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The latest developments from US FDA drug, biologic, and medical device advisory committee meetings.

Today's Headline: Near Unanimous Support for Pfizer's Paxlovid for Mild-to-Moderate COVID-19

March 16, 2023
Meeting Begin Time: 9:00 a.m. | **End Time:** 3:56 p.m.

IN THIS ISSUE

Antimicrobial Drugs Advisory Committee Meeting

AdComm Profiles and Voting Histories—Drugs/Biologics (IDRAC 175864)

Subject: New drug application (NDA) 217188: Paxlovid (nirmatrelvir and ritonavir) co-packaged tablets for oral use, submitted by Pfizer Inc for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

Announced in the Federal Register February 27, 2023 (IDRAC 360744) (Volume 88, Number 38)

Decision/Voting

The Antimicrobial Drugs Advisory Committee (AMDAC) solidly agreed that the overall benefit-risk profile for Paxlovid (nirmatrelvir and ritonavir) co-packaged tablets, submitted by Pfizer Inc, is favorable for adults with mild-to-moderate coronavirus disease 19 (COVID-19) who are at high risk for progression to severe COVID-19. On the whole, panelists agreed with the FDA that the clinical trial data demonstrated that Paxlovid was effective and safe in this population. However, additional data would be needed to determine whether Paxlovid would be beneficial in other patient populations (e.g., immunocompromised individuals).

FDA Question(s) to the Committee	Vote		Comments
	Yes	No	
Is the overall benefit-risk assessment favorable for Paxlovid when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death?	**16**	1	
NOTE: The FDA is not obligated to follow the voting recommendation of the advisory committee, but it may do so once all information is considered.			

The new drug application (IDRAC 34571) (NDA) for Paxlovid was primarily backed by a single pivotal trial, EPIC-HR, with supportive data from trials EPIC-SR and EPIC-PEP. Real-world evidence (RWE) for Paxlovid was also available since the FDA granted an emergency use authorization (IDRAC 238910) (EUA) to the product in December 2021 for the treatment of mild-to-moderate COVID-19. In the FDA's review of the NDA, the agency found that the data supported the proposed indication for Paxlovid. Panelists agreed with the agency's evaluation that Paxlovid treatment demonstrated an absolute risk reduction and relative risk reduction in COVID-19–related hospitalizations or deaths in high-risk adults.

The AMDAC also shared the FDA's view on the safety data for Paxlovid. Because ritonavir is a cytochrome P450 (CYP) 3A4 inhibitor, the agency had concerns related to drug-drug interactions (DDIs). The FDA and the sponsor noted that they would aim to appropriately

describe the risk for serious adverse reactions due to DDIs in the Paxlovid drug label, and the panel members agreed with this risk mitigation strategy. They also encouraged the FDA and the sponsor to support prescribers in managing DDIs by updating the label in a timely manner and providing clear instructions on how to manage them.

Based on the efficacy and safety data, almost all of the panelists voted to support Paxlovid. The patient representative who voted "no" was concerned that prescribers may not be well-informed on the drug and that they would not manage it correctly. Many panel members acknowledged that there is misinformation on Paxlovid across social media and in the press that can mislead prescribers and patients. This issue was also discussed in terms of "COVID-19 rebound," or the recurrence of COVID-19 symptoms after treatment with Paxlovid.

As noted by the FDA, there have been widespread reports in the media on the potential relationship between COVID-19 rebound and Paxlovid treatment. These reports have also raised concern that the rebound is associated with more severe symptoms. The FDA and the sponsor conducted assessments on COVID-19 rebound and demonstrated that there is no clear association between Paxlovid use and virologic or symptomatic rebound. Panelists were reassured by these data that COVID-19 rebound is likely not a major issue but advised the sponsor to collect more data on the frequency of rebound and the severity of symptoms when rebound occurs. They also encouraged the agency to publish these data to help deter misinformation on the subject.

The panel also gave advice regarding the effectiveness of Paxlovid in specific populations, including individuals who have been previously vaccinated or infected with SARS-CoV-2. While the clinical trials showed some benefit in vaccinated participants, several AMDAC members noted that the effect was "small." They suggested that the sponsor collect more data to broaden this finding and determine if people with prior immunity would benefit from the drug.

