was a sizeable percentage of individuals who stopped treatment due to tolerability in both arms (11.3% and 8.4%, respectively). As an SSRI, fluvoxamine also carries an FDA drug class warning for increased risk of suicidal thinking for children, adolescents, and young adults taking antidepressants for major depressive disorder and other psychiatric disorders.[48] For these reasons, we do not feel we can have high certainty in the overall net health benefits of fluvoxamine and have assigned a draft ICER Evidence Rating of "*Comparable or Incremental*" (C+).

Table 3.4. Evidence Ratings

Treatment	Comparator	Evidence Rating
Sotrovimab	Usual care	B+
Molnupiravir*	Usual care	C+
Paxlovid	Usual care	B+
Fluvoxamine	Usual care	C+

*Note: Population excludes individuals who are pregnant or who have childbearing potential.

4. Long-Term Cost Effectiveness

4.1. Methods Overview

The primary aim of this analysis was to estimate the cost effectiveness of REGEN-COV, sotrovimab, molnupiravir, Paxlovid, and fluvoxamine for the treatment of COVID-19. At the posting of this draft Evidence Report, REGEN-COV was judged by US authorities to no longer be effective against the dominant Omicron COVID-19 variant. Therefore, economic analyses for REGEN-COV as an intervention are not included in this Report, but we have included those findings based on pre-Omicron data in Supplement E. We continue to use evidence from the usual care arm of the REGEN-COV pivotal trial to inform the comparator arm of our economic model due to its large percentage of US patients.

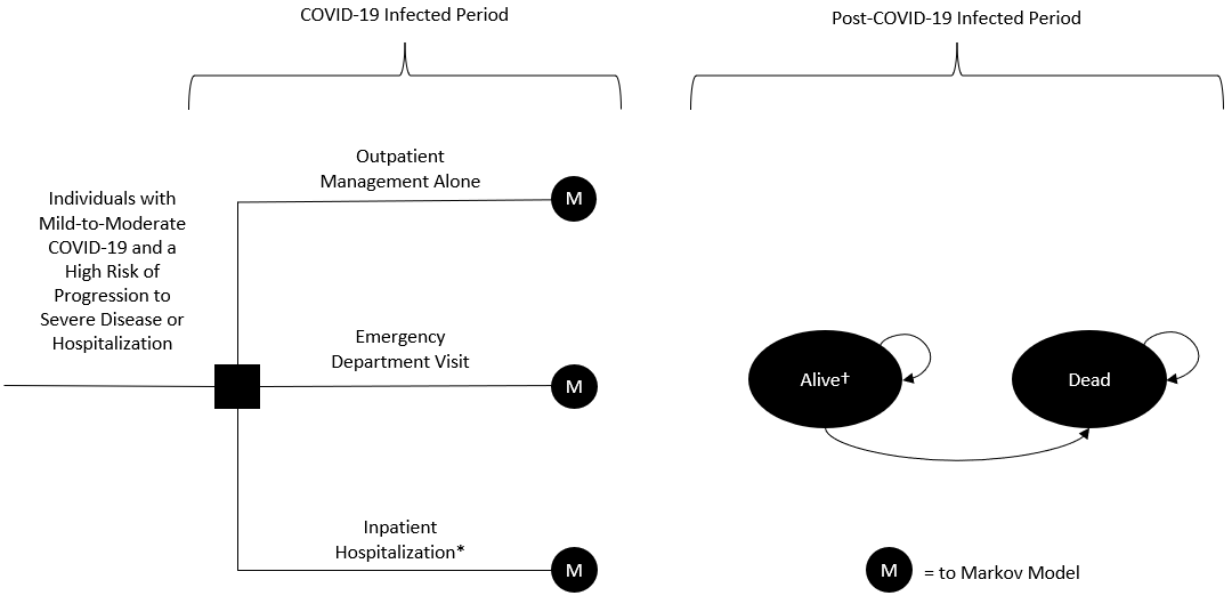
We developed a decision analytic model for this evaluation, informed by ICER's inpatient model for COVID-19,[67] key clinical trials, and other prior relevant economic models.[68-70] Additional components were added to the model structure to account for the outpatient setting of these interventions of interest. The base-case analysis utilized a lifetime time horizon, with future costs and outcomes discounted at 3% per year, and a health care sector perspective. Productivity changes and the potential for other indirect costs and effects were considered using a modified societal perspective as a scenario analysis.

The model focused on an intention-to-treat analysis, with a hypothetical cohort of patients with mild-to-moderate COVID-19 being treated in an outpatient setting entering the model. The target population mirrored that in the pivotal trials and consisted of individuals with mild-to-moderate COVID-19 who also had clinical characteristics denoting a high risk of progression to severe disease or hospitalization. The outcomes in the usual care arm of the model were derived as a weighted average (based on US sample size) across the control arms of the pivotal trials. Given these trials occurred prior to the emergence of the Omicron variant, it is likely these probabilities of hospitalization, respiratory support, and death may be high in comparison to the current landscape in the US. This approach would overvalue the cost effectiveness of these outpatient interventions. Another difference between the data in the trials and the likely real-world cost effectiveness of treatment is related to the vaccination status of patients in the pivotal trials. The key clinical trials enrolled primarily unvaccinated individuals with COVID-19. For our base case, we chose to model a population including both unvaccinated and vaccinated individuals to reflect what we believe will be the true real-world population of patients treated in the US once these treatments are widely available.

The model was developed in Microsoft Excel, Version 2111. A cohort of patients transitioned between health states during cycles of one month over a lifetime time horizon, modeling patients from treatment initiation until death. The model consisted of an acute phase decision tree followed

by a lifetime Markov model. The acute phase decision tree represented the COVID-19 infected period and tracked the highest setting of care received (e.g., outpatient management; emergency department visit; or inpatient hospitalization, with stratifications for level of respiratory support received). The acute phase decision tree had a duration of one month in alignment with the typical follow-up period from the pivotal trials. The lifetime Markov model consisted of health states for alive and dead. Individuals in the alive health state who did not experience any long-term sequelae of COVID-19 had costs and consequences characteristic of the general population throughout the Markov model. Individuals who experienced long-term sequelae of COVID-19 had additional utility decrements, costs, and mortality as suggested by evidence. Patients remained in the model until they died. All patients transitioned to death due to all-cause or COVID-19-specific mortality. The model structure is presented below in Figure 4.1.

Figure 4.1. Model Structure



*Model included stratifications based on level of respiratory support received.
†The alive health state tracked long-term sequelae and its associated costs and consequences, as data suggested.

Cost effectiveness was estimated using incremental cost-effectiveness ratios, with incremental analyses comparing each intervention to usual care. Health outcomes and costs were dependent on the highest setting of care received, respiratory support received if hospitalized, time spent in each health state, clinical events, adverse events, and direct medical costs. Model outcomes included costs, life years, quality-adjusted life years (QALYs), equal-value life years (evLYs), and inpatient hospitalizations.

The evidence for the comparator was based on a pooling of the usual care arms from each pivotal trial. Pooling was based on a weighted average across the trials, where the weight assigned was

based on the US sample size (i.e., trial overall sample size multiplied by the percent of trial participants from the US). If a model input from the usual care arm of an individual trial was not available, that trial was excluded from the pooling of comparator evidence for that input. If the input was missing from more than 50% of the weighted comparator, literature was used to estimate the model input for those trials that did not report the input. More detail on how missing data were accounted for in the pooling of comparator evidence is explained within the "Model Inputs" section of Supplement E.

4.2. Key Model Assumptions and Inputs

Our model includes several key assumptions stated in Table 4.1. Additional assumptions may be found in Supplement E.

Table 4.1. Key Model Assumptions

Assumption	Rationale
The comparator arm was consistent across all interventions studied. The evidence for the comparator was based on a pooling of the usual care arms from each pivotal trial. Pooling was based on a weighted average across the trials, where the weight assigned was based on the US sample size (i.e., trial overall sample size multiplied by the percent of trial participants from the US).	Pooling across the usual care arms from each pivotal trial provided a more generalizable finding to the outcomes experienced by patients receiving usual care by accounting for different time periods within the pandemic, patient populations, and variants.
The relative treatment effects reported in each trial were applied to the outcomes from the pooled usual care evidence. The relative effectiveness seen in the trial population was generalizable to the comparator arm in the model that was constructed based on pooling evidence across the usual care arms in the pivotal trials. If a trial did not report a specific treatment effect, or the reported treatment effect was not statistically significant, a treatment effect of 1.0 was assumed.	The systematic differences in the trial populations should not affect the relative effectiveness of any of the drugs relative to usual care. We did not compare the cost effectiveness between the interventions given the systematic differences in the trial populations and design.
The baseline characteristics of the cohort modeled was consistent across all intervention arms and the comparator arm. The baseline characteristics of the cohort modeled was based on a pooling of the baseline characteristics from each pivotal trial. Pooling was based on a weighted average across the trials, where the weight assigned was based on the US sample size (i.e., trial overall sample size multiplied by the percent of trial participants from the US).	The US population eligible for each treatment is expected to be similar based on clinical expert consultation. Pooling across each pivotal trial was likely to provide a more generalizable finding to the population of individuals with mild-to-moderate COVID-19 and a high risk of progression to severe disease or hospitalization.
Adjustments were made to the risk of hospitalization and death observed in the usual care arms in the pivotal trials to account for the effectiveness of the vaccine in reducing hospitalization and death for the percent of infected patients that were vaccinated.	The trials were either conducted prior to an available vaccine or predominately included unvaccinated individuals. Given that a vaccine is now available, more than 70% of US adults have received at least one dose[71] and the vaccine is effective at reducing hospitalization and death even for breakthrough cases,[72] the evidence from the trials was weighted by the effectiveness of the vaccine for those individuals who were infected but also vaccinated. Clinical experts advised that these treatments, once widely available, are unlikely to be reserved solely for unvaccinated patients, and, in fact, would likely be widely prescribed for patients who are not at high risk of progression, leading to lower absolute risks of hospitalization and death than those seen in the clinical trials.

Assumption	Rationale
Patients were hospitalized prior to dying from COVID-19. Any deaths averted between the intervention and the comparator arm resulted from reductions in the severity of the hospitalization associated with the treatment.	Deaths in patients who only received outpatient management or an emergency department visit are not common.[73] Further, evidence suggested an increased probability of death with higher levels of respiratory support required during the hospitalization.[74] Therefore, we modeled deaths averted indirectly based on hospitalizations averted and higher levels of respiratory support within a hospitalization averted. Trial estimates of the mortality in the intervention arm were not used given the small numbers and clinical rationale that the deaths averted should result from a treatment's effect on averting hospitalizations or reducing the severity of hospitalizations.
The model accounted for the long-term sequelae of COVID-19 for those who were discharged alive following a hospitalization that required mechanical ventilation. These long-term sequelae consisted of an additional disutility, cost, and mortality risk.	Recommendations in the US report the occurrence and features characteristic of the long-term sequelae possible after a COVID-19 infection.[70]

Key model inputs are described in Table 4.2. The population characteristics used in the model equated to a baseline age of 49 years, and 52% of the population was female. Recent data (from November 2021) suggest that approximately 17% of COVID-19 cases are among individuals who are fully vaccinated, and thus our model included a population that was 17% vaccinated and 83% unvaccinated.[71] For each posting of this Report, we will review surveillance data and update this input as needed to track current experience. We anticipate this percent will increase for our next version of the Report given early evidence around the Omicron variant. Using this current mix of vaccinated/unvaccinated, the model finds that among patients receiving usual care, 1.5% are treated in the emergency department, 4.1% are hospitalized, and the remaining are managed with an outpatient visit alone.

In the model, each intervention could reduce the probability of receiving an emergency department visit or being hospitalized, with the relative risk associated with each intervention reported in Table 4.2. For the four interventions included within this review, the pivotal trials did not suggest a treatment effect of the intervention on reducing emergency department visits, potentially because the effect was not statistically significant, the effect was not reported, or emergency department visits were assumed to be included as an outpatient visit.

An intervention could also reduce the severity of the respiratory support received, with the relative risk associated with each treatment also reported in Table 4.2. For the four interventions included within this review, the evidence for one intervention (e.g., sotrovimab) suggested a significant treatment effect on reducing progression to higher levels of respiratory support. The evidence for the other three interventions did not suggest a treatment effect of the intervention on reducing the respiratory support required, either because the effect was not statistically significant or the effect

was not reported. Among those hospitalized in the comparator arm of the model, the respiratory support received equated to 26% requiring no oxygen support, 35% requiring low-flow oxygen, 29% requiring high-flow oxygen or non-invasive ventilation, and 10% requiring mechanical ventilation.

The probability of death among the comparator arm of the model, after pooling across trials and adjusting for the vaccinated population, equated to 0.48%. A treatment could only reduce mortality by way of preventing a hospitalization and/or reducing the severity of the hospitalization. Using recommendations from recent COVID-19 research, our model included post-acute costs and consequences for patients who were discharged alive after being mechanically ventilated. Our model included an increased probability of death for five years (hazard ratio of 1.33), a decrease in quality of life for five years (-0.13 in the first year and -0.04 in years 2 to 5), and an increase in health care costs for one year ($7,859 in the first year) for patients discharged alive after being mechanically ventilated.[70]

Table 4.2. Key Model Inputs

Parameter	Sotrovimab	Molnupiravir	Paxlovid	Fluvoxamine
Relative Risk of an ED Visit	1.0	1.0	1.0	1.0
Relative Risk of a Hospitalization	0.21	0.70	0.12	0.68†
Relative Risk of Respiratory Support Required	0.26	1.0	1.0	1.0
Cost of a Treatment Course	$2,100*	$707	$529	$12
Primary Source	Gupta et al., 2021[2,4]	Jayk Bernal et al., 2021[8]	FDA EUA Label[9]	TOGETHER[3]

ED: emergency department, EUA: Emergency Use Authorization, FDA: Food and Drug Administration

*Excludes administration, monitoring, or markup-related costs.

†Using the outcome of retention in a COVID-19 emergency setting or transfer to a tertiary hospital, which was suggested by clinical experts as a reasonable proxy for hospitalization in the US.

Detail on all inputs used in the model, along with their respective reference, can be found in Supplement E.

4.3. Results

Base-Case Results

The total discounted costs, hospitalizations, QALYs, life years, and evLYs over the lifetime time horizon are detailed in Table 4.3. Each outpatient intervention resulted in additional costs, but also resulted in fewer inpatient hospitalizations, resulting in more QALYs, life years, and evLYs.

Table 4.3. Results for the Base Case, Health Care Sector Perspective

Treatment	Treatment Cost*	Total Cost	Inpatient Hospitalizations	QALYs	Life Years	evLYs
Sotrovimab	$2,100	$300,700	0.87%	15.9645	19.5056	15.9663
Molnupiravir	$707	$298,600	2.90%	15.9356	19.4712	15.9362
Paxlovid	$529	$298,500	0.50%	15.9633	19.5042	15.9651
Fluvoxamine	$12	$297,900	2.82%	15.9366	19.4723	15.9372
Usual Care	--	$297,800	4.14%	15.9213	19.4541	15.9213

evLY: equal-value life year, QALY: quality-adjusted life year

*Excludes administration, monitoring, or markup-related costs.

Table 4.4 presents the incremental cost-effectiveness ratios from the base-case analysis, which includes estimates for the incremental cost per QALY gained, incremental cost per life year gained, incremental cost per evLY gained, and incremental cost per inpatient hospitalization averted.

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case, Health Care Sector Perspective

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Inpatient Hospitalization Averted
Sotrovimab	Usual care	$69,000	$58,000	$66,000	$91,000
Molnupiravir	Usual care	$55,000	$46,000	$53,000	$63,000
Paxlovid	Usual care	$18,000	$15,000	$17,000	$21,000
Fluvoxamine	Usual care	$6,000	$5,000	$6,000	$7,000

evLY: equal-value life year, QALY: quality-adjusted life year

Sensitivity Analyses

To demonstrate the effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors where available or reasonable ranges) to evaluate changes in findings. Supplement Figures E1-E4 present the results from the one-way sensitivity analysis for each intervention as compared to usual care. Notably, the most influential inputs on the cost effectiveness included the relative risk of hospitalization for each intervention, the probability of hospitalization among usual care, and the

cost of a hospitalization. Supplement Tables E15-E18 present the inputs and results for each input that appeared in the tornado diagrams.

One-way sensitivity analyses were conducted to vary one input at a time across a plausible range. From these one-way sensitivity analyses, the incremental cost-effectiveness ratios for sotrovimab were mostly beneath common cost-effectiveness thresholds. Molnupiravir ranged from incremental cost-effectiveness ratios that were beneath common cost-effectiveness thresholds to incremental cost-effectiveness ratios that far exceeded common cost-effectiveness thresholds when the relative risk of hospitalization was near 1.0. Cost-effectiveness estimates for Paxlovid and fluvoxamine ranged from cost-saving to beneath common cost-effectiveness thresholds. Paxlovid was cost-saving at a probability of hospitalization greater than 7.0% for usual care. Fluvoxamine was cost-saving at a probability of hospitalization greater than 5.2% for usual care.

A probabilistic sensitivity analysis was conducted to vary all inputs with noted uncertainty simultaneously. Tables 4.5 and 4.6 present the percent of the 1,000 iterations that were beneath thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY gained and evLY gained. The majority of the iterations were beneath thresholds of $100,000 per QALY gained or per evLY gained. Additional results from the probabilistic sensitivity analyses can be found in Supplement Tables E19-E20 and Supplement Figures E5-E8.

Table 4.5. Probabilistic Sensitivity Analysis Incremental Cost per QALY Gained Results

Treatment	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Sotrovimab	15%	72%	92%	97%
Molnupiravir	34%	73%	84%	88%
Paxlovid	98%	100%	100%	100%
Fluvoxamine	100%	100%	100%	100%

QALY: quality-adjusted life year

Table 4.6. Probabilistic Sensitivity Analysis Incremental Cost Per evLY Gained Results

Treatment	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Sotrovimab	19%	74%	93%	97%
Molnupiravir	36%	74%	85%	89%
Paxlovid	98%	100%	100%	100%
Fluvoxamine	100%	100%	100%	100%

evLY: equal-value life year

Threshold Analyses

Threshold analyses were conducted to identify at what treatment course price each intervention would meet certain cost-effectiveness thresholds. Tables 4.7 and 4.8 present the findings from these threshold analyses using outcomes of both the QALY and evLY, respectively. The prices presented in this table do not include administration, monitoring, or markup-related costs and therefore represent threshold prices for the intervention alone.

Table 4.7. QALY-Based Threshold Analysis Results, Health Care Sector Perspective

Treatment	Treatment Course Price*	Treatment Course* Price to Achieve $50,000 per QALY	Treatment Course* Price to Achieve $100,000 per QALY	Treatment Course* Price to Achieve $150,000 per QALY	Treatment Course* Price to Achieve $200,000 per QALY
Sotrovimab	$2,100	$1,300	$3,400	$5,400	$7,400
Molnupiravir	$707	$640	$1,400	$2,100	$2,800
Paxlovid	$529	$1,900	$4,000	$6,100	$8,200
Fluvoxamine	$12	$680	$1,400	$2,200	$3,000

QALY: quality-adjusted life year

*Excludes administration, monitoring, or markup-related costs.

Table 4.8. evLY-Based Threshold Analysis Results, Health Care Sector Perspective

Treatment	Treatment Course Price*	Treatment Course* Price to Achieve $50,000 per evLY	Treatment Course* Price to Achieve $100,000 per evLY	Treatment Course* Price to Achieve $150,000 per evLY	Treatment Course* Price to Achieve $200,000 per evLY
Sotrovimab	$2,100	$1,400	$3,500	$5,700	$7,800
Molnupiravir	$707	$670	$1,400	$2,200	$2,900
Paxlovid	$529	$2,000	$4,200	$6,300	$8,500
Fluvoxamine	$12	$710	$1,500	$2,300	$3,100

evLY: equal-value life year

*Excludes administration, monitoring, or markup-related costs.

Scenario Analyses

We conducted numerous scenario analyses to assess the robustness of the results across different economic perspectives and different assumptions about critical features of the evolving epidemiology of COVID-19 and corresponding health care utilization.

Scenario Analysis 1: Modified Societal Perspective

In the modified societal perspective, we included societal costs and outcomes associated with productivity gains/losses and ICU capacity. Supplement E provides information on the methods and inputs used to generate estimates from the modified societal perspective. Table 4.9 reports the

model outcomes from the modified societal perspective. Tables 4.10 and 4.11 report the threshold prices from the modified societal perspective using outcomes of both the QALY and evLY, respectively. The threshold prices were higher in the societal perspective as compared to the health care sector perspective for treatments.

Table 4.9. Model Outcomes, Modified Societal Perspective

Treatment	Treatment Cost*	Total Cost†	ICU Admissions	QALYs†	Life Years†	evLYs†
Sotrovimab	$2,100	$303,800	0.09%	15.9843	19.5300	15.9871
Molnupiravir	$707	$301,200	1.13%	15.9419	19.4790	15.9428
Paxlovid	$529	$301,500	0.19%	15.9818	19.5269	15.9845
Fluvoxamine	$12	$300,500	1.10%	15.9433	19.4806	15.9443
Usual Care	--	$300,200	1.62%	15.9213	19.4541	15.9213

evLY: equal-value life year, ICU: intensive care unit, QALY: quality-adjusted life year

*Excludes administration, monitoring, or markup-related costs.

†Includes costs/outcomes for the treated patient and any excess death averted as a societal benefit.

Table 4.10. QALY-Based Threshold Analysis Results, Societal Perspective

Treatment	Treatment Course Price*	Treatment Course* Price to Achieve $50,000 per QALY	Treatment Course* Price to Achieve $100,000 per QALY	Treatment Course* Price to Achieve $150,000 per QALY	Treatment Course* Price to Achieve $200,000 per QALY
Sotrovimab	$2,100	$1,700	$4,700	$7,700	$10,600
Molnupiravir	$707	$770	$1,800	$2,800	$3,900
Paxlovid	$529	$2,300	$5,300	$8,300	$11,300
Fluvoxamine	$12	$820	$1,900	$3,000	$4,100

QALY: quality-adjusted life year

*Excludes administration, monitoring, or markup-related costs.

Table 4.11. evLY-Based Threshold Analysis Results, Societal Perspective

Treatment	Treatment Course Price*	Treatment Course* Price to Achieve $50,000 per evLY	Treatment Course* Price to Achieve $100,000 per evLY	Treatment Course* Price to Achieve $150,000 per evLY	Treatment Course* Price to Achieve $200,000 per evLY
Sotrovimab	$2,100	$1,800	$5,000	$8,100	$11,200
Molnupiravir	$707	$810	$1,900	$3,000	$4,000
Paxlovid	$529	$2,400	$5,600	$8,700	$11,900
Fluvoxamine	$12	$870	$2,000	$3,200	$4,300

evLY: equal-value life year

*Excludes administration, monitoring, or markup-related costs.

Scenario Analysis 2: Unvaccinated Population Only

In this scenario analysis, we restricted the population to unvaccinated individuals and therefore did not make any adjustments to the usual care arms from the pivotal trials used in the pooled comparator arm of our model. Table 4.12 reports the incremental cost-effectiveness ratios for this subpopulation. Cost-effectiveness estimates for this subpopulation were slightly more favorable than the base-case estimates that included vaccinated individuals.

Table 4.12. Incremental Cost-Effectiveness Ratios for Unvaccinated Only Subpopulation

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Inpatient Hospitalization Averted
Sotrovimab	Usual care	$61,000	$52,000	$59,000	$74,000
Molnupiravir	Usual care	$48,000	$41,000	$46,000	$51,000
Paxlovid	Usual care	$15,000	$12,000	$14,000	$15,000
Fluvoxamine	Usual care	$4,000	$3,000	$3,800	$4,000

evLY: equal-value life year, QALY: quality-adjusted life year

Scenario Analysis 3: Lower Probability of Hospitalization

In this scenario analysis, we reduced the probability of hospitalization among usual care by half of what was used in the base case. Recent research has suggested that the Omicron variant of COVID-19 may be associated with a reduced risk of severe clinical endpoints (e.g., hospitalization) by approximately half.[50] Thus, in this scenario analysis, we assumed a probability of hospitalization among usual care of approximately 2%. Table 4.13 reports the incremental cost-effectiveness ratios for this subpopulation. Not surprisingly, cost-effectiveness estimates for this scenario were less favorable than our base-case estimates that assumed a higher probability of hospitalization, but all incremental results remained lower than $100,000 per additional QALY/evLY.

Table 4.13. Incremental Cost-Effectiveness Ratios for Unvaccinated Only Subpopulation

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Inpatient Hospitalization Averted
Sotrovimab	Usual care	$83,000	$68,000	$79,000	$214,000
Molnupiravir	Usual care	$69,000	$57,000	$66,000	$156,000
Paxlovid	Usual care	$32,000	$26,000	$30,000	$71,000
Fluvoxamine	Usual care	$20,000	$16,000	$19,000	$44,000

evLY: equal-value life year, QALY: quality-adjusted life year

Model Validation

We used several approaches to validate the model. First, we provided the preliminary model structure, methods, and assumptions to manufacturers. Based on feedback from these groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging model transparency, we will share the model with relevant manufacturers for external verification around the time of publishing this draft Evidence Report. Finally, we compared results to other cost-effectiveness models in this therapy area. The outputs from the model were validated against the trial/study data of the interventions.

Uncertainty and Controversies

The COVID-19 pandemic continues to evolve, as new variants emerge, vaccination uptake slowly increases, and the role of booster vaccinations becomes a major issue. Linked to these factors, the rate of new infections changes across seasons of the year and region of the country. The management of more serious disease also evolves, resulting in ever-changing approaches to the "usual care" of patients in emergency room and hospital settings. And all these evolving factors also affect overall hospital capacity in different regions of the country as well as broader considerations of policies such as management of infections in school and business settings.

As these factors evolve, the impact and the cost effectiveness of new therapies for outpatient treatment change. To capture this uncertainty and variability, we have conducted numerous sensitivity and scenario analyses. Key analyses are described above and further details on these analyses and others can be found in Supplement E.

Our base-case analysis used a common pooled comparator for each intervention. If we had chosen to compare each intervention to its own usual care arm in its pivotal trial, we would have provided very context-specific results. Pooling across the usual care arms of these pivotal trials allowed us to be more generalizable to the eligible population and representative of various secular trends observed. Given the wide differences in usual care outcomes across the trials, we believe the pooled comparator approach we used will be less likely to provide results that could be misinterpreted.

Another reason for our selection of a pooled comparator approach was driven by input from clinical experts. Experts advised us that, with the exception of the pregnancy limitations on molnupiravir and drug-drug interaction concerns with Paxlovid, clinicians will view these drugs as possible choices for the same population of patients. We therefore pooled the demographic characteristics (e.g., age and sex) across the pivotal trials to unify the population characteristics in the economic model. Given that we pooled the demographic characteristics, it was imperative that we also pool

the outcomes (hospitalization, death) given the documented relationship between age and these outcomes.

Our current approach to estimate the hospitalization risk, a key driver of model findings, was based on what was observed in the pooling of the pivotal trials. However, we understand the pandemic rapidly evolves and the hospitalization risk may change based on which variant(s) exist and which are dominant. At the time of the posting of this draft Evidence Report, we are aware of early evidence suggesting a lower risk of hospitalization with the currently dominant Omicron COVID-19 variant. We will continue to review evidence throughout the remaining time course of this review and may adjust the hospitalization risk observed in pivotal trials to a value more representative of the most recent data.

Our justification for a pooled approach notwithstanding, any pooling of data introduces its own degree of uncertainty due to systematic differences among the trials (e.g., definition of hospitalization, symptom days to start treatment, etc.) that could influence the relative effectiveness estimate for each intervention. All stakeholders should be aware that due to all of the factors that make this Report a "Special Assessment," we advise heightened caution in making inferences of intervention versus intervention cost effectiveness and suggest that stakeholders make use of ICER Analytics to update analyses with new data on relative clinical effectiveness and health care utilization as they become available.

Our model captures the long-term sequelae of COVID-19 through an increased mortality, increased cost, and decreased quality of life for individuals that are discharged alive after being mechanically ventilated. This approach follows recently published recommendations, but we understand that uncertainty and variability in these long-term sequelae exists, and the evidence is continuing to evolve, especially as it relates to the prevalence, duration, associated consequences, and the influence of an outpatient COVID-19 treatment on these sequelae.

Our modified societal perspective has important limitations and assumptions to consider when interpreting the estimates. In the modified societal perspective, we included productivity gains/losses for the patient treated during the time of the COVID-19 infection and indirect costs and benefits to society associated with alleviating ICU capacity. We heard from stakeholders that these outpatient COVID-19 treatments could play an important role in reducing ICU capacity, and reducing health system overload is undoubtedly a good outcome for society. Capturing these system-level capacity constraints is challenging, but we attempted to do so. In our approach, we attempt to extrapolate evidence around system-level capacity outcomes to an indirect societal benefit at the per-treated patient level to quantify this in the model. We had to make numerous methodological assumptions to do so, and thus this is an area we are hopeful to receive public comment on and we anticipate revisions and refinements in our approach. First, we assumed societal outcomes (e.g., excess deaths averted) based on a static 75% ICU occupancy, although we heard from clinical experts of the likely shift downward in ICU capacity concerns as the Omicron

variant begins to fade. Second, we assumed that the excess deaths averted at the national-level occupancy could be divided evenly among each ICU admission to estimate a per-treated patient effect. We acknowledge that in the real-world, numerous ICU admissions may need to be prevented (i.e., a drop in ICU capacity by X%) for excess deaths to be prevented. Due to these methodological assumptions, input from clinical experts suggesting that capacity concerns are not a long-term issue, and that the incremental cost-effectiveness ratios did not cross a decision-making threshold between the two perspectives, the modified societal perspective is not presented as a co-base-case. Further, the influence of COVID-19-driven ICU capacity on excess deaths is an area where additional research is needed, and the estimates of the influence of ICU capacity on excess deaths should be updated as additional evidence is identified.

4.4 Summary and Comment

Our analyses suggest that each outpatient intervention produces improved clinical outcomes. At their current prices, each intervention is estimated to meet standard cost-effectiveness levels in the US health care system, even under a scenario with a lower hospitalization risk that may reflect the current Omicron wave. The cost effectiveness findings are primarily driven by a treatment's ability to reduce hospitalization and the baseline probability of hospitalization.

5. Contextual Considerations and Potential Other Benefits

Our reviews seek to provide information on potential other benefits offered by the intervention(s) to the individual patient, caregivers, the delivery system, other patients, or the public that were not captured in clinical trials and may not be fully captured within the cost-effectiveness model. These elements are listed in the table below and on the following page, with related information gathered from patients and other stakeholders.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	The acuity of need for treatment is low given the relatively low rates of hospitalization and death from COVID-19 in the population of interest.
Magnitude of the lifetime impact on individual patients of the condition being treated	The magnitude of lifetime impact is expected to be low. While a certain proportion of patients experience long-term symptoms, the large majority of patients no longer experience symptoms by 12 weeks.[65,75]

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	COVID-19 has a low impact on patients' ability to achieve life goals. While the acute phase of infection limits activities of daily living, this phase is short.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	COVID-19 has low impact on caregivers' quality of life and ability to achieve life goals, given the limited duration of acute illness.
Patients' ability to manage and sustain treatment given the complexity of regimen	All treatments are short term and not expected impose a substantial burden for administration.
Society's goal of reducing health inequities	Non-White COVID-19 patients appear to be less likely to receive neutralizing antibody treatment for COVID-19.[76] If the oral drugs of interest (molnupiravir, Paxlovid, and fluvoxamine) are fairly distributed, these drugs would reduce access inequities since sotrovimab requires administration by a health care professional typically in an infusion facility or hospital. Therefore, access to sotrovimab may reflect inequities in local health system capacity.
Preventing spread of COVID-19	By reducing viral loads, sotrovimab, molnupiravir, and Paxlovid could theoretically reduce the likelihood of treated individuals spreading SARS-CoV-2. However, this may be counteracted by symptom improvements among treated individuals that result in more social interactions than in untreated individuals.
Improving hospital capacity	Surges in hospitalizations for COVID-19 strains available capacity of local health systems to appropriately care for COVID-19 patients as well as patients with other conditions who require hospitalization.[77,78] The drugs of interest have a potential other benefit of alleviating hospital capacity by reducing hospitalization rates among the treated. We have sought to capture this quantitatively in the societal perspective analysis, but further consideration may be warranted.
Providing support for policies to manage the pandemic with fewer restriction on schools and businesses	Effective outpatient treatments for mild-moderate COVID-19 may help provide psychological reassurance allowing for broader opening of schools and workplaces.
Drug-Specific Potential Benefits/Disadvantages	
Sotrovimab	Sotrovimab requires IV administration, which may limit its access to certain patients. If a onetime intramuscular administration option becomes available, it may offer a helpful alternative for patients for whom adherence to a longer course of therapy is more doubtful.
Molnupiravir	Molnupiravir cannot be used in people who are attempting to conceive or who are pregnant.
Paxlovid	Paxlovid is a combination therapy containing ritonavir. Ritonavir has a large number of known drug-drug interactions that pose a safety risk. These include interactions with certain anticoagulants, antiplatelets, antiarrhythmics, anticonvulsants and immunosuppressants.[9] These interactions are especially important among patients who are at particularly high risk for severe COVID-19 disease (e.g., immunosuppressed patients).[23]
Fluvoxamine	Fluvoxamine affects a different phase in COVID-19 pathophysiology and therefore it may be possible to combine its use with other agents.

6. Health-Benefit Price Benchmarks

ICER does not provide health-benefit price benchmarks as part of draft Evidence Report because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the "Threshold Prices" section of this draft Evidence Report will match the health-benefit price benchmarks that will be presented in the next version of this Report.

7. Potential Budget Impact

A potential budget impact analysis was not conducted for this Special Assessment. Due to the narrow margins of cost and survival benefit, a potential budget impact analysis was not considered policy relevant.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Intervention Definitions

Casirivimab/imdevimab (REGEN-COV) is a cocktail of two recombinant human monoclonal antibodies administered as a onetime IV infusion or subcutaneous injection of 600 mg of each antibody. It works by binding to the receptor-binding domain of the SARS-CoV-2 spike protein, inhibiting either attachment or fusion to human cells. As of January 2022, REGEN-COV's EUA has been revoked by the FDA.

Outcome Measure Definitions

COVID-19 progression: Progression of signs and symptoms of COVID-19 (i.e., cough, body ache, and fever) that gives insight into course of the disease and resources required during the illness.[79]

WHO 11-Point Clinical Progression Scale: An ordinal scale used to represent clinical progression of COVID-19 from mild, moderate, and severe stages, with a score of 0 being assigned to people who are uninfected and have no detectable viral RNA and a score of 10 being assigned to people who die.[79]

Viral clearance: Period when a patient is determined to have a negative nasopharyngeal or polymerase chain reaction (PCR) test (two negative tests may be required to be confirmed as being negative).[80] Phase IIa clinical trial for molnupiravir determined clearance to be when viral levels met a threshold of <1,018 copies/mL.[36]

InFLUenza Patient-Reported Outcome (FLU-PRO): A standardized measure of symptom severity for influenza patient-reported outcomes that requires a patient to record symptoms twice daily for 14 days to assess the presence, severity, and duration of symptoms across six body systems.[81]

SARS-CoV-2 antigen test: A diagnostic test that can generate results in approximately 15 minutes at the point-of-care. These tests tend to have high diagnostic specificity but lower sensitivity than molecular diagnostic tests.

Molecular diagnostic tests: A category of laboratory-based nucleic acid amplification tests that include reverse-transcription PCR tests. Molecular diagnostic tests are considered the gold standard for diagnostic COVID-19 testing and are also used for quantifying COVID-19 viral load.

Oxygen saturation: Defined as the percentage of hemoglobin in the blood that is bound to oxygen as oxyhemoglobin relative to total hemoglobin in the blood. This is typically measured using a

rapid, noninvasive pulse oximeter. Hospitalization with oxygen saturation below 94% is considered severe disease.[29]

Variant of concern: Defined by the CDC as a variant "for which there is evidence of an increase in transmissibility, more severe disease, significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures."[82]

COVID-19 viral load: Measures SARS-CoV-2 concentration after nucleic acid amplification. Viral load is typically used as secondary or surrogate measures for more clinically relevant measures such as hospitalization or death.

A2. Potential Cost-Saving Measures in COVID-19

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by therapies for COVID-19 (e.g., hospitalizations), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of COVID-19 beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with COVID-19 that could be reduced, eliminated, or made more efficient. No suggestions were received.

B. Patient Perspectives: Supplemental Information

B1. Methods

We spoke with three COVID-19 patients, a physician-scientist who maintains a COVID-19 patient registry to track longitudinal quality of life trends, and the Chief Executive Officer of Solve ME, a non-profit organization whose goal is to promote research on chronic fatigue and long-term COVID-19. We supplemented our understanding with a published systematic review that documented the diversity of symptoms associated with COVID-19.[30] The three patients were identified through Savvy Cooperative, patient-owned public benefit cooperative focused on connecting health care researchers to patients.

We spoke to these stakeholders individually for 30 to 45 minutes. The conversations were informed by a semi-structured interview guide, which focused the conversation on several themes:

1. What is it like to live with this condition? What is the experience of caregivers?
2. What is the diversity of experience with the condition; what are the differences of those who have a mild versus a serious case? How does racial and socioeconomic status factor in the diversity of the patient journey?
3. What outcomes matter most to patients? Are there some clinical outcome measures in the clinical trials that are more relevant to what patients care about most? What outcomes are missing entirely from the "evidence" base?
4. What are the most important "potential other benefits" and "contextual considerations" that payers and other policymakers should be aware of in judgments of value?
5. What is the experience with insurance access and affordability for treatments for this condition?

After each of these conversations, patient comments were transcribed, collated, organized, and summarized. We drew upon themes that emerged from our conversations and our summaries for the patient perspective sections of this Report.

C. Clinical Guidelines

Treatment guidelines for COVID-19 are rapidly changing, in part reflecting the changing treatment evidence and prevalence of different variants. We highly recommend that readers refer to current guidelines from the Infectious Diseases Society of America (IDSA). We briefly summarize this guideline—current as of January 2022—below.

IDSA Guidelines as of January 18, 2022

For non-hospitalized outpatients with mild-to-moderate disease who are at high risk of progression to severe disease (defined in Table C1), the IDSA recommends treatment with Paxlovid, remdesivir, or sotrovimab.[83] For this same population, the IDSA recommends molnupiravir for patients who have no other treatment options, citing concerns with low certainty regarding efficacy, the small effect size, potential viral mutagenesis as well as safety among persons of reproductive age. The IDSA recommends fluvoxamine only in the context of a clinical trial, citing the need for more precise estimates of efficacy and the need for greater generalizability of the results, as a key fluvoxamine trial was performed with patients having extended stays in mobile hospitals as part of the primary endpoint.[3]

Table C1. Factors or Conditions that Place Individuals at High Risk for Progression to Severe COVID-19 Disease[45,84,85]

Age ≥65 years
Obesity or being overweight
Pregnancy
Chronic kidney disease
Diabetes
Immunosuppressive disease or immunosuppressive treatment
Cardiovascular disease or hypertension
Chronic lung diseases
Sickle cell disease
Neurodevelopmental disorders
Having a medical-related technological dependence (e.g., tracheostomy)
Other conditions that confer medical complexity (e.g., genetic syndromes)
Other conditions or factors (e.g., race) that may place individual patients at high risk

National Institutes of Health COVID-19 Treatment Guidelines as of January 14, 2022

For non-hospitalized outpatients with mild-to-moderate disease who are at high risk of progression to severe disease (Table C1), the National Institutes of Health recommends treatment with Paxlovid (AIIa: strong recommendation based on other randomized trials or subgroup analyses of randomized trials), sotrovimab (AIIa: strong recommendation based on other randomized trials or subgroup analyses of randomized trials), remdesivir (BIIa: moderate recommendation based on other randomized trials or subgroup analyses of randomized trials).[86] Molnupiravir (CIIa: optional recommendation based on other randomized trials or subgroup analyses of randomized trials) is recommended only when none of the above options can be used. The National Institutes of Health panel's judgment is that there is insufficient evidence to recommend either for or against the use of fluvoxamine for this population.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for the review is adults and adolescents ages 12 and older with mild-to-moderate COVID-19 (confirmed with a positive SARS-CoV-2 PCR or antigen test) and a high risk of progression to severe disease.

