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A review of clinical efficacy data supporting emergency use authorization for COVID-19 therapeutics and lessons for future pandemics

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Abstract

Emergency Use Authorization (EUA) allows the US Food and Drug Administration (FDA) to expedite the availability of therapeutics in the context of a public health emergency. To date, an evidentiary standard for clinical efficacy to support an EUA has not yet been established. This review examines the clinical data submitted in support of EUA for antiviral and anti-inflammatory therapeutics for coronavirus disease 2019 (COVID-19) through December of 2021 and the resilience of the authorization as new clinical data arose subsequent to the authorization. In the vast majority of cases, EUA was supported by at least one well-powered randomized controlled trial (RCT) where statistically significant efficacy was demonstrated. This included branded medications already approved for use outside of the context of COVID-19. When used, the standard of a single RCT seemed to provide adequate evidence of clinical efficacy, such that subsequent clinical studies generally supported or expanded the EUA of the therapeutic in question. The lone generic agent that was granted EUA (chloroquine/hydroxychloroquine) was not supported by a well-controlled RCT, and the EUA was withdrawn within 3 months time. This highlighted not only the ambiguity of the EUA standard, but also the need to provide avenues through which high quality clinical evidence for the efficacy of a generic medication could be obtained. Therefore, maintaining the clinical trial networks assembled during the COVID-19 pandemic could be a critical component of our preparation for future pandemics. Consideration could also be given to establishing a single successful RCT as regulatory guidance for obtaining an EUA.

INTRODUCTION

On January 31, 2020, the US Secretary of Health and Human Services (HHS) declared a public health emergency due to coronavirus disease 2019 (COVID-19).[1] Subsequently, the Emergency Use Authorization (EUA) for COVID-19[2] medical products has been in effect since March 27, 2020, allowing the US Food and Drug Administration (FDA) to authorize repurposed and newly developed medical products for temporary use prior to undergoing the full approval process. Each EUA

requires that the FDA assess the following: that the medical product is appropriate for use as an emergency countermeasure, its potential benefits outweigh the risks of authorization, and there are no formally approved alternatives currently available. The data quality standard to obtain an EUA has been somewhat ambiguous, and has been particularly noted as a concern for diagnostics authorization.[3–5] For therapeutics, the typical requirement for FDA approval of a new therapeutic is two well-controlled, adequately powered randomized controlled trials (RCTs).[6] Herein, we review the clinical data that were obtained to pursue EUA for antiviral and anti-inflammatory medications during the COVID-19 pandemic, with a focus on evidence of clinical efficacy and the resilience of the authorization decision as additional clinical studies of the drug were conducted. We also examine the consistency of such evidence as it was obtained across different therapeutic classes and between branded and generic medications.

METHODS

This review examines "Drugs and Non-Vaccine Biological Products" with EUA for COVID-19, classifying them as

(1) novel or repurposed and (2) by mechanism—antiviral monoclonal antibodies, small molecule antivirals, and anti-inflammatory drugs (Figure 1). All clinical trials found were registered on ClinicalTrials.gov and searched by keywords, including "COVID-", and drug names were extracted for review on January 4, 2022. Related publications or official press releases for data from each clinical trial were found on ClinicalTrials.gov, Medline, PubMed, and Google Scholar. Company websites were also used to find press-releases; BioRxiv and MedRXiv were used to find preprints.