Similarly, panel members noted that more data should be collected in immunocompromised populations. The sponsor shared that it is conducting a trial with immunocompromised subjects (EPIC-IC; see *Clinical Issues*), but some panelists had concerns that the inclusion criteria were too broad. They stated that multiple studies may be needed to evaluate different subsets of immunosuppressed individuals to best determine their treatment regimen. Moreover, severely immunocompromised populations should be monitored for emerging resistant strains because they cannot clear the virus as easily, a member remarked.

There were fewer concerns related to the use of Paxlovid in individuals infected with the SARS-CoV-2 omicron variant. The non-clinical and clinical data were supportive that the drug had antiviral activity versus multiple variants. In addition, panelists were encouraged that Paxlovid targets a highly conserved region in the virus. However, they suggested that the sponsor should have appropriate pharmacovigilance activities to account for new and emerging variants.

Background Information

During this meeting, the Antimicrobial Drugs Advisory Committee (AMDAC) discussed new drug application (IDRAC 34571) (NDA) 217188 for Paxlovid (nirmatrelvir and ritonavir [J05AE]) co-packaged tablets for oral use, submitted by Pfizer Inc for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. Nirmatrelvir is a peptidomimetic inhibitor that targets the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease (M^{pro}). By inhibiting SARS-CoV-2 M^{pro}, nirmatrelvir prevents it from processing polyprotein precursors that are important for viral replication. Ritonavir is a human immunodeficiency virus (HIV)-1 protease inhibitor that helps to increase the plasma concentrations of nirmatrelvir.

In December 2021, the FDA granted Paxlovid an emergency use authorization (IDRAC 238910) (EUA) for the treatment of adults and pediatric patients (aged ≥12 years weighing ≥40 kg) with mild-to-moderate COVID-19 who are at high risk of progression to severe COVID-19, including hospitalization or death. This EUA was primarily supported by adult interim data from EPIC-HR, a phase 2/3 study. The sponsor included EPIC-HR as the pivotal clinical trial for the Paxlovid NDA, with supportive data from 2 other clinical studies: EPIC-SR and EPIC-PEP.

As covered in the Event Materials (IDRAC 361596), the FDA found that the clinical trial results from EPIC-HR and EPIC-SR supported the proposed indication for Paxlovid. However, the agency noted some issues for the panel to consider, including the effectiveness of Paxlovid in immunocompromised individuals. This population, along with other vulnerable groups (e.g., older adults), are more susceptible to severe illness due to COVID-19. Because <1% of the participants in the clinical trials were classified as having immunosuppression, it is unknown whether they would benefit from Paxlovid treatment.

COVID-19 rebound, which is characterized by a relapse of symptoms or SARS-CoV-2 detection after initial recovery, has also been described as a potential effect of Paxlovid treatment. Several publications, case reports, and stories in the media have described patients who experienced this after receiving Paxlovid. While there are speculations on why this occurs, the FDA remarked that it has been "challenging" to determine whether there is a direct correlation between Paxlovid treatment and virologic rebound.

Regarding safety, the overall safety profile for Paxlovid was favorable, but the FDA noted that ritonavir, a cytochrome P450 (CYP) 3A4 inhibitor, may induce serious adverse reactions due to drug-drug interactions (DDIs). The clinical trials did not provide information on this safety concern because it excluded subjects on medications with clinically significant DDIs. However, additional analyses conducted by the agency suggested that prescribers should be aware of the risk of DDIs. At the meeting, panel members discussed this safety risk in their overall benefit-risk assessment of Paxlovid. They also considered the effectiveness of Paxlovid in certain populations and the potential association between Paxlovid treatment and COVID-19 rebound.

Proposed Indication

- *Paxlovid (nirmatrelvir and ritonavir) for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.*

Proposed Dose

- *Paxlovid co-packaged oral tablets, given as nirmatrelvir 300 mg and ritonavir 100 mg, twice daily (BID) for 5 days. In patients with moderate renal impairment (defined as an estimated glomerular filtration rate [eGFR] ≥30 to <60 mL/min), the proposed dosage is nirmatrelvir 150 mg with ritonavir 100 mg BID for 5 days.*