Interventions

The list of interventions evaluated includes:

- Sotrovimab (GlaxoSmithKline and Vir Biotechnology)
- Molnupiravir (Merck)
- PF-07321332/ritonavir (Paxlovid, Pfizer)
- Fluvoxamine (investigator initiated)

Comparators

We compared each treatment to outpatient "usual care" involving only symptomatic treatments, as found in the clinical trials of each product. Data permitting, we also included real-world evidence as appropriate. Differences in patient populations and the natural history of care and outcomes for patients with COVID-19 have been evolving rapidly, making formal quantitative indirect comparisons challenging.

Outcomes

The outcomes of interest are described in the list below.

- Patient-important outcomes
    - Time to symptom resolution
    - Return to work or usual activities
    - Symptom severity
    - Progression to severe or critical illness

    - Degree of respiratory support
        - Conventional oxygen therapy
        - High-flow nasal cannula
        - Noninvasive positive pressure ventilation
        - Mechanical ventilation
    - Medically attended visit
    - Hospitalization
        - Length of stay
        - Readmission
    - Intensive care unit admission
    - Long COVID-19
    - Death
    - Adverse events including:
        - Side effects
        - Anaphylaxis
- Other outcomes
    - Viral load
    - SARS-CoV-2 clearance
    - Oxygen saturation
    - Antiviral resistance
    - Inflammatory markers
    - Adverse events including:
        - Treatment-emergent adverse events and serious adverse events

Timing

Evidence on intervention effectiveness and harms were derived from studies of any duration**.**

Settings

The primary focus was on care settings in the US, but relevant clinical outcomes data from international settings were included. We paid particular attention to the geography and timing of the studies in considering differences among patient populations, viral variants, and outcomes.

Table D1. PRISMA 2009 Checklist

Checklist Items		
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of Bias across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.

Checklist Items		
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on outpatient treatments for mild-to-moderate COVID-19 followed established best research methods.[87,88] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[89] The PRISMA guidelines include a checklist of 27 items, which are described further in Table D1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE) as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/).

Table D2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

1	exp COVID-19/ or exp SARS-COV-2/
2	(COVID* or coronovir* or coronavir* or SARS* or 2019-nCoV or "2019 nCoV" or 2019nCoV or nCov 2019 or "Severe Acute Respiratory Syndrome Coronavirus 2" or HCoV* or ((corona* or corono*) adj1 (virus* or viral* or virinae*))).ti,ab
3	1 or 2
4	exp "Antibodies, monoclonal"/
5	((antibod* or mAb or nAb*) adj2 (therap* or treatment)).ti,ab or ("monoclonal antibody").ti,ab
6	4 or 5
7	("casirivimab and imdevimab" or casirivimab-imdevimab or "casirivimab plus imdevimab" or (casirivimab ADJ3 imdevimab) or casirivimab or imdevimab or (regn10933 adj3 regn10987) or regn10933 or regn10987 or regn-10933 or regn-10987 or regen10933 or regen10987 or regen-10933 or regen-10987 or regen-COV* or "regen COV2" or regn-COV* or "regn COV2").ti,ab
8	(sotrovimab or "vir 7831" or vir-7831 or "gsk 4182136" or gsk-4182136).ti,ab
9	(molnupiravir or "mk 4482" or mk-4482 or "eidd 2801" or eidd-2801).ti,ab
10	(pf-07321332 or "pf 07321332" or (pf-07321332 adj3 (ritonavir or "a 84538" or "a-84538" or "abt 538" or abt538 or "abt-538" or norvir or RTV))).ti,ab
11	exp Fluvoxamine/
12	("ratio fluvoxamine" or "fluvoxamine maleate" or luvox or floxyfral or fevarin or dumirox or faverin or desiflu or du-23000 or "du 23000" or "luvox cr").ti,ab
13	11 or 12
14	6 or 7 or 8 or 9 or 10 or 13
15	3 and 14
16	(addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt
17	15 not 16
18	animals.mp. not (humans and animals).sh.
19	17 not 18
20	Limit 19 to English language
21	remove duplicates from 20

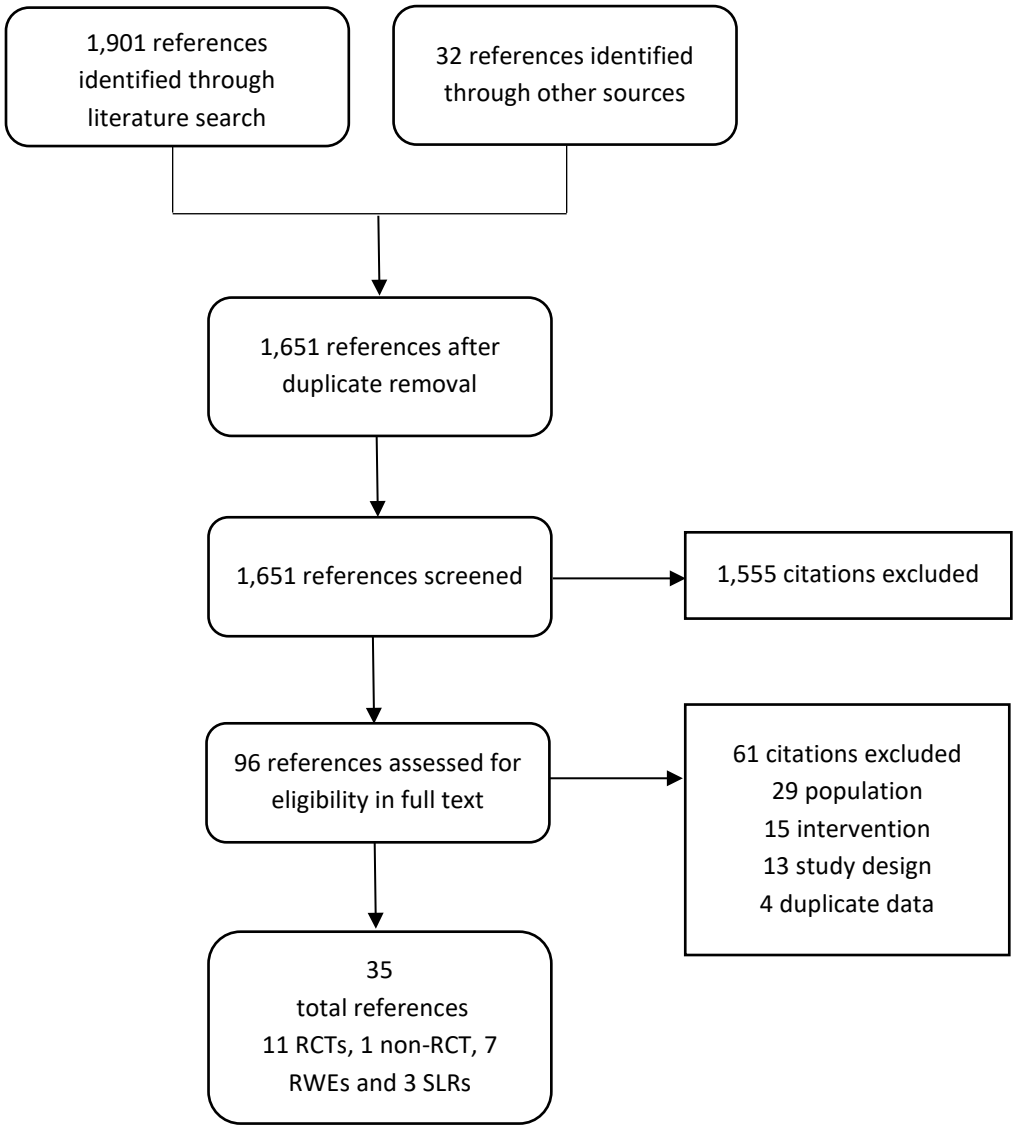
*Search last updated on September 21, 2021.

Table D3. Search Strategy of EMBASE SEARCH

#1	'coronavirus disease 2019'/exp OR 'coronavirus disease 2019'
#2	(COVID* OR coronavir* OR coronovir* OR SARS* OR HCoV* OR 'nCov 2019' OR '2019-nCoV infection' OR '2019 nCoV' OR 2019nCoV OR 'severe acute respiratory syndrome 2' OR ((corona* or corono*) NEAR/1 (virus* or viral* or virinae*))):ti,ab
#3	#1 OR #2
#4	'monoclonal antibody therapy'/exp OR 'monoclonal antibody therapy'
#5	('monoclonal antibody' OR ((antibod* or mAb* or nAb*) NEAR/2 (therap* or treatment*))):ti,ab
#6	#4 OR #5
#7	neutralizing:ti,ab
#8	#6 NOT #7
#9	'casirivimab plus imdevimab'/exp OR casirivimab/exp OR imdevimab/exp
#10	('casirivimab-imdevimab' OR 'casirivimab/imdevimab' OR 'casirivimab and imdevimab' OR 'imdevimab and casirivimab' OR regn10933 OR regn10987 OR 'regn-10933' OR 'regn-10987' OR regen10933 OR regen10987 OR 'regen-10933' OR 'regen-10987' OR 'regen-COV*' OR 'regn-COV*' OR 'regn COV2'):ti,ab OR (casirivimab NEAR/3 imdevimab):ti,ab
#11	#9 OR #10
#12	sotrovimab/exp
#13	('vir-7831' OR 'vir 7831'):ti,ab
#14	#12 OR #13
#15	molnupiravir/exp
#16	('mk-4482' OR 'mk 4482' OR 'eidd-2801' OR 'eidd 2801'):ti,ab
#17	#15 OR #16
#18	('pf-07321332' OR 'pf 07321332' OR ('pf-07321332' NEAR/3 (Ritonavir OR 'abt 538' OR abt538 OR 'abt-538' OR 'a-84538' OR 'abt 84538' OR 'abt-84538' OR norvir OR RTV))):ti,ab
#19	fluvoxamine/exp
#20	(luvox OR fluoxamine OR 'fluvoxamine maleate' OR 'du 23000' OR 'fluroxamine'):ti,ab
#21	#19 OR #20
#22	#8 OR #11 OR #14 OR #17 OR #18 OR #21
#23	#3 AND #22
#24	('case report'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#25	#23 NOT #24
#26	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#27	#25 NOT #26
#28	#27 AND [english]/lim

*Search last updated on September 21, 2021.

Figure D1. PRISMA Flowchart Showing Results of Literature Search for COVID-19 Treatments



Study Selection

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to products approved under EUA. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions, if relevant. All literature that did not undergo a formal peer review process is described separately.

Data Extraction and Quality Assessment

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2). Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention-to-treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention-to-treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[90,91] The main report summarizes the ratings and rationale for sotrovimab, molnupiravir, Paxlovid, and fluvoxamine.

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these newer treatments, we performed an assessment of publication bias for REGEN-COV, sotrovimab, molnupiravir, Paxlovid, and fluvoxamine using the ClinicalTrials.gov website. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias. We provided qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature. The primary concern is the lack of peer-reviewed, published data for the molnupiravir and Paxlovid trials.

Data Synthesis and Statistical Analyses

The studies and their results were summarized in evidence tables and synthesized qualitatively in the body of the review. Analyses were descriptive only, as differences in entry criteria, patient populations, outcome assessments, and other factors, precluded formal quantitative direct or indirect assessments of sotrovimab, molnupiravir, Paxlovid, and fluvoxamine versus usual care.

D2. Additional Clinical Evidence

Evidence Base

REGEN-COV

The discussion of the evidence of REGEN-COV in this Report Supplement summarizes studies conducted early in the pandemic, prior to the Delta and Omicron variants and should be interpreted with caution. Evidence informing our review of REGEN-COV in outpatients with mild-to-moderate COVID-19 was derived from one multi-center RCT with three phases. Our systematic literature review also identified several real-world studies of REGEN-COV, which are summarized below.

Weinreich 2021 was a multi-center Phase III trial that randomized 2,519 patients to 1200 or 2400 mg IV REGEN-COV or placebo.[47] Non-hospitalized adults were eligible to participate if they had tested positive no more than 72 hours prior with symptom onset no more than seven days prior to

randomization. On November 12, 2020, the trial was amended to include only patients with at least one risk factor for severe COVID-19. Patients were excluded if they had been admitted to a hospital prior to randomization due to COVID-19, had received any other treatments for COVID-19, or were pregnant, breastfeeding, or could become pregnant. Participants received REGEN-COV or placebo intravenously and completed a symptom questionnaire daily and regular virologic testing for 29 days. The primary outcome was COVID-19-related hospitalization or death for any cause through day 29. Secondary outcomes included COVID-19-related hospitalization or death from day four through 29, time to COVID-19 symptom resolution, and adverse events. Mean age of the trial participants at baseline was 48 years, and 52% were female. The majority (84%) of participants were White and a minority (5%) were Black. The most common risk factor for severe COVID-19 was obesity (57%) (Evidence Table D6).

Benefits and Harms

In the Phase III trial of REGEN-COV, COVID-19-related hospitalization or death from any cause by day 29 occurred in 7/736 (1.0%) of participants in the REGEN-COV 1200 mg arm and in 24/748 (3.2%) of participants in the concurrent placebo group, a 70.4% risk reduction (95% CI: 31.6 to 87.1; p=0.002). There was one death (from any cause) in both groups. Among those hospitalized, median length of stay was 4.0 days (IQR: 3 to 6 days) in the REGEN-COV 1200 mg group and 5.5 days (IQR: 4 to 10.5 days) in the placebo group. Three (0.4%) patients in the REGEN-COV 1200 mg arm were admitted to the ICU and one (0.1%) required mechanical ventilation, while seven (0.9%) in the placebo group were admitted to the ICU and two (0.3%) required mechanical ventilation. Median time to symptom resolution was 10 days in the REGEN-COV 1200 mg group and 14 days in the placebo group (p<0.001).

Adverse events were more common in the placebo group (safety population, N=1,843) and the majority were COVID-19-related. In the placebo group, 74 (4.0%) participants experienced serious adverse events compared to nine (1.1%) in the REGEN-COV 1200 mg group. No patients in the REGEN-COV 1200 mg group withdrew or discontinued treatment, however, one (0.1%) participant had an infusion-related reaction.

Real-World Studies of REGEN-COV

We identified seven US-based real-world evidence studies of REGEN-COV in our population of interest (non-hospitalized patients with mild-moderate COVID-19 symptoms).[34,51-58] Five out of seven studies were retrospective clinical data extraction studies. All studies included a group of patients who either received REGEN-COV or who were not treated acting as the control group. Of note, the Delta variant was first reported in March 2021 and became the most prominent variant in the US in June 2021.[92,93] Five studies completed data collection by April 2021, thus patients in these studies likely contracted earlier variants COVID-19, but two studies, using the same data source, included patients with COVID-19 from July to October 2021, all of whom had contracted the Delta

variant.[34,57] In the review of the real-world evidence, we focused on three commonly reported outcomes: hospitalization, emergency department visits, and death, at day 14 or day 28-30.

14-Day Outcomes

Two studies examined clinical outcomes at day 14 in individuals who received REGEN-COV compared to a control group of patients who did not receive this agent.[51,52]

Razonable et al. (2021) was a retrospective study of 1,392 adults (696 who received REGEN-COV and 696 matched controls) from Mayo Clinic sites in five states in the US.[52] All patients had confirmed COVID-19 using PCR tests with symptomatic disease and symptom onset within no more than 10 days, and had at least one medical risk factor; around 50% of patients were >65 years of age, had obesity, or had hypertension. The primary endpoint was hospitalizations at 14, 21, and 28 days, and ICU admission and death at 14, 21, and 28 days were secondary endpoints. By day 14, 9/679 (1.3%) of the patients who received REGEN-COV had been hospitalized for any cause, compared to 22/679 (3.3%) of the control group, representing an absolute 2.0% risk difference (95% CI: 0.5%, 3.7%) in favor of REGEN-COV. There was one death (0.15%) in the group of patients who received REGEN-COV, as a result of issues secondary to COVID-19, and three deaths (0.44%) in the control group, representing a non-significant absolute risk difference of 0.29% (95% CI: -0.3%, 0.9%). By day 28, a total of 11/668 (1.6%) of the patients who received REGEN-COV had been hospitalized for any cause, compared to 32/671 (4.8%) of the control group, representing an absolute 3.2% risk difference (95% CI: 1.4%, 5.1%) in favor of REGEN-COV. At day 28, mortality remained at 1/668 (0.15%) in those who received REGEN-COV, and there was a total of four deaths (0.59%) in the control group, representing a non-significant absolute risk difference of 0.33% (95% CI: -0.2%, 1.1%). Safety data were only reported for treated patients, with seven patients (1%) reporting adverse events that were all Grade 1.

Webb et al. (2021) was a retrospective study of 6,130 patients (115 received REGEN-COV, 479 received bamlanivimab [not reviewed here], and 5,536 were untreated contemporaneous controls) in the Intermountain Healthcare system in Utah and Southeastern Idaho in the US.[51] Similar to Razonable et al. (2021), all patients were over 18 years of age and had confirmed COVID-19 with symptomatic disease and symptom onset within no more than seven days before infusion.[52] However, patients in this trial were required to meet specific criteria for high risk constituting a risk score of ≥7.5. For example, a score of two points was assigned to individuals who identified as either non-White race or Hispanic/Latinx ethnicity, had diabetes mellitus, were severely immunocompromised, or had obesity (BMI >30), and a score of one point was given if patients had hypertension, coronary artery disease, chronic liver disease, amongst others. As a result, the patients in this study had more comorbidities compared to other real-world studies, such as reported in Razonable et al. (2021). The median number of total comorbidities was four (IQR 3 to 5); the most common comorbidities were hypertension (79-89%), obesity (54-62%), and diabetes (48-64%). The primary outcome was a composite of emergency department visits or

hospitalizations at day 14. Secondary endpoints were mortality and adverse events at day 14. In this review, only data from patients treated with REGEN-COV or untreated were included. At day 14, 1/115 (0.9%) patient who received REGEN-COV had been hospitalized, compared to 538/5,536 (9.7%) of the control group. In the REGEN-COV group, 9/115 (7.8%) patients visited the emergency room, compared to 944/5,536 (17.1%) in the control group. Thus, 10/115 (8.7%) patients receiving REGEN-COV met the composite endpoint of hospitalization/emergency department visit in this study, compared to 1,482/5,536 (26.8) in the control group. The statistical significance of these differences was not reported. There were no deaths in those patients who received REGEN-COV, compared to 57/5,536 deaths (1.0%) in the control group. Safety data were only reported for those who received REGEN-COV, and one patient reported an infusion-related reaction.

28-30 Day Outcomes

Six real-world evidence studies examined clinical outcomes at days 28, 29, or 30.[34,52-58] Day 28 outcomes from Razonable et al. (2021) are described above.

Polk et al. (2021) was a retrospective study of 324 patients (125 received REGEN-COV, 199 were untreated controls) in a single health system in the US.[58] All patients had confirmed COVID-19 and were assessed and infused within 10 days of symptom onset. Nearly half (43% in the REGEN-COV group vs. 53% in the control group) of the patients had more than one comorbidity; hypertension was the most common comorbidity (45% in REGEN-COV group and 58% of the control group). The study focused on several outcomes at day 30: COVID-19-related hospitalizations, COVID-19-related emergency department visits, ICU admission, mechanical ventilation, death, and adverse events. At day 30, 1/125 (2%) patient who received REGEN-COV had a COVID-19 related hospitalization, compared to 25/199 (12%) of the untreated control group, and 1/125 (1%) patient who received REGEN-COV had a COVID-19-related emergency department visit, compared to 18/199 (9%) of the untreated control group. At day 30, there were no deaths in the group of patients who received REGEN-COV and 4/199 (2%) deaths in the group of untreated controls. All four deaths were deemed to be related to COVID-19. No safety data were reported specifically for patients receiving REGEN-COV. Note that this was a poster presented at IDWeek Conference 2021 and has not been peer-reviewed.

Piccicacco et al. (2021) was a retrospective single-center study of 48 patients who received REGEN-COV and 200 control patients who were randomly selected from the high-risk COVID-19 patients but did not receive REGEN-COV and either declined or were not offered REGEN-COV during the candidacy window.[54-56] Patients were 12 years of age and older (only one patient in the control group was under the age of 18), had mild-to-moderate COVID-19 symptoms for 10 days or fewer before infusion, and were considered high risk for progression to severe COVID-19. The primary outcome was a composite of COVID-19-related hospitalization and emergency department visits at day 29 and secondary outcomes were incidence of hospitalization, emergency department visits, death, and serious adverse events at day 29. At day 29, 5/48 (10.4%) patients were reported to

have had a COVID-19-related emergency department visit or hospitalization, compared to 81/200 (40.5%) in the control group. When examining the individual components of the composite score, all five of the cases in the patients who received REGEN-COV were related to emergency department visits and 26/200 (13%) patients in the control group visited the emergency department for COVID-19-related issues. Thus, no patients who received REGEN-COV were hospitalized for COVID-19 compared to 60/200 (30%) patients in the control group. There were also no deaths in the group of patients who received REGEN-COV, compared to 7/200 deaths (3.5%) in the control group. One serious adverse event was reported for the patients who received REGEN-COV.

Chilimuri et al. (2021) was a single-center retrospective study aimed to provide an inner-city experience of the implementation of infusion therapy in the BronxCare Health System in the South Bronx, New York.[53] The study included patients who received monoclonal antibody therapy, including REGEN-COV (N=22), or who were untreated as they declined therapy (N=11). The sample was more racially diverse than the earlier studies, with 50% of patients who received REGEN-COV identified as Hispanic/Latinx and 27.2% identified as Black/African American. Demographics for the untreated control group were not reported. The primary outcome was hospitalization or death by day 30. At day 30, 1/22 (4.5%) patients who received REGEN-COV had been hospitalized due to COVID-19, compared to 6/11 (54.5%) in the control group. There were no deaths among the patients who received REGEN-COV and there were 2/11 (18.1%) deaths in the control group. No safety data were reported.

A pre-print published by McCreary et al. (2021) describes a prospective quality improvement project that utilized electronic health record data from a 40-hospital health system in Pennsylvania in the US. The study aimed to evaluate the real-world effectiveness of REGEN-COV, administered subcutaneously, in preventing all-cause hospitalization and death at 28 days in patients with the Delta variant of COVID-19, as compared to an untreated control group.[57] The study also aimed to evaluate the effectiveness of REGEN-COV as administered by IV injection compared to subcutaneous injection. All patients were 12 years of age or older, had a positive COVID-19 test, had not been hospitalized due to COVID-19, and were at risk for progression to severe disease. Patients were younger than earlier real-world studies (mean age of 54 years) and the most common comorbidities were hypertension (46%) and asthma (31%), percentages sufficiently lower than the other real-world studies reviewed. The primary outcome of the study was hospitalization or death at day 28, and secondary outcomes were the rate of hospitalization, death, emergency department admission and hospitalization, and adverse events at day 28. To examine the real-world effectiveness of REGEN-COV given subcutaneously, the study obtained data from 652 patients who were treated were given REGEN-COV via subcutaneous injection and 1,304 propensity-score matched nontreated control patients. The symptom status of the nontreated patients was unknown, such that patients in this group may have been asymptomatic. At day 28, 22/652 (3.4%) patients who received REGEN-COV had been hospitalized, compared to 85/1,304 (6.5%) in the

control group. This difference was statistically significant (p=0.005) providing support for the use of subcutaneous infusion of REGEN-COV. There was one death (0.2%) in the group of patients who received REGEN-COV as compared to 29 deaths (2.2%) in the untreated control group (p=0.009). No initial safety data were available. To examine whether the subcutaneous injection was clinically similar to IV of REGEN-COV, data was obtained from 969 patients treated with REGEN-COV via subcutaneous injection and 1,216 treated via IV. Around half of the patients in this analysis reported having been given a COVID-19 vaccine, with a higher rate of vaccination in those treated subcutaneously (55.5%) compared to those treated intravenously (44.1%), and such vaccination status was adjusted for within the analysis. At day 28, 27/969 (2.8%) patients who received REGEN-COV subcutaneously had been hospitalized, compared to 20/1,216 (1.6%) of those treated intravenously (p: 0.05). There was one reported death (0.1%) in the group of patients treated subcutaneously as compared to three deaths (0.2%) in the intravenously treated group, which was not statistically significant. Initial safety data reported two serious adverse events in those who were treated intravenously, and none reported in those treated subcutaneously.

Finally, a pre-print published by Huang et al. (2021) used the same electronic medical record data as McCreary et al. (2021) to evaluate the real-world effectiveness of REGEN-COV on patients with the Delta variant of COVID-19, compared to a matched control group.[34] The study also examined the effectiveness of sotrovimab compared to a matched control group, which is described in the sotrovimab section below. The study only reported combined demographic information for patients who received REGEN-COV and sotrovimab. Patients had a mean age of 54 years and a lower proportion of patients had medical comorbidities than the earlier reviewed studies, with obesity (59%) and hypertension (30%) as the most common comorbidities. The study obtained data from 712 patients who received REGEN-COV and 2,046 propensity-matched nontreated control patients. The primary outcome was hospitalization or death at 28 days and secondary outcomes were the rate of hospitalization, ICU admission, mechanical ventilation, and mortality at day 28. At day 28, 19/712 (2.7%) patients who received REGEN-COV had been hospitalized, compared to 134/2,046 (6.6%) in the control group, representing a risk ratio of 0.41 (95% CI: 0.25 to 0.65) (p<0.001), in favor of REGEN-COV. There was one death (0.1%) in the group of patients who received REGEN-COV as compared to 60 deaths (2.9%) in the untreated control group, representing a risk ratio of 0.05 (95% CI: 0.01 to 0.34) group (p: 0.003), in favor of REGEN-COV. No safety data were available.

The real-world evidence studies provide support for the association between the use of REGEN-COV and lower rates of both all-cause and COVID-19-related hospitalization, emergency visits, and death for patients with mild-to-moderate COVID-19 symptoms. Intravenous infusion of REGEN-COV appeared to be more effective than subcutaneous injection in preventing hospitalizations, but not deaths, although more research is needed to be conclusive. In general, patients in the real-world studies were older than those in the RCTs. The higher overall mortality and hospitalization rates in the real-world evidence studies, as compared to the RCTs, may be explained by this age difference.

Additionally, due to the nature of real-world studies that utilize retrospective clinical data, there were several uncontrolled factors that may have led to this increased rate of hospitalization/death, such as non-random group assignment, lack of blinding, and potential loss of longitudinal data (e.g., if a patient sought care outside of the particular health system) that should be considered when interpreting the studies. Finally, adverse events may be underreported in real-world studies and safety data should be reviewed with caution.

Sotrovimab

Evidence for sotrovimab in the Report mainly focuses on the primary outcomes for COMET-ICE and COMET-TAIL. The secondary endpoint from COMET-ICE included a change in total symptom score, which was evaluated using the FLU-PRO assessment tool. When compared to the placebo arm, participants that received IV administration of sotrovimab reported a higher mean reduction of -1.07 in their FLU-PRO score, which is consistent with the primary outcome.

We identified one additional real-world study of monoclonal antibodies, including REGEN-COV and sotrovimab. Huang 2021 is a prospective observational and propensity-matched cohort study that compared 311 patients who received 500 mg IV single infusion of sotrovimab to a placebo arm of 2,046 patients. Participants enrolled in this study had mild-to-moderate COVID-19 (Delta variant) and were enrolled between July 14, 2021 and September 29, 2021. A comparative analysis of sotrovimab with another monoclonal antibody was also performed in this real-world study but is not the focus of our review. Details of the study are described above.[34]

As previously mentioned in the Report, the primary outcome for the real-world study was hospitalization or death by day 28. In the sotrovimab arm, 16/311 (5.1%) of patients met this endpoint compared to 174/2,046 (8.5%) of patients in the placebo arm (RR: 0.60, 95% CI: 0.37 to 1.00, p=0.05). There were no deaths in the treatment arm and 60/2,046 (2.9%) deaths in the placebo arm. In the sotrovimab arm, 16/131 (5.1%) of patients were hospitalized and 134/2,046 (6.6%) of patients were hospitalized in the placebo group (RR: 0.79, 95% CI: 0.47 to 1.30, p-value: 0.35).[34]

Molnupiravir

In the Report, evidence for molnupiravir focused on the primary outcomes from the full population analysis and interim analysis of the Phase III portion of the MOVe-OUT trial. One of the secondary endpoint outcome measures in MOVe-OUT is the change in the WHO 11-point scale. The WHO 11-point scale measures the progression of COVID-19 through the mild, moderate, and severe stages with a higher numerical value being assigned to more severe patients. As measured by this outcome, patients in the molnupiravir group were less likely to have clinical progression of the disease by days three, five, 10, and 15. This secondary outcome of clinical progression was only

statistically significant at day 10 and day 15, with the maximum difference occurring at day 10 (odds ratio [OR] 1.58, 95% CI: 1.14 to 2.20).[8]

The Phase IIa portion of the MOVe-OUT trial functioned primarily as a dose-finding trial and evaluated three doses of molnupiravir (200 mg, 400 mg, and 800 mg) compared to placebo. Outcomes were reported primarily in participants in the 800 mg dose that was carried forward into the Phase III portion of the MOVe-OUT trial.[36]

The primary endpoint of this study was time to clearance of viral RNA in nasopharyngeal swabs confirmed by PCR detection. Median time to viral clearance was 14 days in the 800 mg molnupiravir group compared to 15 days in the placebo group (p-value: 0.013). This primary outcome was not statistically significant when compared to placebo in the 200 mg and 400 mg molnupiravir treatment arms.[36]

The secondary endpoint of the study was the percentage of participants in each treatment arm that had infectious virus isolations via nasopharyngeal swabs from baseline through days three and five. By the third day of treatment, infectious virus was isolated from 1/53 (1.9%) participants in the 800 mg molnupiravir group and in 9/54 participants in the placebo group (p-value: 0.016). This outcome was consistent with the results on day five, in which 0/53 (0%) participants in the 800 mg molnupiravir group had infectious virus isolated compared to 6/54 (16.7%) participants in the placebo group (p-value: 0.027). The median time to symptom resolution was not statistically significant across all treatment arms and placebo.[36]

Paxlovid

The Report discusses the primary source of data to inform our comparison of Paxlovid to usual care, the EPIC-HR trial, a Phase II/III randomized trial in non-hospitalized patients with mild-to-moderate COVID-19 at high risk of disease progression. At the time of this Report, full details on the trial participants and outcomes were not yet published. In December 2021, the manufacturer released top-line, interim data from the EPIC-SR trial, a Phase II/III randomized trial of Paxlovid in non-hospitalized patients with mild-to-moderate COVID-19 at standard risk for disease progression (including those who were vaccinated with at least one risk factor for progression).[6]

<u>EPIC-SR</u>

The primary outcome of the EPIC-SR trial was a self-reported sustained alleviation of all COVID-19 symptoms for four consecutive days. Secondary outcomes included a composite outcome of hospitalization and no death, viral load, and adverse events. In the interim analysis including 45% of the trial's planned enrollment, the primary endpoint for Paxlovid compared to placebo was not met and not reported.[6] However, in a follow-on analysis including 80% of enrolled patients the secondary outcome of hospitalization and no death was 70% lower in the Paxlovid group compared to the placebo group, with 3/428 hospitalized (0.7%) in the Paxlovid group and 10/329 (2.4%) in the

placebo group (p: 0.051). Treatment-emergent adverse events were similar across treatment groups (22% in the Paxlovid group and 21% in placebo), as were serious adverse events (1.4% in the Paxlovid group and 1.9% in placebo). Discontinuation rates due to adverse events were 2.1% in the Paxlovid group and 1.2% in placebo. Based on the totality of the data available at the time of the interim results, the Data Monitoring Committee recommended that the trial continue.[6]

Fluvoxamine

The Report discusses the primary source of data to inform our comparison of fluvoxamine to usual care, the TOGETHER trial. In addition to the TOGETHER trial, our systematic review identified two additional trials of fluvoxamine, STOP-COVID 1 and STOP-COVID 2.

STOP-COVID 1

STOP-COVID 1 was a double-blind, single-site US-based trial that randomized 181 non-hospitalized adults with mild-to-moderate COVID-19 and symptom onset within seven days to 100 mg of fluvoxamine or placebo three times daily for 15 days.[94] The trial was conducted early in the pandemic (April 2020 to August 2020). The primary outcome was clinical deterioration within 15 days of randomization (defined as shortness of breath or hospitalization for shortness of breath or pneumonia or oxygen saturation <92% or need for supplemental oxygen). Secondary outcomes included symptom severity, hospitalization, or emergency department visit (self-reported), and adverse events. Of the 181 patients who were randomized, 152 were included in the study analysis. Mean age of the participants was 46 years at baseline, 25% were Black, and the majority were female (70-74%). The most frequent risk factors for severe disease were obesity (54-58%), hypertension (19-21%), asthma (13-21%), and diabetes (11%).

In the STOP-COVID 1 trial, 0/80 participants in the fluvoxamine arm and 6/72 (8.3%) in the placebo arm met both criteria for clinical deterioration, the primary outcome (absolute difference 8.7, 95% CI: 1.8 to 16.4, p: 0.009).[94] Symptom severity, as measured on a 7-point scale (lower is better) was 0.22 points lower in the fluvoxamine group (95% CI: -0.41 to -0.04, p: 0.02). There was no difference in hospitalization or emergency department visits (self-reported) between the two groups. Serious adverse events were reported by one (1.3%) patient in the fluvoxamine group and five (6.9%) in the placebo group.

STOP-COVID 2

STOP-COVID 2 was a double-blind, multi-center US and Canada-based trial that randomized 547 non-hospitalized adults with mild-to-moderate COVID-19 and at least one risk factor for severe disease and symptom onset within seven days to 100 mg of fluvoxamine or placebo twice daily for 15 days.[66] Enrollment occurred between December 2020 and May 2021. Like the STOP-COVID 1 trial, the primary outcome was clinical deterioration within 15 days of randomization. Secondary outcomes included hospitalization and adverse events. Mean age of the participants was 48 years

at baseline and 62% were female; approximately 8% were Black and 13% were Hispanic/Latino. Like STOP-COVID 1, the most frequent risk factors for severe disease were obesity (42-45%), hypertension (20-23%), asthma (12-15%), and diabetes (9-10%).

The STOP-COVID 2 trial was stopped early due to low power for the primary outcome. In the interim analysis, 13/272 (4.8%) participants in the fluvoxamine arm and 15/275 (5.5%) in the placebo arm met both criteria for clinical deterioration, the primary outcome (absolute difference 0.0058, 95% CI: -0.034 to 0.045, p: 0.758).[66] In the fluvoxamine arm, nine (3.3%) participants had a COVID-19-related hospitalization compared to 10 (3.6%) in the placebo arm. Adverse events were not reported.

D3. Evidence Tables

Table D4. Study Quality Table

Trial	USPSTF Rating									
	Comparable Groups	Non-Differential Follow-Up	Patient/ Investigator Blinding	Clear Definition of Intervention	Clear Definitions of Outcomes	Selective Outcome Reporting	Measurements Valid	ITT Analysis	Approach to Missing Data	USPSTF Overall Rating
REGEN-COV										
Phase III COV-2067	Yes	Yes	Yes	Yes	Yes	No	Yes	mITT	NRI, LW	Good
Phase I/II COV-2067	Yes	Yes	Yes	Yes	Yes	No	Yes	mITT	NRI	Good
Sotrovimab										
COMET-ICE*	Yes	Yes	Yes	Yes	Yes	No	Yes	ITT	MAR	Good
Molnupiravir										
Phase III MOVe-OUT	Yes	Yes	Yes	Yes	Yes	No	Yes	mITT	NRI	Good
Phase IIa Study 2003* (Fischer 2021)	Yes	Yes	Yes	Yes	Yes	No	Yes	mITT	LOCF	Good
Fluvoxamine										
STOP-COVID	Yes	Yes	Yes	Yes	Yes	No	Yes	mITT	LOCF	Good
STOP-COVID 2*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	mITT	LOCF	Fair
TOGETHER	Yes	No	Yes	Yes	Yes	No	Yes	PP, ITT, mITT	MM	Fair

ITT: intention-to-treat analysis, LOCF: last observation carried forward, LW: listwise deletion, MAR: missing at random, mITT: modified intention-to-treat analysis, MM: mixed-methods model, NRI: non-responder imputation, PP: per-protocol analysis, USPSTF: United States Preventive Service Task Force
*Pre-print.