RESULTS

Novel agents

Monoclonal antibodies

Imdevimab and casirivimab (REGEN-COV)
Data supporting authorization. REGEN-COV is a combination of two noncompeting monoclonal antibodies (mAbs) imdevimab and casirivimab, targeting the severe
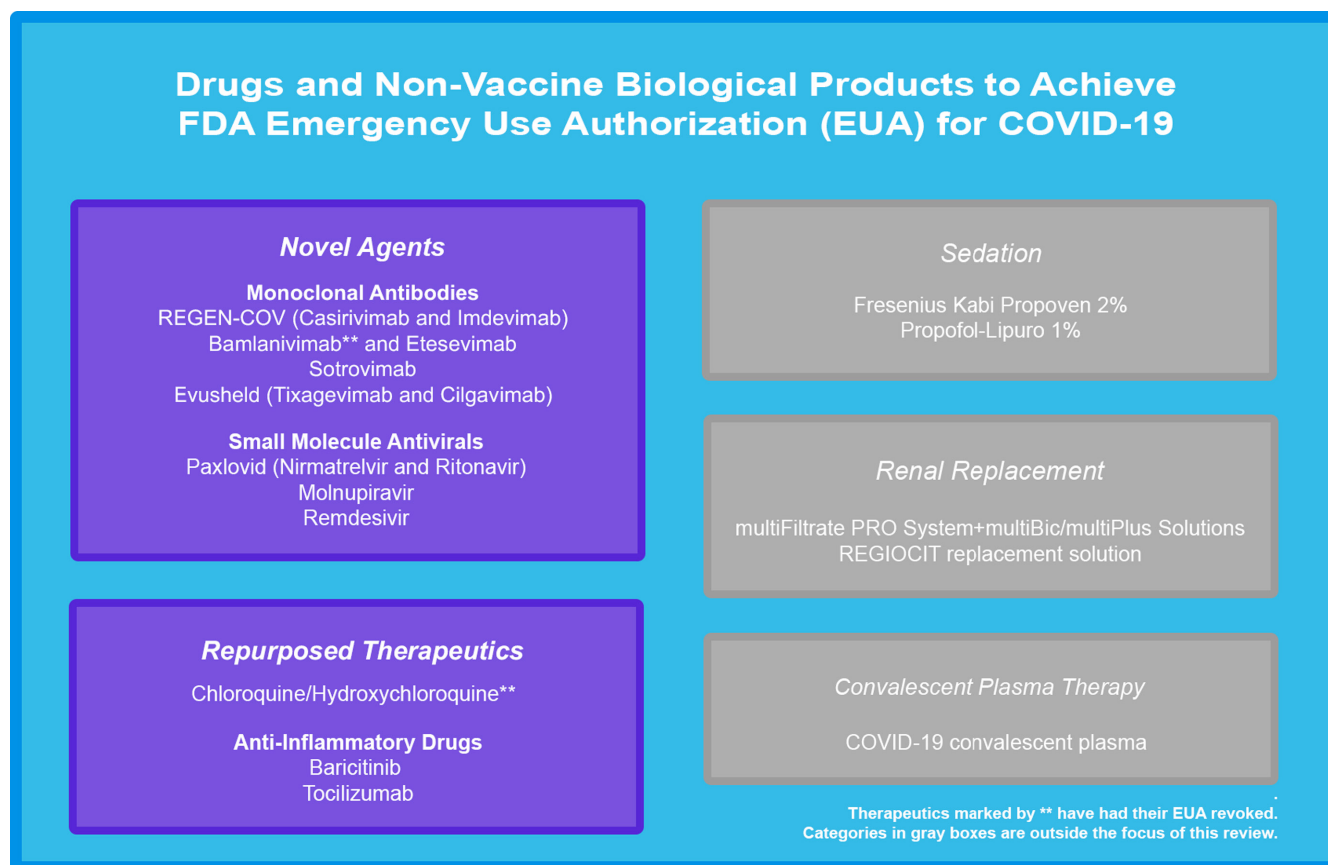

FIGURE 1 All drugs and non-vaccine biological products to have achieved FDA COVID-19 EUA have been sorted into categories that reflect their intended purpose. All therapeutics encompassed by categories in purple will be explored by this review. COVID-19, coronavirus disease 2019; EUA, Emergency Use Authorization; FDA, US Food and Drug Administration.

acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) spike protein.[7] The FDA granted EUA to imdevimab-casirivimab for treatment of mild-to-moderate COVID-19 and postexposure prophylaxis via intravenous infusion or subcutaneous injection in November 2020. The FDA EUA letter cited COV-2067 (NCT04425629) sponsored by Regeneron[7] (Table 1). This trial of 799 patients demonstrated that patients treated with REGEN-COV versus placebo saw a larger reduction in viral load through day 7 ($p = 0.0003$).[8] Clinically, imdevimab-casirivimab reduced virus-related medical visits by 57% through day 29 ($p = 0.024$), especially among patients with risk factors for severe COVID-19.[9]

Post authorization. Subsequent studies were consistent with findings used to file the EUA for imdevimab-casirivimab and expanded its use. The RECOVERY trial evaluated the efficacy of imdevimab-casirivimab in over 9000 patients hospitalized with COVID-19 and demonstrated significant reduction in mortality in those seronegative at baseline when compared with usual care (24% vs. 30%, $p = 0.0010$).[10] The EUA was expanded for subcutaneous injection when intravenous administration is impossible and for postexposure prophylaxis in patients 12 years or older at risk of severe COVID-19. The EUA was reissued seven times between February 2020 and January 2022. Based on diminished potency against Omicron,[11] imdevimab-casirivimab's EUA was limited to geographic areas where Omicron is not dominant. As a result, imdevimab-casirivimab is not currently authorized in any US region, so it may not be administered until further notice[12] (Table S1.1).

Bamlanivimab and etesevimab
Data supporting authorization. Bamlanivimab-etesevimab is a combination of two monoclonal antibodies binding distinct but overlapping epitopes on the SARS-CoV-2 spike protein.[13,14] EUA was given to bamlanivimab alone in November 2020, then revoked April 2021 due to resistant COVID-19 viral variants.[15] At the time, bamlanivimab-etesevimab was already distributed more widely than bamlanivimab alone, and the cocktail was authorized in February 2021 to treat mild-to-moderate COVID-19 and individuals with high risk for serious COVID-19.[16] The FDA cites BLAZE-1 (NCT04427501) with 3290 participants and BLAZE-4 (NCT04634409) with 1631 participants, which reported a statistically significant drop in both COVID-19-related hospitalizations (2.1% vs. 7.0%) and deaths (0% and 1.7%) in patients treated with bamlanivimab-etesevimab versus placebo ($p < 0.001$[17,18]; Table 1).