Regulatory History

January 31, 2020	The secretary of the US Department of Health and Human Services (HHS) declared a public health emergency due to COVID-19.
March 7, 2020	The HHS secretary declared that the COVID-19 pandemic justified the authorization of the emergency use of drugs and biologics under section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act (IDRAC 17027) (FD&C Act).
December 22, 2021	The FDA issued an EUA for Paxlovid [FDA Press Release (IDRAC 339982)].
February 17, 2022	The FDA granted fast track designation (IDRAC 37909) to Paxlovid.
March 17, 2022	The FDA reissued the EUA letter of authorization for Paxlovid.
April 14, 2022	
June 29, 2022	The sponsor submitted NDA 217188 for Paxlovid to the FDA [Application, Format, Content and Submission (IDRAC 34571)].
July 6, 2022	The FDA announced that it revised the EUA for Paxlovid to authorize state-licensed pharmacists to prescribe the drug to eligible patients [FDA Press Release (IDRAC 349770)].
August 5, 2022	The FDA reissued the EUA letter of authorization for Paxlovid.
October 27, 2022	
December 20, 2022	The sponsor announced that the FDA extended the review period for the Paxlovid NDA, extending the Prescription Drug User Fee Act (IDRAC 9046) (PDUFA) target action date by 3 months.
February 1, 2023	The FDA reissued the EUA letter of authorization for Paxlovid.
May 28, 2023	The revised PDUFA target action date, according to the sponsor.

Regulatory Issues

Paxlovid is currently available for the treatment of COVID-19 under an EUA. During public health emergencies, the FDA can authorize medical countermeasures (MCMs) to strengthen public health protections in the US against chemical, biological, radiological, and nuclear (CBRN) threats. As noted in section 564 of the FD&C Act, the FDA may issue an EUA if statutory requirements are met. Under an EUA, the FDA may authorize unapproved medical products or unapproved uses of approved medical products to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threats.

The FDA has published multiple guidances on DDIs including the Guidance for Industry: Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions, January-2020 (IDRAC 305298). This guidance includes recommendations for evaluating CYP-mediated DDIs and labeling considerations. The agency advises that sponsors develop DDI management and prevention strategies if a clinically significant DDI is identified. These strategies may include contraindicating concomitant use and modifying the dosage of the new drug. DDI information is largely included under the Drug Interactions and Clinical Pharmacology sections of a drug label, but it may also appear under other sections (e.g., Warnings and Precautions) if it has "direct implications for the safe and effective use of the drug."

In terms of COVID-19 drug development programs, a relevant FDA resource is the Guidance for Industry: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention (Updated), February-2021 (IDRAC 325821). It focuses on different elements regarding phase 2 and phase 3 clinical trials, such as trial design, efficacy endpoints, safety considerations, and statistical considerations. As noted in the guidance, the FDA "strongly" recommends that drugs to treat COVID-19 be assessed in randomized, placebo-controlled, double-blind clinical trials using a superiority design. Moreover, sponsors should evaluate a range of populations in their clinical trials, including groups of individuals at high risk of complications.

Clinical Issues

NDA 217188 is supported by 3 clinical trials, EPIC-HR, EPIC-SR, and EPIC-PEP, with differing enrollment criteria. EPIC-HR included participants who were unvaccinated against COVID-19 and at high risk for progression to severe disease, while EPIC-SR included participants who were either vaccinated against COVID-19 and at high risk for progression to severe disease or unvaccinated and with no risk factors for progression to severe disease. EPIC-PEP evaluated the postexposure prophylaxis of symptomatic SARS-CoV-2 infection in adults. It enrolled subjects with a negative SARS-CoV-2 rapid antigen test (RAT) result who were also asymptomatic household contacts of a symptomatic individual who recently tested positive for SARS-CoV-2. The Event Materials (IDRAC 361596) and Table 1 include more information on the 3 studies.

Table 1. Paxlovid Clinical Program

Trial	Design	Regimen	No. Patients	Primary Endpoint
EPIC-HR	Randomized, multicenter, double-blind, placebo-controlled, phase 2/3 study	1:1 randomization: Paxlovid* ***or*** placebo every 12 hours for 5 days	2,113	Proportion of participants with COVID-19–related hospitalization or death from any cause through day 28
EPIC-SR			1,075	Time to sustained alleviation of all targeted COVID-19 signs/ symptoms through day 28

EPIC-PEP	Randomized, multicenter, double-blind, placebo-controlled, double-dummy phase 2/3 study	1:1:1 randomization: Paxlovid* every 12 hours for 5 days followed by placebo every 12 hours for 5 days; Paxlovid* every 12 hours for 10 days; ***or*** placebo every 12 hours for 10 days	2,736	Proportion of participants who develop a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through day 14 among participants who have a negative RT-PCR result at baseline
RT-PCR = reverse transcription-polymerase chain reaction * nirmatrelvir 300 mg and ritonavir 100 mg				