Table D5. Key Features: RCTs

Trial & NCT	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
REGEN-COV2 (Casirivimab/Imdevimab)					
Phase III COV-2067 (non-hospitalized)[47,95] NCT04425629	MC, DB, PC, RCT Location: Chile, US, Mexico, Romania Date(s) of Enrollment: September 2020-January 2021	Cohort 1: Outpatients ages ≥18 years old with COVID-19 and at least one risk factor for severe COVID-19 N=4,057 (modified full analysis set)	(BASED ON PROTOCOL AMENDMENT 5) **At day 1 for 1 hour:** REGEN-COV 1200 mg (IV infusion) (n=736) REGEN-COV 2400 mg (IV infusion) (n=1,355) Placebo (n=1,341)	**(BASED ON PROTOCOL AMENDMENT 8)** **Inclusion Criteria:** -Cohort 1: ≥18 years of age and not pregnant; Cohort 2: <18 years of age and not pregnant; Cohort 3: pregnant -SARS-CoV-2-positive diagnostic test from sample collected ≤72 hours prior to randomization, using validated SARS-CoV-2 test -Symptoms consistent with COVID-19 with onset ≤7 days before randomization -Maintains O2 saturation ≥93% on room air -Cohort 1 and Cohort 2 only: has ≥1 risk factor for severe COVID-19 (age ≥50 years, obesity, BMI ≥30 kg/m2, BMI (kg/m2) ≥95th percentile for age and sex based on CDC growth charts (cohort 2 only), CVD, chronic lung disease, type 1 or 2 diabetes, CKD, chronic liver disease, immunosuppressed, or underlying genetic condition, neurologic condition, metabolic condition, or congenital heart disease deemed to be risk factor for severe COVID-19 (cohort 2 only) **Exclusion Criteria:** -Hospitalized prior to or during randomization for COVID-19 -Use of or participation in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG, systemic steroids, or COVID-19 treatments within 3 months or within 5 half-lives of investigational product	**Primary Endpoint:** -Proportion of patients with at least one COVID-19-related hospitalization or death (through day 29) **Secondary Endpoints (through day 29 unless otherwise stated):** -Time to resolution of COVID-19 symptoms -Change from baseline in viral shedding (log10 copies/mL) from day 1 to day 22 -Proportion of patients with ≥1/≥2 COVID-19 related medically-attended visit -Days of hospitalization due to COVID-19 -Hospital/outpatient or telemedicine visit/ICU/requiring mechanical ventilation due to COVID-19 -Proportion of patients with all-cause mortality -Treatment-emergent SAEs, infusion-related reactions, or hypersensitivity reactions

Trial & NCT	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
				-Discharged to quarantine center -Has known positive SARS-CoV-2 serologic test or positive SARS-CoV-2 antigen or molecular diagnostic test from sample collected >72 hours prior to randomization -Has active infection with influenza or other non-SARS-CoV-2 respiratory pathogen -Participation in clinical research study evaluating a COVID-19 vaccine	
Phase I/II COV-2067 (non-hospitalized)[96] NCT04425629	MC, DB, PC, RCT Location: US Date(s) of Enrollment: June 2020-August 2020	Symptomatic Cohort: Outpatients ages ≥18 years old with COVID-19 N=275	(BASED ON PROTOCOL AMENDMENT 5) **At day 1 for 1 hour:** REGEN-COV 2400 mg (IV infusion) (n=92) REGEN-COV 8000 mg (IV infusion) (n=90) Placebo (n=93)	(BASED ON PROTOCOL AMENDMENT 5) **Inclusion Criteria** -Male or female & ≥18 years of age -Has SARS-CoV-2-positive antigen or molecular diagnostic test -a) Symptomatic cohort (all phases): COVID-19 symptoms onset ≤7 days before randomization or b) asymptomatic cohort (Phase 2): no COVID-19 symptoms at any time <2 months prior to randomization, no positive SARS-CoV-2 test results >7 days prior to randomization, and no contact with individual with COVID-19 or positive SARS-COV-2 test result >14 days prior to randomization. -Maintains O2 saturation ≥93% on room air **Exclusion Criteria** -Hospitalized prior to or at randomization, due to COVID-19 -Use of or participation in study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, IVIG, systemic corticosteroids, or COVID-19 EUA-approved treatments -Discharged to quarantine center	**Primary Endpoints (through Day 29 unless otherwise indicated):** -Change from baseline in viral load (log10 copies/mL) (day 7) -Treatment-emergent SAEs, infusion-related or hypersensitivity reactions **Secondary Endpoints (through day 29 unless otherwise stated):** -Concentration of REGN10933 and REGN10987 in serum over time -≥1 COVID-19 related medically attended visit or all-cause death -Time to negative RT-qPCR -COVID-19-related medically-attended visits -Hospital/outpatient or telemedicine visit/ICU/requiring mechanical ventilation due to COVID-19 -Days of hospitalization due to COVID-19 -All-cause mortality

Trial & NCT	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
				-Pregnant or breastfeeding women -Continued sexual activity in women of childbearing potential or sexually active men unwilling to practice highly effective contraception	
Sotrovimab					
Phase II/III COMET-ICE[2,4,33,97] NCT04545060	MC, QB, PC, RCT Location: Austria, Brazil, Canada, Peru, Spain, UK, US Date(s) of Enrollment: August 2020-March 2021	Non-hospitalized adults with COVID-19 N=1,057	**At day 1 for 1 hour:** Sotrovimab 500 mg (IV infusion) (n=528) Placebo (n=529)	**(BASED ON PROTOCOL AMENDMENT 1)** **Inclusion Criteria** -Participants aged ≥18 years AND at high risk of progression of COVID-19 from ≥1 risk factor: diabetes, obesity (BMI>35), CKD, CHF (NYHA class II or more), COPD, chronic obstructive lung disease, emphysema with dyspnea on physical exertion, and moderate to severe asthma, OR participant ≥55 years -Have positive SARS-CoV-2 test result (by any validated diagnostic test) -Oxygen saturation ≥94% on room air -Has COVID-19 symptoms and enrolled ≤5 days from onset of symptoms -Female participants not pregnant or breastfeeding, or using effective contraception **Exclusion Criteria** -Currently hospitalized or likely to require hospitalization in next 24 hours -Symptoms consistent with severe COVID-19 -Participants likely to die in next 7 days -Severely immunocompromised participants -Previous anaphylaxis or hypersensitivity to mAb -Enrollment in any investigational study within 180 days -Receipt of any vaccine within 48 hours prior	**Primary Endpoint:** -Proportion of participants who have progression of COVID-19 (up to day 29) **Secondary Endpoints (Up to 24 weeks unless otherwise indicated):** -Occurrence of adverse events and SAEs -Severity and duration of symptoms of COVID-19 related illness using the FLU-PRO patient-reported outcome instrument (Up to 12 weeks) -%AUCextrap -all-cause mortality -A-UCinf, AUClast, CL, Clast, Cmax -Detection of SARS-CoV-2 in nasal secretions by PCR -Incidence and titers of serum ADA to VIR-7831 -Proportion of participants who progress to develop severe and/or critical respiratory COVID-19 (supplemental oxygen) at day 8, day 15, day 22, or day 29

Trial & NCT	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
				to enrollment or convalescent plasma or SARS-CoV-2 mAb within last 3 months	
Phase III COMET-TAIL[27,35] NCT04913675	MC, OL, randomized Location: France, Ukraine, US Date(s) of Enrollment: June 2021-NR	Adolescent and adult outpatients with mild-to-moderate COVID-19 at a risk of progression to severe disease N=983	Sotrovimab 500 mg (IM injection) (n=376) Sotrovimab 500 mg (IV infusion) (n=378)	**Inclusion Criteria** -Participant aged 12 years or older at time of consent AND at high risk of progression of COVID-19 or ≥55 years old -Participants must have positive SARS-CoV-2 test result and oxygen saturation ≥94% on room air and have COVID-19 symptoms and be less than or equal to 7 days from onset of symptoms **Exclusion Criteria** -Currently hospitalized or judged by investigator as likely to require hospitalization in next 24 hours -Symptoms consistent with severe COVID-19 -Participants who, in judgment of investigator are likely to die in next 7 days -Known hypersensitivity to any constituent present in the investigational product	**Primary Endpoint:** -Proportion of participants who have progression of COVID-19 (up to day 29) **Secondary Endpoints (up to 24 weeks unless otherwise stated):** -AEs, AESIs, and SAEs -Incidence and titers of serum ADA to sotrovimab -%AUCextrap, AUCinf, AUClast, CL/F, Clast, Cmax, t1/2, Tlast, Tmax, Vz/F (IV, IM) -Mean AUC of SARS-CoV-2 viral load (up to day 8) -Proportion of participants with a persistently high SARS-CoV-2 viral load at day 8 by qRT-PCR (up to day 8) -Change from baseline in viral load by qRT-PCR (up to day 8)
Molnupiravir					
Phase III - MOVe-OUT[5,7,8,38] NCT04575597	MC, DB, PC, RCT Location: Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Italy, Japan, Mexico,	Non-hospitalized adults with COVID-19 N=1,550	**Day 1-5 (twice daily):** Molnupiravir 800 mg (oral) (n=716) Placebo (n=717)	**Inclusion Criteria** -SARS-CoV-2 infection with sample collection ≤5 days prior to day of randomization -Had initial onset of COVID-19 signs/symptoms ≤5 days prior to day of randomization and ≥1 COVID-19 sign/symptom day of randomization -Has mild or moderate COVID-19 -Has at least 1 characteristic or underlying medical condition associated with increased risk of severe illness from COVID-19 -Participants are not pregnant or	**Primary Endpoints:** -Percentage of participants who are hospitalized and/or die (up to 29 days) -Rates of AEs and discontinuation due to AEs (Up to ~7 months) **Secondary Endpoints:** -Time to sustained resolution or improvement of each targeted COVID-19 sign/symptom (up to 29 days)

Trial & NCT	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
	Philippines, Russia, South Africa, Spain, Taiwan, Ukraine, US Date(s) of Enrollment: NR			breastfeeding, using contraception or abstinent -For Phase III: unvaccinated **Exclusion Criteria** -Hospitalized for COVID-19 within 48 hours -On dialysis or has reduced eGFR <30 mL/min/1.73m^2 by modification of diet in renal disease equation -Has any of following: HIV with recent viral load >50 copies/mL or AIDS-defining illness in past 6 months, participants with HIV may only be enrolled if on stable antiretroviral regimen; a neutrophilic granulocyte absolute count <500/mm^3 -History of HBV or HCV with cirrhosis, ESRD, hepatocellular carcinoma, AST, and/or ALT >3X ULN -Platelet count <100,000/µL or received platelet transfusion in 5 days prior to randomization -Participation with another clinical study with an investigational compound including COVID-19 therapies -Any condition making participation not in best interest of participant: those who are not expected to survive longer than 48 hours after randomization, or those with recent history of mechanical ventilation, or participants with conditions that could limit GI absorption of capsule contents	-Time to progression of each targeted COVID-19 sign/symptom (up to 29 days) -WHO 11-point outcomes score on a scale (up to 29 days)
Phase IIa Study 2003 Fishcer 2021[36]	MC, DB, PC, RCT Location: US	Symptomatic adult outpatients with COVID-19	**Day 1-5 (twice daily):** Molnupiravir 200 mg (oral) (n=23)	**Inclusion Criteria** -≥18 years of age at screening -Study treatment is expected to begin within ≤168 hours from first symptom onset	**Primary Endpoint:** -Number of participants with any AEs as assessed by Kaplan Meier approach (28 days)

Trial & NCT	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
NCT04405570	Date(s) of Enrollment: June 2020-January 2021	N=204	Molnupiravir 400 mg (oral) (n=62) Molnupiravir 800 mg (oral) (n=55) Placebo	-Documentation of confirmed active SARS-CoV-2 infection, as determined by molecular test conducted at any US clinic or laboratory or equivalent from an NP swab collected ≤96 hours prior to study entry -≥1 SARS-CoV-2 infection symptoms: fever OR signs/symptoms of respiratory illness (including upper respiratory congestion, loss of sense of smell or taste, sore throat, cough, shortness of breath) -No participation in another interventional clinical trial for SARS-CoV-2 treatment or other investigational medicine unless hospitalized -Participants must not be of childbearing potential, have surgical sterilization, not be pregnant, use contraception, or have an azoospermic partner -Males must refrain from donating sperm **Exclusion Criteria** -Need for hospitalization or immediate medical attention in general or due to COVID-19 -Hb <10 g/dL in men and <9 g/dL in women, platelet count <125,000/L, eGFR <60 mL/min/1.73m2, AST/ALT≥3x ULN -History of kidney disease, liver disease, active HBV, HCV, HIV, or blood dyscrasia -Use of therapeutic interventions with possible anti-SARS-CoV-2 activity within 30 days prior to study entry -Receipt of SARS-CoV-2 vaccination -History of hemorrhagic cerebrovascular accident or major bleed	-Virologic efficacy: days until first non-detectable SARS-CoV-2 in NP swabs (28 days) **Secondary Endpoint:** -AEs, Grade 2 or higher (28 days)

Trial & NCT	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
Paxlovid (Nirmatrelvir/Ritonavir)					
Phase II/III - EPIC-HR (Nonhospitalized Symptomatic)[9,98,99] NCT04960202	MC, QB, PC, RCT Location: Argentina, Brazil, Bulgaria, Colombia, Czechia, Hungary, India, Japan, Korea, Malaysia, Mexico, Poland, Puerto Rico, Russia, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine, US Date(s) of Enrollment: July 2021-November 2021	Non-hospitalized symptomatic COVID-19 adults with high risk of progression to severe disease N=2,246	**Day 1-5:** Nirmatrelvir 300 mg + ritonavir 100 mg (oral) twice daily (n=1,039) Placebo (n=1,046)	**Inclusion Criteria** -Confirmed SARS-CoV-2 infection and onset of symptoms within 5 days prior to randomization -≥1 COVID-19 signs/symptoms present on day of randomization -Fertile participants on contraception -≥1 risk of developing severe COVID-19 **Exclusion Criteria** -Hospitalization for COVID-19 -Known history of active liver disease, receiving dialysis or have known renal impairment, or HIV infection with a viral load >400 copies/mL or taking prohibited medications for treatment -Concurrent active systemic non-COVID infection -Use of any medications dependent on or are strong inducers of CYP3A4 -Receive dose of a SARS-CoV-2 vaccine before day 34 or convalescent COVID-19 plasma -Participating in other clinical study with investigational product, including PF-07321332 -Oxygen saturation of <92% on room air, or on standard home oxygen supplementation for those who receive supplementary oxygen for an underlying lung condition -Females who are pregnant or breastfeeding	**Primary Endpoint:** -COVID-19 related hospitalization or death (all cause) (up to day 28) **Secondary Endpoints:** -AEs, TEAEs and SAEs (day 1 through day 34) -Duration and severity of each COVID-19 sign/symptom (day 1 through day 28) -Death (all cause) (day 1 through week 24) -Pharmacokinetics in plasma and whole blood of PF-07321332 (day 1 through day 5) -Viral titers measured by RT-PCR in nasal swabs (day 1 through day 14) -Number of COVID-19 related medical visits other than hospitalization (day 1 through day 34) -Number of days in hospital and ICU for the treatment of COVID-19 (day 1 through day 34)
Phase II/III - EPIC-SR[6]	MC, QB, PC, RCT Location:	Non-hospitalized symptomatic COVID-19 adults	**Day 1-5:** Nirmatrelvir 300 mg + ritonavir 100 mg (oral)	**Inclusion Criteria** -SARS-CoV-2 infection and onset COVID-19 symptoms within 5 days prior to	**Primary Outcome:** -Time to alleviation of COVID-19 symptoms (day 28)

Trial & NCT	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
NCT05011513	Argentina, Brazil, Bulgaria, Colombia, Czechia, Hungary, Japan, Korea, Malaysia, Mexico, Poland, Puerto Rico, Russia, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine, US Date(s) of Enrollment: August 2021-NR	with low/ standard risk of progression to severe disease N~>1,140	twice daily (n=338) Placebo (n=355)	randomization -Fertile participants on contraception **Exclusion Criteria** -Received any COVID-19 vaccine, except for patients with increased risk of developing severe COVID-19, therefore making patients low risk -History of or need for hospitalization for COVID-19 -Previous SARS-CoV-2 infection or active systemic infection other than COVID-19 -Liver disease, has HIV infection with viral load >400 copies/ml, taking prohibited medications for HIV, receiving dialysis or has renal impairment -Use of medications dependent on CYP3A4 for clearance -Receive mAb treatment, convalescent COVID-19 plasma, SARS-COV-2 vaccine -Participation in clinical study with other investigational compound or PF-07321332 -Oxygen saturation of <92% on room air -Pregnant or breastfeeding	**Secondary Outcomes (up to day 28 unless otherwise stated):** -AEs, SAEs, AEs leading to discontinuation (day 34) -Participants with severe COVID-19 symptoms -Duration of COVID-19 symptoms -Progression to a worsening status in COVID-19 symptoms -Participants with resting peripheral oxygen saturation ≥95% (days 1, 5) -Number of COVID-19 related medical visits -Number of days in hospital and ICU -Participants with COVID-19 related hospitalization or all-cause death
Fluvoxamine					
Phase III TOGETHER[3] NCT04727424	MC, QB, PC, Randomized Adaptive Trial Location: Brazil Date(s) of Enrollment: January 2021-August 2021 (for	Non-hospitalized adults with mild COVID-19 and high risk of complications N~3,645	**Day 1-10:** Fluvoxamine 100 mg (oral) twice daily (n=739) Doxazosin (1 or 2 mg once daily (days 0-3), titration up to 8 mg/day (days 3-13) (oral)	**Inclusion Criteria** -Patients over 18 years old with acute flu-like symptoms <7 days -≤1 enhancement criteria: age >50 years, diabetes, hypertension, CVD, lung disease, asthma, fever >38C, obesity, transplant patients, stage IV CKD, immunosuppressive or corticosteroid therapy, cancer, chronic renal disease KDIGO IV or ESRD on therapy -Patient with positive rapid test for SARS-	**Primary Endpoints (through day 28):** -Need for and evaluation of ED visits and observation unit stay >6 hours -Hospitalization due to COVID-19 progression and related complications **Secondary Endpoints (through day 28 unless otherwise stated):** -Change in viral load on day 3 and 7 after randomization (day 3 and 7)

Trial & NCT	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
	fluvoxamine arm)		Ivermectin 6 mg (oral) once daily Placebo (n=733)	CoV2 antigen at screening or diagnostic test within 7 days of symptom onset **Exclusion Criteria** -Negative SARS-CoV2 test, flu-like symptom onset 8+ days, or >14 days of SARS-CoV-2 vaccination -Hospitalization due to COVID-19 -Non-COVID-19 acute respiratory conditions -Patients with moderate disease or hospitalized -Use of medications in last 14 days: SSRIs, MAOIs, alpha-1 antagonists, sotalol, clonidine, methyldopa, phosphodiesterase 5 inhibitors, prazosin, terazosin, doxazosin, antiretroviral agents -Patients with severe psychiatric disorders or major uncontrolled depression -Pregnant or breastfeeding patients -History of cardiac arrythmia, long QT syndrome, hypotension, syncope, POTS, cerebrovascular accident, MI, CV intervention, mitral or aortic stenosis, seizures, liver cirrhosis or Child-Pugh C classification -Surgical procedure during treatment -Patients with known severe degenerative neurological/serious mental diseases	-Time to clinical changes (>50%) -Time to hospitalization -Number of days with respiratory symptoms -All-cause hospitalizations -COVID-19 hospitalizations -Number of days on mechanical ventilator -Number of days on ICU -Number of days on hospitalizations -Health and functioning after COVID-19 disease using PROMIS Global Health Score (day 14 and 28) -WHO ordinal scale for clinical improvement -Number of days on respiratory Symptoms -Adherence
Phase II STOP COVID[94] NCT04342663	MC, TB, PC, RCT Location: US Date(s) of Enrollment:	Non-hospitalized adults with known SARS-COV-2 N=152	**Day 0:** Fluvoxamine 50 mg (oral) **Day 1-2:** Fluvoxamine 100 mg (oral) twice daily	**Inclusion Criteria** -Men and woman ages 18 and older -Not hospitalized -Has recently tested SARS-CoV-2 (COVID-19 virus) positive -Currently symptomatic with one or more of one or more of the following symptoms:	**Primary Endpoint:** -Number of participants who met clinical worsening, defined as presence of dyspnea and/or hospitalization for shortness of breath or pneumonia, AND decrease in O2 saturation (<92%) on room air and/or

Trial & NCT	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
	April 2020-August 2020		Placebo **Day 3-15:** Fluvoxamine 100 mg (oral) 3 times daily (n=80) Placebo (n=72)	fever, cough, myalgia, mild dyspnea, diarrhea, vomiting, anosmia, ageusia, sore throat **Exclusion Criteria** -Illness severe enough to require hospitalization or already meeting study's primary endpoint for clinical worsening -Unstable medical comorbidities including, but not limited to: severe underlying lung disease (COPD on home oxygen, interstitial lung disease, pulmonary hypertension), decompensated cirrhosis, CHF (stage 3 or 4 per patient report and/or medical records) -Already enrolled in another COVID-19 trial, or currently taking chloroquine, hydroxychloroquine, azithromycin or colchicine -Immunocompromised (solid organ transplant, BMT, AIDS, on biologics and/or high-dose steroids (>20 mg prednisone per day)	supplemental oxygen requirement in order to keep O2 saturation >92% (~15 days) **Secondary Endpoint:** -Clinical deterioration on a Likert-type scale (0-6) (~15 days) -Symptomatic severity using a continuous scale of each patient's most severe baseline symptom on an 11-point scale (~15 days)
Phase III STOP COVID 2[66,100] NCT04668950	MC, TB, PC, RCT Location: Canada and US Date(s) of Enrollment: December 2020-May 2021	Non-hospitalized symptomatic adults ages 30+ with SARS-COV-2 and high risk of clinical deterioration N~880	**Day 0:** Fluvoxamine 50 mg (oral) **Day 1-15:** Fluvoxamine 100 mg (oral) twice daily (n=276) Placebo (n=275)	**Inclusion Criteria** -Men and woman age 30 and older and not currently hospitalized -Proven SARS-CoV-2 positive (per lab or physician report) - Able to provide informed consent -Currently symptomatic with one or more of following symptoms: fever, cough, myalgia, mild dyspnea, chest pain, diarrhea, nausea, vomiting, anosmia, ageusia, sore throat, nasal congestion -Reports one of the following risk factors for clinical deterioration: age ≥40, racial/ethnic	**Primary Endpoint:** -Clinical deterioration, defined as both presence of dyspnea and/or hospitalization for shortness of breath or pneumonia AND decrease in O2 saturation (<92% on room air) and/or supplemental oxygen requirement to keep O2 saturation ≥92%) (~15 days) **Secondary Endpoint:** -Post covid functioning via PROMIS

Trial & NCT	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
				group African American, Hispanic, or Native American, or 1+ medical condition increasing risk for moderate-severe COVID-19 illness: obesity, hypertension, diabetes, heart disease, lung disease, immune disorder **Exclusion Criteria:** -Illness severe enough to require hospitalization or already meeting study's primary endpoint for clinical worsening -Unstable medical comorbidities -Immunocompromised from following: solid organ transplant, BMT, high-dose steroids (>20 mg prednisone per day), or tocilizumab -Already enrolled in another COVID-19 treatment trial or received COVID-19 vaccine -Taking donepezil, sertraline, warfarin, phenytoin, clopidogrel, and St John's wort -Taking SSRIs, SNRIs, tricyclic antidepressants, bipolar medication, theophylline, tizanidine, clozapine, or olanzapine -Individuals unwilling to cut alprazolam or diazepam medication by 25%	Global Health Scale (day 15 and day 90)

ADA: anti-drug antibody, AE: adverse event, AIDS: acquired immunodeficiency syndrome, ALT: alanine aminotransferase, AST: aspartate aminotransferase, AUC_{extrap}: area under the curve extrapolated as a percentage of the total, AUC_{inf}: area under the curve to infinity, AUC_{last}: area under the curve to the last measurable concentration, BMI: body mass index, BMT: blood or marrow transplant, CKD: chronic kidney disease, CL: drug clearance, CL/F: apparent oral clearance, C_{last}: last measurable concentration (above the quantification limit), C_{max}: maximum plasma concentration, CVD: cardiovascular disease, CYP3A4: Cytochrome P450 3A4, DB: double-blind, dL: deciliter, eGFR: estimated glomerular filtration rate EUA: Emergency Use Authorization, g: gram, HBV: hepatitis B, HCV: hepatitis C, HIV: human immunodeficiency virus, ICU: intensive care unit, IM: intramuscular, IV: intravenous, IVIG: intravenous immune globin, kg: kilogram, L: liter, m: meter, mAb: monoclonal antibody, MC: multi-center, mg: milligram, mL: mililiter, n: number, N: total number, NCT: National Clinical Trial Identifier, NR: not reported, NYHA: New York Heart Association, OL: open-label, O_2: oxygen, PC: placebo-controlled, POTS: postural orthostatic tachycardia syndrome, QB: quadruple-blind, QT: interval representing the time it takes for the heart muscle to contract and then recover, RCT: randomized controlled trial, RT-qPCR: quantitative reverse transcription polymerase chain reaction, SAE: serious adverse event, SNRI: serotonin and norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor, TB: triple-blindTEAE: treatment-emergent adverse event, T_{last}: time of last measurable concentration, T_{max}: time to maximum plasma concentration (C_{max}), t½: half-life, uL: microliter, U.K.: United Kingdom, ULN: upper limit normal, U.S.: United Status, V_Z/F: apparent volume of distribution during terminal phase, WHO: World Health Organization

Table D6. Baseline Characteristics: Phase III Trials (Monoclonal Antibodies)[2,4,47,95]

Drug Name		REGEN-COV2 (Casirivimab/Imdevimab)				Sotrovimab			
Trial		Phase III COV-2067 (Non-Hospitalized)				COMET-ICE		COMET-TAIL	
Arms		REGEN-COV 2400 mg	PBO 2400 mg	REGEN-COV 1200 mg	PBO 1200 mg	Sotrovimab 500 mg	PBO	Sotrovimab 500 mg (IM)	Sotrovimab 500 mg (IV)
N		1355	1341*	736	748	528	529	983	
Age, Median Years (IQR)		50 (39-60)	50 (37-58)	48.5 (37-57.5)	48 (35-57)	53 (18-96)	53 (17-88)	NR	NR
Age Group, n/N (%)	≥50 Years	715/1355 (52.8)	678/1341 (50.6)	357/736 (48.5)	356/748 (47.6)	NR	NR	NR	NR
	<65 Years	1141/1355 (84.2)	1197/1341 (89.3)	632/736 (87.4)	660/748 (88.2)	423/528 (80)	421/529 (80)	NR	NR
	≥65 Years	214/1355 (15.8)	144/1341 (10.7)	93/736 (12.6)	88/748 (11.8)	105/528 (20)	108/529 (20)	NR	NR
Gender, n/N (%)	Male	656/1355 (48.4)	633/1341 (47.2)	364/736 (49.5)	352/748 (47.1)	229/528 (43)	256/529 (48)	NR	NR
	Female	699/1355 (51.6)	707/1341 (52.8)	372/736 (50.5)	396/748 (52.9)	299/528 (57)	273/529 (52)	NR	NR
Race, n/N (%)	White	1161/1355 (85.7)	1136/1341 (84.7)	595/736 (80.8)	611/748 (81.7)	458/528 (87)	463/529 (88)	NR	NR
	Black or African American	67/1355 (4.9)	66/1341 (4.9)	38/736 (5.2)	38/748 (5.1)	40/528 (8)	42/529 (8)	NR	NR
	Asian	52/1355 (3.8)	56/1341 (4.2)	38/736 (5.2)	36/748 (4.8)	24/528 (5)	21/529 (4)	NR	NR
	American Indian or Alaska Native	19/1355 (1.4)	13/1341 (1.0)	17/736 (2.3)	10/748 (1.3)	1/528 (<1)	2/529 (<1)	NR	NR
	Hispanic or Latino	NR	NR	NR	NR	NR	NR	NR	NR
	Mixed Race	NR	NR	NR	NR	4/528 (<1)	0	NR	NR
	Other	NR	NR	NR	NR	NR	NR	NR	NR
	Unknown	28/1355 (2.1)	43/1341 (3.2)	36/736 (4.9)	37/748 (4.9)	NR	NR	NR	NR
	Not Reported	24/1355 (1.8)	26/1341 (1.9)	10/736 (1.4)	15/748 (2.0)	NR	NR	NR	NR
Ethnicity, n/N (%)	Hispanic or Latino	464/1355 (34.2)	471/1341 (35.1)	312/736 (42.4)	295/748 (39.4)	345/528 (65)	346/529 (65)	NR	NR

Drug Name		REGEN-COV2 (Casirivimab/Imdevimab)				Sotrovimab			
Trial		Phase III COV-2067 (Non-Hospitalized)				COMET-ICE		COMET-TAIL	
Arms		REGEN-COV 2400 mg	PBO 2400 mg	REGEN-COV 1200 mg	PBO 1200 mg	Sotrovimab 500 mg	PBO	Sotrovimab 500 mg (IM)	Sotrovimab 500 mg (IV)
N		1355	1341*	736	748	528	529	983	
	Not Hispanic or Latino	891/1355 (65.8)	870/1341 (64.9)	424/736 (57.6)	453/748 (60.6)	183/528 (35)	183/529 (35)	NR	NR
Weight, Median kg (IQR)		87.5 (75.2-102.1)	87.9 (74.3-103)	86.2 (74.4-102.1)	86.2 (72.8-102.4)	NR	NR	NR	NR
BMI Mean kg/m² (SD)		31.1 (6.3)	31.2 (6.6)	31.5 (7.3)	31.1 (6.5)	32.3 (6.7)	32.2 (6.6)	NR	NR
BMI, n/N (%)	<30 kg/m²	568/1355 (41.9)	569/1341 (42.4)	326/736 (44.3)	321/748 (42.9)	198/528 (37)	188/529 (36)	NR	NR
	≥30 kg/m²	787/1355 (58.1)	772/1341 (57.6)	410/736 (55.7)	427/748 (57.1)	330/528 (63)	341/529 (64)	NR	NR
Overweight, n/N (%)		567/2091 (27.1)†	339/1341 (25.3)	567/2091 (27.1)†	NR	NR	NR	NR	NR
Positive Baseline Qualitative RT-PCR, n/N (%)		1353/1355 (99.9)	1333/1341 (99.4)	734/736 (99.7)	744/748 (99.5)	NR	NR	NR	NR
SARS-COV-2 Variant, n/N (%)	Alpha	NR	NR	NR	NR	NR	NR	NR	NR
	Gamma	NR	NR	NR	NR	NR	NR	NR	NR
	Delta	NR	NR	NR	NR	NR	NR	NR	NR
	Mu	NR	NR	NR	NR	NR	NR	NR	NR
	Lambda	NR	NR	NR	NR	NR	NR	NR	NR
Time from Symptom Onset to Randomization, Median Days (Range)		3.0 (2-5)	3.0 (2-5)	3.0 (2-5)	3.0 (2-4)	NR	NR	NR	NR
Time from Symptom Onset to Randomization, n/N (%)	0-3 Days	NR	NR	NR	NR	314/528 (59)	310/529 (59)	NR	NR
	4-5 Days	NR	NR	NR	NR	213/528 (40)	219/529 (41)	NR	NR
	4-7 Days	NR	NR	NR	NR	NR	NR	NR	NR
	Unspecified	NR	NR	NR	NR	NR	NR	NR	NR
Duration of Follow-Up, Median Days (SD)		45‡				103 (5-178)§	102 (3-176)§	NR	NR

Drug Name		REGEN-COV2 (Casirivimab/Imdevimab)				Sotrovimab			
Trial		Phase III COV-2067 (Non-Hospitalized)				COMET-ICE		COMET-TAIL	
Arms		REGEN-COV 2400 mg	PBO 2400 mg	REGEN-COV 1200 mg	PBO 1200 mg	Sotrovimab 500 mg	PBO	Sotrovimab 500 mg (IM)	Sotrovimab 500 mg (IV)
N		1355	1341*	736	748	528	529	983	
≥1 Risk Factor for Progression to Severe Disease, n/N (%)		1355/1355 (100)	1341/1341 (100)	736/736 (100)	748/748 (100)	525/528 (>99)	526/529 (>99)	983/983 (100)	
Any Risk Factor for Progression to Severe Disease, n/N (%)	Age ≥55 Years	715/1355 (52.8)#	678/1341 (50.6)#	357/736 (48.5)#	356/748 (47.6)#	243/528 (46)	256/529 (48)	NR	NR
	Obesity (BMI>30)	787/1355 (58.1)	772/1341 (57.6)	410/736 (55.7)	427/748 (57.1)	330/528 (63)	341/529 (64)	NR	NR
	CVD or Hypertension	520/1355 (38.4)	473/1341 (35.3)	282/736 (38.3)	NR	4/528 (<1)¤	3/529 (<1)¤	NR	NR
	COPD	NR	NR	NR	NR	34/528 (6)	27/529 (5)	NR	NR
	Asthma	216/1355 (15.9)**	219/1341 (16.3)**	139/736 (18.9)**	NR	90/528 (17)††	88/529 (17)††	NR	NR
	CKD	19/1355 (1.4)	9/1341 (0.7)	8/736 (1.1)	NR	5/528 (<1)	8/529 (2)	NR	NR
	Diabetes (Type 1/2)	202/1355 (14.9)	210/1341 (15.7)	94/736 (12.8)	NR	119/528 (23)	109/529 (21)	NR	NR
	Immunosup. Disease	46/1355 (3.4)‡‡	34/1341 (2.5)‡‡	24/736 (3.3)	NR	NR	NR	NR	NR
	Neurological Disorder	NR	NR	NR	NR	NR	NR	NR	NR
	Liver Disease	14/1355 (1.0)	8/1341 (0.6)	3/736 (0.4)	NR	NR	NR	NR	NR
	High Cholesterol	NR	NR	NR	NR	NR	NR	NR	NR
	Any Other Risk Factors or Comorbidities	NR	NR	NR	NR	NR	NR	NR	NR
Baseline Serum Antibody Status, n/N (%)	Negative	940/1355 (69.4)	930/1341 (69.4)	500/736 (67.9)	519/748 (69.4)	NR	NR	NR	NR
	Positive	323/1355 (23.8)	297/1341 (22.1)	177/736 (24.0)	164/748 (21.9)	NR	NR	NR	NR
	Unknown	NR	NR	NR	NR	NR	NR	NR	NR

Drug Name		REGEN-COV2 (Casirivimab/Imdevimab)				Sotrovimab			
Trial		Phase III COV-2067 (Non-Hospitalized)				COMET-ICE		COMET-TAIL	
Arms		REGEN-COV 2400 mg	PBO 2400 mg	REGEN-COV 1200 mg	PBO 1200 mg	Sotrovimab 500 mg	PBO	Sotrovimab 500 mg (IM)	Sotrovimab 500 mg (IV)
N		1355	1341*	736	748	528	529	983	
Baseline Viral Load in Nasopharyngeal Swab, Median Log_{10} Copies/ml (Range)		7.01 (2.6-10)§§	6.95 (2.6-10.2)##	6.92 (2.6-10.5)¤¤	6.85 (2.6-10.2)***	NR	NR	NR	NR
Geography of Enrollment, n/N (%)	US	2004/2091 (95.8)†	1285/1341 (95.8)	2004/2091 (95.8)†	NR	NR	NR	NR	NR
	Non-US	87/2091 (4.2)†	56/1341 (4.2)	87/2091 (4.2)†	NR	NR	NR	NR	NR

BMI: body mass index, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, IM: intramuscular, IV: intravenous, IQR: interquartile range, kg: kilogram, m: meter, mg: milligram, mL: milliliter, n: number, N: total number, NR: not reported, PBO: placebo, RT-PCR: reverse transcription polymerase chain reaction, SD: standard deviation, US: United States

*Number includes patients in the placebo 1200 mg arm.

†Pooled data from the two intervention arms.

‡No SD available.

§Median (range).

#Age ≥50 years.

¤Congestive heart failure (NYHA class II or more).

**Chronic lung disease including asthma.

††Moderate-to-severe asthma

‡‡Immunocompromised.

§§N=1,353.

##N=1,333.

¤¤N=734.

***N=744.

Table D7. Baseline Characteristics: Phase III Trials (Oral Antivirals)[5,6,8,9]

Drug Name		Molnupiravir		Paxlovid (Nirmatrelvir/Ritonavir)			
Trial		Phase III MOVe-OUT		Phase II/III EPIC-HR		Phase II/III EPIC-SR (Interim)	
Arms		Molnupiravir 800 mg	PBO	Nirmatrelvir 300 mg + Ritonavir 100 mg	PBO	Nirmatrelvir 300 mg + Ritonavir 100 mg	PBO
N		716	717	1,039	1,046	NR	NR
Age, Median Years (IQR)		42 (18-90)*	44 (18-88)*	46†		NR	NR
Age Group, n/N (%)	≥50 Years	232/716 (32)	252/717 (35)	NR	NR	NR	NR
	<65 Years	643/716 (90)	635/717 (89)	NR	NR	NR	NR
	≥65 Years	73/716 (10)	82/717 (11)	NR	NR	NR	NR
Gender, n/N (%)	Male	332/716 (46.4)	366/717 (51)	51%		NR	NR
	Female	384/716 (53.6)	351/717 (49)	49%		NR	NR
Race, n/N (%)	White	400/716 (55.9)	413/717 (57.6)	72%		NR	NR
	Black or African American	40/716 (5.6)	35/717 (4.9)	5%		NR	NR
	Asian	26/716 (3.6)	23/717 (3.2)	14%		NR	NR
	American Indian or Alaska Native	60/716 (8.4)	44/717 (6.1)	NR	NR	NR	NR
	Hispanic or Latino	NR	NR	NR	NR	NR	NR
	Mixed Race	190/716 (26.5)	202/717 (28.2)	NR	NR	NR	NR
	Other	NR	NR	NR	NR	NR	NR
	Unknown	NR	NR	NR	NR	NR	NR
	Not Reported	NR	NR	NR	NR	NR	NR
Ethnicity, n/N (%)	Hispanic or Latino	355/716 (49.6)	356/717 (49.7)	45%		NR	NR
	Not Hispanic or Latino	355/716 (49.6)	358/717 (49.9)	55%		NR	NR
Weight, Median kg (IQR)		NR	NR	NR	NR	NR	NR
BMI Mean kg/m² (SD)		NR	NR	NR	NR	NR	NR
BMI, n/N (%)	<30 kg/m²	178/716 (24.9)	199/717 (27.8)	NR	NR	NR	NR

Drug Name		Molnupiravir		Paxlovid (Nirmatrelvir/Ritonavir)			
Trial		Phase III MOVe-OUT		Phase II/III EPIC-HR		Phase II/III EPIC-SR (Interim)	
Arms		Molnupiravir 800 mg	PBO	Nirmatrelvir 300 mg + Ritonavir 100 mg	PBO	Nirmatrelvir 300 mg + Ritonavir 100 mg	PBO
N		716	717	1,039	1,046	NR	NR
	≥30 kg/m²	538/716 (75.1)	518/717 (72.2)	NR	NR	NR	NR
Overweight, n/N (%)		NR	NR	NR	NR	NR	NR
Positive Baseline Qualitative RT-PCR, n/N (%)		NR	NR	NR	NR	NR	NR
SARS-COV-2 Variant, n/N (%)	Alpha	12/716 (1.7)	9/717 (1.3)	NR	NR	NR	NR
	Gamma	37/716 (5.2)	48/717 (6.7)	NR	NR	NR	NR
	Delta	237/716 (33.1)	223/717 (31.1)	NR	NR	NR	NR
	Mu	76/716 (10.6)	86/717 (12)	NR	NR	NR	NR
	Lambda	14/716 (2)	7/717 (1)	NR	NR	NR	NR
Time from Symptom Onset to Randomization, Median Days (Range)		4†	4†	NR	NR	NR	NR
Time from Symptom Onset to Randomization, n/N (%)	0-3 Days	342/716 (47.8)	342/717 (47.7)	66%		NR	NR
	4-5 Days	374/716 (52.2)	375/717 (52.3)	34%		NR	NR
	4-7 Days	NR	NR	NR	NR	NR	NR
	Unspecified	NR	NR	NR	NR	NR	NR
Duration of Follow-Up, Median Days (SD)		NR	NR	NR	NR	NR	NR
≥1 Risk Factor for Progression to Severe Disease, n/N (%)		712/716 (99.4)	712/717 (99.3)	1039/1039 (100)	1046/1046 (100)	NR	NR
Any Risk Factor for Progression to Severe Disease, n/N (%)	Age ≥55 Years	119/716 (16.6)‡	127/717 (17.7)‡	194/1039 (18.7)‡	225/1046 (21.5)‡	NA	NA
	Obesity (BMI>30)	538/716 (75.1)	518/717 (72.2)	371/1039 (35.7)	373/1046 (35.7)	NA	NA
	CVD or Hypertension	86/716 (12)§	81/717 (11.3)§	NR	NR	NA	NA
	COPD	22/716 (3.1)	35/717 (4.9)	NR	NR	NA	NA
	Asthma	NR	NR	NR	NR	NA	NA

Drug Name		Molnupiravir		Paxlovid (Nirmatrelvir/Ritonavir)			
Trial		Phase III MOVe-OUT		Phase II/III EPIC-HR		Phase II/III EPIC-SR (Interim)	
Arms		Molnupiravir 800 mg	PBO	Nirmatrelvir 300 mg + Ritonavir 100 mg	PBO	Nirmatrelvir 300 mg + Ritonavir 100 mg	PBO
N		716	717	1,039	1,046	NR	NR
	CKD	38/716 (5.3)	46/717 (6.4)	NR	NR	NA	NA
	Diabetes (Type 1 and 2)	107/716 (14.9)	121/717 (16.9)	125/1039 (12)	127/1046 (12.1)	NA	NA
	Immunosuppressive Disease	NR	NR	NR	NR	NA	NA
	Neurological Disorder	NR	NR	NR	NR	NA	NA
	Liver Disease	NR	NR	NR	NR	NA	NA
	High Cholesterol	NR	NR	NR	NR	NA	NA
	Any Other Risk Factors or Comorbidities	NR	NR	NR	NR	NA	NA
Baseline Serum Antibody Status, n/N (%)	Negative	541/716 (75.6)	521/717 (72.7)	47%		NR	NR
	Positive	137/716 (19.1)#	147/717 (20.5)#	53%		NR	NR
	Unknown	38/716 (5.3)	49/717 (6.8)	NR	NR	NR	NR
Baseline Viral Load in Nasopharyngeal Swab, Median log_{10} Copies/mL (Range)		NR	NR	4.63 (2.87)		NR	NR
Geography of Enrollment, n/N (%)	US	45/716 (6.3)	46/717 (6.4)	41%**		NR	NR
	Non-US	671/716 (93.7)	671/717 (93.6)	59%††		NR	NR

BMI: body mass index, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, IQR: interquartile range, kg: kilogram, m: meter, mg: milligram, mL: milliliter, n: number, N: total number, NA: not applicable, NR: not reported, PBO: placebo, RT-PCR: reverse transcription polymerase chain reaction, SD: standard deviation, US: United States

*Median (range). †No SD, IQR, or range available. ‡Age ≥60 years. §Serious heart condition. #These data do not reflect prior vaccination status. ¤Mean (SD). **North America. ††Regions not in North America.