Post authorization. Data from subsequent studies were consistent with studies supporting the EUA (Table S1.2).

On December 3, 2021, the FDA extended authorization under the same conditions to the treatment of all pediatric patients, including those under 12 years of age.[16] However, on December 29, 2021, the HHS paused bamlanivimab-etesevimab allocation anywhere with greater than 80% Omicron prevalence. After the National Institutes of Health (NIH) published on the variability of Omicron prevalence, the HHS allowed all states and territories to order the cocktail. The FDA reissued the EUA late January 2022 to limit use in areas with a high prevalence of nonsusceptible variants.[12,16]

Sotrovimab
Data supporting authorization. Sotrovimab is an mAb targeting a conserved epitope across SARS-CoV and SARS-CoV-2 developed with the aim of creating an antibody with a high barrier to resistance as well as activity across different corona viruses.[19] The FDA granted sotrovimab EUA in May 2021 for treatment of mild-to-moderate adult and pediatric patients that test positive for SARS-CoV-2 and are at risk of severe COVID-19, based on COMET-ICE (NCT04545060).[20] COMET-ICE enrolled 1057 adult patients with symptomatic COVID-19 designated as high risk for COVID-19 progression. Interim analysis indicated that sotrovimab treatment led to an 85% reduction in death or need for hospitalization for over 24 h versus placebo ($p = 0.002$).[21]

Post authorization. In June 2021, Vir's final COMET-ICE results stated that sotrovimab reduced risk of hospitalization for more than 24 h or death by day 29 by 79% ($p < 0.001$). Safety results were consistent with interim analyses.[22] Notable trials in progress are COMET-PEAK and COMET-TAIL, follow-up trials to COMET-ICE, and BLAZE-4 (NCT04634409).[23] Both evaluate intravenous versus intramuscular administration, and, to date, indicate equivalent virological response from intravenous and intramuscular injections have been observed.[23] Sotrovimab retains potency against the Omicron variant.[24,25] The NIH currently recommends the use of sotrovimab over imdevimab-casirivimab and bamlanivimab-etesevimab due to its higher efficacy[26] (Table S1.3).

Tixagevimab and cilgavimab (Evusheld)
Data supporting authorization. Evusheld is a combination of tixagevimab and cilgavimab, two long-acting IgG1 mAbs targeting nonoverlapping epitopes of the SARS-CoV-2 spike protein.[27] In December 2021, the FDA granted tixagevimab-cilgavimab EUA for pre-exposure prophylaxis of COVID-19 in adults and children 12 years of age or older with no known recent exposure nor current infection

TABLE 1 A summary of clinical trials cited as evidence of clinical efficacy and safety in obtaining EUA for treatment of COVID-19 through December 31, 2021

Type of drug	Intervention (sponsor)	Trials (ID)	Study description	Study population	Primary outcome measures	Key findings	References
Antiviral monoclonal antibody	Imdevimab-casirivimab (Regeneron Pharmaceuticals)	COV-2067[10] (NCT04425629)	Sponsored by Regeneron: double-blinded, placebo-controlled, randomized phase I-III clinical trial with reported results for 799 total patients (at the time of EUA in November 2020)	Three cohorts. Over 18 at randomization, less than 18 at randomization, pregnant at randomization: outpatients with symptomatic COVID-19 that maintain O2 saturation ≥93% on room air	Proportion of patients with AEs, infusion-related and hypersensitivity reactions; change in viral load; proportion of patients with COVID-related hospitalization or death; concentration of antibodies in serum over time	Larger reduction in viral load through day 7 than those receiving placebo ($p = 0.0003$). Reduced virus-related medical visits by 57% through day 29 ($p = 0.024$), with effects more pronounced among patients with risk factors for severe COVID-19	8,9,104
	Bamlanivimab-etesevimab (Eli-Lilly)	BLAZE-1 (NCT04427501)	Sponsored by Eli Lilly and Company: Double-blinded, placebo-controlled, randomized phase II/III clinical trial with 3290 participants	Over 18 at randomization, less than 18 at randomization, pregnant at randomization: outpatients with mild to moderate cases of COVID-19 treated with bamlanivimab monotherapy	Percent of participants who experience COVID-related hospitalization, ED visit, or death; percent of participants with viral load greater than prespecified threshold through day 7, percent of participants who experience serious adverse effect(s) by any cause; time until symptoms are resolved	No significant difference in viral load with 3 doses of bamlanivimab monotherapy compared with placebo	105–107
		BLAZE-4 (NCT04634409)	Sponsored by Eli Lilly and Company: Double-blinded, placebo-controlled, randomized phase II clinical trial with 1631 participants	18 years and older: patients with mild to moderate COVID-19 treated with bamlanivimab-etesevimab dual therapy	Percent of participants with viral load (>5.27; cycle threshold value <27.5) at day 7, percent of patients experiencing COVID-19 related hospitalization or death, percent of participants demonstrating symptom resolution/improvement	Statistically significant drop in COVID-19-related hospitalizations and deaths compared with placebo ($p < 0.001$)	17,18
	Sotrovimab (Vir Biotechnology)	COMET-ICE (NCT04545060)	Sponsored by Vir Biotechnology, Inc.: Multicenter, double-blind, phase III trial, with 583 patients (at time of interim analyses)	18 years and older: high-risk (defined as at least one underlying risk factor or older age) patients with a positive reverse-transcriptase–PCR or antigen SARS-CoV-2 test result and onset of symptoms within the prior 5 days	Proportion of patients with hospitalization for more than 24 h or death, due to any cause, through day 29	Statistically significant drop in risk of COVID-19 progression, as defined as hospitalization for >24 h or death, by 85% ($p = 0.002$)	19,21
	Tixagevimab-cilgavimab (AstraZeneca)	PROVENT (NCT04625725)	Sponsored by AstraZeneca: Double-blinded, placebo-controlled, randomized phase III clinical trial with 5197 participants	18 years and older: unvaccinated participants that are negative for SARS-CoV-2 testing at screening and can benefit from passive immunization with antibodies	Incidence of the first case of positive SARS-CoV-2 PCR test and symptomatic illness, AES, SAEs, MAAEs, and AESIs postdose of IMP	Statistically significant reduced risk of developing positive SARS-CoV-2 with symptomatic COVID-19 illness by 83% (November 2021), 77% (December 2021) compared to placebo ($p < 0.001$)	29,30,108,109