As the FDA noted in the event materials, the original EUA review document for Paxlovid included analyses from EPIC-HR and EPIC-SR. However, the FDA excluded data from 4 clinical trial sites (2 EPIC-HR clinical trial sites and 2 EPIC-SR clinical trial sites) after conducting inspections and other review actions to ensure data reliability. The overall efficacy and safety conclusions did not change after excluding these data, the agency noted. In addition, 2 clinical trial sites from EPIC-PEP that matched the 4 EPIC-HR and EPIC-SR sites were also excluded.

Safety

Safety data were derived across phase 1, 2, and 3 trials, including EPIC-HR, EPIC-SR, and EPIC-PEP. The safety analysis included >2,400 participants from EPIC-HR, EPIC-SR, and EPIC-PEP who received the proposed dose of Paxlovid. The FDA also evaluated post-authorization adverse event (AE) reports to examine safety signals outside of the clinical trial setting.

Overall, the FDA found that Paxlovid demonstrated a favorable safety profile. The incidences of AEs were similar between treatment groups in EPIC-HR, EPIC-SR, and EPIC-PEP. For severe AEs, serious AEs (SAEs), and AEs leading to permanent discontinuation of the study drug, the placebo groups had similar or higher incidences compared to the Paxlovid groups. No deaths were reported in the Paxlovid arms. The most common treatment-emergent AEs (TEAEs) (≥2% incidence) for the EPIC-HR Paxlovid group were dysgeusia and diarrhea; these TEAEs were consistent with those reported in EPIC-SR and EPIC-PEP. In Paxlovid-treated subjects in EPIC-HR, the most common SAEs (≥2 subjects) were COVID-19 and COVID-19 pneumonia, while the most common discontinuations due to AEs (≥2 subjects) included nausea, vomiting, and dysgeusia. The SAEs and discontinuations due to AEs observed in EPIC-SR and EPIC-PEP were consistent with those in EPIC-HR.

Since Paxlovid was authorized in December 2021, the FDA's Office of Surveillance and Epidemiology (OSE) has been monitoring for safety signals following Paxlovid treatment through the FDA Adverse Events Reporting System, the FDA American College of Medical Toxicology (ACMT) COVID-19 Toxicology Investigators Consortium (ToxIC) Pharmacovigilance Project Sub-registry, and the medical literature. Adverse reactions that have been identified by the OSE or the sponsor to date during use of Paxlovid under EUA fell into the following categories of disorders: immune system disorders (e.g., anaphylaxis), nervous system disorders (headache), vascular disorders (hypertension), gastrointestinal disorders (e.g., pain), and general disorders and administration site conditions (malaise). Because these reactions are reported voluntarily, the FDA noted that it may not be possible to estimate their frequency or determine if they are caused by drug exposure.

As mentioned previously, the FDA expressed concern that Paxlovid may increase the risk for serious adverse reactions due to DDIs, largely caused by the ritonavir component. The current Paxlovid EUA Fact Sheet for Healthcare Providers includes a list of 143 drugs that have DDIs with Paxlovid, and it includes a statement that the list is not considered comprehensive, the agency noted.

Because the available clinical trial data could not provide information on risk of serious adverse reactions due to DDIs, the OSE conducted 3 analyses regarding post-authorization use of Paxlovid. Using the Medicare and Veteran Affairs databases, one analysis evaluated the proportion of Paxlovid-eligible adults who also took concomitant medications that have DDIs with Paxlovid. In a second analysis, the OSE used the Symphony Health Metys database to assess the types of healthcare providers who are prescribing Paxlovid in the US. An evaluation of AEs reported to the FDA that were possibly related to Paxlovid DDIs was the OSE's third analysis.

Overall, these analyses revealed that many Paxlovid-eligible patients are taking medications that have DDIs with Paxlovid, a majority of prescribers are adult primary care practitioners who may not have experience with managing ritonavir DDIs, and serious adverse reactions related to Paxlovid DDIs have occurred, including death. Based on these data, the FDA suggested that the Paxlovid label should appropriately describe the risk of serious adverse reactions due to DDIs. Prescribers need to be aware of the potential for these risks to properly manage them and safely prescribe the drug to a patient, the agency remarked.