Table D8. Baseline Characteristics: Phase III Trials (Fluvoxamine)[3,66,94,100]

Drug Name		Fluvoxamine					
Trial		TOGETHER		STOP COVID 1		STOP COVID 2	
Arms		Fluvoxamine 100 mg	PBO	Fluvoxamine 100 mg	PBO	Fluvoxamine 100 mg	PBO
N		741	756	80	72	272	275
Age, Median Years (IQR)		50 (39-56)	49 (38-56)	46 (35-58)	45 (36-54)	47 (40-55)	48 (41-56)
Age Group, n/N (%)	≥50 Years	327/741 (44)	328/756 (43)	NR	NR	NR	NR
	<65 Years	NR	NR	NR	NR	NR	NR
	≥65 Years	NR	NR	NR	NR	NR	NR
Gender, n/N (%)	Male	332/741 (45)	303/756 (40)	24/80 (30)	19/72 (26)	103/272 (38)	105/275 (38.2)
	Female	409/741 (55)	453/756 (60)	56/80 (70)	53/72 (74)	169/272 (62)	170/275 (61.8)
Race, n/N (%)	White	6/741 (1)	6/756 (1)	56/80 (70)	50/72 (69)	197/272 (72.4)	201/275 (73.1)
	Black or African American	5/741 (1)	5/756 (1)	18/80 (23)	20/72 (28)	22/272 (8.1)	23/275 (8.4)
	Asian	NR	NR	3/80 (4)	1/72 (1)	8/272 (2.9)	5/275 (1.8)
	American Indian or Alaska Native	NR	NR	0/80 (0)	1/72 (1)	6/272 (2.2)	8/275 (2.9)
	Hispanic or Latino	NR	NR	NR	NR	NR	NR
	Mixed Race	709/741 (96)	719/756 (95)	NR	NR	NR	NR
	Other	NR	NR	2/80 (3)	1/72 (1)	29/272 (10.7)	21/275 (7.6)
	Unknown	21/741 (3)	26/756 (3)	1/80 (1)	0/72 (0)	17/272 (6.3)	22/275 (8)
	Not Reported	NR	NR	NR	NR		
Ethnicity, n/N (%)	Hispanic or Latino	NR	NR	3/80 (4)	2/72 (3)	35/272 (12.7)	37/275 (13.5)
	Not Hispanic or Latino	NR	NR	75/80 (94)	66/72 (92)	234/272 (86)	236/275 (85.8)
Weight, Median kg (IQR)		NR	NR	NR	NR	NR	NR
BMI Mean kg/m² (SD)		NR	NR	NR	NR	NR	NR
BMI, n/N (%)	<30 kg/m²	355/741 (48)	373/756 (49)	38/80 (46)	30/72 (42)	NR	NR
	≥30 kg/m²	376/741 (51)	375/756 (50)	43/80 (54)	42/72 (58)	115/272 (42.3)	123/275 (44.7)
Overweight, n/N (%)		NR	NR	22/80 (28)	22/72 (31)	86/272 (31.6)	90/275 (32.7)
Positive Baseline Qualitative RT-PCR, n/N (%)		NR	NR	NR	NR	NR	NR
SARS-COV-2 Variant, n/N (%)	Alpha	NR	NR	NR	NR	NR	NR
	Gamma	NR	NR	NR	NR	NR	NR
	Delta	NR	NR	NR	NR	NR	NR

Drug Name		Fluvoxamine					
Trial		TOGETHER		STOP COVID 1		STOP COVID 2	
Arms		Fluvoxamine 100 mg	PBO	Fluvoxamine 100 mg	PBO	Fluvoxamine 100 mg	PBO
N		741	756	80	72	272	275
	Mu	NR	NR	NR	NR	NR	NR
	Lambda	NR	NR	NR	NR	NR	NR
Time from Symptom Onset to Randomization, Median Days (Range)		3.8 (1.87)*		4 (3-5)	4 (3-5)	5 (4-6)	5 (4-6)
Time from Symptom Onset to Randomization, n/N (%)	0-3 Days	328/741 (44)	310/756 (41)	NR	NR	NR	NR
	4-5 Days	NR	NR	NR	NR	NR	NR
	4-7 Days	239/741 (32)	267/756 (35)	NR	NR	NR	NR
	Unspecified	174/741 (23)	179/756 (24)	NR	NR	NR	NR
Duration of Follow-Up, Median Days (SD)		NR	NR	NR	NR	NR	NR
≥1 Risk Factor for Progression to Severe Disease, n/N (%)		741/741 (100)	733/733 (100)	NR	NR	NR	NR
Any Risk Factor for Progression to Severe Disease, n/N (%)	Age ≥55 years	327/741 (44)†	328/756 (43)†	NR	NR	NR	NR
	Obesity (BMI>30)	376/741 (51)	375/756 (50)	NR	NR	115/272 (42.3)	123/275 (44.7)
	CVD or Hypertension	115/741 (15)‡	95/756 (13)‡	15/80 (19)	15/72 (21)	59/272 (21.7)‡	66/275 (24)‡
	COPD	6/741 (1)§	3/756 (<1)§	NR	NR	2/272 (0.7)#	2/275 (0.7)#
	Asthma	12/741 (2)	16/756 (2)	17/80 (21)	9/72 (13)	40/272 (15.4)	33/275 (12)
	CKD	2/741 (<1)	2/756 (<1)	NR	NR	1/272 (0.4)¤	2/275 (0.7)¤
	Diabetes (Type 1 and 2)	129/741 (17)	114/756 (12)	9/80 (11)	8/72 (11)	23/272 (8.5)	28/275 (10.2)
	Immunosuppressive Disease	0/741 (0)**	2/756 (<1)**	NR	NR	14/272 (5.2)	4/275 (1.5)
	Neurological Disorder	NR	NR	NR	NR	NR	NR
	Liver Disease	NR	NR	NR	NR	1/272 (0.4)	1/275 (0.4)
	High Cholesterol	NR	NR	7/80 (9)	7/72 (10)	NR	NR
	Any Other Risk Factors or Comorbidities	25/741 (3)	24/756 (3)	NR	NR	42/272 (15.2)††	54/275 (19.6)††
Baseline Serum Antibody Status, n/N (%)	Negative	NR	NR	NR	NR	NR	NR
	Positive	NR	NR	NR	NR	NR	NR
	Unknown	NR	NR	NR	NR	NR	NR

Drug Name		Fluvoxamine					
Trial		TOGETHER		STOP COVID 1		STOP COVID 2	
Arms		Fluvoxamine 100 mg	PBO	Fluvoxamine 100 mg	PBO	Fluvoxamine 100 mg	PBO
N		741	756	80	72	272	275
Baseline Viral Load in Nasopharyngeal Swab, Median log_{10} Copies/mL (Range)		NR	NR	NR	NR	NR	NR
Geography of Enrollment, n/N (%)	US	NA	NA	80/80 (100)	72/72 (100)	272/272 (100)‡‡	275/275 (100)‡‡
	Non-US	741/741 (100)	756/756 (100)	NA	NA	NA	NA

BMI: body mass index, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, IQR: interquartile range, kg: kilogram, m: meter, mg: milligram, mL: milliliter, n: number, N: total number, NA: not applicable, NR: not reported, PBO: placebo, RT-PCR: reverse transcription polymerase chain reaction, SD: standard deviation, US: United States

*Mean (SD).

†Age ≥50 years.

‡Cardiac disease and hypertension summed.

§Chronic pulmonary disease

#Lung disease.

¤Kidney disease.

**Autoimmune disease.

††Other medical condition.

‡‡North America (US and Canada).

Table D9. Baseline Characteristics: Phase I/II Trials (REGEN-COV)[96]

Drug Name		REGEN-COV2 (Casirivimab/Imdevimab)			
Trial		Phase I/II COV-2067 (Non-Hospitalized)			
Arms		REGEN-COV2 2.4 g	REGEN-COV2 8.0 g	REGEN-COV2 Combined	PBO
N		92	90	182	93
Age, Median Years (IQR)		43 (33.5-51)	44 (36-53)	43 (35-52)	45 (34-54)
Age Group, n/N (%)	≥50 Years	NR	NR	NR	NR
	<65 Years	NR	NR	NR	NR
	≥65 Years	NR	NR	NR	NR
Gender, n/N (%)	Male	46/92 (50)	38/90 (42)	84/182 (46)	50/93 (54)
	Female	46/92 (50)	52/90 (58)	98/182 (54)	43/90 (46)
Race, n/N (%)	White	74/92 (80)	78/90 (87)	152/182 (84)	72/93 (77)
	Black or African American	15/92 (16)	6/90 (7)	21/182 (12)	14/93 (15)
	Asian	0/92 (0)	1/90 (1)	1/182 (1)	2/93 (2)
	American Indian or Alaska Native	0/92 (0)	0/90 (0)	0/182 (0)	2/93 (2)
	Hispanic or Latino	NR	NR	NR	NR
	Mixed Race	NR	NR	NR	NR
	Other	NR	NR	NR	NR
	Unknown	0/92 (0)	1/90 (1)	1/182 (1)	2/93 (2)
	Not Reported	3/92 (3)	4/90 (4)	7/182 (4)	1/93 (1)
Ethnicity, n/N (%)	Hispanic or Latino	52/92 (57)	55/90 (61)	107/182 (59)	46/93 (49)
	Not Hispanic or Latino	40/92 (43)	35/90 (39)	75/182 (41)	47/93 (51)
Weight, Median kg (IQR)		85.7 (72.2-97.1)	86.3 (72.6-98.3)	86.1 (72.6-97.3)	83.9 (72.9-97.7)
BMI Mean kg/m² (SD)		30.4 (6.6)	30.6 (7.2)	30.5 (6.9)	29.7 (7.1)
BMI, n/N (%)	<30 kg/m²	53/92 (58)	48/90 (53)	101/182 (55)	59/93 (63)
	≥30 kg/m²	39/92 (42)	42/90 (47)	81/182 (45)	34/93 (37)
Overweight, n/N (%)		NR	NR	NR	NR
Positive Baseline Qualitative RT-PCR, n/N (%)		73/92 (79)	74/90 (82)	147/182 (81)	81/93 (87)
SARS-COV-2 Variant, n/N (%)	Alpha	NR	NR	NR	NR
	Gamma	NR	NR	NR	NR
	Delta	NR	NR	NR	NR
	Mu	NR	NR	NR	NR
	Lambda	NR	NR	NR	NR
Time from Symptom Onset to Randomization, Median Days (range)		3.5 (0-7)	3.0 (0-8)	3.0 (0-8)	3.0 (0-8)

Drug Name		REGEN-COV2 (Casirivimab/Imdevimab)			
Trial		Phase I/II COV-2067 (Non-Hospitalized)			
Arms		REGEN-COV2 2.4 g	REGEN-COV2 8.0 g	REGEN-COV2 Combined	PBO
N		92	90	182	93
Time from Symptom Onset to Randomization, n/N (%)	0-3 Days	NR	NR	NR	NR
	4-5 Days	NR	NR	NR	NR
	4-7 Days	NR	NR	NR	NR
	Unspecified	NR	NR	NR	NR
Duration of Follow-Up, Median days (SD)		NR	NR	NR	NR
≥1 Risk Factor for Progression to Severe Disease, n/N (%)		57/92 (62)	61/90 (68)	118/182 (65)	58/93 (62)
Any Risk Factor for Progression to Severe Disease, n/N (%)	Age ≥55 Years	NR	NR	NR	NR
	Obesity (BMI>30)	39/92 (42)	42/90 (47)	81/182 (45)	34/93 (37)
	CVD or Hypertension	NR	NR	NR	NR
	COPD	NR	NR	NR	NR
	Asthma	NR	NR	NR	NR
	CKD	NR	NR	NR	NR
	Diabetes (Type 1 and 2)	NR	NR	NR	NR
	Immunosuppressive Disease	NR	NR	NR	NR
	Neurological Disorder	NR	NR	NR	NR
	Liver Disease	NR	NR	NR	NR
	High Cholesterol	NR	NR	NR	NR
	Any Other Risk Factors or Comorbidities	NR	NR	NR	NR
Baseline Serum Antibody Status, n/N (%)	Negative	41/92 (45)	39/90 (43)	80/182 (44)	33/93 (35)
	Positive	37/92 (40)	39/90 (43)	76/182 (42)	47/93 (51)
	Unknown	14/92 (15)	12/90 (13)	26/182 (14)	13/93 (14)
Baseline Viral Load in Nasopharyngeal Swab, Median log_{10} Copies/mL (Range)		5.41 (0.0-7.9)*	5.29 (0.0-7.9)†	5.30 (0.0-7.9)‡	4.70 (0.0-7.9)§
Geography of Enrollment, n/N (%)	US	92/92 (100)	90/90 (100)	182/182 (100)	93/93 (100)
	Non-US	NA	NA	NA	NA

BMI: body mass index, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, g: gram, IQR: interquartile range, kg: kilogram, m: meter, mL: milliliter, n: number, N: total number, NA: not applicable, NR: not reported, PBO: placebo, RT-PCR: reverse transcription polymerase chain reaction, SD: standard deviation, US: United States

*N=84. †N=83. ‡N=167. §N=91.

Table D10. Baseline Characteristics: Phase I/II Trials (Molnupiravir)[36]

Drug Name		Molnupiravir							
Trial		Phase II MOVe-OUT				Phase IIa Study 2003 (Fischer 2021)			
Arms		Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo
N		75	77	76	74	23	62	55	62
Age, Median Years (IQR)		NR	NR	NR	NR	32.0 (19-65)	42.5 (19-82)	42.0 (18-68)	39.0 (19-71)
Age Group, n/N (%)	≥50 Years	NR	NR	NR	NR	NR	NR	NR	NR
	<65 Years	NR	NR	NR	NR	22/23 (95.7)	59/62 (95.2)	51/55 (92.7)	59/62 (95.2)
	≥65 Years	NR	NR	NR	NR	1/23 (4.3)	3/62 (4.8)	4/55 (7.3)	3/62 (4.8)
Gender, n/N (%)	Male	NR	NR	NR	NR	12/23 (52.2)	30/62 (48.4)	28/55 (50.9)	28/62 (45.2)
	Female	NR	NR	NR	NR	11/23 (47.8)	32/62 (51.6)	27/55 (49.1)	34/62 (54.8)
Race, n/N (%)	White	NR	NR	NR	NR	17/23 (73.9)	56/62 (90.3)	49/55 (89.1)	54/62 (87.1)
	Black or African American	NR	NR	NR	NR	3/23 (13.0)	3/62 (4.8)	3/55 (5.5)	2/62 (3.2)
	Asian	NR	NR	NR	NR	1/23 (4.3)	2/62 (3.2)	1/55 (1.8)	2/62 (3.2)
	American Indian or Alaska Native	NR	NR	NR	NR	NR	NR	NR	NR
	Hispanic or Latino	NR	NR	NR	NR	NR	NR	NR	NR
	Mixed Race	NR	NR	NR	NR	0/23 (0)	1/62 (1.6)	0/55 (0)	3/62 (4.8)
	Other	NR	NR	NR	NR	2/23 (8.7)	0/62 (0)	2/55 (3.6)	1/62 (1.6)
	Unknown	NR	NR	NR	NR	NA	NA	NA	NA
	Not Reported	NR	NR	NR	NR	NA	NA	NA	NA
Ethnicity, n/N (%)	Hispanic or Latino	NR	NR	NR	NR	7/23 (30.4)	23/62 (37.1)	33/55 (60)	23/62 (37.1)
	Not Hispanic or Latino	NR	NR	NR	NR	16/23 (69.6)	39/62 (62.9)	22/55 (40)	39/62 (62.9)
Weight, Median kg (IQR)		NR	NR	NR	NR	NR	NR	NR	NR
BMI Mean kg/m² (SD)		NR	NR	NR	NR	25.5*	26.7*	27*	27.1*
BMI, n/N (%)	<30 kg/m²	NR	NR	NR	NR	16/23 (69.6)	44/62 (71)	40/55 (72.7)	46/62 (74.2)
	≥30 kg/m²	NR	NR	NR	NR	7/23 (30.4)	18/62 (29)	15/55 (27.3)	16/62 (25.8)
Overweight, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Positive Baseline Qualitative RT-PCR, n/N (%)		NR	NR	NR	NR	11/22 (50.0)	18/43 (41.9)	20/52 (38.5)	25/53 (47.2)
	Alpha	NR	NR	NR	NR	NR	NR	NR	NR
	Gamma	NR	NR	NR	NR	NR	NR	NR	NR

Drug Name		Molnupiravir							
Trial		Phase II MOVe-OUT				Phase IIa Study 2003 (Fischer 2021)			
Arms		Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo
N		75	77	76	74	23	62	55	62
SARS-COV-2 Variant, n/N (%)	Delta	NR	NR	NR	NR	NR	NR	NR	NR
	Mu	NR	NR	NR	NR	NR	NR	NR	NR
	Lambda	NR	NR	NR	NR	NR	NR	NR	NR
Time from Symptom Onset to Randomization, Median Days (Range)		NR	NR	NR	NR	4.0 (1.8-7.0)	4.9 (2.5-7.1)	4.6 (1.4-7.1)	4.6 (1.8-7.5)
Time from Symptom Onset to Randomization, n/N (%)	0-3 Days	NR	NR	NR	NR	NR	NR	NR	NR
	4-5 Days	NR	NR	NR	NR	NR	NR	NR	NR
	4-7 Days	NR	NR	NR	NR	NR	NR	NR	NR
	Unspecified	NR	NR	NR	NR	NR	NR	NR	NR
Duration of Follow-Up, Median Days (SD)		NR	NR	NR	NR	NR	NR	NR	NR
≥1 Risk Factor for Progression to Severe Disease, n/N (%)		NR	NR	NR	NR	15/23 (65.2)	37/62 (59.7)	33/55 (60.0)	37/62 (59.7)
Any Risk Factor for Progression to Severe Disease, n/N (%)	Age ≥55 Years	NR	NR	NR	NR	NR	NR	NR	NR
	Obesity (BMI>30)	NR	NR	NR	NR	NR	NR	NR	NR
	CVD or Hypertension	NR	NR	NR	NR	NR	NR	NR	NR
	COPD	NR	NR	NR	NR	NR	NR	NR	NR
	Asthma	NR	NR	NR	NR	NR	NR	NR	NR
	CKD	NR	NR	NR	NR	NR	NR	NR	NR
	Diabetes (Type 1/2)	NR	NR	NR	NR	NR	NR	NR	NR
	Immunosuppressive Disease	NR	NR	NR	NR	NR	NR	NR	NR
	Neurological Disorder	NR	NR	NR	NR	NR	NR	NR	NR
	Liver disease	NR	NR	NR	NR	NR	NR	NR	NR
	High Cholesterol	NR	NR	NR	NR	NR	NR	NR	NR
	Any Other Risk Factors or Comorbidities	NR	NR	NR	NR	NR	NR	NR	NR
	Negative	NR	NR	NR	NR	NR	NR	NR	NR

Drug Name		Molnupiravir							
Trial		Phase II MOVe-OUT				Phase IIa Study 2003 (Fischer 2021)			
Arms		Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo
N		75	77	76	74	23	62	55	62
Baseline Serum Antibody Status, n/N (%)	Positive	NR	NR	NR	NR	3/20 (15.0)	15/50 (30.0)	18/51 (35.3)	10/55 (18.2)
	Unknown	NR	NR	NR	NR	NR	NR	NR	NR
Baseline Viral Load in Nasopharyngeal Swab, Median log_{10} Copies/mL (Range)		NR	NR	NR	NR	7.25 (3.0-9.5)	6.72 (3.0-9.9)	6.12 (3.0-9.4)	6.40 (3.0-9.3)
Geography of Enrollment, n/N (%)	US	NR	NR	NR	NR	23/23 (100)	62/62 (100)	55/55 (100)	62/62 (100)
	Non-US	NR	NR	NR	NR	NR	NR	NR	NR

BMI: body mass index, COPD: chronic obstructive pulmonary disease, IQR: interquartile range, kg: kilogram, m: meter, mg: milligram, mL: milliliter, n: number, N: total number, NA: not applicable, NR: not reported, RT-PCR: reverse transcription polymerase chain reaction, SD: standard deviation, US: United States

*No SD available.

Table D11. Efficacy Outcomes Phase III Trials[2,4,27,47,95]

Drug Name		REGEN-COV2 (Casirivimab/Imdevimab)				Sotrovimab			
Trial		Phase III COV-2067 (Non-Hospitalized)				COMET-ICE		COMET-TAIL	
Arms		REGEN-COV 2400 mg	Placebo 2400 mg	REGEN-COV 1200 mg	Placebo 1200 mg	Sotrovimab 500 mg	Placebo	Sotrovimab 500 mg (IM)	Sotrovimab 500 mg (IV)
N		1355	1341*	736	748	528	529	376	378
Timepoint		29 Days				29 Days		29 Days	
≥1 Any-Cause Medically-Attended Visit, n/N (%)		43/1355 (3.2)	109/1341 (8.1)	20/736 (2.7)	51/748 (6.8)	NR	NR	NR	NR
Type of Any-Cause Medically-Attended Visit, n/N (%)	ED	NR	NR	NR	NR	6/528 (1)	10/529 (2)	NR	NR
	Hospitalization	NR	NR	NR	NR	7/528 (1)	29/529 (5)	NR	NR
	ICU Admission	6/1355 (0.4)	18/1341 (1.3)	3/736 (0.4)	7/738 (0.9)	0/528 (0)	10/529 (1.9)	NR	NR
≥1 COVID-Related Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Type of COVID-19 Related Medically-Attended Visit, n/N (%)	Outpatient Visit	13/1355 (1)†	24/1341 (1.8)†	10/736 (1.4)†	12/748 (1.6)†	NR	NR	NR	NR
	Urgent Care	3/1355 (0.2)	7/1341 (0.5)	1/736 (0.1)	5/748 (0.7)	NR	NR	NR	NR
	ED	9/1355 (0.7)	16/1341 (1.2)	2/736 (0.3)	10/748 (1.3)	NR	NR	NR	NR
	Hospitalization	17/1355 (1.3)	59/1341 (4.4)	6/736 (0.8)	23/748 (3.1)	3/528 (0.6)	NR	NR	NR
	ICU Admission	NR	NR	NR	NR	NR	NR	NR	NR
COVID-Related Hospitalization or Any-Cause Death, n/N (%)		18/1855 (1.3)	62/1341 (4.6)	7/736 (1)	24/748 (3.2)	NR	NR	NR	NR
Relative Risk Reduction vs. Placebo of Primary Outcome (Hospitalization or All-Cause Death), % (95% CI)		71.3 (51.7 - 82.9)‡		70.4 (31.6 - 87.1)‡		79 (50-91)§		NR	NR
Hospitalized or Death from Any Cause, n/N (%)		20/1355 (1.5)	66/1341 (4.9)	7/736 (1)	26/748 (3.5)	7/528 (1)	30/529 (6)	10/376 (2.7)§	5/378 (1.3)§
Time to Hospitalization, Median Days (IQR)		NR	NR	NR	NR	NR	NR	NR	NR
Hospital Length of Stay, Median Days (IQR)		6 (3-11)	7 (5-13)	4 (3-6)	5.5 (4-10.5)	NR	NR	NR	NR

Drug Name		REGEN-COV2 (Casirivimab/Imdevimab)				Sotrovimab			
Trial		Phase III COV-2067 (Non-Hospitalized)				COMET-ICE		COMET-TAIL	
Arms		REGEN-COV 2400 mg	Placebo 2400 mg	REGEN-COV 1200 mg	Placebo 1200 mg	Sotrovimab 500 mg	Placebo	Sotrovimab 500 mg (IM)	Sotrovimab 500 mg (IV)
N		1355	1341*	736	748	528	529	376	378
Timepoint		29 Days				29 Days		29 Days	
ED Observation for ≥6 Hours or Hospitalization from COVID-19, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Time to ED Visit for ≥6 Hours, Median Days (IQR)		NR	NR	NR	NR	NR	NR	NR	NR
Mortality, n/N (%)		1 (<0.1)	3 (0.2)	1 (0.1)	1 (0.1)	0/528 (0)	2/529 (<1)	NR	NR
Time to Death, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR	NR
Time to Symptom Resolution, Mean Days (SD)		10#	14#	10#	14#	NR	NR	NR	NR
Ventilation Requirement, n/N (%)	Non-Invasive Ventilation	NR	NR	NR	NR	0/528 (0)	10/529 (2)	NR	NR
	Mechanical Ventilation	1/1355 (<0.1)	6/1341 (0.4)	1/736 (0.1)	2/748 (0.3)	0/528 (0)	4/529 (<1)	NR	NR
Time to SARS-Cov-2 Clearance, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR	NR
Viral Clearance, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Change from Baseline in SARS-CoV-2 Viral Load, LSM log_{10} Copies/mL (SE)	Day 5	NR	NR	NR	NR	NR	NR	NR	NR
	Day 7	-3.52 (0.08)††	-2.67 (0.08)‡‡	-3.35 (0.08)§§	NR	-2.59¤ (-2.71, -2.47) **	-2.36¤ (-2.48, -2.24) **	NR	NR
Difference from Placebo in Change from Baseline in SARS-CoV-2 Viral Load, log10 Copies/mL (95% CI)		NR	NR	NR	NR	NR	NR	NR	NR
Adherence, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR

CI: confidence interval, ER: emergency room, ICU: intensive care unit, IQR: interquartile range, IM: intramuscular, IV: intravenous, LSM: least squares mean, mg: milligram, mL: milliliter, n: number, N: total number, NR: not reported, SD: standard deviation, SE: standard error, vs.: versus

*Number includes patients in the placebo 1200 mg arm. †Physician office/telemedicine visit. ‡Primary outcome is COVID-19-related hospitalization or death. §Primary outcome is hospitalization >24 hours or death. #Median (no SD available). ¤Day 8 timepoint. **LSM (95% CI). ††N=736. ‡‡N=744. §§N=734.

Table D12. Efficacy Outcomes: Phase III Trials (Oral Antivirals)[5-9]

Drug Name		Molnupiravir		Paxlovid (Nirmatrelvir/Ritonavir)			
Trial		Phase III MOVe-OUT		Phase II/III EPIC-HR		Phase II/III EPIC-SR (Interim)	
Arms		Molnupiravir 800 mg	Placebo	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
N		709	699	1,039	1,046	333	329
Timepoint		29 Days		28 Days		28 Days	
≥1 Any-Cause Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	NR	NR
Type of Any-Cause Medically-Attended Visit, n/N (%)	ED	NR	NR	NR	NR	NR	NR
	Hospitalization	48/709 (6.8)	67/699 (9.6)	NR	NR	NR	NR
	ICU Admission	NR	NR	NR	NR	NR	NR
≥1 COVID-Related Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	NR	NR
Type of COVID-19 Related Medically-Attended Visit, n/N (%)	Outpatient Visit	NR	NR	NR	NR	NR	NR
	Urgent Care	NR	NR	NR	NR	NR	NR
	ED	NR	NR	NR	NR	NR	NR
	Hospitalization	NR	NR	8/1039 (0.8)	66/1046 (6.3)	2/333 (0.6)	8/329 (2.4)
	ICU Admission	NR	NR	NR	NR	NR	NR
COVID-Related Hospitalization or Any-Cause Death, n/N (%)		45/709 (6.3)	64/699 (9.2)	8/1039 (0.8)	66/1046 (6.3)	2/333 (0.6)	8/329 (2.4)
Relative Risk Reduction vs. Placebo of Primary Outcome (Hospitalization or All-Cause Death), % (95% CI)		30%*		88%*†		70%*†	
Hospitalized or Death from Any Cause, n/N (%)		48/709 (6.8)	68/699 (9.7)	NR	NR	NR	NR
Time to Hospitalization, Median Days (IQR)		NR	NR	NR	NR	NR	NR
Hospital Length of Stay, Median Days (IQR)		NR	NR	NR	NR	NR	NR
ED Observation for ≥6 Hours or Hospitalization from COVID-19, n/N (%)		NR	NR	NR	NR	NR	NR

Drug Name		Molnupiravir		Paxlovid (Nirmatrelvir/Ritonavir)			
Trial		Phase III MOVe-OUT		Phase II/III EPIC-HR		Phase II/III EPIC-SR (Interim)	
Arms		Molnupiravir 800 mg	Placebo	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
N		709	699	1,039	1,046	333	329
Timepoint		29 Days		28 Days		28 Days	
Time to ED Visit for ≥6 Hours, Median Days (IQR)		NR	NR	NR	NR	NR	NR
Mortality, n/N (%)		1/709 (0.1)	9/699 (1.3)	0/1039 (0)	12/1046 (1.1)	0/333 (0)	0/329 (0)
Time to Death, Mean Days (SD)		NR	NR	NR	NR	NR	NR
Time to Symptom Resolution, Mean Days (SD)		NR	NR	NR	NR	NR	NR
Ventilation Requirement, n/N (%)	Non-Invasive Ventilation	NR	NR	NR	NR	NR	NR
	Mechanical Ventilation	NR	NR	NR	NR	NR	NR
Time to SARS-Cov-2 Clearance, Mean Days (SD)		NR	NR	NR	NR	NR	NR
Viral Clearance, n/N (%)		NR	NR	NR	NR	NR	NR
Change from Baseline in SARS-CoV-2 Viral Load, LSM log_{10} Copies/mL (SE)	Day 5	NR	NR	NR	NR	NR	NR
	Day 7	NR	NR	NR	NR	NR	NR
Difference from Placebo in Change from Baseline in SARS-CoV-2 Viral Load, log10 Copies/mL (95% CI)		-0.33 (-0.5, -0.16)‡	REF	-0.93†‡	REF	-1†‡	REF
Adherence, n/N (%)		NR	NR	NR	NR	NR	NR

CI: confidence interval, ER: emergency room, ICU: intensive care unit, IQR: interquartile range, IM: intramuscular, IV: intravenous, LSM: least squares mean, mg: milligram, mL: milliliter, n: number, N: total number, NR: not reported, REF: reference, SD: standard deviation, SE: standard error, vs: versus

*Primary outcome is COVID-19-related hospitalization or death.

†No 95% CI available.

‡Day 5 timepoint.

Table D13. Efficacy Outcomes: Phase III Trials (Fluvoxamine)[3,66,94]

Drug Name		Fluvoxamine					
Trial		TOGETHER		STOP COVID 1		STOP COVID 2	
Arms		Fluvoxamine 100 mg	Placebo	Fluvoxamine 100 mg	Placebo	Fluvoxamine 100 mg	Placebo
N		741	756	80	72	272	275
Timepoint		28 Days		15 Days		15 Days	
≥1 Any-Cause Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	NR	NR
Type of Any-Cause Medically-Attended Visit, n/N (%)	ED	7/741 (1)*	36/756 (5)*	NR	NR	NR	NR
	Hospitalization	76/741 (10)	99/756 (13)	NR	NR	11/272 (4.0)	12/275 (4.4)
	ICU Admission	NR	NR	NR	NR	NR	NR
≥1 COVID-Related Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	NR	NR
Type of COVID-19 Related Medically-Attended Visit, n/N (%)	Outpatient Visit	NR	NR	NR	NR	NR	NR
	Urgent Care	NR	NR	NR	NR	NR	NR
	ED	NR	NR	NR	NR	NR	NR
	Hospitalization	75/741 (10)	97/756 (13)	NR	NR	9/272 (3.3)	10/275 (3.6)
	ICU Admission	NR	NR	NR	NR	NR	NR
COVID-Related Hospitalization or Any-Cause Death, n/N (%)		NR	NR	NR	NR	NR	NR
Relative Risk Reduction vs. Placebo of Primary Outcome (Hospitalization or All-Cause Death), % (95% CI)		32 (12-48)†		NR	NR	NR	NR
Hospitalized or Death from Any Cause, n/N (%)		NR	NR	NR	NR	NR	NR
Time to Hospitalization, Median Days (IQR)		5 (3-7)	5 (3-7.5)	NR	NR	NR	NR
Hospital Length of Stay, Median days (IQR)		8 (5-13)	6 (3-10.75)	NR	NR	NR	NR
ED Observation for ≥6 Hours or Hospitalization from COVID-19, n/N (%)		79/741 (11)	119/756 (16)	NR	NR	NR	NR

Drug Name		Fluvoxamine					
Trial		TOGETHER		STOP COVID 1		STOP COVID 2	
Arms		Fluvoxamine 100 mg	Placebo	Fluvoxamine 100 mg	Placebo	Fluvoxamine 100 mg	Placebo
N		741	756	80	72	272	275
Timepoint		28 Days		15 Days		15 Days	
Time to ED Visit for ≥6 Hours, Median Days (IQR)		4 (3-7)	5 (3-8.25)	NR	NR	NR	NR
Mortality, n/N (%)		17/741 (2)	25/756 (3)	NR	NR	NR	NR
Time to Death, Mean Days (SD)		17 (9-21)‡	14 (8-20)‡	NR	NR	NR	NR
Time to Symptom Resolution, Mean Days (SD)		NR	NR	NR	NR	NR	NR
Ventilation Requirement, n/N (%)	Non-Invasive Ventilation	NR	NR	0/80 (0)	0/72 (0)	NR	NR
	Mechanical Ventilation	26§	34§	0/80 (0)	1/72 (1.4)	NR	NR
Time to SARS-Cov-2 Clearance, Mean Days (SD)		NR	NR	NR	NR	NR	NR
Viral Clearance, n/N (%)		40/207 (19)#	58/221 (26)#	NR	NR	NR	NR
Change from Baseline in SARS-CoV-2 Viral Load, LSM log_{10} copies/mL (SE)	Day 5	NR	NR	NR	NR	NR	NR
	Day 7	NR	NR	NR	NR	NR	NR
Difference from Placebo in Change from Baseline in SARS-CoV-2 Viral Load, log10 Copies/mL (95% CI)		NR	NR	NR	NR	NR	NR
Adherence, n/N (%)		548/741 (74)	618/738 (82)	NR	NR	NR	NR

CI: confidence interval, ER: emergency room, ICU: intensive care unit, IQR: interquartile range, IM: intramuscular, IV: intravenous, LSM: least squares mean, mg: milligram, mL: milliliter, n: number, N: total number, NR: not reported, SD: standard deviation, SE: standard error, vs.: versus

*ED visits ≥6 hours. †Primary outcome is ED visits ≥6 hours or COVID-related hospitalization, ‡Median (IQR). §Unclear in publication whether these values were reported as percentages or numbers of patients. #Day 7 timepoint.

Table D14. Efficacy Outcomes: Phase I/II Trials (REGEN-COV)[96]

Drug Name		REGEN-COV2 (Casirivimab/Imdevimab)			
Trial		Phase I/II COV-2067 (Non-Hospitalized)			
Arms		REGEN-COV2 2.4 g	REGEN-COV2 8.0 g	REGEN-COV2 Combined	Placebo
N		92	90	182	93
Timepoint		29 Days			
≥1 Any-Cause Medically-Attended Visit, n/N (%)		NR	NR	NR	NR
Type of Any-Cause Medically-Attended Visit, n/N (%)	ED	NR	NR	NR	NR
	Hospitalization	NR	NR	NR	NR
	ICU Admission	NR	NR	NR	NR
≥1 COVID-Related Medically-Attended Visit, n/N (%)		3/92 (3)	3/90 (3)	6/182 (3)	6/93 (6)
Type of COVID-19 Related Medically-Attended Visit, n/N (%)	Outpatient Visit	NR	NR	NR	NR
	Urgent Care	NR	NR	NR	NR
	ED	NR	NR	NR	NR
	Hospitalization	NR	NR	NR	NR
	ICU Admission	NR	NR	NR	NR
COVID-Related Hospitalization or Any-Cause Death, n/N (%)		NR	NR	NR	NR
Relative Risk Reduction vs. Placebo of Primary Outcome (Hospitalization or All-Cause Death), % (95% CI)		NR	NR	NR	NR
Hospitalized or Death from Any Cause, n/N (%)		NR	NR	NR	NR
Time to Hospitalization, Median Days (IQR)		NR	NR	NR	NR
Hospital Length of Stay, Median Days (IQR)		NR	NR	NR	NR
ED Observation for ≥6 Hours or Hospitalization from COVID-19, n/N (%)		NR	NR	NR	NR
Time to ED Visit for ≥6 Hours, Median Days (IQR)		NR	NR	NR	NR
Mortality, n/N (%)		NR	NR	NR	NR
Time to Death, Mean Days (SD)		NR	NR	NR	NR
Time to Symptom Resolution, Mean Days (SD)		NR	NR	NR	NR
Ventilation Requirement, n/N (%)	Non-Invasive Ventilation	NR	NR	NR	NR
	Mechanical Ventilation	NR	NR	NR	NR
Time to SARS-Cov-2 Clearance, Mean Days (SD)		NR	NR	NR	NR
Viral Clearance, n/N (%)		NR	NR	NR	NR
Change from Baseline in SARS-CoV-2 Viral Load, LSM log_{10} Copies/mL (SE)	Day 5	NR	NR	NR	NR
	Day 7	-1.60 (0.14)	-1.90 (0.14)	-1.74 (0.11)	-1.34 (0.13)

Drug Name	REGEN-COV2 (Casirivimab/Imdevimab)			
Trial	**Phase I/II COV-2067 (Non-Hospitalized)**			
Arms	**REGEN-COV2 2.4 g**	**REGEN-COV2 8.0 g**	**REGEN-COV2 Combined**	**Placebo**
N	**92**	**90**	**182**	**93**
Timepoint	**29 Days**			
Difference from Placebo in Change from Baseline in SARS-CoV-2 Viral Load, log10 Copies/mL (95% CI)	NR	NR	NR	NR
Adherence, n/N (%)	NR	NR	NR	NR

CI: confidence interval, ER: emergency room, g: gram, ICU: intensive care unit, IQR: interquartile range, IM: intramuscular, IV: intravenous, LSM: least squares mean, mL: milliliter, n: number, N: total number, NR: not reported, SD: standard deviation, SE: standard error, vs: versus

Table D15. Efficacy Outcomes: Phase I/II Trials (Molnupiravir)[5,36]

Drug Name		Molnupiravir							
Trial		Phase II MOVe-OUT				Phase IIa Study 2003 (Fischer 2021)			
Arms		Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo
N		75	77	76	74	23	62	55	62
Timepoint		29 Days				28 Days			
≥1 Any-Cause Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Type of Any-Cause Medically-Attended Visit, n/N (%)	ED	NR	NR	NR	NR	NR	NR	NR	NR
	Hospitalization	NR	NR	NR	NR	NR	NR	NR	NR
	ICU Admission	NR	NR	NR	NR	NR	NR	NR	NR
≥1 COVID-Related Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	3/23 (13)	4/62 (6.5)	5/55 (9.1)	5/62 (8.1)
Type of COVID-19 Related Medically-Attended Visit, n/N (%)	Outpatient visit	NR	NR	NR	NR	NR	NR	NR	NR
	Urgent Care	NR	NR	NR	NR	NR	NR	NR	NR
	ED	NR	NR	NR	NR	NR	NR	NR	NR
	Hospitalization	NR	NR	NR	NR	NR	NR	NR	NR
	ICU Admission	NR	NR	NR	NR	NR	NR	NR	NR
COVID-Related Hospitalization or Any-Cause Death, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Relative Risk Reduction vs. Placebo of Primary Outcome (Hospitalization or All-Cause Death), % (95% CI)		NR	NR	NR	NR	NR	NR	NR	NR
Hospitalized or Death from Any Cause, n/N (%)		1/74 (1.4)	3/77 (3.9)	3/74 (4.1)	4/74 (5.4)	NR	NR	NR	NR
Time to Hospitalization, Median Days (IQR)		NR	NR	NR	NR	NR	NR	NR	NR
Hospital Length of Stay, Median Days (IQR)		NR	NR	NR	NR	NR	NR	NR	NR
ED Observation for ≥6 Hours or Hospitalization from COVID-19, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR

Drug Name		Molnupiravir							
Trial		Phase II MOVe-OUT				Phase IIa Study 2003 (Fischer 2021)			
Arms		Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo
N		75	77	76	74	23	62	55	62
Timepoint		29 Days				28 Days			
Time to ED Visit for ≥6 Hours, Median Days (IQR)		NR	NR	NR	NR	NR	NR	NR	NR
Mortality, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Time to Death, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR	NR
Time to Symptom Resolution, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR	NR
Ventilation Requirement, n/N (%)	Non-Invasive Ventilation	NR	NR	NR	NR	NR	NR	NR	NR
	Mechanical Ventilation	NR	NR	NR	NR	NR	NR	NR	NR
Time to SARS-Cov-2 Clearance, Mean Days (SD)		NR	NR	NR	NR	22.0 (15.0, 28.0)*	27.0 (15.0, 28.0)*	14.0 (13.0, 14.0)*	15.0 (15.0, 27.0)*
Viral Clearance, n/N (%)		NR	NR	NR	NR	21/23 (91.3)	49/62 (78.7)	51/55 (92.5)	50 (80.3)
Change from Baseline in SARS-CoV-2 Viral Load, LSM log_{10} Copies/mL (SE)	Day 5	NR	NR	NR	NR	-1.47 (0.21)	-1.75 (0.13)†	-1.87 (0.13)‡	-1.32 (0.15)§
	Day 7	NR	NR	NR	NR	-2.03 (0.20)	-2.26 (0.12)#	-2.49 (0.11)¤	-1.95 (0.16)†
Difference from Placebo in Change from Baseline in SARS-CoV-2 Viral Load, log10 Copies/mL (95% CI)		NR	NR	NR	NR	-0.08 (-0.59, 0.44)	-0.31 (-0.7, 0.08)	-0.53 (-0.91, -0.16)	REF
Adherence, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR

CI: confidence interval, ER: emergency room, ICU: intensive care unit, IQR: interquartile range, IM: intramuscular, IV: intravenous, LSM: least squares mean, mg: milligram, mL: milliliter, n: number, N: total number, NR: not reported, REF: reference, SD: standard deviation, SE: standard error, vs: versus
*Median (95% CI). †N=56. ‡N=52. §N=57. #N=52. ¤N=49.