TABLE 1 (Continued)

Type of drug	Intervention (sponsor)	Trials (ID)	Study description	Study population	Primary outcome measures	Key findings	References
Small molecule antiviral	Remdesivir (Gilead Sciences)	ACTT-1 (NCT04280705)	Sponsored by the NIAID: double-blinded, randomized, placebo-controlled phase III clinical trial with 1062 participants	18 years and older: patients hospitalized with COVID-19 infection and at least one of the following: radiographic infiltrates, SpO2 <= 94%, requiring supplemental oxygen, or requiring mechanical ventilation	Time to recovery through day 29 (either hospitalized and not requiring supplemental oxygen or not hospitalized)	Patients in the remdesivir group had a shorter time to recovery with a median 10 days as compared to the placebo group with a median 15 days (risk ratio: $p < 0.0001$), and fewer SAEs due to respiratory failure	[36,81]
		(NCT04292899)	Sponsored by Gilead Sciences: Non-blinded, randomized (not stratified) phase III clinical trial with 397 participants	Age limit was amended to 12 years and older on March 15, 2020 after enrollment started on March 6, 2020 with initial limit of 18 years and older: participants with COVID-19 that are hospitalized, SpO2 <= 94% or requiring supplemental oxygen, and radiographic evidence of pulmonary infiltrates	Clinical status at day 14 on a 7-point ordinal scale ranging from 1- death to 7- not hospitalized	The investigators stated that after adjustment for baseline imbalances in treatment group characteristics, no significant difference in efficacy was detected between a 5- and 10-day dose	[37]
CQ/HCQ	Nirmatrelvir plus ritonavir (Pfizer)	None EPIC-HR (NCT04960202)	N/A Sponsored by Pfizer: Double-blinded, placebo-controlled, randomized Phase 2/3 clinical trial with 2246 participants	N/A 18 years and older: patients with at least one characteristic/ underlying medical condition associated with increased risk of severe COVID-19 and confirmed SARS-CoV-2 infection/ symptoms within 5 days prior to randomization	N/A Proportion of participants with COVID-19 related hospitalization or death from any cause through day 28 based on treatment initiated within 3 days of first symptoms	N/A Statistically significant reduction of risk of hospitalization or death by 89% compared to placebo within 3 days and 88% within 5 days of symptom onset, decreased viral load by 10-fold	[88,110]
	Molnupiravir (Merck and Ridgeback Biotherapeutics)	MOVe-OUT (NCT04575597)	Sponsored by Merck Sharpe and Dohme Corp.: Double-blinded, placebo-controlled, randomized phase II/III clinical trial with 1433 participants	18 years and older; patients with mild or moderate COVID-19 and at least 1 characteristic/underlying medical condition associated with increased risk of severe COVID-19	Percentage of participants who are hospitalized and/or die by day 29 based on treatment initiated within 3 days of first symptoms, percentage of participants with AEs, percentage of patients who discontinue study participation due to AEs	Statistically significant decrease in hospitalization by 48% compared to placebo in interim analysis ($p = 0.001$), 30% decrease in hospitalization compared to placebo in full data set due to decrease in hospitalization rate of placebo arm	[51,52,111]

TABLE 1 (Continued)