Efficacy

EPIC-HR. The primary efficacy endpoint was evaluated in 1) the modified intent-to-treat (mITT) population that included randomized subjects who took ≥1 dose of study intervention, did not receive nor were expected to receive COVID-19 monoclonal antibody (mAb) treatment at baseline, and were dosed ≤3 days at COVID-19 symptom onset; 2) the mITT1 population that included randomized subjects who took ≥1 dose of study intervention, did not receive nor were expected to receive COVID-19 mAb treatment at baseline, and were dosed ≤5 days at COVID-19 symptom onset; and 3) the mITT2 population that included randomized subjects who took ≥1 dose of study intervention and were dosed ≤5 days at COVID-19 symptom onset. Table 2 summarizes the efficacy results for EPIC-HR.

Table 2. Proportion of Subjects with COVID-19–Related Hospitalization or Death From Any Cause Through Day 28 in EPIC-HR

	Paxlovid	Placebo
mITT, N	**N = 671**	**N = 647**
Subjects with event, n (%)	5 (0.7)	44 (6.8)
COVID-19 hospitalization	5 (0.7)	44 (6.8)
Death	0	9 (1.4)
Estimated difference in proportion % (95% CI)[1]	-6.1 (-8.2, -4.1)	
2-sided nominal p-value	<0.0001	
mITT1, N	**N = 977**	**N = 989**
Subjects with event, n (%)	9 (0.9)	64 (6.5)
COVID-19 hospitalization	9 (0.9)	63 (6.4)
Death	0	12 (1.2)
Estimated difference in proportion % (95% CI)[1]	-5.6 (-7.3, -4.0)	
2-sided nominal p-value	<0.0001	
mITT2, N	**N = 1,038**	**N = 1,053**
Subjects with event, n (%)	10 (1.0)	66 (6.3)
COVID-19 hospitalization	10 (1.0)	65 (6.2)
Death	0	12 (1.1)
Estimated difference in proportion % (95% CI)[1]	-5.4 (-7.0, -3.8)	
2-sided nominal p-value	<0.0001	

CI = confidence interval

[1]The estimated cumulative proportion of subjects hospitalized for the treatment of COVID-19 or death by day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through day 28 were censored at the time of study discontinuation.

EPIC-SR. EPIC-SR did not demonstrate a meaningful difference for its primary efficacy endpoint. The FDA further analyzed a prespecified secondary endpoint of COVID-19–related hospitalization or death from any cause through day 28 in the mITT1 population. Although there was not a statistically significant difference in this endpoint between the Paxlovid arm and the placebo arm, there were numerically lower rates of hospitalization and death in the Paxlovid arm. Table 3 shows the results for the secondary endpoint across all randomized subjects and in the subgroup of vaccinated high-risk participants.

Table 3. Proportion of Subjects with COVID-19–Related Hospitalization or Death From Any Cause Through Day 28 in EPIC-SR

	Paxlovid	Placebo
mITT1, N	**N = 540**	**N = 528**
Subjects with event, n (%)	5 (0.9)	10 (1.9)
COVID-19 hospitalization	5 (0.9)	10 (1.9)
Death	0	1 (0.2)

Estimated difference in proportion % (95% CI)[1]	-1.0 (-2.4, 0.5)	
2-sided nominal p-value	0.1815	
Vaccinated high-risk subgroup of mITT1, n	**n = 317**	**n = 314**
Subjects with event, n (%)	3 (0.9)	7 (2.2)
COVID-19 hospitalization	3 (0.9)	7 (2.2)
Death	0	1 (0.3)
Estimated difference in proportion % (95% CI)[1]	-1.3 (-3.3, 0.7)	
2-sided nominal p-value	0.1970	

[1]The estimated cumulative proportion of subjects hospitalized for the treatment of COVID-19 or death by day 28 was calculated for each treatment group using the Kaplan-Meier method, where subjects without hospitalization and death status through day 28 were censored at the time of study discontinuation.

EPIC-PEP. There were no clinically meaningful differences between the Paxlovid group and the placebo group in EPIC-PEP. Each arm also had 1 COVID-19–related hospitalization event. No deaths were reported in the study.