Table D16. Subgroup Efficacy: Primary Outcome[6,7,9]

Study Name	Subgroup Category	Arms	N	Timepoint	Hospitalization or Any-Cause Death, n/N (%)†
Molnupiravir					
Phase III MOVe-OUT	**Time from Symptom Onset ≤3 Days**	**Molnupiravir 800 mg**	339	29 days	25/339 (7.4)
		Placebo	335		28/335 (8.4)
	Time from Symptom Onset >3 days	**Molnupiravir 800 mg**	370	29 days	23/370 (6.2)
		Placebo	364		40/364 (11)
	Age ≤60 Years	**Molnupiravir 800 mg**	591	29 days	36/591 (6.1)
		Placebo	572		52/572 (9.1)
	Age >60 Years	**Molnupiravir 800 mg**	118	29 days	12/118 (10.2)
		Placebo	127		16/127 (12.6)
	Obesity (BMI ≥30)	**Molnupiravir 800 mg**	535	29 days	29/535 (5.4)
		Placebo	507		46/507 (9.1)
	No Obesity (BMI <30)	**Molnupiravir 800 mg**	174	29 days	19/174 (10.9)
		Placebo	192		22/192 (11.5)
	Diabetes	**Molnupiravir 800 mg**	107	29 days	17/107 (15.9)
		Placebo	117		17/117 (14.5)
	No Diabetes	**Molnupiravir 800 mg**	602	29 days	31/602 (5.1)
		Placebo	582		51/582 (8.8)
	Mild COVID Severity	**Molnupiravir 800 mg**	395	29 days	19/395 (4.8)
		Placebo	376		27/376 (7.2)
	Moderate COVID Severity	**Molnupiravir 800 mg**	311	29 days	29/311 (9.3)
		Placebo	321		40/321 (12.5)
	Gamma Variant	**Molnupiravir 800 mg**	37	29 days	0/37 (0)
		Placebo	47		9/47 (19.1)
	Delta Variant	**Molnupiravir 800 mg**	237	29 days	18/237 (7.6)
		Placebo	221		22/221 (10)
	Mu Variant	**Molnupiravir 800 mg**	75	29 days	6/75 (8)
		Placebo	82		13/82 (15.9)
	Positive Antibody Status	**Molnupiravir 800 mg**	136	29 days	5/136 (3.7)
		Placebo	146		2/146 (1.4)
	Negative Antibody Status	**Molnupiravir 800 mg**	541	29 days	39/541 (7.2)
		Placebo	520		64/520 (12.3)
	North America Region	**Molnupiravir 800 mg**	42	29 days	4/42 (9.5)

Study Name	Subgroup Category	Arms	N	Timepoint	Hospitalization or Any-Cause Death, n/N (%)†
		Placebo	45		5/45 (11.1)
	Latin America Region	**Molnupiravir 800 mg**	329	29 days	22/329 (6.7)
		Placebo	321		34/321 (10.6)
	European Region	**Molnupiravir 800 mg**	229	29 days	13/229 (5.7)
		Placebo	233		18/233 (7.7)
	Africa Region	**Molnupiravir 800 mg**	90	29 days	4/90 (4.4)
		Placebo	84		7/84 (8.3)
Phase II MOVe-OUT	**Symptom Onset ≤5 Days and 1 Risk Factor**	**Molnupiravir 200 mg**	38	29 days	1/38 (2.6)
		Molnupiravir 400 mg	38		2/38 (5.3)
		Molnupiravir 800 mg	31		1/31 (3.2)
		Placebo	34		4/34 (11.8)
	Age >60 Years	**Molnupiravir 200 mg**	18	29 days	0/18 (0)
		Molnupiravir 400 mg	17		1/17 (5.9)
		Molnupiravir 800 mg	20		1/20 (5)
		Placebo	14		3/14 (21.4)
Paxlovid					
Phase II/III EPIC-HR*	**Time from Symptom Onset ≤3 Days**	**Nirmatrelvir 300 mg + Ritonavir 100 mg**	697	28 days	5/697 (0.7)
		Placebo	682		44/682 (6.5)
	Time from Symptom Onset >3 Days	**Nirmatrelvir 300 mg + Ritonavir 100 mg**	342	28 days	3/342 (0.9)
		Placebo	364		22/364 (6)
	Age ≥65 Years	**Nirmatrelvir 300 mg + Ritonavir 100 mg**	94	28 days	1/94 (1.1)
		Placebo	98		16/98 (16.3)
	Age ≤65 Years	**Nirmatrelvir 300 mg + Ritonavir 100 mg**	845	28 days	7/845 (0.8)
		Placebo	821		37/821 (4.5)
	Age >60 Years	**Nirmatrelvir 300 mg + Ritonavir 100 mg**	194	28 days	1/194 (0.5)
		Placebo	225		29/225 (12.9)
	No Obesity (BMI <30)	**Nirmatrelvir 300 mg + Ritonavir 100 mg**	667	28 days	4/667 (0.6)
		Placebo	673		37/673 (5.5)

Study Name	Subgroup Category	Arms	N	Timepoint	Hospitalization or Any-Cause Death, n/N (%)†
	Obesity (BMI ≥30)	**Nirmatrelvir 300 mg + Ritonavir 100 mg**	371	28 days	4/371 (1.1)
		Placebo	373		29/373 (7.8)
	Diabetes	**Nirmatrelvir 300 mg + Ritonavir 100 mg**	125	28 days	2/125 (1.6)
		Placebo	127		9/127 (7.2)
	No Diabetes	**Nirmatrelvir 300 mg + Ritonavir 100 mg**	913	28 days	6/913 (0.7)
		Placebo	919		57/919 (6.2)
	Negative Antibody Status	**Nirmatrelvir 300 mg + Ritonavir 100 mg**	487	28 days	7/487 (1.4)
		Placebo	505		58/505 (11.5)
	Positive Antibody Status	**Nirmatrelvir 300 mg + Ritonavir 100 mg**	540	28 days	1/540 (0.2)
		Placebo	528		8/528 (1.5)

BMI: body mass index, mg: milligram, n: number, N: total number

*Primary outcome in Paxlovid trial is COVID-19-related hospitalization or death.

†Primary outcome was not available in subgroups of fluvoxamine and sotrovimab trials.

Table D17. Patient-Reported Outcomes (PROs)[2-4,100]

Drug Name	Sotrovimab		Fluvoxamine			
Trial*	**COMET-ICE**		**STOP COVID 2**		**TOGETHER**	
Arms	**Sotrovimab 500 mg**	**Placebo**	**Fluvoxamine 100 mg**	**Placebo**	**Fluvoxamine 100 mg**	**Placebo**
N	**528**	**529**	**272**	**275**	**739**	**733**
Timepoint	**7 Days**		**15 Days**		**28 Days**	
PROMIS Global Health Scale, Mean (SD)	NR	NR	No difference		No difference	
Change in FLU-PRO Plus Total Score, Mean (95% CI)	3.1 (-3.3, -2.4)†	-2.0 (-2.2, -1.8)	NR	NR	NR	NR

CI: confidence interval, IM: intramuscular, IV: intravenous, mg: milligram, N: total number, NR: not reported, SD: standard deviation

*There were no PRO data available for REGEN-COV, molnupiravir, or Paxlovid trials.

†N=412.

‡N=399.

Table D18. Adverse Events: Phase III Trials (Monoclonal Antibodies)[2,4,27,47]

Drug Name		REGEN-COV2 (Casirivimab/Imdevimab)				Sotrovimab			
Trial		Phase III COV-2067 (Non-Hospitalized)				COMET-ICE		COMET-TAIL	
Arms		REGEN-COV 1200 mg	REGEN-COV 2400 mg	REGEN-COV 8000 mg	Placebo 1200 mg	Sotrovimab 500 mg	Placebo	Sotrovimab 500 mg (IM)	Sotrovimab 500 mg (IV)
N		827	1849	1012	1843	523	526	376	378
Timepoint		29 Days				24 Weeks		24 Weeks	
≥1 AE, n/N (%)		59/827 (7.1)	142/1849 (7.7)	85/1012 (8.4)	189/1843 (10.3)	114/523 (22)	123/526 (23)	NR	NR
≥1 TEAE, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Drug-Related AE, n/N (%)		NR	NR	NR	NR	8/523 (2)	9/526 (2)	NR	NR
AE Leading to Discontinuation, n/N (%)		0/827 (0)	1/1849 (<0.1)	2/1012 (0.2)	1/1843 (<0.1)	0/523 (0)	0/526 (0)	NR	NR
AE Leading to Dose Interruption, n/N (%)		1/827 (0.1)	0/1849 (0)	1/1012 (0.1)	0/1843 (0)	2/523 (<1)	0/526 (0)	NR	NR
≥1 Serious AE, n/N (%)		9/827 (1.1)	24/1849 (1.3)	17/1012 (1.7)	74/1843 (4)	11/523 (2)	32/526 (6)	≤1%	≤1%
Serious AE Related to Treatment, n/N (%)		NR	NR	NR	NR	0/523 (0)	2/526 (<1)	NR	NR
Fatal AE, n/N (%)		1/827 (0.1)	1/1849 (<0.1)	0/1012 (0)	5/1843 (0.3)	0/523 (0)	4/526 (<1)	NR	NR
All-Cause Mortality, n/N (%)		NR	NR	NR	NR	0/523 (0)	4/526 (<1)	NR	NR
Grade 3 or 4 AE, n/N (%)		11/827 (1.3)	18/1849 (1)	15/1012 (1.5)	62/1843 (3.4)	15/523 (3)	36/526 (7)	≤1%	≤1%
TEAE Severity, n/N (%)	Grade 1	NR	NR	NR	NR	NR	NR	NR	NR
	Grade 2	NR	NR	NR	NR	NR	NR	NR	NR
	Grade 3	NR	NR	NR	NR	NR	NR	NR	NR
	Grade 4	NR	NR	NR	NR	NR	NR	NR	NR
	Grade 5	NR	NR	NR	NR	NR	NR	NR	NR
Infusion-Related AE, n/N (%)	Any	NR	NR	NR	NR	6/523 (1)	6/526 (1)	NR	NR
	Grade ≥2	2/827 (0.2)*	1/1849 (<0.1)*	3/1012 (0.3)*	0/1843 (0)*	NR	NR	NR	NR
	Grade 3 or 4	NR	NR	NR	NR	NR	NR	NR	NR
	Related to Treatment	NR	NR	NR	NR	0/523 (0)	3/526 (<1)	NR	NR

Drug Name		REGEN-COV2 (Casirivimab/Imdevimab)				Sotrovimab			
Trial		Phase III COV-2067 (Non-Hospitalized)				COMET-ICE		COMET-TAIL	
Arms		REGEN-COV 1200 mg	REGEN-COV 2400 mg	REGEN-COV 8000 mg	Placebo 1200 mg	Sotrovimab 500 mg	Placebo	Sotrovimab 500 mg (IM)	Sotrovimab 500 mg (IV)
N		827	1849	1012	1843	523	526	376	378
Timepoint		29 Days				24 Weeks		24 Weeks	
	Leading to Discontinuation	NR	NR	NR	NR	0/523 (0)	0/526 (0)	NR	NR
	Leading to Dose Interruption	NR	NR	NR	NR	0/523 (0)	0/526 (0)	NR	NR
≥1 Hypersensitivity Reaction, n/N (%)		0/827 (0)†	1/1849 (<0.1)†	0/1012 (0)†	1/1843 (<0.1)†	10/523 (2)	5/526 (1)	NR	NR
Dyspnea, n/N (%)		0/827 (0)	1/1512 (<0.1)	0/1012 (0)	1/1476 (<0.1)	NR	NR	NR	NR
Diarrhea, n/N (%)		NR	NR	NR	NR	8/523 (2)	4/526 (<1)	NR	NR
Nausea n/N (%)		2/827 (0.2)	0/1849 (0)	1/1012 (<0.1)	0/1843 (0)	5/523 (<1)	9/526 (2)	NR	NR
Vomiting, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Dizziness, n/N (%)		2/827 (0.2)	1/1849 (<0.1)	0/1012 (0)	1/1843 (<0.1)	NR	NR	NR	NR
Headache, n/N (%)		2/827 (0.2)	1/1849 (<0.1)	1/1012 (<0.1)	2/1843 (0.1)	4/523 (<1)	11/526 (2)	NR	NR
Hypoxia, n/N (%)		1/827 (0.1)	1/1849 (<0.1)	1/1012 (<0.1)	6/1843 (0.3)	NR	NR	NR	NR
COVID-19 Pneumonia, n/N (%)		2/827 (0.2)	4/1849 (0.2)	5/1012 (0.5)	14/1843 (0.8)	5/523 (<1)	22/526 (4)	NR	NR
Rash, n/N (%)		NR	NR	NR	NR	1%	NR	NR	NR

AE: adverse event, IM: intramuscular, IV: intravenous, mg: milligram, n: number, N: total number, NR: not reported, TEAE: treatment emergent adverse event

*Experienced within 4 days.

†Severity ≥2.

Table D19. Adverse Events: Phase III Trials (Oral Antivirals)[5,6,8,9]

Drug Name		Molnupiravir		Paxlovid (Nirmatrelvir/Ritonavir)			
Trial		Phase III MOVe-OUT		Phase II/III EPIC-HR		Phase II/III EPIC-SR (Interim)	
Arms		Molnupiravir 800 mg	Placebo	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
N		710	701	1,109	1,115	NR	NR
Timepoint		19 Days		34 Days		34 Days	
≥1 AE, n/N (%)		216/710 (30.4)	231/701 (33)	NR	NR	NR	NR
≥1 TEAE, n/N (%)				255/1109 (23)	268/1115 (24)	22%	21%
Drug-Related AE, n/N (%)		57/710 (8)	59/701 (8.4)	NR	NR	NR	NR
AE Leading to Discontinuation, n/N (%)		10/710 (1.4)	20/701 (2.9)	23/1109 (2.1)	47/1115 (4.2)	2.1%	1.2%
AE Leading to Dose Interruption, n/N (%)		NR	NR	NR	NR	NR	NR
≥1 Serious AE, n/N (%)		49/710 (6.9)	67/701 (9.6)	18/1109 (1.6)	74/1115 (6.6)	1.4%	1.9%
Serious AE Related to Treatment, n/N (%)		0/710 (0)	1/701 (0.1)	NR	NR	NR	NR
Fatal AE, n/N (%)		NR	NR	NR	NR	NR	NR
All-Cause Mortality, n/N (%)		2/710 (0.3)	12/701 (1.7)	NR	NR	NR	NR
Grade 3 or 4 AE, n/N (%)				NR	NR	NR	NR
TEAE Severity, n/N (%)	Grade 1	NR	NR	NR	NR	NR	NR
	Grade 2	NR	NR	NR	NR	NR	NR
	Grade 3	NR	NR	NR	NR	NR	NR
	Grade 4	NR	NR	NR	NR	NR	NR
	Grade 5	NR	NR	NR	NR	NR	NR
Infusion-Related AE, n/N (%)	Any	NA	NA	NA	NA	NA	NA
	Grade ≥2	NA	NA	NA	NA	NA	NA
	Grade 3 or 4	NA	NA	NA	NA	NA	NA
	Related to Treatment	NA	NA	NA	NA	NA	NA
	Leading to Discontinuation	NA	NA	NA	NA	NA	NA
	Leading to Dose Interruption	NA	NA	NA	NA	NA	NA
≥1 Hypersensitivity Reaction, n/N (%)		NR	NR	NR	NR	NR	NR
Dyspnea, n/N (%)		NR	NR	NR	NR	NR	NR
Diarrhea, n/N (%)		16/710 (2.3)	21/701 (3)	33/1109 (3)	22//1115 (2)	NR	NR
Nausea n/N (%)		13/710 (1.8)	6/701 (0.9)	NR	NR	NR	NR

Drug Name	Molnupiravir		Paxlovid (Nirmatrelvir/Ritonavir)			
Trial	Phase III MOVe-OUT		Phase II/III EPIC-HR		Phase II/III EPIC-SR (Interim)	
Arms	Molnupiravir 800 mg	Placebo	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo
N	710	701	1,109	1,115	NR	NR
Timepoint	19 Days		34 Days		34 Days	
Vomiting, n/N (%)	NR	NR	NR	NR	NR	NR
Dizziness, n/N (%)	NR	NR	NR	NR	NR	NR
Headache, n/N (%)	NR	NR	NR	NR	NR	NR
Hypoxia, n/N (%)	NR	NR	NR	NR	NR	NR
COVID-19 Pneumonia, n/N (%)	45/710 (6.3)	67/701 (9.6)	NR	NR	NR	NR
Rash, n/N (%)	NR	NR	NR	NR	NR	NR

AE: adverse event, mg: milligram, n: number, N: total number, NA: not applicable, NR: not reported, TEAE: treatment emergent adverse event

*During treatment period (5 days) and 14 days after end of treatment period.

Table D20. Adverse Events: Phase III Trials (Fluvoxamine)[3,100]

Drug Name		Fluvoxamine					
Trial		TOGETHER		STOP COVID 1		STOP COVID 2	
Arms		Fluvoxamine 100 mg	Placebo	Fluvoxamine 100 mg	Placebo	Fluvoxamine 100 mg	Placebo
N		741	756	80	72	272	275
Timepoint		28 Days		45 Days*		NR	
≥1 AE, n/N (%)		NR	NR	11/80 (13.8)	6/72 (8.3)	NR	NR
≥1 TEAE, n/N (%)		NR	NR	NR	NR	NR	NR
Drug-Related AE, n/N (%)		NR	NR	NR	NR	NR	NR
AE Leading to Discontinuation, n/N (%)		NR	NR	NR	NR	NR	NR
AE Leading to Dose Interruption, n/N (%)		NR	NR	NR	NR	NR	NR
≥1 Serious AE, n/N (%)		NR	NR	1/80 (1.3)	5/72 (6.9)	NR	NR
Serious AE Related to Treatment, n/N (%)		NR	NR	NR	NR	NR	NR
Fatal AE, n/N (%)		NR	NR	NR	NR	NR	NR
All-Cause Mortality, n/N (%)		17/741 (2)	25/756 (3)	NR	NR	NR	NR
Grade 3 or 4 AE, n/N (%)		59/741 (8)	70/756 (9)	NR	NR	NR	NR
TEAE Severity, n/N (%)	Grade 1	20/741 (3)	11/756 (1)	NR	NR	NR	NR
	Grade 2	72/741 (10)	81/756 (11)	NR	NR	NR	NR
	Grade 3	38/741 (5)	50/756 (7)	NR	NR	NR	NR
	Grade 4	21/741 (3)	20/756 (3)	NR	NR	NR	NR
	Grade 5	18/741 (2)	26/756 (3)	NR	NR	NR	NR
Infusion-Related AE, n/N (%)	Any	NA	NA	NA	NA	NA	NA
	Grade ≥2	NA	NA	NA	NA	NA	NA
	Grade 3 or 4	NA	NA	NA	NA	NA	NA
	Related to Treatment	NA	NA	NA	NA	NA	NA
	Leading to Discontinuation	NA	NA	NA	NA	NA	NA
	Leading to Dose Interruption	NA	NA	NA	NA	NA	NA
≥1 Hypersensitivity Reaction, n/N (%)		NR	NR	NR	NR	NR	NR
Dyspnea, n/N (%)		NR	NR	NR	NR	NR	NR
Diarrhea, n/N (%)		NR	NR	NR	NR	NR	NR
Nausea n/N (%)		NR	NR	1/80 (1.3)†‡	5/72 (6.9)†‡	NR	NR
Vomiting, n/N (%)		NR	NR			NR	NR
Dizziness, n/N (%)		NR	NR	NR	NR	NR	NR
Headache, n/N (%)		NR	NR	2/80 (2.5)†‡	1/72 (1.4)‡	NR	NR

Drug Name	Fluvoxamine					
Trial	**TOGETHER**		**STOP COVID 1**		**STOP COVID 2**	
Arms	**Fluvoxamine 100 mg**	**Placebo**	**Fluvoxamine 100 mg**	**Placebo**	**Fluvoxamine 100 mg**	**Placebo**
N	**741**	**756**	**80**	**72**	**272**	**275**
Timepoint	**28 Days**		**45 Days***		**NR**	
Hypoxia, n/N (%)	NR	NR	0/80 (0)‡	6/72 (8.3)‡	NR	NR
Covid-19 Pneumonia, n/N (%)	NR	NR	3/80 (3.8)‡§	6/72 (8.3)‡§	NR	NR
Rash, n/N (%)	NR	NR	NR	NR	NR	NR

AE: adverse event, mg: milligram, n: number, N: total number, NA: not applicable, NR: not reported, TEAE: treatment emergent adverse event

*During treatment period (15 days) and 30 days after end of treatment period.

†Gastroenteritis, nauseas, or vomiting

‡Reported as number of instances of each individual AE, not the number of patients who experienced them.

§General pneumonia.

Table D21. Adverse Events: Phase I/II Trials (REGEN-COV)[96]

Drug Name		REGEN-COV2 (Casirivimab/Imdevimab)			
Trial		Phase I/II COV-2067 (Non-Hospitalized)			
Arms		REGEN-COV2 2.4 g	REGEN-COV2 8.0 g	REGEN-COV2 Combined	Placebo
N		88	88	176	93
Timepoint		29 Days			
≥1 AE, n/N (%)		NR	NR	NR	NR
≥1 TEAE, n/N (%)		NR	NR	NR	NR
Drug-Related AE, n/N (%)		NR	NR	NR	NR
AE Leading to Discontinuation, n/N (%)		0/88 (0)	0/88 (0)	0/176 (0)	0/93 (0)
AE Leading to Dose Interruption, n/N (%)		0/88 (0)	1/88 (1)	1/176 (1)	1/93 (1)
≥1 Serious AE, n/N (%)		1/88 (1)	0/88 (0)	1/176 (1)	2/93 (2)
Serious AE Related to Treatment, n/N (%)		NR	NR	NR	NR
Fatal AE, n/N (%)		0/88 (0)	0/88 (0)	0/176 (0)	0/93 (0)
All-Cause Mortality, n/N (%)		NR	NR	NR	NR
Grade 3 or 4 AE, n/N (%)		1/88 (1)	0/88 (0)	1/176 (1)	1/93 (1)
TEAE Severity, n/N (%)	Grade 1	NR	NR	NR	NR
	Grade 2	NR	NR	NR	NR
	Grade 3	NR	NR	NR	NR
	Grade 4	NR	NR	NR	NR
	Grade 5	NR	NR	NR	NR
Infusion-Related AE, n/N (%)	Any	NR	NR	NR	NR
	Grade ≥2	0/88 (0)*	2/88 (2)*	2/176 (1)*	1/93 (1)*
	Grade 3 or 4	NR	NR	NR	NR
	Related to Treatment	NR	NR	NR	NR
	Leading to Discontinuation	NR	NR	NR	NR
	Leading to Dose Interruption	NR	NR	NR	NR
≥1 Hypersensitivity Reaction, n/N (%)		0/88 (0)	1/88 (1)	1/176 (1)	2/93 (2)
Dyspnea, n/N (%)		NR	NR	NR	NR
Diarrhea, n/N (%)		NR	NR	NR	NR
Nausea n/N (%)		1/88 (1.1)	0/88 (0)	1/176 (0.6)	0/176 (0)
Vomiting, n/N (%)		1/88 (1.1)	0/88 (0)	1/176 (0.6)	0/176 (0)
Dizziness, n/N (%)		0/88 (0)	0/88 (0)	0/176 (0)	1/93 (1.1)
Headache, n/N (%)		0/88 (0)	0/88 (0)	0/176 (0)	1/93 (1.1)

Drug Name	REGEN-COV2 (Casirivimab/Imdevimab)			
Trial	Phase I/II COV-2067 (Non-Hospitalized)			
Arms	REGEN-COV2 2.4 g	REGEN-COV2 8.0 g	REGEN-COV2 Combined	Placebo
N	88	88	176	93
Timepoint	29 Days			
Hypoxia, n/N (%)	0/88 (0)	0/88 (0)	0/176 (0)	1/93 (1.1)
Covid-19 Pneumonia, n/N (%)	NR	NR	NR	NR
Rash, n/N (%)	0/88 (0)	0/88 (0)	0/176 (0)	1/93 (1)

AE: adverse event, g: gram, n: number, N: total number, NR: not reported, TEAE: treatment emergent adverse event

*Experienced within 4 days.

Table D22. Adverse Events: Phase I/II Trials (Molnupiravir)[36-38]

Drug Name		Molnupiravir							
Trial		Phase II MOVe-OUT				Phase IIa Study 2003 (Fischer 2021)			
Arms		Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo
N		75	77	76	74	23	62	55	62
Timepoint		19 Days*				28 Days			
≥1 AE, n/N (%)		NR	NR	NR	NR	11/23 (47.8)	20/62 (32.3)	11/55 (20.0)	18/62 (29.0)
≥1 TEAE, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Drug-Related AE, n/N (%)		14/225 (6.2)			5/74 (6.8)	4/23 (17.4)	13/62 (21)	1/55 (1.8)	8/62 (12.9)
AE Leading to Discontinuation, n/N (%)		3/228 (1.3)			1/74 (1.4)	0/23 (0)	1/62 (1.6)	1/55 (1.8)	1/62 (1.6)
AE Leading to Dose Interruption, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
≥1 Serious AE, n/N (%)		8/228 (3.6)			4/74 (5.4)	0/23 (0)	2/62 (3.2)	1/55 (1.8)	1/62 (1.6)
Serious AE Related to Treatment, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Fatal AE, n/N (%)		NR	NR	NR	NR	0/23 (0)	0/62 (0)	0/55 (0)	1/62 (1.6)
All-Cause Mortality, n/N (%)		NR	NR	NR	1/74 (1.4)	NR	NR	NR	NR
Grade 3 or 4 AE, n/N (%)		NR	NR	NR	NR	1/23 (4.3)†	2/62 (3.2)†	4/55 (7.3)†	5/62 (8.1)†
TEAE Severity, n/N (%)	Grade 1	NR	NR	NR	NR	NR	NR	NR	NR
	Grade 2	NR	NR	NR	NR	NR	NR	NR	NR
	Grade 3	NR	NR	NR	NR	NR	NR	NR	NR
	Grade 4	NR	NR	NR	NR	NR	NR	NR	NR
	Grade 5	NR	NR	NR	NR	NR	NR	NR	NR
Infusion-Related AE, n/N (%)	Any	NA	NA	NA	NA	NA	NA	NA	NA
	Grade ≥2	NA	NA	NA	NA	NA	NA	NA	NA
	Grade 3 or 4	NA	NA	NA	NA	NA	NA	NA	NA
	Related to Treatment	NA	NA	NA	NA	NA	NA	NA	NA
	Leading to Discontinuation	NA	NA	NA	NA	NA	NA	NA	NA
	Leading to Dose Interruption	NA	NA	NA	NA	NA	NA	NA	NA

Drug Name	Molnupiravir							
Trial	Phase II MOVe-OUT				Phase IIa Study 2003 (Fischer 2021)			
Arms	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo
N	75	77	76	74	23	62	55	62
Timepoint	19 Days*				28 Days			
≥1 Hypersensitivity Reaction, n/N (%)	NR	NR	NR	NR	NR	NR	NR	NR
Dyspnea, n/N (%)	NR	NR	NR	NR	0/23 (0)	1/62 (1.6)	0/55 (0)	0/62 (0)
Diarrhea, n/N (%)	NR	NR	NR	4/74 (5.4)	0/23 (0)	1/62 (1.6)	0/55 (0)	1/62 (1.6)
Nausea n/N (%)	NR	NR	NR	NR	1/23 (4.3)	2/62 (3.2)	0/55 (0)	1/62 (1.6)
Vomiting, n/N (%)	NR	NR	NR	NR	NR	NR	NR	NR
Dizziness, n/N (%)	NR	NR	NR	NR	2/23 (8.7)	1/62 (1.6)	0/55 (0)	0/62 (0)
Headache, n/N (%)	NR	NR	NR	NR	1/23 (4.3)	3/62 (4.8)	2/55 (3.6)	3/62 (4.8)
Hypoxia, n/N (%)	NR	NR	NR	NR	0/23 (0)	0/62 (0)	0/55 (0)	1/62 (1.6)
Covid-19 Pneumonia, n/N (%)	NR	NR	4/76 (5.4)	NR	0/23 (0)†	1/62 (1.6)‡	1/55 (1.8)‡	0/62 (0)†
Rash, n/N (%)	NR	NR	NR	NR	0/23 (0)	1/62 (1.6)	1/55 (1.8)	0/62 (0)

AE: adverse event, mg: milligram, n: number, N: total number, NA: not applicable, NR: not reported, TEAE: treatment emergent adverse event

*During treatment period (5 days) and 14 days after end of treatment period.

†Grade 3 or higher severity.

‡General pneumonia.

Table D23. Key Features: Real-World Studies

Trial & Author	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
RW Study Webb et al. 2021[51]	Retrospective clinical data extraction Location: Intermountain Healthcare in UT and Southeastern ID, US Dates: 11/20-1/21	Ambulatory patients ages ≥18 years with COVID-19 N=115 (combined both bamlanivimab and casirivimab/ imdevimab)	Casirivimab/ imdevimab Control cohort	**Key Inclusion Criteria** -At or above the risk score threshold (set at ≥7.5 points, which identified approximately top decile of estimated risk among COVID-19-positive patients) -Confirmed COVID-19 -Symptomatic disease with symptom onset within no more than 7 days -Over 18 years of age **Key Exclusion Criteria** -Hospitalized due to COVID-19 -New COVID-related hypoxemia (defined as peripheral oxygen saturation <90% at rest or new supplemental oxygen requirement, or for those with chronic hypoxia, a new change in baseline saturation or oxygen demand) -Pregnant -Hypersensitivity to other mAbs	**Primary Endpoint (through day 14):** - Number of hospitalizations/ED visits (composite) **Secondary Endpoints (at day 14):** - Adverse events - Mortality
RW Study Razonable et al. 2021[52]	Retrospective clinical data extraction Location: Patients from several geographic Mayo Clinic sites, e.g., AZ, FL, MN, and WI; US Dates: 12/20-4/21	Ambulatory patients ages ≥18 years with COVID-19 N=696 patients w/ casirivimab/ imdevimab	Casirivimab/ imdevimab Control cohort	**Key Inclusion Criteria** -Patients 18 years and older -Had symptoms of mild-to-moderate COVID-19 -Within 10 days of symptom onset -Had at least one of following criteria: age 65 years, BMI 35, diabetes mellitus, CKD, immunosuppressive medication use, or an immunocompromising condition; patients 55 years and older qualified if they had hypertension, CVD, or chronic lung disease **Key Exclusion Criteria** -Patients with clinical manifestations of severe COVID-19 (e.g., new or worsening hypoxemia)	**Primary Endpoint (through day 14, 21, and 28):** - Rates of hospitalizations **Secondary Endpoints (day 14, 21, and 28):** - ICU admissions - Mortality

Trial & Author	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
				and those requiring hospitalization for COVID-19 were excluded -Received bamlanivimab with or without etesevimab -Have canceled casirivimab/imdevimab order -Were in hospice or comfort care -Have a DNI, DNR, or DNH status -Had SpO2 of <93%; were currently hospitalized at the time of positive PCR test or casirivimab/ imdevimab infusion	
RW Study Polk et al. 2021[58]	Retrospective clinical data extraction Location: NR Dates: 12/16/20-3/5/21	Patients with COVID-19 N=125 patients w/ casirivimab/ imdevimab n=199 untreated patients	Casirivimab/ imdevimab Untreated cohort	**Key Inclusion Criteria:** -Patients who had COVID-19 -Assessed and infused within 10 days of symptom onset -Screened between 12/16/20 and 3/5/21	**Primary Endpoints (through day 30):** -Completion of treatment and reasons not treated -Rates of hospitalizations -ED visits -ICU stays -Mechanical ventilation required -Death
RW Study Chilimuri et al. 2021[53]	Retrospective observational study Location: South-Bronx, NY, US Dates: 11/27/20-3/17/21	Patients with COVID-19 N=22 patients w/ casirivimab/ imdevimab n=11 control patients (declined therapy)	Casirivimab/ imdevimab Control group	**Key Inclusion Criteria** -Patients >18 years of age -Diagnosed with mild-moderate COVID-19 -Symptoms <10 days duration -≥1 high-risk conditions for progression to severe disease, including BMI ≥35 kg/m^2, CKD, diabetes, immunosuppressive disease, or treatment, ≥65 years of age **Exclusion** -Patients who required admission for COVID-19, patients with severe disease, patients requiring oxygen, or increasing oxygen requirements in patients on long-term oxygen therapy for non-COVID-19 causes	**Primary Endpoints:** -Symptom improvement at day 1 and day 14 -30-day all-cause hospitalization -30-day hospitalization related to COVID-19 -30-day mortality

Trial & Author	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
RW Study Piccaccio et al. 2021[54-56]	Retrospective cohort study Location: Single-center in FL, US Dates: 11/18/20-1/5/21	Patients with COVID-19 N=48 patients w/ casirivimab/ imdevimab n=200 control patients	Casirivimab/ imdevimab Control group	**Key Inclusion Criteria** -Confirmed COVID-19 infection ->12 years of age -Weighed at least 40 kg -Mild-to-moderate symptoms for 10 days of less -Considered high-risk based on EUA document **Exclusion** -No documentation from clinic after initial diagnoses or mAb administration	**Primary Endpoints (through day 29)**: -Composite of COVID-19 related hospitalization (>24-hour acute stay) and ED visits **Secondary Endpoints (day 29)**: -COVID-19 hospitalizations -COVID-19 ED visit -All-cause mortality -SAEs in the mAb cohort
RW Study McCreary et al. 2021[57] NCT04790786	Prospective quality improvement project using electronic health record data Location: UPMC Health System Dates: Project was from 3/21- 9/21; but data in analysis was from 7/14/21 -10/26/21	Patients with COVID-19 in the OPTIMISE-C19 QI project First analysis: -N=969 SC casirivimab/ imdevimab (N=652 matched) N=4,353 non-treated eligible controls (N=1,304 matched) Second analysis: N=969 SC w/ casirivimab/ imdevimab (N=652 matched) N=1,216 IV w/ casirivimab/ imdevimab	Casirivimab/ imdevimab (SC and IV) Untreated cohort	**Key Inclusion Criteria**: -Confirmed COVID-19 infection ->12 years of age -Considered high risk based on EUA document **Exclusion**: -Admission to ED or hospital on date of positive COVID-19 test results	**Primary Endpoints**: -28-day adjusted RR or adjusted risk difference for hospitalization or death **Secondary Endpoints**: -28-day adjusted RR/differences of hospitalizations, death, composite endpoint of ED admissions and hospitalizations, and rates of AEs

Trial & Author	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
RW Study Huang et al. 2021[34] NCT04790786	Prospective quality improvement project using electronic health record data Location: UPMC Health System Dates: 7/14/21 - 9/10/21	Patients with COVID-19 in the OPTIMISE-C19 QI project First analysis: N=717 casirivimab/ imdevimab (N=712 when matched) N=5,171 non-treated matched controls (N=2,046 when matched) Second analysis: N=311 sotrovimab (N=311 matched) N=5,171 non-treated matched controls (N=2,046 matched)	Casirivimab/ imdevimab IV Sotrovimab IV Untreated cohort	**Key Inclusion Criteria** -Confirmed COVID-19 infection -Considered high-risk based on EUA document **Exclusion** -Admission to hospital	**Primary Endpoints**: -28-day hospitalization or death **Secondary Endpoints**: -28-day rate of hospitalizations, ICU admission, mechanical ventilation, and death

BMI: body mass index, ED: emergency department, e.g.: exempli gratia (for example), ER: emergency room, EUA: Emergency Use Authorization, FDA: Food and Drug Administration, ICU: intensive care unit, IV: intravenous, kg: kilogram, mAb: monoclonal antibody, n: number, N: total number, NCT: National Clinical Trial Identifier, QI: Quality Improvement, RW: real-world, SAE: serious adverse event, SC: subcutaneous, UPMC: University of Pittsburgh Medical Center

Table D24. Baseline Characteristics: RWE Studies I[51,52]

Drug Name		REGEN-COV			
Trial		Webb et al. 2021		Razonable et al. 2021	
Arms		Casirivimab/Imdevimab	Contemporaneous Controls	Casirivimab/Imdevimab	Controls
N		115	5536	696	696
Age, Median Years (IQR)		66 (15)	62 (15)	63 (52-71)	63 (52-71)
Age Group, n/N (%)	≥50 Years	NR	NR	NR	NR
	<65 Years	NR	NR	378/696 (54.3)	386/696 (55.5)
	≥65 Years	NR	NR	NR	NR
Gender, n/N (%)	Male	61/115 (53)	3005/5536 (54.3)	340/696 (48.9)	321/696 (46.1)
	Female	54/115 (47)	2531/5536 (45.7)	356/696 (51.1)	375/696 (53.9)
Race, n/N (%)	White	108/115 (93.9)	4787/5536 (86.5)	645/696 (92.7)	646/696 (92.8)
	Black or African American	1/115 (0.9)	170/5536 (3.1)	26/696 (3.7)	28/696 (4.0)
	Asian	1/115 (0.9)	89/5536 (1.6)	8/696 (1.1)	5/696 (0.7)
	American Indian or Alaska Native	0/115 (0)	77/5536 (1.4)	3/696 (0.4)	2/696 (0.3)
	Native Hawaiian or Pacific Islander	1/115 (0.9)	170/5536 (3.1)	NR	NR
	South Asian	NR	NR	NR	NR
	Hispanic or Latino	NR	NR	NR	NR
	Mixed Race	NR	NR	NR	NR
	Communities of Color	19/115 (16.5)	1494 (27.0)	NR	NR
	Other	NR	NR	8/696 (1.1)	10/696 (1.4)
	Unknown	NR	NR	6/696 (0.9)	5/696 (0.7)
	Not Reported	NR	NR	NA	NA
Ethnicity, n/N (%)	Hispanic or Latino	15/115 (13.0)	933/5536 (16.9)	29/696 (4.2)	32/696 (4.6)
	Not Hispanic or Latino	100/115 (87)	4603/5536 (83.1)	655/696 (94.1)	653/696 (93.8)
Weight, Median kg (IQR)		NR	NR	NR	NR
BMI, Mean kg/m² (SD)		NR	NR	NR	NR
BMI, n/N (%)	<30 kg/m²	53/115 (46.1)	2120/5536 (39.3)	214/696 (31)	216/696 (31)
	≥30 kg/m²	62/115 (53.9)	3416/5536 (61.7)	340/696 (49)	347/696 (50)
Overweight, n/N (%)		NR	NR	145/696 (20.8)	147/696 (21.1)
Positive Baseline Qualitative RT-PCR, n/N (%)		NR	NR	696/696 (100)	696/696 (100)

Drug Name		REGEN-COV			
Trial		Webb et al. 2021		Razonable et al. 2021	
Arms		Casirivimab/Imdevimab	Contemporaneous Controls	Casirivimab/Imdevimab	Controls
N		115	5536	696	696
Previous Anti-SARS-COV-2 Vaccination, n/N (%)		NR*	NR*	NR	NR
Time from Symptom Onset to Infusion, Median Days (Range)		2.2 (1.8-3.1)	NR	2.61 (1.25)†	NR
Time from Symptom Onset to Infusion, n/N (%)	0-3 Days	NR	NR	NR	NR
	4-5 Days	NR	NR	NR	NR
	>5 Days	NR	NR	NR	NR
	>7 Days	NR	NR	NR	NR
	Unspecified	NR	NR	NR	NR
Duration of Follow-Up, Median Days (SD)		NR	NR	NR	NR
Any Risk Factor for Progression to Severe Disease, n/N (%)	Age ≥55 Years	NR	NR	318/696 (45.7)‡	310/696 (44.5)‡
	Obesity (BMI >30)	62/115 (53.9)	3416/5536 (61.7)	340/696 (48.9)	347/696 (50.0)
	Hypertension	102/115 (88.7)	4392/5536 (79.3)	363/696 (52.5)	365/696 (52.4)
	Cardiovascular Disease	16/115 (13.9)§	529/5536 (9.6)§	NR	NR
	Heart failure	19/115 (16.5)	827/5536 (14.9)	53/696 (7.6)	37/696 (5.3)
	COPD	65/115 (56.5)	2928/5536 (52.9)	151/696 (21.7)	135/696 (19.4)
	Asthma	NR	NR	NR	NR
	CKD	35/115 (30.4)	1077/5536 (19.5)	NR	NR
	Diabetes (Type 1 and 2)	73/115 (63.5)	2656/5536 (48.0)	164/696 (23.6)	130/696 (18.7)
	Immunosuppressive Disease	6/115 (5.2)	236/5536 (4.3)	6.7%#	
	Neurological Disorder	0/115 (0)	903/5536 (16.3)	NR	NR
	Liver Disease	34/115 (29.6)	1476/5536 (26.7)	65/696 (9.3)	48/696 (6.9)
	High Cholesterol	NR	NR	NR	NR
	Any Other Risk Factors or Comorbidities	NR	NR	NR	NR
Total Comorbidities, Median (IQR)		4 (3-5)	4 (3-5)	NR	NR
≥1 Risk Factor for Progression to Severe Disease, n/N (%)		NR	NR	696/696 (100)	NR
Baseline Serum Antibody Status, n/N (%)	Negative	NR	NR	NR	NR
	Positive	NR	NR	NR	NR
	Other	NR	NR	NR	NR

Drug Name		REGEN-COV			
Trial		Webb et al. 2021		Razonable et al. 2021	
Arms		Casirivimab/Imdevimab	Contemporaneous Controls	Casirivimab/Imdevimab	Controls
N		115	5536	696	696
	Unknown	NR	NR	NR	NR
Baseline Viral Load in Nasopharyngeal Swab, Median log_{10} Copies/mL (Range)		NR	NR	NR	NR
Geography of Enrollment	US (%)	100%	100%	100%	100%
	Non-US (%)	NA	NA	NA	NA

BMI: body mass index, COPD: chronic obstructive pulmonary disease, IQR: interquartile range, kg: kilogram, m: meter, mL: milliliter, n: number, N: total number, NA: not applicable, NR: not reported, RT-PCR: reverse transcription polymerase chain reaction, SD: standard deviation, US: United States

*All patients had a positive PCR or antigen COVID-19 test.