Type of drug	Intervention (sponsor)	Trials (ID)	Study description	Study population	Primary outcome measures	Key findings	References
Anti-inflammatory	Baricitinib (Eli Lilly and Incyte Corporation)	ACTT-2 (NCT04401579)	Sponsored by NIAID: Double-blinded, placebo-controlled, randomized phase III clinical trial of 1033 participants	18 years and older: patients admitted to the hospital with symptoms suggestive of COVID-19 and laboratory confirmed SARS-CoV-2; particularly those requiring supplemental oxygen or ECMO	Time to recovery through day 29 (not hospitalized or not requiring supplemental oxygen/ongoing care)	Baricitinib with remdesivir is superior to remdesivir alone, associated with fewer SAEs, those on baricitinib had a median recovery time of 7 days whereas those on just remdesivir 8 days (rate ratio for recovery: $p = 0.03$)	65,66,112
		COV-BARRIER (NCT04421027)	Sponsored by Eli Lilly: Double-blinded, placebo-controlled, randomized phase III clinical trial with 1585 participants	18 years and older: patients hospitalized with COVID-19 and requiring supplemental oxygen at randomization, have indicators of progression	Percentage of participants who die or require noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation (including ECMO) through day 28	Statistically significant decrease in death by any cause compared to placebo ($p = 0.0018$), no significant difference in progression to supplemental oxygen and invasive mechanical ventilation	66,67,113,114
Tocilizumab (Hoffman-La Roche)		RECOVERY (NCT04381936)	Sponsored by the University of Oxford: Open-label, randomized phase II/III clinical trial with 4116 participants in the tocilizumab arm	18 years and older: patients with hypoxia (oxygen saturation <92% on room air or requiring supplemental oxygen), systemic inflammation, and no clear evidence of active infection other than SARS-CoV-2	All-cause mortality, duration of hospital stay, composite end point of death or need for either mechanical ventilation or ECMO	All-cause mortality within 28 days of randomization was improved compared to placebo ($p = 0.0028$). Treated patients were also more likely to be discharged from the hospital in 28 days	71,81
		COVACTA (NCT04320615)	Sponsored by Hoffmann-La Roche: Double-blinded, placebo-controlled, randomized phase III clinical trial with 452 participants	18 years and older: patients hospitalized with COVID-19 pneumonia confirmed per WHO criteria and evidenced by chest X-ray or CT scan	Clinical status (assessed using 7-category ordinal scale at day 28), incidence of ICU stays by day 28 (week 4)	No benefit in 28-day mortality rate compared to placebo ($p = 0.94$)	115,116
		EMPACTA (NCT04372186)	Sponsored by Genentech: Double-blinded, placebo-controlled, randomized phase III clinical trial with 377 participants	18 years and older: patients hospitalized with COVID-19 pneumonia confirmed by a positive PCR of any specimen and radiographic imaging	Proportion of participants who died or required mechanical ventilation by day 28, time to "ready for discharge" (via body temp, respiratory rate, and oxygen saturation).	Did not impact day-to-day quality of life but did reduce likelihood of severe disease progression (leading to death or mechanical ventilation)	117,118
		REMDACTA (NCT04409262)	Sponsored by Hoffmann-La Roche: Double-blinded, placebo-controlled, randomized phase III clinical trial with 649 participants	12 years and older: patients hospitalized with COVID-19 pneumonia confirmed by a positive PCR of any specimen and evidenced by chest X-ray or CT scan	Time from randomization to hospital discharge, "ready for discharge," first occurrence of mechanical ventilation or death up to day 28	Not yet available	119

Abbreviations: AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; CQ, chloroquine; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; ED, emergency department; EUA, Emergency Use Authorization; HCQ, hydroxychloroquine; ICU, intensive care unit; IMP, investigational medicinal product; MAAE, medically attended adverse event; NIAID, National Institute of Allergy and Infectious Diseases; PCR, polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2; WHO, World Health Organization.

with COVID-19. Use is limited to moderately/severely immunocompromised individuals or those with a history of severe adverse reactions supporting inappropriate response to the COVID-19 vaccination.[28] Tixagevimab-cilgavimab EUA letter cites PROVENT (NCT04625725), a trial of 5197 unvaccinated adult participants which demonstrated in two reports that tixagevimab-cilgavimab reduced the risk of developing symptomatic COVID-19 by 83% and 77% compared to placebo ($p < 0.001$[29,30]; Table 1).

Post authorization. Due to tixagevimab-cilgavimab's more recent authorization, subsequent data are limited. Several trials are in progress and focus on treatment and postexposure prophylaxis: PROVENT, TACKLE (NCT04723394), and STORMCHASER (NCT04625972). Primary analysis of TACKLE in October 2021 based on 822 patients found that tixagevimab-cilgavimab reduced the risk of developing severe COVID-19 or death by 50% in outpatients and 67% in participants who received treatment from the onset of symptoms. Ninety percent of participants were at high risk of severe COVID-19.[31] Tixagevimab-cilgavimab has retained laboratory efficacy against Omicron, and AstraZeneca stated that it had neutralizing capacity comparable to that of patients who had recovered naturally from COVID-19, leading to no change in its EUA[32,33] (Table S1.4).