Efficacy Issues. In addition to reviewing the 3 trials, the FDA conducted further analyses to address various efficacy issues. One assessment evaluated the efficacy of Paxlovid in high-risk adults who were previously vaccinated against COVID-19 or infected with SARS-CoV-2. The proposed indication for Paxlovid is for the treatment of COVID-19 regardless of COVID-19 vaccination status or prior SARS-CoV-2 infection. However, the pivotal trial, EPIC-HR, enrolled high-risk adults who had not received the vaccine or were previously infected with SARS-CoV-2. This is important, the FDA noted, because an "overwhelming majority" of adults in the US have received ≥1 COVID-19 doses or have been infected before. After analyzing 3 subgroups across all 3 trials, the agency concluded that the EPIC-HR and EPIC-SR clinical trial results support the efficacy of Paxlovid regardless of vaccination status or prior SARS-CoV-2 infection.

The FDA also assessed the efficacy of Paxlovid against the SARS-CoV-2 omicron variant. EPIC-HR began enrollment when the delta variant was predominant in the US, and the trial was completed before omicron replaced delta and became the prevalent circulating variant. Although clinical trial data are lacking to determine the efficacy of Paxlovid in high-risk adults infected with the omicron variant, the FDA noted that nonclinical and clinical data show that the drug has antiviral activity against it. This is likely due to high conservation of SARS-CoV-2 M^{pro} and M^{pro} cleavage site amino acid sequences across the SARS-CoV-2 variants and that nirmatrelvir is likely to retain activity against circulating and emerging variants of SARS-CoV-2, the agency stated.

As noted previously, the FDA stated concerns relating to the efficacy of Paxlovid in immunocompromised individuals and its potential association with COVID-19 rebound. EPIC-HR enrolled <1% of subjects who were classified as having immunosuppression. Patients with immunosuppression may benefit from a longer treatment course of Paxlovid, but there are limited data to support this. The agency noted that data from an ongoing clinical trial, EPIC-IC, will help determine the optimal duration in this population. EPIC-IC is a randomized, double-blind clinical trial in which immunocompromised subjects with mild-to-moderate COVID-19 are randomized to 5, 10, or 15 days of Paxlovid treatment.

In regard to COVID-19 rebound, the FDA conducted comprehensive tests using virology and symptom data from EPIC-HR and EPIC-SR. Based on these analyses as well as assessments from the sponsor, a "clear association" between Paxlovid treatment and COVID-19 rebound was not identified. This suggests that virologic and/or symptomatic rebound may occur as "part of the natural progression and resolution of COVID-19 disease, irrespective of Paxlovid treatment," the agency noted.

Medical Issues

SARS-CoV-2, a zoonotic coronavirus that emerged in late 2019, is the causative agent for COVID-19. An enveloped, positive-sense, single-stranded RNA virus, SARS-CoV-2 shares >70% of its sequence with severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus) and approximately (~) 50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV). Various SARS-CoV-2 variants have emerged over time. In November 2021, the omicron variant was detected. As the FDA noted in the Event

Materials (IDRAC 361596), the omicron variant was estimated to be responsible for >99% of SARS-CoV-2 infections in the US by late January 2022.

Patients with COVID-19 can present varying symptoms. Many have asymptomatic or mild disease, but older adults or immunocompromised individuals are more likely to progress to severe respiratory tract disease. Severe illnesses (e.g., pneumonia, acute respiratory distress syndrome) can emerge and increase the chance of hospitalization and death. The FDA noted that hospitalizations and deaths related to COVID-19 continue to be a major issue, especially in vulnerable populations. In January 2023, there were approximately (~) 4,000 COVID-19 related deaths and 35,000 COVID-19 related hospitalizations each week in the US, according to the Centers for Disease Control and Prevention (CDC).

Pharmacology Issues

Paxlovid is composed of nirmatrelvir tablets co-packaged with ritonavir tablets. According to the sponsor, nirmatrelvir inhibits SARS-CoV-2 M^{pro} by forming a covalent interaction with a cysteine residue at the active site of the protease. After evaluating pharmacokinetic data with nirmatrelvir alone, the sponsor included ritonavir to provide sustained elevated plasma levels of nirmatrelvir. The proposed dose of nirmatrelvir 300 mg and ritonavir 100 mg BID for 5 days was chosen to achieve a nirmatrelvir plasma concentration above the 90% effective concentration (EC_{90}) of 292 ng/mL for anti–SARS-CoV-2 activity.