†Mean (SD).

‡Age ≥65 years.

§Coronary artery disease.

#Compromised immune function.

Table D25. Baseline Characteristics: RWE Studies II[53-56,58]

Drug Name		REGEN-COV					
Trial		Polk et al. 2021		Chilimuri et al. 2021		Piccicacco et al. 2021	
Arms		Casirivimab/ Imdevimab	Untreated	Casirivimab/ Imdevimab	Control Group	Casirivimab/ Imdevimab	Controls
N		125	199	22	11	48	200
Age, Median Years (IQR)		59 (19-98)	62 (20-92)	65 (55-65)	NR	65 (52.8-74.3)	65 (56-73.3)
Age Group, n/N (%)	≥50 Years	NR	NR	NR	NR	41/48 (85.4)	174/200 (87)
	<65 Years	NR	NR	NR	NR	23/48 (47.9)	96/200 (48)
	≥65 Years	38/125 (30)	85/199 (44)	NR	NR	25/48 (52.1)	104/200 (52)
Gender, n/N (%)	Male	62/125 (50)	87/199 (44)	9/22 (40.9)	NR	23/48 (48)	91/200 (45.5)
	Female	63/125 (50)	112/199 (56)	13/22 (59)	NR	25/48 (52)	109/200 (54.5)
Race, n/N (%)	White	97/125 (78)	119/199 (60)	3/22 (13.6)	NR	30/48 (62.5)	110/200 (55)
	Black or African American	17/125 (14)	56/199 (28)	6/22 (27.2)	NR	8/48 (16.7)	42/200 (21)
	Asian	2/125 (1)	7/199 (3)	2/22 (0.9)	NR	1/48 (2.1)	3/200 (1.5)
	American Indian or Alaska Native	NR	NR	NR	NR	NR	NR
	Native Hawaiian or Pacific Islander	NR	NR	NR	NR	NR	NR
	South Asian	NR	NR	NR	NR	NR	NR
	Hispanic or Latino	7/125 (6)	12/199 (6)	11/22 (50)	NR	4/48 (8.3)	23/200 (11.5)
	Mixed Race	NR	NR	NR	NR	NR	NR
	Communities of Color	NR	NR	NR	NR	NR	NR
	Other	2/125 (1)	5/199 (2)	NR	NR	5/48 (10.4)	22/200 (11)
	Unknown			NR	NR		
	Not Reported	NA	NA	NA	NR	NA	NA
Ethnicity, n/N (%)	Hispanic or Latino	NR	NR	NR	NR	NR	NR
	Not Hispanic or Latino	NR	NR	NR	NR	NR	NR
Weight, Median kg (IQR)		NR	NR	NR	NR	NR	NR
BMI, Mean kg/m² (SD)		NR	NR	30.1 (26.1-35.0)	NR	30.7 (6.9)	31.3 (7.3)
BMI, n/N (%)	<30 kg/m²	83/125 (66)*	133/199 (67)*	NR	NR	23/48 (47.9)	99/200 (49.5)
	≥30 kg/m²	42/125 (34)†	66/199 (33)†	NR	NR	23/48 (47.9)	96/200 (48)

Drug Name		REGEN-COV					
Trial		Polk et al. 2021		Chilimuri et al. 2021		Piccicacco et al. 2021	
Arms		Casirivimab/ Imdevimab	Untreated	Casirivimab/ Imdevimab	Control Group	Casirivimab/ Imdevimab	Controls
N		125	199	22	11	48	200
Overweight, n/N (%)		NR	NR	NR	NR	NR	NR
Positive Baseline Qualitative RT-PCR, n/N (%)		NR	NR	22/22 (100)	NR	NR	NR
Previous Anti-SARS-COV-2 Vaccination, n/N (%)		NR	NR	NR	NR	NR	NR
Time from Symptom Onset to Infusion, Median Days (Range)		5 (1-10)‡	NR	6 (4-7)	NR	4.9 (2.1)§	NR
Time From Symptom Onset to Infusion, n/N (%)	0-3 Days	NR	NR	NR	NR	NR	NR
	4-5 Days	NR	NR	NR	NR	NR	NR
	>5 Days	48/125 (38)	NR	NR	NR	NR	NR
	>7 Days	NR	NR	NR	NR	NR	NR
	Unspecified	NR	NR	NR	NR	NR	NR
Duration of Follow-Up, Median Days (SD)		NR	NR	NR	NR	NR	NR
Any Risk Factor for Progression to Severe Disease, n/N (%)	Age ≥55 years	38/125 (30)#	85/199 (44)#	NR	NR	35/48 (72.9)	161/200 (80.5)
	Obesity (BMI >30)	42/125 (34)†	66/199 (33)†	NR	NR	23/48 (47.9)	96/200 (48)
	Hypertension	56/125 (45)	116/199 (58)	18/22 (81.8)	NR	25/48 (52.1)¤	120/200 (60)¤
	CVD	12/125 (10)	19/199 (9)	8/22 (36.4)	NR	5/48 (10.4)**	29/200 (14.5)**
	Heart Failure	NR	NR	NR	NR	NR	NR
	COPD	19/125 (15)	28/199 (14)	NR	NR	2/48 (4.2)††	32/200 (16) ††
	Asthma	NR	NR	9/22 (40.9)‡‡	NR	NR	NR
	CKD	13/125 (10)	19/199 (9)	3/22 (13.6)	NR	3/48 (6.3)§§	17/200 (8.5)§§
	Diabetes (Type 1 and 2)	36/125 (29)	57/199 (29)	10/22 (45.4)	NR	16/48 (33.3)	85/200 (42.5)
	Immunosuppressive Disease	19/125 (15)	20/199 (10)	4/22 (18.2)	NR	9/48 (18.8)	15/200 (7.5)
	Neurological Disorder	NR	NR	NR	NR	NR	NR
	Liver Disease	NR	NR	NR	NR	NR	NR
	High cholesterol	NR	NR	NR	NR	NR	NR

Drug Name		REGEN-COV					
Trial		Polk et al. 2021		Chilimuri et al. 2021		Piccicacco et al. 2021	
Arms		Casirivimab/ Imdevimab	Untreated	Casirivimab/ Imdevimab	Control Group	Casirivimab/ Imdevimab	Controls
N		125	199	22	11	48	200
	Any Other Risk Factors or Comorbidities	NR	NR	NR	NR	NR	NR
Total Comorbidities, Median (IQR)		NR	NR	NR	NR	2 (1.2)§ ¤¤	2.3 (1.2)§ ¤¤
≥1 Risk Factor for Progression to Severe Disease, n/N (%)		54/125 (43)	105/199 (53)	22/22 (100)	NR	48/48 (100)	200/200 (100)
Baseline Serum Antibody Status, n/N (%)	Negative	NR	NR	NR	NR	NR	NR
	Positive	NR	NR	NR	NR	NR	NR
	Other	NR	NR	NR	NR	NR	NR
	Unknown	NR	NR	NR	NR	NR	NR
Baseline Viral Load in Nasopharyngeal Swab, Median log_{10} Copies/mL (Range)		NR	NR	NR	NR	NR	NR
Geography of Enrollment	US (%)	100%	100%	100%	NR	100%	100%
	Non-US (%)	NA	NA	NA	NA	NA	NA

BMI: body mass index, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease, ESRD: end-stage renal disease, IQR: interquartile range, kg: kilogram, m: meter, mL: milliliter, n: number, N: total number, NA: not applicable, NR: not reported, RT-PCR: reverse transcription polymerase chain reaction, SD: standard deviation, US: United States

*BMI ≤35 kg/m^2. †BMI >35 kg/m^2. ‡Mean (range). §Mean (SD). #Age >65 years. ¤55 years of age with hypertension. **55 years of age with CVD. ††55 years of age with chronic lung disease. ‡‡Chronic respiratory disease. §§CKD and ESRD. ¤¤Number of risk factors.

Table D26. Baseline Characteristics: RWE Studies III[34,57]

Drug Name		REGEN-COV				REGEN-COV and Sotrovimab		
Trial		McCreary et al. 2021				Huang et al. 2021		
Arms		SC: Casirivimab/ Imdevimab	IV: Casirivimab/ Imdevimab	SC Matched: Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Sotrovimab	Control Group
N		969	1216	652	1304*	712	311	2046
Age, Median Years (IQR)		53.8 (16.7)†	54.3 (16.6)†	53.7 (16.9)†	53.0 (19.3)†	53.2 (16.4)†		52.8 (19.5)†
Age Group, n/N (%)	≥50 Years	NR	NR	NR	NR	NR	NR	NR
	<65 Years	NR	NR	NR	NR	NR	NR	NR
	≥65 Years	NR	NR	NR	NR	NR	NR	NR
Gender, n/N (%)	Male	422/969 (43.6)	544/1216 (45.6)	264/652 (50.5)	519/1304 (39.8)	454/1023 (44.4)		889/2046 (43.7)
	Female	547/969 (56.4)	672/1216 (54.4)	388/652 (59.5)	785/1304 (60.2)	569/1023 (55.6)		1157/2046 (56.6)
Race, n/N (%)	White	852/969 (89.8)	1071/1216 (89.4)	NR	NR	NR	NR	NR
	Black or African American	49/969 (5.2)	83/1216 (6.9)	35/652 (5.4)	50/1304 (3.8)	61/1023 (6.0)		112/2046 (5.5)
	Asian	NR	NR	NR	NR	NR	NR	NR
	American Indian or Alaska Native	NR	NR	NR	NR	NR	NR	NR
	Native Hawaiian or Pacific Islander	NR	NR	NR	NR	NR	NR	NR
	South Asian	NR	NR	NR	NR	NR	NR	NR
	Hispanic or Latino	NR	NR	NR	NR	NR	NR	NR
	Mixed Race	NR	NR	NR	NR	NR	NR	NR
	Communities of Color	NR	NR	NR	NR	NR	NR	NR
	Other	48/969 (5.1)	44/1216 (3.7)	NR	NR	NR	NR	NR
	Unknown	NR	NR	NR	NR	NR	NR	NR
	Not Reported	NR	NR	NR	NR	NR	NR	NR
Ethnicity, n/N (%)	Hispanic or Latino	NR	NR	NR	NR	NR	NR	NR
	Not Hispanic or Latino	NR	NR	NR	NR	NR	NR	NR
Weight, Median kg (IQR)		NR	NR	NR	NR	NR	NR	NR
BMI, Mean kg/m² (SD)		31.8 (7.5)	32.8 (8.4)	32.0 (7.6)	32.1 (7.7)	32.5 (7.4)		32.6 (7.8)
BMI, n/N (%)	<30 kg/m²	NR	NR	NR	NR	NR	NR	NR

Drug Name		REGEN-COV				REGEN-COV and Sotrovimab		
Trial		McCreary et al. 2021				Huang et al. 2021		
Arms		SC: Casirivimab/ Imdevimab	IV: Casirivimab/ Imdevimab	SC Matched: Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Sotrovimab	Control Group
N		969	1216	652	1304*	712	311	2046
	≥30 kg/m²	NR	NR	NR	NR	NR	NR	NR
Overweight, n/N (%)		NR	NR	NR	NR	NR	NR	NR
Positive Baseline Qualitative RT-PCR, n/N (%)		NR	NR	NR	NR	NR	NR	NR
Previous Anti-SARS-COV-2 Vaccination, n/N (%)		447/969 (55.5)‡	485/1216 (44.1)‡	NR	NR	NR	NR	NR
Time from Symptom Onset to Infusion, Median Days (Range)		6.1 (1.9)†	6.1 (2.0)†	NR	NA	NR	NR	NR
Time from Symptom Onset to Infusion, n/N (%)	0-3 Days	170/969 (21.2)‡	257/1216 (23.4)‡	NR	NA	NR	NR	NR
	4-5 Days			NR	NA	NR	NR	NR
	>5 Days	293/969 (36.5)§	352/1216 (32.0)§	NR	NA	NR	NR	NR
	>7 Days	339/969 (42.3)	491/1216 (44.6)	NR	NA	NR	NR	NR
	Unspecified	NR	NR	NR	NR	NR	NR	NR
Duration of Follow-Up, Median Days (SD)		NR	NR	NR	NR	NR	NR	NR
Any Risk Factor for Progression to Severe Disease, n/N (%)	Age ≥55 Years	NR	NR	NR	NR	NR	NR	NR
	Obesity (BMI >30)	NR	NR	NR	NR	NR	NR	NR
	Hypertension	314/969 (47.0)**	408/1216 (43.3)**	303/652 (46.5)**	591/1304 (45.3)**	423/1023 (41.4)**		861/2046 (42.1)**
	CVD	73/969 (10.9)#**	105/1216 (11.1)#**	71/652 (10.9)#**	142/1304 (10.9)#**	103/1023 (10.1)#**		188/2046 (9.2)#**
	Heart Failure	36/969 (5.4)**	50/1216 (5.3)**	32/653 (4.9)**	85/1304 (6.4)**	46/1023 (4.5)**		93/2046 (4.6)**
	COPD	115/969 (17.2)**	151/1216 (16.0)**	108/653 (16.6)**	202/1304 (15.5)**	146/1023 (14.3)**		272/2046 (13.3)**
	Asthma	220/969 (32.9)**	283/1216 (30.0)**	213/652 (32.7)**	387/1304 (29.7)**	311/1023 (30.4)**		593/2046 (29.0)**
	CKD	34/969 (5.1)**	63/1216 (6.7)**	27/652 (4.1)**	80/1304 (6.1)**	53/1023 (5.2)**		117/2046 (5.7)**
	Diabetes (Type 1 and 2)	112/969 (16.8)**	161/1216 (17.1)**	107/652 (16.4)**	203/1304 (15.6)**	166/1023 (16.2)**		331/2046 (16.2)**

Drug Name		REGEN-COV				REGEN-COV and Sotrovimab		
Trial		McCreary et al. 2021				Huang et al. 2021		
Arms		SC: Casirivimab/ Imdevimab	IV: Casirivimab/ Imdevimab	SC Matched: Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Sotrovimab	Control Group
N		969	1216	652	1304*	712	311	2046
	Immunosup. Disease	NR	NR	NR	NR	NR	NR	NR
	Neurological Disorder	NR	NR	NR	NR	NR	NR	NR
	Liver Disease	28/969 (4.2)¤**	23/1216 (2.4)¤**	28/652 (4.3)¤**	42/1304 (3.2)¤**	34/1023 (3.3)¤**		59/2046 (2.9)¤**
	High Cholesterol	NR	NR	NR	NR	NR	NR	NR
	Any Other Risk Factors or Comorbidities	NR	NR	NR	NR	NR	NR	NR
Total Comorbidities, Median (IQR)		NR	NR	NR	NR	NR	NR	NR
≥1 Risk Factor for Progression to Severe Disease, n/N (%)		NR	NR	NR	NR	NR	NR	NR
Baseline Serum Antibody Status, n/N (%)	Negative	NR	NR	NR	NR	NR	NR	NR
	Positive	NR	NR	NR	NR	NR	NR	NR
	Other	NR	NR	NR	NR	NR	NR	NR
	Unknown	NR	NR	NR	NR	NR	NR	NR
Baseline Viral Load in Nasopharyngeal Swab, Median log_{10} Copies/mL (Range)		NR	NR	NR	NR	NR	NR	NR
Geography of Enrollment	US (%)	100%	100%	100%	100%	100%	100%	100%
	Non-US (%)	NA	NA	NA	NA	NA	NA	NA

BMI: body mass index, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, CVD: cardiovascular disease, IQR: interquartile range, IV: intravenous, kg: kilogram, m: meter, mL: milliliter, n: number, N: total number, NA: not applicable, NR: not reported, RT-PCR: reverse transcription polymerase chain reaction, SC: subcutaneous, SD: standard deviation, US: United States

*Matched controls. †Mean (SD). ‡Fully vaccinated patients. ‡1-4 days. §5-6 days. #Coronary artery disease. ¤Fatty liver disease. **Having a history of the condition/risk factor.

Table D27. Efficacy Outcomes: RWE Studies I[51,52]

Drug Name		REGEN-COV							
Trial		Webb et al. 2021		Razonable et al. 2021					
Arms		Casirivimab/ Imdevimab	Contemporaneous Controls	Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Controls
N		115	5,536	679	679	673	674	668	671
Timepoint		Day 14		Day 14		Day 21		Day 28	
≥1 Any-Cause Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Type of Any-Cause Medically-Attended Visit, n/N (%)	Outpatient Visit	NR	NR	NR	NR	NR	NR	NR	NR
	Urgent Care	NR	NR	NR	NR	NR	NR	NR	NR
	ED	9/115 (7.8)	944/5536 (17.1)	NR	NR	NR	NR	NR	NR
	Hosp.	1/115 (0.9)	538/5536 (9.7)	9/679 (1.3)	22/679 (3.3)	9/673 (1.3)	28/674 (4.2)	11/668 (1.6)	32/671 (4.8)
	ICU Admission	NR	NR	5/679 (0.7)	6/679 (0.9)	5/673 (0.7)	6/674 (0.9)	5/668 (0.7)	7/671 (1.0)
≥1 COVID-Related Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Type of COVID-19 Related Medically-Attended Visit, n/N (%)	Outpatient Visit	NR	NR	NR	NR	NR	NR	NR	NR
	Urgent Care	NR	NR	NR	NR	NR	NR	NR	NR
	ED	NR	NR	NR	NR	NR	NR	NR	NR
	Hosp.	NR	NR	NR	NR	NR	NR	NR	NR
	ICU Admission	NR	NR	NR	NR	NR	NR	NR	NR
COVID-19-Related Hospitalization or Any-Cause Death, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Hospitalized or Death from Any Cause, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Time to First ED Visit or Hospitalization, Median Days (IQR)		NR	6.7 (5.8)	NR	NR	NR	NR	NR	NR

Drug Name		REGEN-COV							
Trial		Webb et al. 2021		Razonable et al. 2021					
Arms		Casirivimab/ Imdevimab	Contemporaneous Controls	Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Controls
N		115	5,536	679	679	673	674	668	671
Timepoint		Day 14		Day 14		Day 21		Day 28	
Hospital Length of Stay, Median Days (IQR)		NR	NR	0.06 (0.64)*	0.14 (0.92)*	0.07 (0.80)*	0.18 (1.20)*	0.07 (0.81)*	0.23 (1.45)*
Relative Risk Reduction vs. Placebo of Primary Outcome (≥1 COVID-19-Related Hospitalization or All-Cause Death), % (95% CI)		NR	NR	NR	NR	NR	NR	NR	NR
ED Observation or Hospitalization from COVID-19, n/N (%)		10/115 (8.7)	1482/5536 (26.8)	NR	NR	NR	NR	NR	NR
ICU Length of Stay, Mean Days (SD)		NR	NR	0.03 (0.46)	0.03 (0.44)	0.03 (0.46)	0.03 (0.49)	0.03 (0.47)	0.03 (0.49)
COVID-19-Related Death, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Overall Mortality, n/N (%)		0/115 (0)	57/5536 (1.0)	1/679 (0.15)	3/679 (0.44)	1/673 (0.15)	3/674 (0.44)	1/668 (0.15)	4/671 (0.59)
Time to Death, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR	NR
Time to Symptom Resolution, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR	NR
Reduction in Time to COVID-19 Symptom Resolution, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR	NR
Time To First Alleviation of Symptoms, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR	NR
Ventilation Requirement, n/N (%)	Non-Invasive Ventilation	NR	NR	NR	NR	NR	NR	NR	NR
	Mechanical Ventilation	NR	NR	NR	NR	NR	NR	NR	NR

Drug Name		REGEN-COV							
Trial		Webb et al. 2021		Razonable et al. 2021					
Arms		Casirivimab/ Imdevimab	Contemporaneous Controls	Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Controls
N		115	5,536	679	679	673	674	668	671
Timepoint		Day 14		Day 14		Day 21		Day 28	
Days on Mechanical Ventilator, Median Days (IQR)		NR	NR	NR	NR	NR	NR	NR	NR
Time to SARS-Cov-2 Clearance, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR	NR
Viral Clearance, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR
Change from Baseline in SARS-Cov-2 Viral Load (log_{10} Copies/mL) LSM (SE)	Day 5	NR	NR	NR	NR	NR	NR	NR	NR
	Day 7	NR	NR	NR	NR	NR	NR	NR	NR
Adherence		NR	NR	NR	NR	NR	NR	NR	NR

CI: confidence interval, ED: emergency department, ED: emergency department, ICU: intensive care unit, IQR: interquartile range, LSM: least squares mean, mL: milliliter, n: number, N: total number, NR: not reported, SD: standard deviation, SE: standard error, vs: versus

*Median (SD).

Table D28. Efficacy Outcomes: RWE Studies II[53,55,56,58]

Drug Name		REGEN-COV					
Trial		Polk et al. 2021		Chilimuri et al. 2021		Piccicacco et al. 2021	
Arms		Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Control Group	Casirivimab/ Imdevimab	Controls
N		125	199	22	11	48	200
Timepoint		Day 30		Day 30		Day 29	
≥1 Any-Cause Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	NR	NR
Type of Any-Cause Medically-Attended Visit, n/N (%)	Outpatient Visit	NR	NR	NR	NR	NR	NR
	Urgent Care	NR	NR	1. NR	NR	NR	NR
	ED	3/125 (2)	21/199 (10)	NR	NR	NR	NR
	Hospitalization	3/125 (2)	25/199 (12)	2/22 (9.1)	6/11 (54.5)	NR	NR
	ICU Admission	0/125 (0)	8/199 (4)	NR	NR	NR	NR
≥1 COVID-19-Related Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	NR	NR
Type of COVID-19 Related Medically-Attended Visit, n/N (%)	Outpatient Visit	NR	NR	NR	NR	NR	NR
	Urgent Care	NR	NR	NR	NR	NR	NR
	ED	1/125 (1)	18/199 (9)	NR	NR	5/48 (10.4)	26/200 (13)
	Hospitalization	3/125 (2)	24/199 (12)	1/22 (4.5)	6/11 (54.5)	0/48 (0)	60/200 (30)
	ICU Admission	0/125 (0)	8/199 (4)	NR	NR	NR	NR
COVID-19-Related Hospitalization or Any-Cause Death, n/N (%)		NR	NR	NR	NR	NR	NR
Hospitalized or Death from Any Cause, n/N (%)		NR	NR	NR	NR	NR	NR
Time to First ED Visit or Hospitalization, Median Days (IQR)		NR	NR	NR	NR	NR	NR
Hospital Length of Stay, Median Days (IQR)		NR	NR	NR	NR	NR	NR
Relative Risk Reduction vs. Placebo of Primary Outcome (≥1 COVID-19-Related Hospitalization or All-Cause Death), % (95% CI)		NR	NR	NR	NR	NR	NR
ED Observation or Hospitalization from COVID-19, n/N (%)		NR	NR	NR	NR	5/48 (10.4)	81/200 (40.5)
ICU Length of Stay, Mean Days (SD)		NR	NR	NR	NR	NR	NR
COVID-Related Death, n/N (%)		0/125 (0)	4/199 (2)	NR	NR	NR	NR

Drug Name		REGEN-COV					
Trial		Polk et al. 2021		Chilimuri et al. 2021		Piccicacco et al. 2021	
Arms		Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Control Group	Casirivimab/ Imdevimab	Controls
N		125	199	22	11	48	200
Timepoint		Day 30		Day 30		Day 29	
Overall Mortality, n/N (%)		0/125 (0)	4/199 (2)	0/22 (0)	2/11 (18.1)	0/48 (0)	7/200 (3.5)
Time to Death, Mean Days (SD)		NR	NR	NR	NR	NR	NR
Time to Symptom Resolution, Mean Days (SD)		NR	NR	NR	NR	NR	NR
Reduction in Time to COVID-19 Symptom Resolution, Mean Days (SD)		NR	NR	NR	NR	NR	NR
Time to First Alleviation of Symptoms, Mean Days (SD)		NR	NR	NR	NR	NR	NR
Ventilation Requirement, n/N (%)	Non-Invasive Ventilation	NR	NR	NR	NR	NR	NR
	Mechanical Ventilation	0/125 (0)	3/199 (1)	NR	NR	NR	NR
Days on Mechanical Ventilator, Median Days (IQR)		NR	NR	NR	NR	NR	NR
Time to SARS-Cov-2 Clearance, Mean Days (SD)		NR	NR	NR	NR	NR	NR
Viral Clearance, n/N (%)		NR	NR	NR	NR	NR	NR
Change from Baseline in SARS-Cov-2 Viral Load (log_{10} Copies/mL) LSM (SE)	Day 5	NR	NR	NR	NR	NR	NR
	Day 7	NR	NR	NR	NR	NR	NR
Adherence		NR	NR	NR	NR	NR	NR

CI: confidence interval, ED: emergency department, ER: emergency room, ICU: intensive care unit, IQR: interquartile range, LSM: least squares mean, mL: milliliter, n: number, N: total number, NR: not reported, SD: standard deviation, SE: standard error, vs: versus

Table D29. Efficacy Outcomes: RWE Studies III[34,57]

Drug Name		REGEN-COV				REGEN-COV & Sotrovimab		
Trial		McCreary et al. 2021				Huang et al. 2021		
Arms		SC: Casirivimab/ Imdevimab	IV: Casirivimab/ Imdevimab	SC matched: Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Sotrovimab	Control Group
N		969	1,216	652	1,304*	712	311	2,046
Timepoint		Day 28				Day 28		
≥1 Any-Cause Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	NR	NR	NR
Type of Any-Cause Medically-Attended Visit, n/N (%)	Outpatient Visit	NR	NR	NR	NR	NR	NR	NR
	Urgent Care	NR	NR	NR	NR	NR	NR	NR
	ED	NR	NR	NR	NR	NR	NR	NR
	Hospitalization	27/969 (2.8)	20/1216 (1.6)	22/652 (3.4)	85/1304 (6.5)	19/712 (2.7)	16/311 (5.1)	134/2046 (6.6)
	ICU Admission	3/969 (0.3)	3/1216 (0.2)	NR	NR	NR	NR	NR
≥1 COVID-19-Related Medically-Attended Visit, n/N (%)		NR	NR	NR	NR	NR	NR	NR
Type of COVID-19 Related Medically-Attended Visit, n/N (%)	Outpatient Visit	NR	NR	NR	NR	NR	NR	NR
	Urgent Care	NR	NR	NR	NR	NR	NR	NR
	ED	NR	NR	NR	NR	NR	NR	NR
	Hospitalization	NR	NR	NR	NR	NR	NR	NR
	ICU Admission	NR	NR	NR	NR	NR	NR	NR
COVID-19-Related Hospitalization or Any-Cause Death, n/N (%)		NR	NR	NR	NR	NR	NR	NR
Hospitalized or Death from Any Cause, n/N (%)		27/969 (2.8)	21/1216 (1.7)	22/652 (3.4)	101/1304 (7.8)	19/712 (2.7)	16/311 (5.1)	174/2046 (8.5)
Time to First ED Visit or Hospitalization, Median Days (IQR)		NR	NR	NR	NR	NR	NR	NR
Hospital Length of Stay, Median days (IQR)		4 (2-8)	3 (4-6.5)	NR	NR	NR	NR	NR
Relative Risk Reduction vs. Placebo of Primary Outcome (≥1 COVID-19-		NR	NR	NR	NR	NR	NR	NR

Drug Name		REGEN-COV				REGEN-COV & Sotrovimab		
Trial		McCreary et al. 2021				Huang et al. 2021		
Arms		SC: Casirivimab/ Imdevimab	IV: Casirivimab/ Imdevimab	SC matched: Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Sotrovimab	Control Group
N		969	1,216	652	1,304*	712	311	2,046
Timepoint		Day 28				Day 28		
Related Hospitalization or All-Cause Death), % (95% CI)								
ED Observation or Hospitalization from COVID-19, n/N (%)		47/969 (4.8)†	71/1216 (5.8)†	40/652 (6.1)†	133/1304 (10.2)†	NR	NR	NR
ICU Length of Stay, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR
COVID-19-Related Death, n/N (%)		NR	NR	NR	NR	NR	NR	NR
Overall Mortality, n/N (%)		1/969 (0.1)	3/1216 (0.2)	1/652 (0.2)	29/1304 (2.2)	1/712 (0.1)	0/311 (0)	60/2046 (2.9)
Time to Death, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR
Time to Symptom Resolution, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR
Reduction in Time to COVID-19 Symptom Resolution, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR
Time to First Alleviation of Symptoms, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR
Ventilation Requirement, n/N (%)	Non-Invasive Ventilation	NR	NR	NR	NR	NR	NR	NR
	Mechanical Ventilation	3/969 (0.3)	2/1216 (0.2)	NR	NR	NR	NR	NR
Days on Mechanical Ventilator, Median Days (IQR)		NR	NR	NR	NR	NR	NR	NR
Time to SARS-Cov-2 Clearance, Mean Days (SD)		NR	NR	NR	NR	NR	NR	NR
Viral Clearance, n/N (%)		NR	NR	NR	NR	NR	NR	NR
Change from Baseline in SARS-Cov-2 Viral Load (log_{10}	Day 5	NR	NR	NR	NR	NR	NR	NR
	Day 7	NR	NR	NR	NR	NR	NR	NR

Drug Name	REGEN-COV				REGEN-COV & Sotrovimab		
Trial	McCreary et al. 2021				Huang et al. 2021		
Arms	SC: Casirivimab/ Imdevimab	IV: Casirivimab/ Imdevimab	SC matched: Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Sotrovimab	Control Group
N	969	1,216	652	1,304*	712	311	2,046
Timepoint	Day 28				Day 28		
Copies/mL) LSM (SE)							
Adherence	NR	NR	NR	NR	NR	NR	NR

CI: confidence interval, ED: emergency department, ER: emergency room, ICU: intensive care unit, IQR: interquartile range, IV: intravenous, LSM: least squares mean, mL: milliliter, n: number, N: total number, NR: not reported, SC: subcutaneous, SD: standard deviation, SE: standard error, vs.: versus

*Matched controls.

†ED observation or any-cause hospitalization.

Table D30. Subgroup Outcomes: RWE Studies[34,57]

Drug Name		REGEN-COV				REGEN-COV & Sotrovimab		
Trial*		McCreary et al. 2021				Huang et al. 2021		
Subgroup Category		Same Site Infused Patients		Unmatched Cohort		Unmatched Cohort		
Arms		SC: Casirivimab/ Imdevimab	IV: Casirivimab/ Imdevimab	SC Matched: Casirivimab/ Imdevimab	Controls	Casirivimab/ Imdevimab	Sotrovimab	Control Group
N		721	441	665	3,821	717	311	5,171
Timepoint		Day 29		Day 29		Day 29		
Hospitalized or Death from Any Cause, n/N (%)		17/721 (2.4)	4/441 (0.9)	23/665 (3.5)	251/3821 (6.6)	19/717 (2.6)	16/311 (5.1)	479/5171 (9.3)
Hospitalization		17/721 (2.4)	4/441 (0.9)	23/665 (3.5)	208/3821 (5.4)	19/717 (2.6)	16/311 (5.1)	357/5171 (6.9)
ICU Admission		3/721 (0.4)	1/441 (0.2)	NR	NR	NR	NR	NR
Hospital Length of Stay, Mean Days (SD)		6 (3,10)	4.5 (2,6)	NR	NR	NR	NR	NR
ED Observation or Hospitalization from COVID-19, n/N (%)		38/721 (5.3)†	26/441 (5.9)†	40/665 (6.0)†	376/3821 (9.8)†	NR	NR	NR
Overall Mortality, n/N (%)		1/721 (0.1)	1/441 (0.2)	1/665 (0.2)	80/3821 (2.1)	1/717 (0.1)	0/311 (0)	184/5171 (3.6)
Ventilation Requirement, n/N (%)	Non-Invasive Ventilation	NR	NR	NR	NR	NR	NR	NR
	Mechanical Ventilation	2/721 (0.3)	1/441 (0.2)	NR	NR	NR	NR	NR

ER: emergency room, ICU: intensive care unit, IV: intravenous, n: number, N: total number, NR: not reported, SC: subcutaneous, SD: standard deviation

*No subgroup data available from Webb et al. 2021, Razonable et al. 2021, Polk et al. 2021, Chilimuri et al. 2021, or Piccicacco et al. 2021.

†ED observation or any-cause hospitalization.

Table D31. Adverse Events: RWE Studies I[51,52]

Drug Name		REGEN-COV			
Trial		Webb et al. 2021		Razonable et al. 2021	
Arms		Casirivimab/Imdevimab	Contemporaneous Controls	Casirivimab/Imdevimab	Controls
N		115	5536	696	696
Timepoint		Day 14		Day 28	
≥ Any AE, n/N (%)		1/115 (0.9)	NR	7/696 (1.0)	NR
≥ Any TEAE, n/N (%)		NR	NR	NR	NR
Drug-Related AE, n/N (%)		NR	NR	NR	NR
AE Leading to Discontinuation, n/N (%)		NR	NR	NR	NR
AE Leading to Dose Interruption, n/N (%)		NR	NR	NR	NR
AE Leading to Death, n/N (%)		NR	NR	NR	NR
Serious AE Related to Treatment, n/N (%)		0/115 (0)	NR	0/696 (0)	NR
≥1 Serious AE, n/N (%)		0/115 (0)	NR	0/696 (0)	NR
Fatal AE, n/N (%)		NR	NR	0/696 (0)	NR
All-Cause Mortality, n/N (%)		NR	NR	0/696 (0)	NR
Grade 3 or 4 AE, n/N (%)		NR	NR	NR	NR
TEAE Severity, n/N (%)	Grade 1	NR	NR	7/696 (1.0)	NR
	Grade 2	NR	NR	0/696 (0)	NR
	Grade 3	NR	NR	0/696 (0)	NR
	Grade 4	NR	NR	0/696 (0)	NR
	Grade 5	NR	NR	0/696 (0)	NR
Infusion-Related AE, n/N (%)	Any	1/115 (0.9)	NR	NR	NR
	Grade ≥2	NR	NR	NR	NR
	Grade 3 or 4	NR	NR	NR	NR
	Related to Treatment	NR	NR	NR	NR
	Leading to Discontinuation	NR	NR	NR	NR
	Leading to Dose Interruption	NR	NR	NR	NR
Hypersensitivity Reactions Grade ≥2, n/N (%)		NR	NR	0/696 (0)	NR
Dyspnea, n/N (%)		NR	NR	NR	NR
Diarrhea, n/N (%)		NR	NR	NR	NR

Drug Name	REGEN-COV			
Trial	Webb et al. 2021		Razonable et al. 2021	
Arms	Casirivimab/Imdevimab	Contemporaneous Controls	Casirivimab/Imdevimab	Controls
N	115	5536	696	696
Timepoint	Day 14		Day 28	
Nausea n/N (%)	NR	NR	2/696 (0.3)	NR
Vomiting, n/N (%)	NR	NR	NR	NR
Dizziness, n/N (%)	NR	NR	NR	NR
Headache, n/N (%)	NR	NR	1/696 (0.1)	NR
Hypoxia, n/N (%)	NR	NR	NR	NR
COVID-19 Pneumonia, n/N (%)	NR	NR	NR	NR
Hives, n/N (%)	1/115 (0.9)	NR	NR	NR

AE: adverse event, n: number, N: total number, NR: not reported, TEAE: treatment emergent adverse event

Table D32. Adverse Events: RWE Studies II[54,57]

Drug Name		REGEN-COV					
Trial*		Piccicacco et al. 2021		McCreary et al. 2021			
Arms		Casirivimab/ Imdevimab	Controls	SC: Casirivimab/ Imdevimab	IV: Casirivimab/ Imdevimab	SC Matched: Casirivimab/ Imdevimab	Controls
N		48	200	969	1216	652	1304†
Timepoint		Day 29		Day 28			
≥ Any AE, n/N (%)		NR	NR	NR	NR	NR	NR
≥ Any TEAE, n/N (%)		NR	NR	NR	NR	NR	NR
Drug-Related AE, n/N (%)		NR	NR	NR	NR	NR	NR
AE Leading to Discontinuation, n/N (%)		NR	NR	NR	NR	NR	NR
AE Leading to Dose Interruption, n/N (%)		NR	NR	NR	NR	NR	NR
AE Leading to Death, n/N (%)		NR	NR	NR	NR	NR	NR
Serious AE Related to Treatment, n/N (%)		NR	NR	NR	NR	NR	NR
≥1 Serious AE, n/N (%)		1/48 (2.1)	NR	0/969 (0)	2/1216 (0.2)	NR	NR
Fatal AE, n/N (%)		NR	NR	NR	NR	NR	NR
All-Cause Mortality, n/N (%)		NR	NR	1/969 (0.1)	3/1216 (0.2)	1/652 (0.2)	29/1304 (2.2)
Grade 3 or 4 AE, n/N (%)		NR	NR	NR	NR	NR	NR
TEAE Severity, n/N (%)	Grade 1	NR	NR	NR	NR	NR	NR
	Grade 2	NR	NR	NR	NR	NR	NR
	Grade 3	NR	NR	NR	NR	NR	NR
	Grade 4	NR	NR	NR	NR	NR	NR
	Grade 5	NR	NR	NR	NR	NR	NR
Infusion-Related AE, n/N (%)	Any	NR	NR	NR	NR	NR	NR
	Grade ≥2	NR	NR	NR	NR	NR	NR
	Grade 3 or 4	NR	NR	NR	NR	NR	NR
	Related to Treatment	NR	NR	NR	NR	NR	NR
	Leading to Discontinuation	NR	NR	NR	NR	NR	NR

Drug Name	REGEN-COV					
Trial*	Piccicacco et al. 2021		McCreary et al. 2021			
Arms	Casirivimab/ Imdevimab	Controls	SC: Casirivimab/ Imdevimab	IV: Casirivimab/ Imdevimab	SC Matched: Casirivimab/ Imdevimab	Controls
N	48	200	969	1216	652	1304†
Timepoint	Day 29		Day 28			
Leading to Dose Interruption	NR	NR	NR	NR	NR	NR
Hypersensitivity Reactions Grade ≥2, n/N (%)	NR	NR	NR	NR	NR	NR
Dyspnea, n/N (%)	NR	NR	NR	NR	NR	NR
Diarrhea, n/N (%)	NR	NR	NR	NR	NR	NR
Nausea n/N (%)	NR	NR	NR	NR	NR	NR
Vomiting, n/N (%)	NR	NR	NR	NR	NR	NR
Dizziness, n/N (%)	NR	NR	NR	NR	NR	NR
Headache, n/N (%)	NR	NR	NR	NR	NR	NR
Hypoxia, n/N (%)	NR	NR	NR	NR	NR	NR
COVID-19 Pneumonia, n/N (%)	NR	NR	NR	NR	NR	NR
Hives, n/N (%)	NR	NR	NR	NR	NR	NR

AE: adverse event, n: number, N: total number, NR: not reported, TEAE: treatment emergent adverse event

*No safety data available for Polk et al. 2021, Chilimuri et al. 2021, or Huang et al. 2021.