Small molecule antivirals

Remdesivir
Data supporting authorization. Remdesivir, previously developed but not authorized for use against Ebola virus, is a nucleoside monophosphate prodrug that causes delayed chain termination, preventing elongation of newly synthesized viral RNA four nucleotides after remdesivir has been incorporated.[34] Initial EUA in May 2020 authorized treatment of severe COVID-19 in hospitalized patients 12 years of age and older through intravenous administration.[35] The EUA cited ACTT-1 (NCT04280705) and NCT04292899 (Table 1). ACTT-1, a trial of 1062 participants, found that the remdesivir group had shorter median days to recovery versus placebo (10 vs. 15, $p < 0.0001$) and lower mortality estimates.[36] Gilead's NCT04292899 trial found no significant difference in efficacy and safety between 5- versus 10-day remdesivir courses among the 397 hospitalized participants.[37]

Post authorization. In October 2020, the FDA approved a New Drug Application (NDA) for remdesivir use in hospitalized patients with COVID-19 12 years of age and older. The EUA was revised to remove NDA-approved uses

and retain EUA for use in younger hospitalized patients. Review of existing studies, including the Solidarity and DisCoVeRy trials, casts doubt on remdesivir's efficacy in reducing mortality and hospital-stay duration. ACTT-1 was targeted for potential bias due to a greater proportion of lower-severity patients in the treatment group than placebo[38] (Table S1.5). Gilead had initiated a phase III study of remdesivir in nonhospitalized patients at high risk for severe COVID-19, but terminated the study due to the requirement for infusion in a healthcare setting.[39] Sequence analysis of the viral RNA polymerase suggested remdesivir would retain activity against the omicron variant.[40] This was subsequently confirmed in a laboratory setting.[41] In January 2022, the NDA was supplemented to approve remdesivir use in nonhospitalized patients 12 years of age and older who have mild-to-moderate COVID-19 but are at high risk for disease progression.[42]

Nirmatrelvir plus ritonavir (Paxlovid)
Data supporting authorization. Paxlovid consists of nirmatrelvir, an SARS-CoV-2 main protease inhibitor and ritonavir, an HIV protease inhibitor and potent CYP 3A/4 inhibitor used to increase nirmatrelvir exposure.[43,44] It became the first authorized oral antiviral in December 2021. Nirmatrelvir plus ritonavir is authorized for adult and pediatric patients over 12 years old with mild-to-moderate COVID-19 confirmed with positive SARS-CoV-2 test and at high risk of severe COVID-19.[43] The EPIC-HR trial (NCT04960202) is the only clinical trial cited by the FDA and found that nirmatrelvir plus ritonavir reduced the risk of hospitalization or death by 89% versus placebo within 3 days, and 88% within 5 days of symptom onset in 2246 nonhospitalized patients with high-risk COVID-19. Nirmatrelvir plus ritonavir was also found to decrease viral load by nearly 10-fold versus placebo[45] (Table 1).

Post authorization. Given the more recent authorization for nirmatrelvir plus ritonavir, limited post authorization data are available. EPIC-HR, EPIC-SR (NCT05011513), and NCT05047601 will examine nirmatrelvir plus ritonavir efficacy in postexposure prophylaxis and treating patients without a risk factor for severe COVID-19. EPIC-SR showed a 70% reduction in hospitalization compared to placebo for unvaccinated adults or those with at least one risk factor for severe COVID-19.[46] Based on in vitro assessments, nirmatrelvir retains activity across SARS-CoV-2 variants, including Omicron[26,41,47] (Table S1.6).

Molnupiravir
Data supporting authorization. Molnupiravir, is a non-chain terminating nucleoside analogue developed as an oral antiviral for treatment of COVID-19.[48] It received

EUA in December 2021. Molnupiravir is authorized for adults with mild-to-moderate COVID-19 and at least one risk factor for severe COVID-19, as well as positive results from SAR-CoV-2 viral testing.[49] Molnupiravir is not recommended for use during pregnancy due to the potential to cause fetal harm.[50] The EUA was initially filed based on results from interim analysis of 762 patients from MOVe-OUT (NCT04575597) where hospitalization was decreased by 48% in molnupiravir vs placebo ($p = 0.001$).[49] Largely driven by a decrease of hospitalization in the placebo arm, relative efficacy of molnupiravir treatment in the full data set presented to the EUA advisory committee was a 30% decrease versus placebo in hospitalization through day 29[51,52] (Table 1).

Post authorization. Although no new clinical data have been reported since the declaration of EUA, data from the MOVe-AHEAD study (NCT04939428), enrolling ~1332 participants exposed to COVID-19 is expected in 2022.[53] Based on in vitro assessments, molnupiravir retains activity across SARS-CoV-2 variants, including Omicron[41,47,54] (Table S1.7).

Repurposed therapeutics

Chloroquine and hydroxychloroquine

Data supporting authorization. Chloroquine (CQ) and hydroxychloroquine (HCQ) have been used to treat malaria, as well as several autoimmune diseases.[55] In vitro screening conducted early in the pandemic demonstrated that CQ was active in cell-based models of SARS-CoV-2 infection and created interest in the value of the medication to treat COVID-19.[56] The Trump administration began championing HCQ/CQ as treatments in early 2020, increasing public demand for investigation.[57] In March 2020, CQ and HCQ received an EUA for treatment of COVID-19. Notably, the EUA letter did not cite supportive data from any clinical trial.[58]

Post authorization. The EUA was immediately controversial.[59] A broadly discussed French study, purported to provide preliminary evidence of efficacy for HCQ,[60] was subsequently renounced by the publishing journal as not meeting their standards.[61,62] Twenty-three of 325 trials of CQ/HCQ registered on ClinicalTrials.gov have reported results. Of those, just two had positive findings for the efficacy. Most trials were underpowered, terminated early, focused on safety rather than efficacy (with mixed conclusions), or concluded no statistically significant improvement of clinical outcomes from HCQ/CQ (Table S2.1). Consequently, general scientific

consensus was reached and, in June 2020, the FDA revoked its COVID-19 EUA for HQC/CQ.

Anti-inflammatory drugs

Baricitinib

Data supporting authorization. Baricitinib is an oral JAK kinase inhibitor indicated for the treatment of moderately to severely active rheumatoid arthritis.[63] It was initially authorized for COVID-19 treatment in combination with remdesivir in November 2020, and subsequently authorized for single agent use in July 2021 for treatment of hospitalized patients with COVID-19 requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[64] The studies leading up to baricitinib's authorization as a single agent cited in the EUA are ACTT-2 (NCT04401579), COV-BARRIER (NCT04421027), and data from NDA 207924.[64] Baricitinib was initially evaluated in combination with remdesivir versus remdesivir alone in 1033 patients hospitalized with COVID-19 through ACTT-2, which found that baricitinib with remdesivir was superior especially among patients on high-flow oxygen or noninvasive ventilation.[65] COV-BARRIER found a significant decrease in death by any cause by day 29 in 1585 hospitalized participants ($p = 0.0018$), leading to baricitinib's authorization as a single agent[66] (Table 1).

Post authorization. Data released since the EUA for baricitinib as a single agent have supported the findings prior to authorization. Further data from the pre-EUA COV-BARRIER study of hospitalized patients showed baricitinib in addition to standard of care (SOC) led to a 38.2% relative reduction in 28-day all-cause mortality ($p = 0.0018$).[67] Similarly, studies of baricitinib in combination with SOC, remdesivir, and dexamethasone, respectively, found decreased ICU admissions (22.3% vs. 36.9%, $p = 0.002$)[68] and invasive mechanical ventilation was avoided in 90% of patients[69] (Table S2.2).

Tocilizumab

Data supporting authorization. Tocilizumab is an IL-6 receptor antagonist indicated for treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis, and cytokine release syndrome. The FDA granted EUA for tocilizumab in June 2021 for the treatment of COVID-19, for hospitalized adult and pediatric patients at least 2 years old receiving systemic corticosteroids and supplemental oxygen, noninvasive or invasive mechanical ventilation, or ECMO.[70] The FDA letter cites four clinical trials: RECOVERY (NCT04381936), COVACTA (NCT04320615), EMPACTA (NCT04372186), and

REMDACTA (NCT04409262). These trials investigated the effects of tocilizumab either alone or in combination with remdesivir in various hospitalized populations that had COVID-19 pneumonia or hypoxia and/or systemic inflammation. RECOVERY found that all-cause mortality within 28 days of randomization was 31% in the 2022 patients receiving tocilizumab and 35% in the 2094 patients receiving the placebo treatment ($p = 0.0028$[71,72]; Table 1).

Post authorization. Little additional clinical data has been released after the EUA, but several trials are registered on ClinicalTrials.gov related to risk stratification with various biomarkers, specific platform trials, and expansion of treatment to other locations. In light of the Omicron variant, the European Commission extended the marketing authorization for tocilizumab to include treating COVID-19 in adults relying on systemic corticosteroids, supplemental oxygen, or other forms of mechanical ventilation.[73,74] However, there has not been a similar authorization for tocilizumab in the United States (Table S2.3).

DISCUSSION

Several common themes emerged upon review of the data. In virtually every case, the EUA was supported by at a minimum one large, RCT and the process included a commercial sponsor (Table 1). This applied to new molecules as well as branded medications with market authorization for other uses. This standard was consistent for both antiviral and anti-inflammatory therapies. When this standard was applied, the EUAs remained in place or were expanded as data from subsequent studies became available. Here, we draw a distinction between the initial EUA decision being based on inadequate information versus viral evolution curtailing efficacy over time. Indeed, were it not for their expedited access, these beneficial medicines would not have been available whereas they remained effective against the circulating strain of SARS-CoV-2.