†Matched controls.

D4. Ongoing Studies

Figure D33. Ongoing Studies

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
Sotrovimab					
Intramuscular VIR-7831 (Sotrovimab) for Mild/Moderate COVID-19 (COMET-TAIL) Vir Biotechnology, Inc; GlaxoSamithKine NCT04913675	Phase III MC, OL, RCT N=983	• Sotrovimab 500 mg IV • Sotrovimab 500 mg IM • Sotrovimab 250 mg IM	Inclusion Criteria: • Participant aged 12+ years AND at high risk of progression of COVID-19 or ≥55 years old • Participants must have a positive SARS-CoV-2 test result and oxygen saturation ≥94% on room air and have COVID-19 symptoms and be less than or equal to 7 days from onset of symptoms Exclusion Criteria: • Currently hospitalized or likely hospitalization in next 24 hours • Symptoms consistent with severe COVID-19 • Participants who are likely to die in the next 7 days	Primary Outcome: • Progression of COVID-19 [day 29] Secondary Outcomes (up to 24 weeks unless otherwise stated): • AEs, SAEs, and AESIs • Incidence and titers of serum ADA to sotrovimab • Cmax, Clast, Tmax, Tlast, AUCinf, AUClast, %AUCextrap, t1/2, Vz/F, CL/F • Mean AUC of SARS CoV-2 viral load [day 8] • Change from baseline in viral load [day 8]	August 2022
Safety, Tolerability and Pharmacokinetics of Second Generation VIR-7831 Material in Non-hospitalized Participants With Mild to Moderate COVID-19 (COMET-PEAK) Vir Biotechnology, Inc; GlaxoSamithKine NCT04779879	Phase II MC, DB, parallel group, RCT N=352	Part A: • Sotrovimab 500 mg IV (Gen 1) • Sotrovimab 500 mg IM (Gen 2) Part B: • Sotrovimab 500 mg IV (Gen 2) Part C: • Sotrovimab 500 mg IV (Gen 2)	Inclusion Criteria: • Part A: Patients ages 18+ years • Parts B and C: Patients ages 18-69 years • Positive SARS-CoV-2 test result ≤7 days prior to enrollment, oxygen saturation ≥94% on room air, has COVID-19 symptoms and ≤7 days from onset of symptoms Exclusion Criteria: • Currently or soon hospitalized	Primary Outcome: • AEs, SAEs and AESIs [day 29, 12 weeks, and 24 weeks] • Occurrence of clinically significant abnormalities on 12-lead ECG [day 29 and 12 weeks] • Disease progression events [day 29 and 24 weeks]	June 2022

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
		• Sotrovimab 250 mg IM	• Symptoms consistent with severe COVID-19 • Likely to die in next 7 days or are severely immunocompromised • Parts A and B: Prior receipt of a SARS-CoV-2 vaccination • Parts B and C: Conditions that would prohibit receipt of IM injections • Any vaccination within 48 hours prior	• Mean AUC of SARS-CoV-2 viral load [day 1-day 8, day 5, and day 11] Secondary Outcomes: • Cmax, Clast, Tmax, Tlast, AUCD0-28, AUCinf, AUClast, %AUCexp, T1/2, Vz, Vss, CL [24 weeks] • Change from baseline in viral load [day 29]	
Molnupiravir					
Phase II AGILE Merck (No NCT provided)	Phase I: OL Phase II: PC, RCT N~198	• Molnupiravir • Placebo	Inclusion Criteria: • Outpatient adults with mild or moderate COVID	NR	NR
Paxlovid					
A Study of PF-07321332/Ritonavir in Non-Hospitalized Low-Risk Adult Participants With COVID-19 (EPIC-SR) Pfizer NCT05011513	Phase II/III DB, PC, RCT N~1,140	• Nirmatrelvir 300 mg + ritonavir 100 mg • Placebo	Inclusion Criteria: • SARS-CoV-2 infection and onset COVID-19 symptoms within 5 days prior to randomization • Fertile participants must be on contraception Exclusion Criteria: • Received any COVID-19 vaccine • History of or need for hospitalization for COVID-19 • Previous SARS-CoV-2 or active infection other than COVID-19 • Has liver disease, HIV infection with viral load >400 copies/ml, taking prohibited medications for HIV, receiving dialysis or has renal impairment • Use of medications dependent on CYP3A4 for clearance	Primary Outcome: • Time to alleviation of COVID-19 symptoms [day 28] Secondary Outcomes (up to day 28 unless otherwise stated): • AEs, SAEs, AEs leading to discontinuation [day 34] • Severe COVID-19 symptoms • Duration of COVID-19 symptoms • Progression to a worsening status in COVID-19 symptoms	April 2022

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
			• Receive monoclonal antibody, convalescent COVID-19 plasma, SARS-COV-2 vaccine • Participation in clinical study with other investigational compound or PF-07321332 • Oxygen saturation of <92% on room air • Pregnant or breastfeeding	• Resting peripheral oxygen saturation ≥95% [days 1, 5] • Number of COVID-19 related medical visits • Number of days in hospital and ICU • COVID-19 related hospitalization or all-cause death	
Fluvoxamine					
Repurposed Approved and Under Development Therapies for Patients With Early-Onset COVID-19 and Mild Symptoms	Phase III QB, PC, RCT Adaptive platform trial N~3,645	• Fluvoxamine 100 mg (oral) twice daily (n=739) • Doxazosin (1 or 2 mg once daily (days 0-3), titration up to 8 mg/day (days 3-13) (oral) Ivermectin 6 mg (oral) once daily Placebo (n=733)	<u>Inclusion Criteria:</u> • Patients 18+ years with acute flu-like symptoms <7 days • ≤1 enhancement criteria: age > 50 years, diabetes, asthma, hypertension, CVD, lung disease, fever >38C, obesity, transplant patients, CKD, immunosuppressive or corticosteroid therapy, cancer, chronic renal disease KDIGO IV or ESRD • Patient with SARS-CoV2 <u>Exclusion Criteria:</u> • Negative SARS-CoV2 test, flu-like symptom onset 8+ days, or >14 days of SARS-CoV-2 vaccination • Non-COVID acute respiratory conditions • Moderate disease or hospitalized due to COVID-19 • Use of medications in 14 days: SSRIs, MAOIs, sotalol, prazosin, alpha-1 antagonists, clonidine, methyldopa, terazosin, PDE5	<u>Primary Outcomes: (through day 28):</u> • Need for ED visits and observation unit stay >6 hours • Hospitalization due to COVID-19 progression <u>Secondary Outcomes (through day 28 unless otherwise stated):</u> • Change in viral load (day 3 and 7) • Time to clinical changes (>50%) • Time to hospitalization • Days with respiratory symptoms • All-cause and COVID-19 hospitalizations • Number of days on mechanical ventilator • Number of days on ICU • Number of days on hospitalizations	March 2022

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
			inhibitors, doxazosin, antiretroviral agents • Have severe psychiatric/mental disorders • Pregnant or breastfeeding • History of cardiac arrythmia, long QT syndrome, syncope, hypotension, POTS, MI, cerebrovascular accident, cardiovascular intervention, mitral or aortic stenosis, seizures, liver cirrhosis • Surgery during treatment	• Health and functioning after COVID-19 disease using PROMIS Global Health Score (day 14 and 28) • WHO ordinal scale for clinical improvement • Number of days on respiratory Symptoms • Adherence	
COVID-OUT: Early Outpatient Treatment for SARS-CoV-2 Infection (COVID-19) University of Minnesota NCT04510194	Phase III DB, PC, RCT N~1350	• Metformin 500/1000 mg • Ivermectin 390-470 mcg/kg • Fluvoxamine 50 mg • Metformin 500/1000 mg + Fluvoxamine 50 mg • Metformin 500/1000 mg + Ivermectin 390-470 mcg/kg	Inclusion Criteria: • Positive lab test for SARS-CoV-2 infection within 3 days of randomization. • No history of SARS-CoV-2 infection • BMI ≥25kg/m2 by self-report height/weight or ≥23kg/m2 in South Asian or Latinx patients • GFR >45ml/min within 2 weeks for patients >75 years old, or with history of heart, kidney, or liver failure. Exclusion Criteria: • Hospitalized, for COVID-19 or other reasons. • Symptom onset >7 days before randomization • Hepatic impairment, alcohol use disorder, severe kidney disease, CKD, bipolar disease, immunocompromised	Primary Outcome: • Clinical progression (day 14) Secondary Outcomes • Maximum symptom severity (days 14 and 28) • Clinical progression Scale (days 14 and 28) • Time to meaningful recovery (days 14 and 28) • Laboratory Outcome – Subsidy & Microbiome (days 1, 5, 10) • Participants with post-acute sequelae of SARS-CoV-2 infection (PASC) (6 and 12 months)	February 2023

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
			• Enrollment in another RCT for COVID-19 or already received effective COVID-19 therapy • Typhoid, BCG, or cholera vaccination within the 14-days		
ACTIV-6: COVID-19 Study of Repurposed Medications NCT04885530	Phase III DB, PC, RCT Adaptive platform trial N~15,000	• Ivermectin 7 mg • Arm A Placebo • Fluvoxamine 50 mg • Arm B Placebo • Fluticasone 200 µg • Arm C Placebo	Inclusion Criteria: • Age ≥30 years old • Confirmed SARS-CoV-2 infection by any authorized or approved PCR or antigen test within 10 days of screening • 2+ current symptoms of acute infection for ≤7 days Exclusion Criteria: • Prior diagnosis of COVID-19 infection (>10 days from screening) • Current or recent hospitalization	Primary Outcomes (Day 14): • Hospitalizations • Death Secondary Outcomes (Day 28 unless otherwise stated): • Change in COVID-19 clinical progression scale • Hospitalizations • Deaths • Number of symptoms • Symptom resolution • PROMIS-29 (days 7, 14, 28, 29)	March 2023
Randomized-controlled Trial of the Effectiveness of COVID-19 Early Treatment in Community NCT05087381	OL, RCT Adaptive platform trial N~1,800	• Fluvoxamine 50 mg • Fluvoxamine 50 mg + Bromhexine 8 mg • Fluvoxamine 50 mg + Cyproheptadine 4 mg • Niclosamide 1000 mg • Niclosamide 1000 mg + Bromhexine 8 mg • Usual care	Inclusion Criteria: • COVID-19 adult patients with mild symptoms and the results were confirmed by antigen test kit or PCR for SARS-CoV-2 • People who have symptoms consistent with COVID-19 and test positive for SARS-CoV-2 infection within 48 hours of being known Exclusion Criteria: • Almost recovered • Previous randomization to an arm of the trial • Pregnant or breastfeeding	Primary Outcomes: • COVID-19-related hospital admission or mortality related to COVID-19 (day 28) • Time to recovery (through final participation day) Secondary Outcomes: • Change in GI viral shedding (days 7, 14) • Change in respiratory viral clearance (days 7, 14)	April 2022

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
			• Severe hepatic or renal impairment. • Currently taking fluvoxamine, bromhexine, cyproheptadine, or niclosamide	• Time to fever resolution (through final participation day) • WHO 5 Well Being Index (days 7, 15, 28, 60)	

AE: adverse event, AIDS: acquired immunodeficiency syndrome, AUC: area under the curve, AUC_{extrap}: area under the curve extrapolated as a percentage of the total, AUC_{inf}: area under the curve to infinity, AUC_{last}: area under the curve to the last measurable concentration, BCG: Bacille Calmette-Guérin, BMI: body-mass index, CKD: chronic kidney disease, CL: drug clearance, CL/F: apparent oral clearance, C_{last}: last measurable concentration (above the quantification limit), C_{max}: maximum plasma concentration, COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease, CYP3A4: Cytochrome P450 3A4, DB: double-blind, ED: emergency department, eGFR: estimated glomerular filtration rate, ESRD: end-stage renal disease, EUA: Emergency Use Authorization, GI: gastrointestinal, Hb: hemoglobin, HIV: human immunodeficiency virus, HCV: hepatitis C virus, HBV: hepatitis B virus, ICU: intensive care unit, IM: intramuscular, IVIG: intravenous immunoglobulin, IV: intravenous, KDIGO: Kidney Disease Improving Global Outcomes, kg: kilogram, m: meter, mAb: monoclonal antibody, MAOI: monoamine oxidase inhibitors, MC: multi-center, mcg: microgram, mg: milligram, MI: myocardial infarction, mL: milliliter, N: total number, NCT: National Clinical Trial Identifier, NR: not reported, NYHA: New York Heart Association, OL: open-label, PC: placebo-controlled, PCR: polymerase, chain reaction, PDE5: phosphodiesterase type 5, POTS: postural orthostatic tachycardia syndrome, QB: quadruple-blind, QT: interval representing the time it takes for the heart muscle to contract and then recover, RCT: randomized controlled trial, SAE: serious adverse event, TEAE: treatment-emergent adverse event, T_{last}: time of last measurable concentration, T_{max}: time to maximum plasma concentration (Cmax), t½: half-life, Vss: steady state volume of distribution, VZ/F: apparent volume of distribution during terminal phase, WHO: World Health Organization
Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies).

D5. Previous Systematic Reviews and Technology Assessments

We identified 17 systematic literature reviews or meta-analyses evaluating therapies for the treatment of COVID-19, three of which evaluated interventions of interest in our population of focus and are summarized below.

Kreuzberger, N., et al. (2021). "SARS-CoV-2-Neutralising Monoclonal Antibodies for Treatment of COVID-19"[101]

This living systematic literature review from the Cochrane database evaluated the effectiveness and safety of SARS-CoV-2 neutralizing monoclonal antibodies for the treatment of patients with COVID-19. The interventions assessed included bamlanivimab, bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, and regdanvimab. Inclusion criteria included studies evaluating SARS-CoV-2 neutralizing monoclonal antibody treatments for patients with COVID-19. By July 2021, investigators identified six RCTs (N=17,495), four studies looking at non-hospitalized patients with no symptoms or mild COVID-19 (N=3,474) and two looking at hospitalized patients with moderate-to-severe COVID-19 (N=10,099). Because of the limited number of studies and events, the level of certainty for all outcomes reported in the non-hospitalized population was low.

For non-hospitalized patients with COVID-19, fewer patients in the bamlanivimab arm were hospitalized compared to those in the placebo arm (RR: 0.17, 95% CI: 0.02 to 1.33; RR: 0.32, 95% CI: 0.07 to 1.47; RR: 0.34, 95% CI: 0.08 to 1.56). The treatment and placebo arms had similar rates of adverse events, and no arms had any deaths. Similarly, patients treated with bamlanivimab/etesevimab had a decreased likelihood of being hospitalized (RR: 0.30, 95% CI: 0.16 to 0.59), but an increased likelihood of experiencing adverse events and serious adverse events; there were also 10 deaths in the placebo arm and none in the treatment arm. Additionally, casirivimab/imdevimab was found to likely reduce the risk of hospitalization or death in non-hospitalized patients (RR: 0.43, 95% CI: 0.08 to 2.19; RR: 0.21, 95% CI: 0.02 to 1.79), but it is uncertain what effect this drug has on adverse events. Sotrovimab may reduce the number of patients requiring oxygen (RR: 0.11, 95% CI: 0.02 to 0.45) and experiencing hospitalization and death (RR: 0.14, 95% CI: 0.04 to 0.48), and serious adverse events, but it is uncertain whether sotrovimab reduces mortality, mechanical ventilation, or death. Regdanvimab may decrease hospitalization or death, but also may increase serious adverse events.

Due to the numerous limitations in the studies, such as lack of blinding, too few events, and serious imprecision, investigators found that the certainty level of evidence for the non-hospitalized COVID patients was low and that this evidence was not sufficient to derive meaningful conclusions about monoclonal antibody treatments for COVID-19.

Siemieniuk, R.A.C., et al. (2021). "Antibody and Cellular Therapies for Treatment of COVID-19: A Living Systematic Review and Network Meta-Analysis"[102]

Investigators conducted a living systematic literature review and network meta-analysis to evaluate the efficacy and safety of antiviral antibody therapies and blood products for the treatment of patients with COVID-19. They included RCTs of non-hospitalized patients and/or outpatients with suspected, probable, or confirmed COVID-19 that assessed blood products and COVID-19 antiviral antibodies. As of July 2021, 47 RCTs meeting inclusion criteria were identified, nine of which focused solely on mild/moderate COVID-19 patients, and 24 of which focused only on severe/critical COVID-19 patients. The interventions included convalescent plasma, IV immunoglobulin, umbilical cord mesenchymal stem cells, bamlanivimab, casirivimab/imdevimab, bamlanivimab/etesevimab, control plasma, peripheral blood non-haematopoetic stem cells, sotrovimab, anti-SARS-CoV-2 IVIG, therapeutic plasma exchange, XAV-19 polyclonal antibody, CT-P59 monoclonal antibody, and INM005 polyclonal antibody. Outcomes were stratified by disease severity, so only findings in the non-severe COVID-19 population are discussed.

For patients with non-severe COVID-19, it was found that those who received the interventions casirivimab/imdevimab (OR: 0.29, 95% CI: 0.17 to 0.47), bamlanivimab (OR: 0.24, 95% CI: 0.06 to 0.86), bamlanivimab/estevimab (OR: 0.31, 95% CI: 0.11 to 0.81), and sotrovimab (OR: 0.17, 95% CI: 0.04 to 0.57) had a lower risk of hospitalization. This level of evidence had low to moderate certainty. Since the risks of both mortality and need for mechanical ventilation are already very low in patients with non-severe disease, no interventions were found to have a significant reduction in either of these outcomes. Casirivimab/imdevimab was found to probably reduce the time to symptom resolution (ratio of means: 0.72, 95% CI: 0.58 to 0.92), while there was no effect for the other three monoclonal antibodies. None of the evaluated interventions seemed to have any effect on viral clearance or time to viral clearance.

In terms of adverse events, investigators did not distinguish findings between non-severe and severe COVID-19. Convalescent plasma and IV immunoglobulin may have an effect on adverse events leading to drug discontinuation, but with low certainty, and bamlanivimab and casirivimab/imdevimab likely do not have an effect on this outcome. Only convalescent plasma was found to cause infusion reactions, transfusion-associated circulatory overload, and transfusion-related acute lung injury, but the risks of these outcomes are very low.

Investigators concluded that monoclonal antibodies seem more effective in patients with non-severe COVID-19 than those with severe disease, given that the monoclonal antibodies appear to lower the risk of hospitalization, but noted that only casirivimab/imdevimab had moderate certainty for this outcome. Convalescent plasma seemed to have no benefit to patients with COVID-19, regardless of severity. Limitations include not enrolling patients with contemporary SARS-CoV-2 variants, such as Delta, using thresholds for imprecision that were determined within

the review team and not based on empirical data, lack of blinding in most of included trials of blood products, and potentially differential administration of cointerventions and supportive care.

Lee, T., et al. (2021). "Fluvoxamine for Outpatient COVID-19 to Prevent Hospitalization: A Systematic Review and Meta-Analysis"[46]

Investigators conducted a systemic literature review and meta-analysis to assess the effectiveness of fluvoxamine in patients with COVID-19. They included completed studies that evaluated fluvoxamine compared to placebo or standard of care in the outpatient COVID-19 population. By November 2021, three RCTs (STOP-COVID, STOP-COVID 2, and TOGETHER) were identified and included, with a total of 2,196 patients and a median age of 46 to 50. Investigators conducted a frequentist DerSimonian-Laird random effects meta-analysis, and two sensitivity analyses with a Bayesian random effects meta-analysis on the log risk ratio scale. The primary outcome in this meta-analysis was all-cause hospitalization.

Both forms of analyses favored fluvoxamine. In the frequentist-meta-analysis, RR: 0.75 (95% CI: 0.57 to 0.97); additionally, there was nearly a 99% probability that fluvoxamine prevents hospitalization with a moderate or greater effect. In the sensitivity analysis, RR: 0.78, (95% CI: 0.58 to 1.08) (weakly neutral prior) and RR: 0.73 (95% CI: 0.53 to 1.01) (moderately optimistic prior). The probability of a moderate effect ranged from 82% to 91%. The risk of bias in all trials was considered low and the evidence was found to have a moderate level of certainty.

Findings indicated that fluvoxamine likely has at least a moderate effect on preventing hospitalizations due to COVID-19. Investigators identified several potential limitations in their analysis, including the difference in baseline event rates due to variability in resource availability, disease variants, and healthcare practices, exclusion of fully vaccinated individuals who have a much lower rate of hospitalization, and inclusion of only three trials in this analysis. Investigators plan to use a living systematic review approach in their future research.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if Quantified), Likely Magnitude & Impact (if Not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	X	X	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	N/A	☐	
	Unpaid caregiver-time costs	N/A	☐	
	Transportation costs	N/A	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	N/A	X	
	Cost of unpaid lost productivity due to illness	N/A	X	
	Cost of uncompensated household production	N/A	☐	
Consumption	Future consumption unrelated to health	N/A	☐	
Social services	Cost of social services as part of intervention	N/A	☐	
Legal/Criminal Justice	Number of crimes related to intervention	N/A	☐	
	Cost of crimes related to intervention	N/A	☐	
Education	Impact of intervention on educational achievement of population	N/A	☐	
Housing	Cost of home improvements, remediation	N/A	☐	
Environment	Production of toxic waste pollution by intervention	N/A	☐	
Other	Other impacts (if relevant)	N/A	X	ICU capacity

N/A: not applicable

Adapted from Sanders et al.,2016[103]

Target Population

The population of focus for the economic evaluation consisted of individuals with mild-to-moderate COVID-19 and a high risk of progression to severe disease or hospitalization. Table E2 presents the baseline population characteristics from each pivotal trial. We calculated a single pooled estimate across these estimates, so the baseline characteristics of the cohort modeled were consistent across all intervention arms and the comparator arm. Pooling was based on a weighted average across the trials, where the weight assigned was based on the US sample size (i.e., trial overall sample size multiplied by the percent of trial participants from the US). The population characteristics used in the model after this pooling equated to a baseline age of 49 years and 52% of the population being female.

Table E2. Baseline Population Characteristics

	REGEN-COV	Sotrovimab	Molnupiravir	Paxlovid	Fluvoxamine
Sample Size	1,484	1,057	1,408	2,246	1,497
Percent US	95.8%	92%	6.2%	41%	0%
Weight for Pooling	42%	29%	3%	27%	0%
Age at Study Enrollment	48 years	53 years	43 years	46 years	50 years
Percent Female	52%	54%	52%	49%	58%
Source	Weinreich et al., 2021[47]	Gupta et al., 2021[2,4]	Jayk Bernal et al., 2021[8]	Pfizer Press Release[6], FDA EUA Label[9]	TOGETHER[3]

EUA: Emergency Use Authorization, FDA: Food and Drug Administration, NR: not reported, UK: United Kingdom, US: United States

The economic model accounted for the vaccination status of the population modeled in the base-case analysis and included both unvaccinated and vaccinated individuals. The trials were conducted prior to an available vaccine or excluded individuals who were vaccinated, and thus real-world evidence was used to estimate the percent of the real-world COVID-19 cases that likely occurred among vaccinated individuals. As of the posting of this Report, approximately 17% of COVID-19 cases are among individuals who were fully vaccinated.[71] This number will be reviewed and updated accordingly for each version of the Evidence Report within this review. A subpopulation including only unvaccinated individuals with mild-to-moderate COVID-19 and at high risk of progression to severe disease or hospitalization was evaluated in a scenario analysis.

Because current clinical and epidemiological evidence for COVID-19 suggests the average age of those that die from COVID-19 is higher than the average age of those infected with COVID-19,[104] the model allows for the average age of the treated population to differ from the average age of the population that died from COVID-19. When a survival benefit is observed, this results in a different average age for those who recovered between the intervention and comparator arm. Trial

evidence was reviewed for the age at death. The trial for REGEN-COV was the only trial that reported an age at death; it reported an age at death of 58 years.[47] Because the evidence for the age at death was available for less than 50% of our comparator weighted average, evidence from outside the trials was sourced for the trials that did not report this model input. A publication from the CDC reported the age of those who died from COVID-19 as 78 years.[105] Therefore, 78 years was used as the age at death for the trials that did not report this model input (e.g., sotrovimab, molnupiravir, Paxlovid, and fluvoxamine). After weighting across all five trials using the weights reported in Table E2, the age at death equated to 69.6 years.

Treatment Strategies

The list of interventions was developed with input from clinicians, manufacturers, and payers on which treatments to include. The list of interventions included:

- REGEN-COV
- Sotrovimab
- Molnupiravir
- Paxlovid
- Fluvoxamine

At the posting of this Report, REGEN-COV has been determined by US authorities to no longer be effective against the dominant Omicron COVID-19 variant. Therefore, economic estimates for REGEN-COV as an intervention are not included in the Report. Economic estimates for REGEN-COV that use evidence from when REGEN-COV was thought to be effective against prior COVID-19 variants can be found within this Supplement. We continue to use evidence from the usual care arm of the REGEN-COV pivotal trial in the comparator arm of our economic model due to its large US population and relevance to the comparator of our model. We also continue to review the evidence and receive stakeholder feedback, and thus the interventions included in the economic section of this report may change throughout the review.

E2. Model Inputs and Assumptions

Our model includes several assumptions stated in Table E3.

Table E3. Key Model Assumptions

Assumption	Rationale
The comparator arm was consistent across all interventions studied. The evidence for the comparator was based on a pooling of the usual care arms from each pivotal trial. Pooling was based on a weighted average across the trials, where the weight assigned was based on the US sample size (i.e., trial overall sample size multiplied by the percent of trial participants from the US).	Pooling across the usual care arms from each pivotal trial provided a more generalizable finding to the outcomes experienced by patients receiving usual care by accounting for different time periods within the pandemic, patient populations, and variants.
The relative treatment effects reported in each trial were applied to the outcomes from the pooled usual care evidence. The relative effectiveness seen in the trial population was generalizable to the comparator arm in the model that was constructed based on pooling evidence across the usual care arms in the pivotal trials. If a trial did not report a specific treatment effect, or the reported treatment effect was not statistically significant, a treatment effect of 1.0 was assumed.	The systematic differences in the trial populations should not affect the relative effectiveness of any of the drugs relative to usual care. We did not compare the cost effectiveness between the interventions given the systematic differences in the trial populations and design.
The baseline characteristics of the cohort modeled was consistent across all intervention arms and the comparator arm. The baseline characteristics of the cohort modeled was based on a pooling of the baseline characteristics from each pivotal trial. Pooling was based on a weighted average across the trials, where the weight assigned was based on the US sample size (i.e., trial overall sample size multiplied by the percent of trial participants from the US).	The US population eligible for each treatment is expected to be similar based on clinical expert consultation. Pooling across each pivotal trial was likely to provide a more generalizable finding to the population of individuals with mild-to-moderate COVID-19 and a high risk of progression to severe disease or hospitalization.
Adjustments were made to the risk of hospitalization and death observed in the usual care arms in the pivotal trials to account for the effectiveness of the vaccine in reducing hospitalization and death for the percent of infected patients that were vaccinated.	The trials were either conducted prior to an available vaccine or predominately included unvaccinated individuals. Given a vaccine is now available, more than 70% of US adults have received at least one dose,[71] and the vaccine is effective at reducing hospitalization and death even for breakthrough cases,[72] the evidence from the trials was weighted by the effectiveness of the vaccine for those individuals who were infected but also vaccinated. Clinical experts advised that these treatments, once widely available, are unlikely to be reserved solely for unvaccinated patients, and in fact would likely be widely prescribed for patients who are not at high risk of progression, leading to lower absolute risks of hospitalization and death than those seen in the clinical trials.

Assumption	Rationale
Death due to COVID-19 occurred at the end of the COVID-19 infected period in the model. Patients that died due to COVID-19 entered the Markov model in the dead health state.	Based on real-world data, death due to COVID-19 occurs later on in the infected period, rather than at the beginning.
The model accounted for the long-term sequelae of COVID-19 for those who were discharged alive following a hospitalization that required mechanical ventilation. These long-term sequelae consisted of an additional disutility, cost, and mortality risk.	Recommendations in the US report the occurrence and features characteristic of the long-term sequelae possible after a COVID-19 infection.[70]
A patient is 100% adherent to each intervention.	Treatment duration is short; for some interventions, treatment is a single administration.
The economic evaluation for REGEN-COV was based on the IV administration and the 1200 mg dose (600 mg of casirivimab and 600 mg of imdevimab) and its associated evidence from before the Omicron variant when it was expected to be effective.	The 1200 mg dose is the dose under EUA. The fact sheet recommends the IV infusion with the subcutaneous injection as an alternative when IV infusion is not possible. Evidence specific to the current Omicron variant is not available.
The economic evaluation for sotrovimab was based on the IV administration and its associated evidence.	The fact sheet specifies the IV infusion.[106]
The economic evaluation for IV-administered treatments assumed a clinic administration, rather than a home administration as well as a 6% markup.	Home administration infusions have historically been relatively low in frequency.[107]
All patients in the intervention arm had an outpatient visit. All patients in the comparator arm with an outpatient visit as their highest setting of care visited their outpatient provider.	All patients in the intervention arm visited their provider in order to get a prescription for these treatments.
Patients were hospitalized prior to dying from COVID-19. Any deaths averted between the intervention and the comparator arm resulted from reductions in the severity of the hospitalization associated with the treatment.	Deaths in patients who only received outpatient management or an emergency department visit are not common.[73] Further, evidence suggested an increased probability of death with higher levels of respiratory support required during the hospitalization.[74] Therefore, we modeled deaths averted indirectly based on hospitalizations averted and higher levels of respiratory support within a hospitalization averted. Trial estimates of the mortality in the intervention arm were not used given the small numbers and clinical rationale that the deaths averted should result from a treatment's effect on averting hospitalizations or reducing the severity of hospitalizations.

ED: emergency department, EUA: emergency use authorization, IV: intravenous, mg: milligram, US: United States

Model Inputs

Key model inputs included clinical probabilities, utility values, and health care costs. The comparator arm was consistent across all interventions and was based on a pooling of the outcomes observed in the usual care arms from each pivotal trial. Pooling was based on a weighted average across the trials, where the weight assigned was based on the US sample size (i.e., trial overall sample size multiplied by the percent of trial participants from the US). Adjustments were

made to the pooled probability of hospitalization and death from the usual care arms of the pivotal trials to account for the effectiveness of the vaccine in reducing hospitalizations and death for the COVID-19 positive cases who are expected to be vaccinated. Relative treatment effectiveness as well as treatment acquisition and associated costs were different among interventions and sourced from best available evidence. The relative treatment effect(s) reported in each trial was applied to the outcomes in the comparator arm (that was derived by pooling evidence from the usual care arms in the trials and adjusting for the effectiveness of the vaccine).

Clinical Inputs

Clinical inputs included probabilities of the highest setting of care a patient received during the COVID-19 infected period, the level of respiratory support received during a hospitalization, the probability of death, total symptoms days until recovery, and condition- and treatment-specific adverse events.

Highest Setting of Care to Manage COVID-19 Infection

The model tracked the highest setting of care a patient received during their COVID-19 infected period. Table E4 presents the highest setting of care from each pivotal trial. Evidence for the comparator arm was calculated based on a pooled estimate across the usual care arms from all pivotal trials, which was then adjusted for the percent of the population assumed to be vaccinated. Pooling was based on a weighted average across the trials, where the weight assigned was based on the US sample size (i.e., trial overall sample size multiplied by percent of trial participants from the US). Three trials did not report the probability of an emergency department visit and thus they were excluded from the pooled average of the emergency department probability. Evidence on the emergency department probability was available for more than 50% of the weighted average so no external sources were sourced for those three trials missing that model input.

Table E4. Highest Setting of Care Inputs, Unvaccinated Population

REGEN-COV			
Parameter	**Comparator**	**Relative Risk**	**Source/Notes**
Outpatient Management Only, %	95.6%	N/A	Weinreich et al., 2021[47]
ED Visit, %	1.3%	0.203	
Hospitalization, %	3.1%	0.265	
Sotrovimab			
Parameter	**Comparator**	**Relative Risk**	**Source/Notes**
Outpatient Management Only, %	92.2%	N/A	Gupta et al., 2021[2]
ED Visit, %	1.9%	1.0	
Hospitalization, %	5.9%	0.21	
Molnupiravir			
Parameter	**Comparator**	**Relative Risk**	**Source/Notes**
Outpatient Management Only, %	90.3%	N/A	Jayk Bernal et al., 2021[8]
ED Visit, %	NR	1.0	
Hospitalization, %	9.7%	0.70	
Paxlovid			
Parameter	**Comparator**	**Relative Risk**	**Source/Notes**
Outpatient Management Only, n (%)	93.7%	N/A	Pfizer press release[6]
ED Visit, n (%)	NR	1.0	
Hospitalization, n (%)	6.3%	0.12	
Fluvoxamine			
Parameter	**Comparator**	**Relative Risk**	**Source/Notes**
Outpatient Management Only, n (%)	84%	N/A	TOGETHER[3]
ED Visit, n (%)	NR	1.0	
Hospitalization, n (%)	16%	0.68	

ED: emergency department, N/A: not available, n: number, NR: not reported

The pooled probabilities of the highest setting of care calculated using evidence from the unvaccinated population in the trials (values reported in Table E4) equated to 93.6% of the cohort treated with an outpatient visit only, 1.5% of the cohort treated with an emergency department visit, and 4.9% of the cohort treated with an inpatient hospitalization. The pooled probability of hospitalization was then adjusted using real-world COVID-19 case data. For the percent of the total COVID-19 cases that occurred among vaccinated individuals (17%),[71] the probability of hospitalization based on the pooled evidence across the usual care arms was multiplied by the effectiveness of the vaccine in reducing hospitalizations (RR of 0.04).[72] No adjustments were made to the pooled probability of hospitalization for the cases that occurred among unvaccinated individuals. After making the adjustments for the vaccinated population, the hospitalization probability among the comparator arm equated to 4.1%. In the one-way sensitivity analysis, the probability of hospitalization was varied using the lower bound from the trial that reported the lowest probability of hospitalization (after adjustments for the vaccinated population) to an upper bound from the trial that reported the highest probability of hospitalization (after adjustments for the vaccinated population).

The relative risk reported in Table E4 observed for each intervention was applied to the evidence used in the comparator arm to estimate the outcomes for each intervention.

Severity of Hospitalizations

Evidence from the usual care arms of the trials that reported information on the severity of hospitalization was used to estimate the respiratory support received for a COVID-19 hospitalization for this population in the comparator arm. If the evidence suggested a statistically significant reduction in the level of respiratory support received associated with an intervention, then the model accounted for this in the respective intervention arm. If the evidence for an intervention did not provide this information, we modeled the same severity in the intervention arm as what was used in the comparator arm (e.g., RR of 1.0). Table E5 presents the level of respiratory support received if an individual was hospitalized as reported in the pivotal trials. Evidence for the comparator arm was calculated based on pooling across the usual care arms from all pivotal trials. Pooling was based on a weighted average across the trials, where the weight assigned was based on the US sample size (i.e., trial overall sample size multiplied by percent of trial participants from the US).

The respiratory support inputs used in the comparator arm of the model after this pooling equated to 26% requiring no oxygen support, 35% requiring low-flow oxygen, 29% requiring high-flow oxygen or non-invasive ventilation, and 10% requiring mechanical ventilation. Three trials did not report the respiratory support required and thus they were excluded from the pooled average of the emergency department probability. Evidence on the respiratory support required was available for more than 50% of the weighted average so no external sources were sourced for those three trials missing these model inputs.

The relative risks reported in Table E5 were applied to the evidence used in the comparator arm to estimate the respiratory support for each intervention.

Table E5. Respiratory Support Received Among Those Hospitalized

REGEN-COV			
Parameter	**Comparator**	**Relative Risk**	**Source/Notes**
No Oxygen, %	33.4%	N/A	Split single evidence data point for low-flow oxygen and high-flow oxygen combined based on distribution observed for sotrovimab; Data on file from Regeneron[95]
Low-Flow Oxygen, %	31.8%	1.0	
High-Flow Oxygen or Non-Invasive Ventilation, %	26.5%	1.0	
Mechanical Ventilation, %	8.3%	1.0	
Sotrovimab			
Parameter	**Comparator**	**Relative Risk**	**Source/Notes**
No Oxygen, %	16.1%	N/A	Gupta et al., 2021[2]
Low-Flow Oxygen, %	38.7%	0.26*	
High-Flow Oxygen or Non-Invasive Ventilation, %	32.3%		
Mechanical Ventilation, %	12.9%		
Molnupiravir			
Parameter	**Comparator**	**Relative Risk**	**Source/Notes**
No Oxygen, %	NR	N/A	Jayk Bernal et al., 2021[8]
Low-Flow Oxygen, %	NR	1.0	
High-Flow Oxygen or Non-Invasive Ventilation, %	NR	1.0	
Mechanical Ventilation, %	NR	1.0	
Paxlovid			
Parameter	**Comparator**	**Relative Risk**	**Source/Notes**
No Oxygen, %	NR	N/A	Pfizer Press Release[6]
Low-Flow Oxygen, %	NR	1.0	
High-Flow Oxygen or Non-Invasive Ventilation, %	NR	1.0	
Mechanical Ventilation, %	NR	1.0	
Fluvoxamine			
Parameter	**Comparator**	**Relative Risk**	**Source/Notes**
No Oxygen, %	NR	N/A	TOGETHER[3]
Low-Flow Oxygen, %	NR	1.0	
High-Flow Oxygen or Non-Invasive Ventilation, %	NR	1.0	
Mechanical Ventilation, %	4.5%	1.0	

n: number, N/A: not available, NR: not reported

*Relative risk is from a composite endpoint for progression to severe and/or critical respiratory COVID-19.

Mortality

Mortality in the model included COVID-19-related mortality and all-cause mortality. COVID-19-related mortality occurred from hospitalizations, with the probability of death based on the level of respiratory support received. Therefore, we modeled deaths averted indirectly based on hospitalizations averted and higher levels of respiratory support averted rather than direct estimates of mortality from the intervention arms of the trials. Direct estimates of mortality for the intervention arm are not used from the pivotal trials given the small numbers and clinical rationale

that the deaths averted should result from a treatment's effect on averting hospitalizations or reducing the severity of the hospitalizations (as measured by respiratory support required). Table E6 presents the probability of mortality conditioned on each level of respiratory support that was applied in the model. Because of the small number of deaths reported across the pivotal trials, these probabilities were sourced from real-world evidence.