Remdesivir presents an interesting case and potential exception. The EUA and subsequent FDA approval were supported by three RCTs, one executed in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) and the other two conducted by Gilead. In terms of evidence supporting clinical efficacy, the NIAID study provided evidence of significant benefit. NCT04292899 was not designed to demonstrate the efficacy of remdesivir versus SOC, and, in NCT04292730, 5 days of remdesivir showed a statistically significant improvement. However, the authors noted the size of the effect was of questionable clinical relevance.[37,75] The

DisCoVeRy and Solidarity trials failed to show benefit of the use of remdesivir versus SOC. One potential explanation is the change in SOC for the latter two trials, in particular the incorporation of dexamethasone as SOC.[76] Notably, remdesivir was later found to be highly effective in preventing hospitalization when given in the outpatient setting, early in illness.[77]

The lone example of an EUA issued for a therapeutic in the absence of a supporting large RCT was CQ/HCQ, and the EUA was rescinded <3 months after it was issued. The decision was roundly criticized citing the data supporting the EUA as inadequate, and the process as overly influenced by political factors.[59] This may also serve as an example of two broader issues—the translational accuracy of non-clinical data, in particular for repurposed molecules (vide infra) and the relative difficulty in generating high quality clinical data to support the use of generic medications when a commercial sponsor is unavailable to run the clinical trials with standard rigor. The dis-coordinated response seen early in the pandemic led to the proliferation of poorly designed and executed small clinical trials, most of which were too underpowered to provide evidence of efficacy[78,79] (Table 1).

Large, publicly supported trials with coordinated research strategies or collective databases for disparate clinical data, such as RECOVERY, ACTIV, REMAP-COVID, and Solidarity, were useful in supporting the development of branded medications, but critical to the assessment of generics. A prominent example was the demonstration of the efficacy of dexamethasone demonstrated within the RECOVERY trial (NCT04381936),[80,81] as well as a clear negative assessment for the effectiveness of a number of other generic medications, such as HCQ, lopinavir-ritonavir, and colchicine.[82–84]

Another benefit of rigorous clinical study was a better understanding of considerations, such as the treatment window post-symptom onset for antiviral medications, and which hospitalized patients would derive benefit from treatment with anti-inflammatory/immunosuppressant medications.[85,86] Both remdesivir[77] and molnupiravir[87] were substantially more effective when given before hospitalization. Antivirals have been relatively more effective in preventing hospitalization in patients with at least one risk factor for severe COVID-19 versus a general population.[88] Such considerations are not unique to COVID-19. Peramivir (a neuraminidase inhibitor [NA]) was granted EUA for treatment of hospitalized patients during the H1N1 influenza outbreak in 2009 due to its i.m. or i.v. route of administration.[89,90] Peramivir had similar or better in vitro potency to the two approved NA inhibitors and, at the time, evidence of clinical efficacy in uncomplicated influenza, but subsequent studies of peramivir efficacy in the hospital setting have been inconclusive.[91]

Although outside the scope of this review, it should be noted that the variability and translational value of in vitro data may vary by mechanism. For direct acting antivirals, the predictive value of preclinical data is relatively high. For example, for antivirals such as protease inhibitors (HIV, hepatitis C virus, and SARS-CoV-2) or NS5A inhibitors in vitro effective concentration 90% (EC_{90}) or higher, corrected for free fraction, has been more predictive of target exposures to obtain an antiviral effect.[92–96] Treatment guidelines for the use of antibody therapies for COVID-19 are based on "current knowledge of the in vitro activities of the available products against the circulating SARS-CoV-2 variants and subvariants."[97] In vitro data were are also prominently noted in the decision to authorize bebtelovimab.[98] Data from repurposing screens for SARS-CoV-2, in particular for host cell targeted molecules, show more variability based on the assay used and the cell type used, making it difficult to estimate if an antiviral effect can be expected at the previously established clinical exposure (for example, maintaining exposure over the anti-viral EC_{90} as noted above).[99–103] This would again support the need for robust clinical investigation, in particular, for generic medicines where the antiviral mechanism is incompletely understood.

CONCLUSION

The EUA provides not only a vehicle to expedite the availability of life-saving medications in the midst of a public health crisis, but also a means to assure the public that the safety and efficacy of that medication has been independently reviewed by the FDA. The authors acknowledge that our observations arise from a retrospective analysis of data for treatments for COVID-19, but many of the lessons may be applicable to future health emergencies. The vast majority of EUAs granted during the COVID-19 pandemic involved a commercial sponsor, and were supported by efficacy demonstrated in at least one large RCT. When this standard was applied, subsequent clinical study was largely supportive of the initial authorization decision. Generics offer the advantages of lower cost, broad availability, and a well-established safety profile, but lack the resources and infrastructure of a commercial sponsor to support thorough evaluation of clinical efficacy. This required the establishment of publicly funded clinical trial networks which played a critical role in COVID-19 in both validating or refuting clinical efficacy suggested from pilot clinical studies or, in some cases, from in vitro data alone. Maintaining the publically funded platform clinical trial infrastructure developed during the pandemic and funds to support the FDA review process as part of the long-term strategy for pandemic preparedness would address many of these issues. Furthermore, establishing formal guidance for the need for an RCT to obtain EUA could help reduce the ambiguity of the current standard and help shield the authorization process for undue political influence. In particular, although not required for access to generics, review and authorization could improve public trust in the medication.

CONFLICT OF INTEREST
M.N.N. has received research support from AbbVie and is a consultant for Arrakis Therapeutics and Axonis and past employee of Alkermes, Vertex Pharmaceuticals, and Cubist. All other authors declare no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.