Table E6. Probability of Death Following COVID-19 Hospitalization

Respiratory Support Received	Probability of Death	Source
No Oxygen	4.6%	Ohsfeldt et al., 2021[74]
Low-Flow Oxygen	7.6%	
High-Flow Oxygen or Non-Invasive Ventilation	25.8%	
Mechanical Ventilation	60.6%	

Table E7 presents the mortality observed in the comparator arms of the pivotal trials. The evidence from Table E7 was used to calibrate the model findings using the probabilities reported in Table E6. A multiplier was applied to each of the probabilities from Table E6 in the model to calibrate the model outcomes so the overall mortality in the acute phase of the comparator arm of the model equated to the weighted overall mortality reported in the usual care arms of the pivotal trials from Table E7. The probability of death after pooling the evidence from Table E7 equated to 0.521%. After accounting for the percent of the eligible population assumed to be vaccinated (17%)[71] and the effectiveness of the vaccine at preventing death following breakthrough infections (hazard ratio of 0.49),[108] the adjusted probability of death for the comparator arm equated to 0.48%.

Table E7. Probability of Death from Pivotal Trials

Intervention	Comparator	Source
REGEN-COV	0.13%	Weinreich et al., 2021[47]
Sotrovimab	0.38%	Gupta et al., 2021[4]
Molnupiravir	1.29%	Jayk Bernal et al., 2021[8]
Paxlovid	1.20%	Pfizer Press Release[6]
Fluvoxamine	3.00%	TOGETHER[3]

All-cause mortality was based on an exponential distribution fit to age- and sex-adjusted mortality from the general population.[109] Differences in life years gained between the intervention and comparator were modeled by way of preventing COVID-19 hospitalizations and by reducing the severity of those hospitalizations if evidence suggests.

Total Symptom Days

Total symptom days (Table E8) were tracked in the model based on the highest setting of care and level of respiratory support received. If evidence for an intervention suggested reductions in symptom days associated with the treatment, the model accounted for that accordingly. The only treatment with evidence suggestive of a reduction in symptom days was for REGEN-COV, which

reported a statistically significant hazard ratio of resolution of symptoms of 1.18 for outpatient management.[47]

Table E8. COVID-19 Symptom Days

	Symptom Days	Notes	Source
Outpatient Management Alone	11 days	Median 8 days of symptoms after positive test plus median 3 days of symptoms prior to test	CDC MMWR, Vol 69, No 30[110]
ED Visit	11 days		
Hospitalization (Without Oxygen)	17 days	Length of stay reported in source plus 9 days, which was the median time from symptom onset to hospitalization	Ohsfeldt et al., 2021[74] & Beigel et al., 2020[111]
Hospitalization (With Low-Flow Oxygen)	19 days		
Hospitalization (With High-Flow Oxygen or Noninvasive Ventilation)	21 days		
Hospitalization (With Mechanical Ventilation)	28 days		

CDC MMWR: Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report, ED: emergency department

Adverse Events

No treatment-related adverse events were included in the model. Condition-specific adverse events, outside of hospitalizations and the receipt of respiratory support, were incorporated in the economic model as data suggested. Condition-specific adverse events included the long-term sequelae some patients experience after the COVID-19 infected period. We used recommendations from COVID-19 research to include post-acute costs and consequences for patients who were discharged alive after being mechanically ventilated.[70] For those individuals, the model accounted for an increased probability of death for five years (hazard ratio of 1.33), a decrease in quality of life for five years (-0.13 in the first year and -0.04 in years 2 to 5), and an increase in health care costs for one year ($7,859 in the first year).[70]

Societal Clinical Inputs

Recent research has reported that when ICUs are near capacity, excess deaths occur over the following weeks.[112] Given these outpatient COVID-19 treatments may be associated with a reduction in ICU admissions, we include the potential indirect benefits of these treatments on ICU capacity in our modified societal perspective. As of November 2021, ICU bed occupancy was at 74% nationally (61,513 of 82,692 ICU beds filled).[113] For each posting of this Report, we will review the evidence for updated occupancy numbers. At an occupancy level of 74% nationally, recent research estimates an additional 12,000 excess deaths would occur within two weeks.[113] The average length of stay for COVID-19 patients admitted to the ICU has been reported as approximately two weeks.[114] Thus we assumed that the excess deaths over a two week period at the national-level occupancy level could be divided evenly among each ICU admission to estimate a per-treated patient effect. Therefore, the 12,000 excess deaths averted nationally translated to 0.195 (12,000/61,513) excess deaths averted per ICU admission averted. We then calculated the number

of ICU admissions averted for each treatment, assuming that hospitalizations that required high-flow oxygen, non-invasive mechanical ventilation, or mechanical ventilation would have been in the ICU. We then multiplied the number of ICU admissions averted for each treatment by 0.195 to calculate the number of excess societal deaths averted. We estimated the lifetime discounted costs, life years, QALYs, and evLYs for an excess societal death averted using the mean age at ICU admission of 78 years[115] and the same general population age-adjusted costs, mortality, and quality-of-life inputs described earlier in the Report. These indirect costs, QALYs, life years, and evLYs resulting from fewer excess deaths were included in the societal costs and societal health outcomes.

We did not include any societal benefits associated with the potential lower viral load associated with a treatment. This decision was the result of numerous conversations with clinical experts who suggested that vaccine uptake in the US is now at such a level that the benefit of these treatments in preventing secondary cases is minor.

Utility Inputs

Health state utilities were derived from publicly available literature. Age-adjusted utilities were applied over the lifetime time horizon.[116] COVID-19-related disutilities were applied during the infected period, with a larger disutility as the setting of care and respiratory support received increases. Table E9 reports the COVID-19-related disutilities. The duration of the disutility was based on the symptom days for each setting of care and respiratory support received.

Table E9. COVID-19-Related Disutilities

	Disutility	Notes	Source
Outpatient Management Alone	-0.19	Calculated disutility from utility reported in source (0.68) from subtracting utility from age-adjusted utility (0.87)[116]	Poteet & Craig, 2021[117] & Sullivan et al., 2020[116]
ED Visit	-0.30	Applied in addition to the outpatient management alone disutility	Barbut et al., 2019 & Campbell et al., 2020[67]
Hospitalization (Without Oxygen or With Low-Flow Oxygen)	-0.30		
Hospitalization (With High-Flow Oxygen or Noninvasive Ventilation)	-0.50		
Hospitalization (With Mechanical Ventilation)	-0.60		

ED: emergency department

Patients who were discharged alive after being mechanically ventilated experienced an additional disutility for five years. This long-term sequelae was associated with a disutility of -0.13 for the first year and a disutility of -0.04 for the second through fifth year.[70]

Economic Inputs

The model included direct medical costs, including but not limited to costs related to treatment acquisition, administration, and monitoring; condition-related care; and general age-adjusted health care costs. In addition, productivity costs were included in a separate analysis. All costs used in the model were updated to 2021 US dollars.

Drug Acquisition Costs

The following inputs were used to model drug utilization and associated costs:

- Dose
- Frequency of administration
- Route of administration

Table E10 reports the regimens that were modeled in this economic evaluation.

Table E10. Recommended Treatment Regimen

	REGEN-COV	Sotrovimab	Molnupiravir	Paxlovid	Fluvoxamine
Manufacturer	Regeneron	GlaxoSmithKline and Vir Biotechnology	Merck and Ridgeback Biotherapeutics	Pfizer	Generic
Dose	1200 mg total (600 mg per active ingredient)	500 mg	800 mg	NR	100 mg
Frequency of Administration	One time	One time	Twice daily for 5 days	Twice daily for 5 days	2 times per day for 10 days
Route of Administration	IV	IV	Oral	Oral	Oral
Source	EUA[118]	EUA[106]	Khoo et al., 2021[119]	Clinicaltrials.gov [39]	TOGETHER[3]

EUA: Emergency Use Authorization, IV: intravenous, mg: milligrams, NR: not reported

Table E11 includes the treatment acquisition costs that were included in the model. The costs reported are per treatment course. The IV-administered treatments included a 6% mark-up in the economic evaluation given these treatments are provider-administered.

Table E11. Treatment Acquisition Costs

	Treatment Course Acquisition Cost	Notes	Source
REGEN-COV	$2,100	In addition to the acquisition cost, the model included a 6% mark-up due to these treatments being provider-administered. Including the 6% mark-up, a treatment course cost $2,226.	Regeneron Press Release[120]
Sotrovimab	$2,100		REDBOOK
Molnupiravir	$707	Based on government-contract price per treatment course	Beasley and O'Donnell, 2021[121]
Paxlovid	$529	Based on government-contract price per treatment course	CBS News, 2021[122]
Fluvoxamine	$12	Lowest price of 20 100 mg tablets	REDBOOK

mg: milligram

Administration and Monitoring Costs

For the IV-administered treatments, an additional cost of $450 was included in the economic evaluation to account for administration and monitoring costs.[123] This cost was based on the Medicare Part B payment for COVID-19 monoclonal antibodies during the public health emergency and is inclusive of the IV infusion and post-administration monitoring.[123] Orally administered treatments did not have any additional costs associated with administration or monitoring outside of the initial office visit to receive the prescription (further detail about this office visit available beneath the heading for COVID-19-related health care utilization).

Condition-Related Care Costs

COVID-19 Related Health Care Utilization

All individuals in the intervention arms had an office visit to receive their prescription for the outpatient treatment. In the comparator arm, we assumed everyone with outpatient management as the highest setting of care had an office visit. The model also included health care utilization costs if a patient was in the emergency department or hospitalized. Hospitalization costs did not vary with length of stay. Table E12 reports the average unit cost for health care utilization that was used in this economic evaluation.

Table E12. Health Care Utilization Costs

Health Care Utilization	Unit Price	Notes	Source
Outpatient Visit	$84	Every individual in the intervention arms received this; every individual in the comparator arm with outpatient management as the highest setting of care received this	CMS Physician Fee Schedule (HCPCS code: 99203 for office visit of moderate complexity)[124]
COVID-19 ED Visit	$563	Any individual that had an ED visit as their highest setting of care received this	Moore and Liang et al., 2020[125]
COVID-19 Hospitalization (No Oxygen)	$16,442	Any individual hospitalized that didn't receive any respiratory support received this; any individual that was re-admitted received an additional COVID-19 hospitalization with no oxygen received	Ohsfeldt et al., 2021[74]
COVID-19 Hospitalization (Low-Flow Oxygen)	$19,706	Any individual hospitalized that received low-flow oxygen as their highest level of respiratory support received this	
COVID-19 Hospitalization (High-Flow Oxygen or Non-Invasive Ventilation)	$35,139	Any individual hospitalized that received high-flow oxygen or non-invasive ventilation as their highest level of respiratory support received this	
COVID-19 Hospitalization (Mechanical Ventilation)	$60,958	Any individual hospitalized that received mechanical ventilation as their highest level of respiratory support received this	

CMS: Centers for Medicare and Medicaid Services, ED: emergency department, HCPCS: Healthcare Common Procedure Coding System

Hospital Readmissions

Recent research has evaluated COVID-19 US hospitalizations and has found 9% of patients discharged alive are re-admitted within two months.[126] The median number of days that elapsed between discharge and readmission was eight days (IQR: 3 to 20 days).[126] In alignment with this evidence, the model included an additional hospitalization for 9% of those individuals who were hospitalized and discharged alive. The model accounted for these readmissions in the first cycle of the Markov model by applying a cost and a disutility for this readmission. The cost, disutility value, and disutility duration were based on the characteristics for a hospitalization that does not require oxygen. Hospital characteristics from a low severity hospitalization were used given the very favorable outcomes associated with these re-admissions.[126]

Long-Term Sequelae

Patients discharged from a hospitalization alive after being mechanically ventilated experienced long-term sequelae that was associated with an additional cost of $7,859 for the first year after discharge.[70]

Other Health Care Costs

Age-adjusted health care costs were applied over the lifetime time horizon.[127] Treatment costs and condition-related care were in addition to these age-adjusted health care costs.

Societal Costs

We included productivity gains/losses associated with the COVID-19 infection. To account for lost productivity while an individual was infected with COVID-19, the model assumed that the patient was not working for the duration of their symptom days. The model accounted for this lost productivity by multiplying the average daily wage (eight hours multiplied by $27.07 per hour) by the number of symptom days experienced for each setting of care and respiratory support received.[128]

E3. Results

Description of evLY Gained Calculations

The cost per evLY gained considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLY gained.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy. [129]
2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained.
3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the evLY for that cycle.
4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.
5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.
6. The evLY for the comparator arm was equivalent to the QALY estimate for that model cycle.

Finally, the evLY gained is the incremental difference in evLY between the intervention and the comparator arms.

Base-Case Results

Base-case results for sotrovimab, molnupiravir, Paxlovid, and fluvoxamine can be found in the Report. In this Supplement, we include economic estimates for REGEN-COV using efficacy data from before the Omicron variant. It is expected that REGEN-COV is not effective against the Omicron variant of COVID-19 and thus it is not included in the Report. However, in Tables E13 and E14, we present economic estimates for REGEN-COV using evidence prior to the Omicron variant.

Table E13. Results for the Base Case, Health Care Sector Perspective

Treatment	Treatment Cost*	Total Cost	Hospitalizations	QALYs	Life Years	evLYs
REGEN-COV	$2,100	$300,600	1.10%	15.9574	19.4959	15.9589
Usual Care	--	$297,800	4.14%	15.9213	19.4541	15.9213

evLY: equal-value life year, QALY: quality-adjusted life year

*Excludes administration, monitoring, or markup-related costs.

Table E14. Incremental Cost-Effectiveness Ratios for the Base Case, Health Care Sector Perspective

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Hospitalization Averted
REGEN-COV	Usual care	$79,000	$68,000	$76,000	$94,000

evLY: equal-value life year, QALY: quality-adjusted life year

E4. Sensitivity Analyses

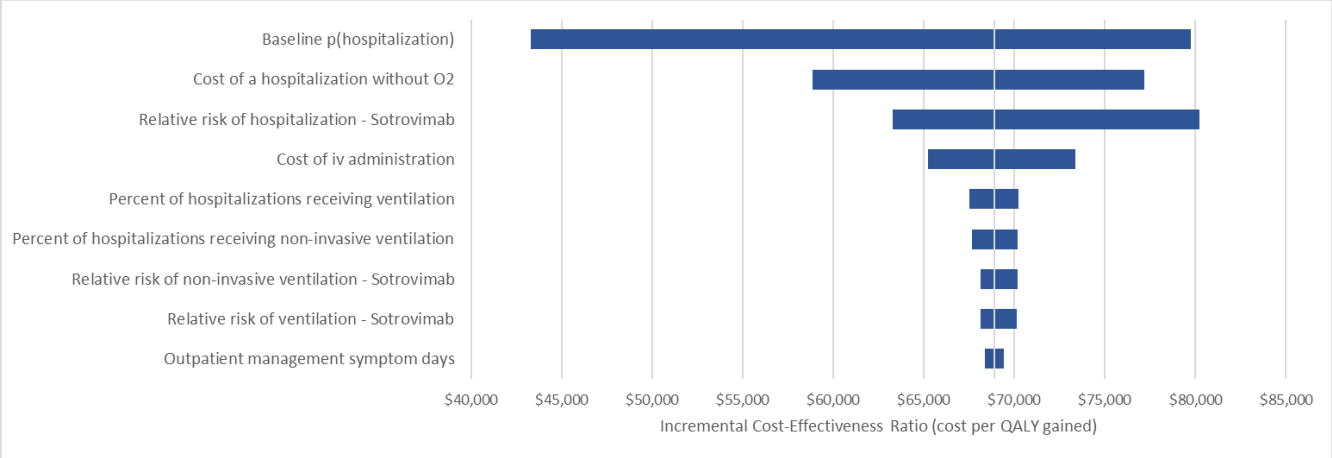
We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. The key inputs and results from the one-way sensitivity analyses can be found in Tables E15-E18. Figures E1-E4 present this information graphically by way of a tornado diagram for each intervention.

Table E15. Tornado Diagram Inputs and Results for Sotrovimab versus Usual Care

Input Name	Lower Input ICER	Upper Input ICER	Lower Input	Upper Input
Baseline P (Hospitalization)	$80,000	$43,000	0.03	0.08
Cost of a Hospitalization without O_2	$77,000	$59,000	$10,6400	$23,485
Relative Risk of Hospitalization – Sotrovimab	$63,000	$80,000	0.06	0.46
Cost of IV Administration	$65,000	$73,000	$291	$643
Percent of Hospitalizations Receiving Ventilation	$70,000	$68,000	0.08	0.12
Percent of Hospitalizations Receiving Non-Invasive Ventilation	$70,000	$68,000	0.23	0.35
Relative Risk of Non-Invasive Ventilation – Sotrovimab	$68,000	$70,000	0.07	0.57
Relative Risk of Ventilation – Sotrovimab	$68,000	$70,000	0.07	0.57
Outpatient Management Symptom Days	$69,000	$68,000	7.12	15.71

ICER: incremental cost-effectiveness ratio, IV: intravenous, O_2: oxygen, P: probability

Figure E1. Tornado Diagram for Sotrovimab versus Usual Care



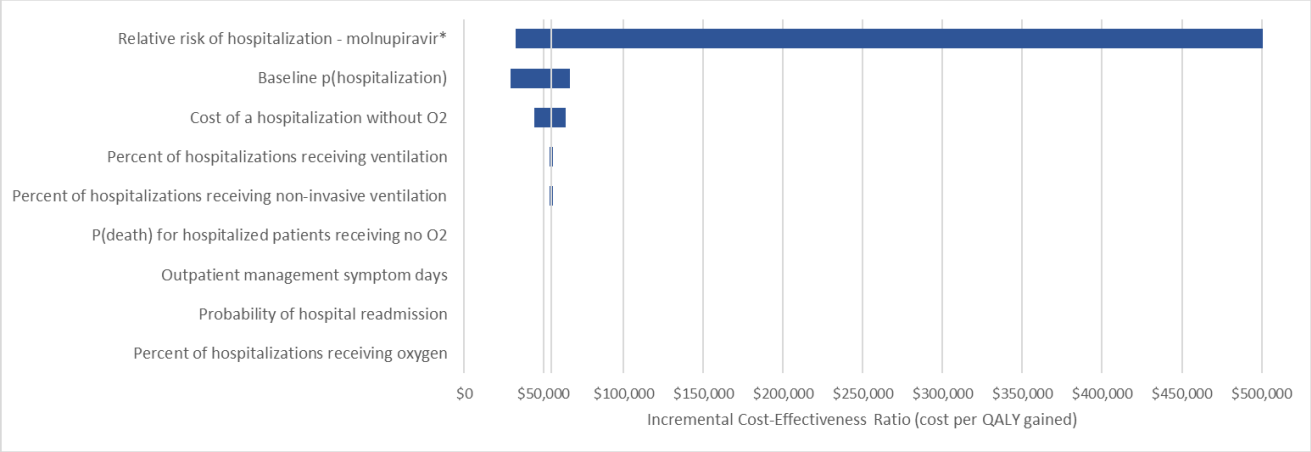
O_2: oxygen, p: probability, QALY: quality-adjusted life year

Table E16. Tornado Diagram Inputs and Results for Molnupiravir versus Usual Care

Input Name	Lower Input ICER	Upper Input ICER	Lower Input	Upper Input
Relative Risk of Hospitalization – Molnupiravir	$32,000	>$1,000,000	0.45	1.00
Baseline P (Hospitalization)	$66,000	$29,000	0.03	0.08
Cost of a Hospitalization without O_2	$64,000	$44,000	$10,640	$23,485
Percent of Hospitalizations Receiving Ventilation	$56,000	$54,000	0.08	0.12
Percent of Hospitalizations Receiving Non-Invasive Ventilation	$56,000	$54,000	0.23	0.35
P (Death) for Hospitalized Patients Receiving no O_2	$55,000	$54,000	0.02	0.04
Outpatient Management Symptom Days	$55,000	$54,000	7.12	15.71
Probability of Hospital Readmission	$55,000	$54,000	0.06	0.13
Percent of Hospitalizations Receiving O_2	$55,000	$55,000	0.28	0.42

ICER: incremental cost-effectiveness ratio, O_2: oxygen, P: probability

Figure E2. Tornado Diagram for Molnupiravir versus Usual Care



O_2: oxygen, P: probability, QALY: quality-adjusted life year

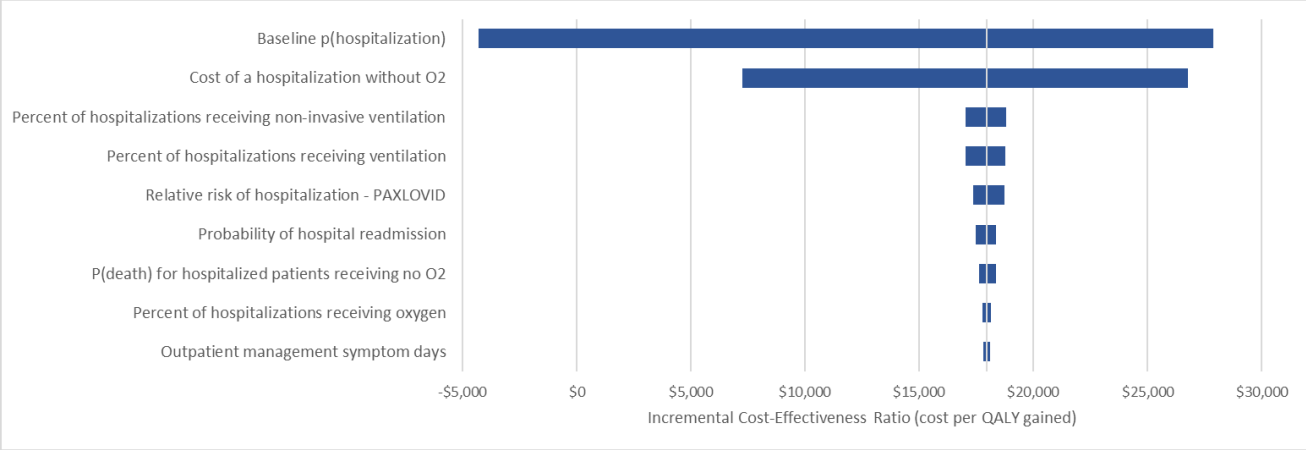
*Incremental cost-effectiveness ratio extends to a very high incremental cost-effectiveness ratio (>$1,000,000) given a near zero denominator. The X axis has been truncated at an upper bound of $500,000 for clarity of the graph.

Table E17. Tornado Diagram Inputs and Results for Paxlovid versus Usual Care

Input Name	Lower Input ICER	Upper Input ICER	Lower Input	Upper Input
Baseline P (Hospitalization)	$28,000	-$4,000	0.03	0.08
Cost of a Hospitalization without O_2	$27,000	$7,000	$10,640	$23,485
Percent of Hospitalizations Receiving Non-Invasive Ventilation	$19,000	$17,000	0.23	0.35
Percent of Hospitalizations Receiving Ventilation	$19,000	$17,000	0.08	0.12
Relative Risk of Hospitalization – Paxlovid	$17,000	$19,000	0.08	0.17
Probability of Hospital Readmission	$18,000	$17,000	0.06	0.13
P (Death) for Hospitalized Patients Receiving No O_2	$18,000	$18,000	0.02	0.04
Percent of Hospitalizations Receiving O_2	$18,000	$18,000	0.28	0.42
Outpatient Management Symptom Days	$18,000	$18,000	7.12	15.71

ICER: incremental cost-effectiveness ratio, O_2: oxygen, P: probability

Figure E3. Tornado Diagram for Paxlovid versus Usual Care



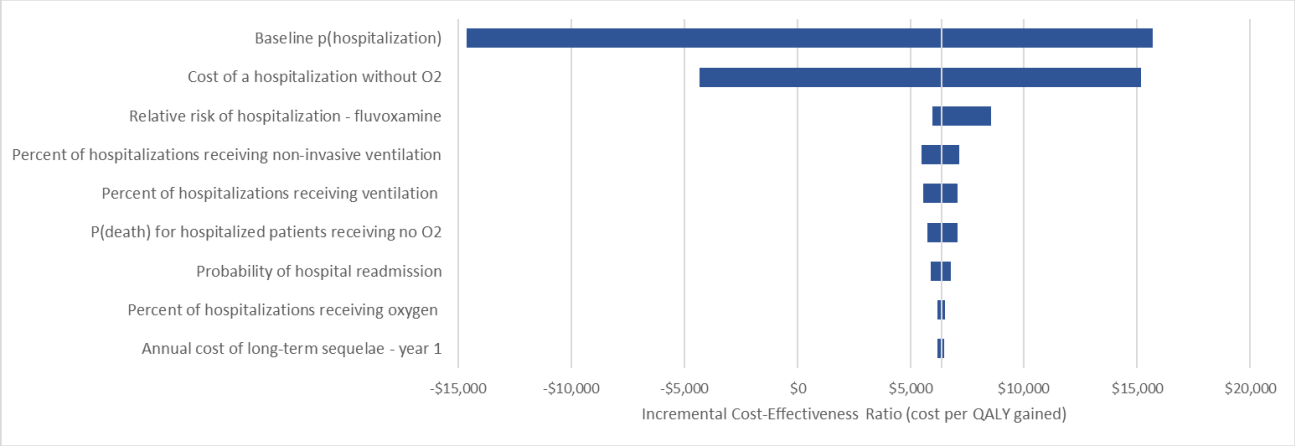
O2: oxygen, QALY: quality-adjusted life year

Table E18. Tornado Diagram Inputs and Results for Fluvoxamine versus Usual Care

Input Name	Lower Input ICER	Upper Input ICER	Lower Input	Upper Input
Baseline P (Hospitalization)	$16,000	-$15,000	0.03	0.08
Cost of a Hospitalization without O_2	$15,000	-$4,000	$10,640	$23,485
Relative Risk of Hospitalization – Fluvoxamine	$6,000	$9,000	0.49	0.89
Percent of Hospitalizations Receiving Non-Invasive Ventilation	$7,000	$5,000	0.23	0.35
Percent of Hospitalizations Receiving Ventilation	$7,000	$6,000	0.08	0.12
P (death) for Hospitalized Patients Receiving No O_2	$6,000	$7,000	0.02	0.04
Probability of Hospital Readmission	$7,000	$6,000	0.06	0.13
Percent of Hospitalizations Receiving O_2	$7,000	$6,000	0.28	0.42
Annual Cost of Long-Term Sequelae – Year 1	$6,000	$6,000	$5,085	$11,225

ICER: incremental cost-effectiveness ratio, O_2: oxygen, P: probability

Figure E4. Tornado Diagram for Fluvoxamine versus Usual Care



O_2: oxygen, P: probability, QALY: quality-adjusted life year

Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Table E19 reports the mean and credible range for each intervention, usual care, and incremental comparisons.

Table E19. Results of Probabilistic Sensitivity Analysis

	Intervention		Usual Care		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Sotrovimab						
Total Costs	$300,706	($300,523, $300,958)	$297,725	($296,643, $298,513)	$2,981	($2,282, $3,990)
Total QALYs	15.99	(15.98, 16.00)	15.95	(15.88, 15.98)	0.04	(0.01, 0.10)
ICER ($/QALY)						$68,100
Molnupiravir						
Total Costs	$298,515	($297,745, $299,069)	$297,725	($296,643, $298,513)	$791	($540, $1,159)
Total QALYs	15.96	(15.91, 15.98)	15.95	(15.88, 15.98)	0.01	(0.00, 0.04)
ICER ($/QALY)						$54,600
Paxlovid						
Total Costs	$298,489	($298,359, $298,588)	$297,725	($296,643, $298,513)	$764	($71, $1,721)
Total QALYs	15.99	(15.98, 16.00)	15.95	(15.88, 15.98)	0.04	(0.01, 0.10)
ICER ($/QALY)						$18,000
Fluvoxamine						
Total Costs	$297,825	($297,079, $298,385)	$297,725	($296,643, $298,513)	$100	(-$161, $465)
Total QALYs	15.96	(15.92, 15.99)	15.95	(15.88, 15.98)	0.02	(0.00, 0.04)
ICER ($/QALY)						$6,500

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year

Table E20 reports the percent of iterations less than commonly used thresholds for each intervention.

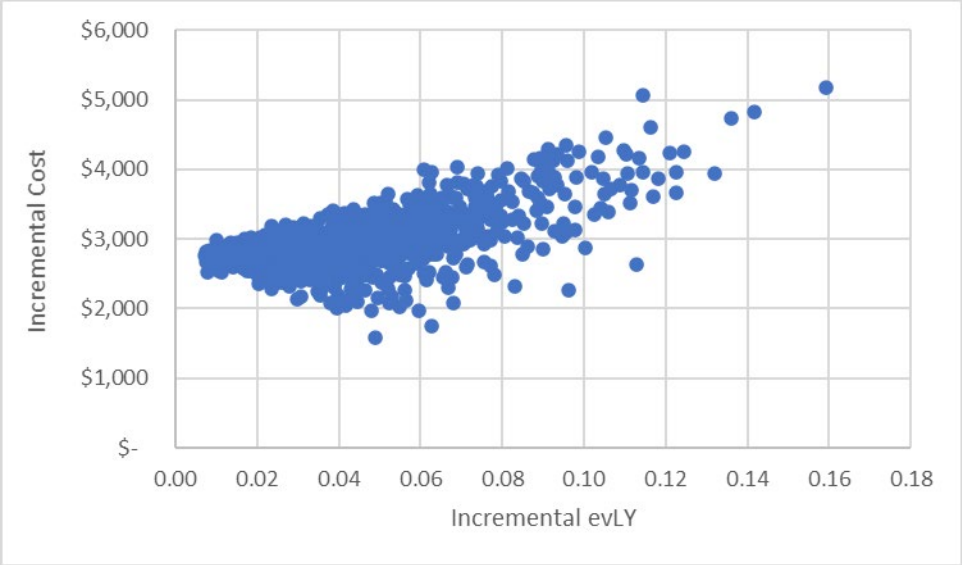
Table E20. Probability of Being Cost Effective at Various Thresholds

Outcome: QALYs Gained	$50,000 per QALY Gained	$100,000 per QALY Gained	$150,000 per QALY Gained	$200,000 per QALY Gained
Sotrovimab	17%	75%	92%	97%
Molnupiravir	37%	73%	84%	90%
Paxlovid	98%	100%	100%	100%
Fluvoxamine	100%	100%	100%	100%
Outcome: evLYs Gained	**$50,000 per evLY Gained**	**$100,000 per evLY Gained**	**$150,000 per evLY Gained**	**$200,000 per evLY Gained**
Sotrovimab	20%	77%	93%	97%
Molnupiravir	40%	75%	85%	91%
Paxlovid	98%	100%	100%	100%
Fluvoxamine	100%	100%	100%	100%

evLY: equal-value life year, QALY: quality-adjusted life year

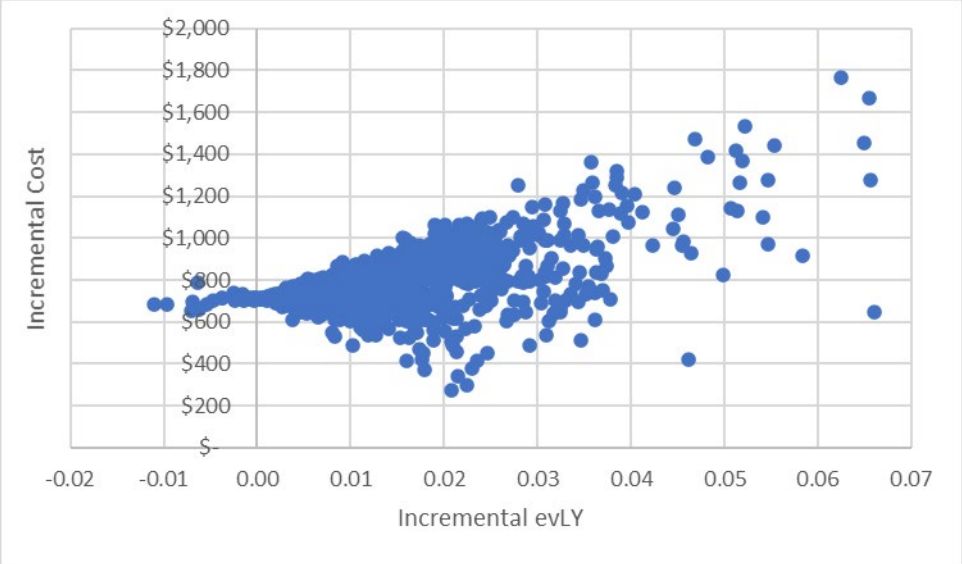
Figures E5-E8 report a scatterplot of each intervention to usual care using the outcome of the evLY gained. The figure using the QALY outcome generates similar findings.

Figure E5. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds, Sotrovimab versus Usual Care



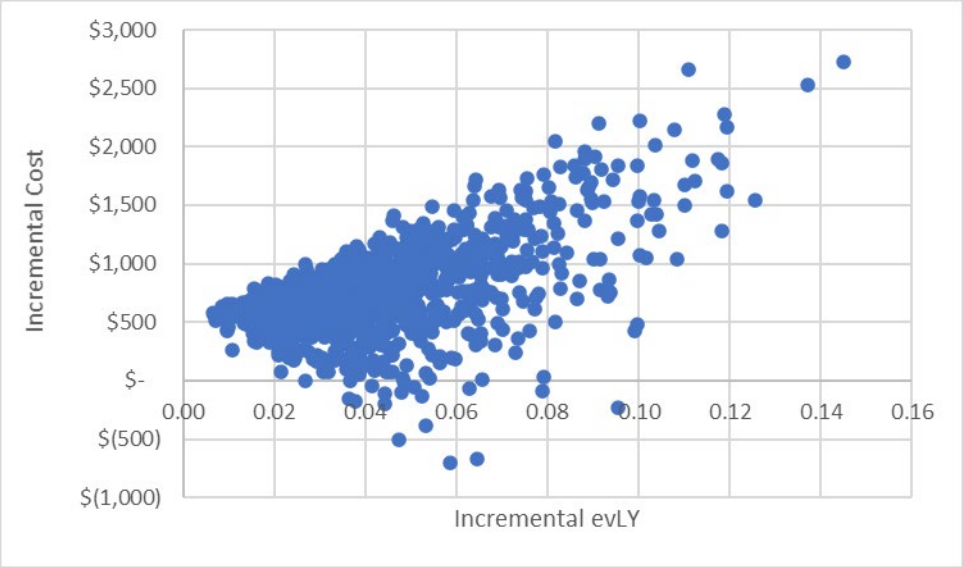
evLY: equal-value life year

Figure E6. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds, Molnupiravir versus Usual Care



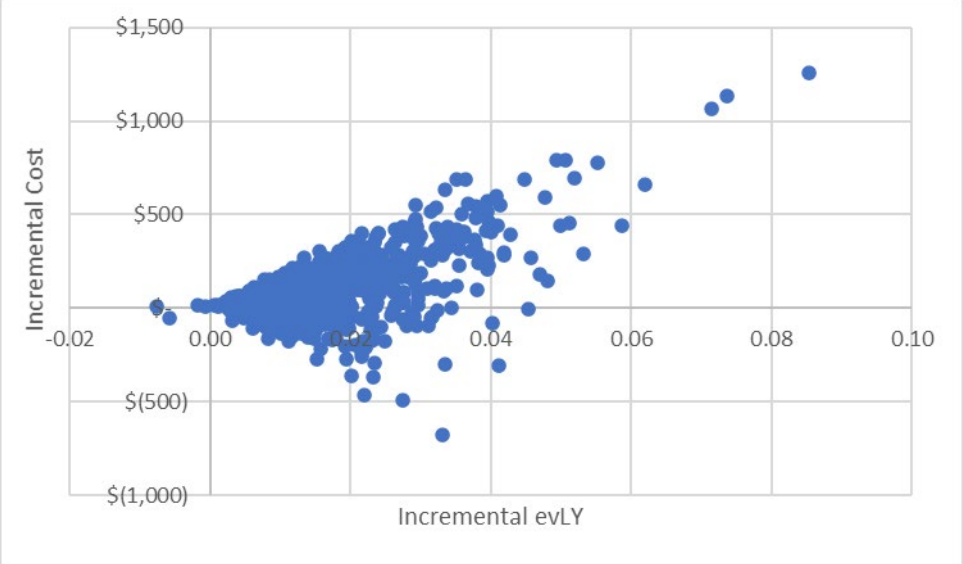
evLY: equal-value life year

Figure E7. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds, Paxlovid versus Usual Care



evLY: equal-value life year

Figure E8. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds, Fluvoxamine versus Usual Care



evLY: equal-value life year

E5. Scenario Analyses

Table E21 reports the incremental cost-effectiveness ratios for Scenario Analysis 1, which expanded the perspective to a modified societal perspective. The incremental cost-effectiveness ratios from the modified societal perspective attenuate to $30,000 per QALY gained across the treatments given the excess deaths averted are associated with an incremental cost-effectiveness ratio of approximately $30,000 per health outcome gained. Given the incremental cost-effectiveness ratios for Paxlovid and fluvoxamine were less than $30,000 per health outcome gained in the health care sector perspective, their incremental cost-effectiveness ratio from the modified societal perspective slightly increases. However, as shown in the Report, the threshold prices for the modified societal perspective are all higher than the threshold prices for the health care sector perspective because the lowest threshold is $50,000 per health outcome gained.

Table E21. Incremental Cost-Effectiveness Ratios for the Modified Societal Perspective

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Sotrovimab	Usual care	$56,500	$46,900	$54,100
Molnupiravir	Usual care	$47,000	$39,000	$45,000
Paxlovid	Usual care	$21,400	$17,700	$20,500
Fluvoxamine	Usual care	$13,300	$11,000	$12,700

evLY: equal-value life year, QALY: quality-adjusted life year

E6. Model Validation

First, we provided the preliminary model structure, methods, and assumptions to manufacturers. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we will also share the model with the relevant manufacturers for external verification around the time of publishing the draft report for this review. Finally, we compared results to other cost-effectiveness models in this therapy area. The outputs from the model were validated against the trial/study data of the interventions and also any relevant observational datasets.

Prior Economic Models

To our knowledge, there are no other published cost-effectiveness analyses that assess the cost effectiveness of outpatient treatments for COVID-19. Mills et al 2021 (pre-print)[130] conducted a cost-consequence analysis assessing fluvoxamine versus placebo for adult patients with symptomatic COVID-19 infection at increased risk of progression to severe infection or hospitalization. The study was conducted from the US health care system perspective over a 28-day

time horizon and consisted of a decision tree modeled according to the highest level of care received (i.e., emergency department visit only, extended emergency room visit, or hospital admission with ICU stay or not). Our model similarly tracked patients according to the highest setting of care received using an upfront acute phase decision tree. In our model, patients were permitted to be managed in the outpatient setting only and included highest setting of care according to oxygen and ventilation status. Our model also used a lifetime time horizon and included quality of life outcomes. The base-case probability of hospitalization used in Mills et al. was 10% and their analysis found that fluvoxamine was a cost-saving treatment ($232 vs. placebo). Our model included a lower base-case hospitalization rate of 4.1%; however, when varied in sensitivity analysis also found that fluvoxamine would be cost-saving versus usual care when hospitalization was greater than 5.2%.

In the absence of other full cost-effectiveness analyses to compare our results, two published papers offer recommendations for assessing the cost effectiveness of COVID-19 interventions, though not specific to outpatient treatments. Sheinson et al 2021[70] published a cost-effectiveness framework for evaluating acute treatments for hospitalized patients with COVID-19. Our model structure is closely aligned with the recommendations in this study consisting of an acute decision tree followed by a lifetime Markov model, model outcomes based on the highest level of care received (i.e., hospitalized with or without oxygen and with non-invasive or mechanical ventilation), the inclusion of long-term sequalae based on the level of respiratory support received, and utilities based on the average US population with disutilities applied for each level of care received. There were differences between our model and Sheinson et al. in terms of how societal costs were measured – authors estimated productivity impacts due to COVID-19 mortality for the full cohort regardless of age whereas our model included lost productivity costs for the duration of COVID-19 symptom days. A white paper published by Elvidge et al 2021[131] also provided guidance for economic evaluations of COVID-19 interventions. Recommendations included using a whole disease pathway model, an individual level simulation (to allow for assessing impact on transmission and system capacity), the inclusion of the long-term impacts of COVID-19, and analyses conducted from the societal and health care system perspective. Our model focused on treatments at one position in the disease pathway – an example of a decision question where the guidelines suggest that a cohort model may be sufficient.