For patients with renal impairment, the proposed dose of Paxlovid is lower (nirmatrelvir 150 mg and ritonavir 100 mg BID for 5 days). The event materials summarized that data from a renal impairment study showed that subjects with moderate renal impairment had increased nirmatrelvir systemic exposure (~87% increase in mean area under the concentration-time curve from time 0 to infinity [AUC_{inf}]) compared to subjects with normal renal function. This exposure was greater in participants with severe renal impairment who had a mean 204% increase in AUC_{inf} compared to subjects with normal renal function. Based on these data, Paxlovid is not recommended in patients with severe renal impairment until additional data are available.

The sponsor noted that *in vitro* studies indicate that nirmatrelvir is a substrate for CYP3A4 and human multidrug resistance gene 1 (MDR1). Although ritonavir is a CYP3A4 inhibitor, it also appears to inhibit CYP2D6 and MDR1. It can also induce CYP13A, CYP1A2, CYP2C9, CYP2C19, CYP2B6, and other enzymes such as glucuronosyl transferase.

Market Issues

If the FDA approves Paxlovid, from Pfizer Inc, it would be the first oral antiviral for the treatment of COVID-19 and the second FDA-approved antiviral for COVID-19. The first antiviral for COVID-19, Veklury (IDRAC 357081) (remdesivir), from Gilead Sciences Inc, was approved by the agency in October 2020 as an intravenous infusion. Table 4 lists these products and several others for the treatment of COVID-19, including those authorized under an EUA.

Table 4. FDA-Approved/Authorized Products for the Treatment of COVID-19

Trade Name	Generic Name	Company
ATC: J05AB—Nucleosides and nucleosides excl. reverse transcriptase inhibitors		
Veklury (IDRAC 357081)*	remdesivir	Gilead Sciences, Inc
Lagevrio	molnupiravir	Merck Sharp & Dohme LLC
ATC: J05AE—Protease inhibitors		
Paxlovid	nirmatrelvir and ritonavir	Pfizer Inc
ATC: L04AA—Selective immunosuppressants		
Olumiant (IDRAC 348797)*	baricitinib	Eli Lilly and Company
ATC: L04AC—Interleukin inhibitors		
Actemra (IDRAC 357395)*	tocilizumab	Genentech, Inc
Kineret	anakinra	Swedish Orphan Biovitrum AB

*Approved by the FDA to treat patients with COVID-19; all other products are available under EUA.

On January 28, 2022, the European Commission granted Paxlovid conditional marketing authorization for treating COVID-19 in adults who do not require supplemental oxygen and

who are at increased risk of the disease becoming severe [EMA EPAR EMEA/H/C/005973 Revision 9: PAXLOVID (PF-07321332 / ritonavir), 21-February-2023 (IDRAC 360588)]. Paxlovid is also authorized for use in >70 countries, according to the sponsor, including Japan, the United Kingdom, Australia, Canada, China, and South Korea.

In the Pipeline

Gilead Sciences is recruiting participants with COVID-19 who have a standard risk of developing severe illness for a randomized, double-blind, placebo-controlled phase 3 study. The study is evaluating the efficacy and safety of GS-5245, an oral nucleoside prodrug inhibitor of the SAR-CoV-2 polymerase. The ~1,900 participants in the study are randomized to receive either GS-5245 350 mg BID or placebo BID for 5 days. The primary outcome measures are the time to COVID-19 symptom alleviation by day 29 and the percentages of participants experiencing TEAEs, laboratory abnormalities, SAEs, and AEs leading to study drug discontinuation up to 35 days. Begun in February 2023, the study is estimated to complete in August 2024.

In a double-blind, randomized, placebo-controlled phase 2/3 study, Laurent Pharmaceuticals Inc is recruiting ~508 hospitalized subjects with COVID-19 who are at a higher risk of complications to assess the efficacy and safety of LAU-7b. The agent is a new oral form of fenretinide, a retinoid previously studied in cancer and other diseases. Participants in the study receive either oral LAU-7b or placebo once daily for up to 14 days. The primary outcome measure is the proportion of participants who require mechanical ventilation and/or are deceased by day 60. The study began in June 2020 and is expected to finish in June 2023.

Pardes Biosciences, Inc, is examining the efficacy and safety of pomotrelvir, a novel inhibitor of the SARS-CoV-2 M^{pro}, in a double-blind, randomized phase 2 study. The 210 non-hospitalized, symptomatic participants with COVID-19 receive either pomotrelvir 350 mg BID or placebo BID for 5 days. The primary outcome measure is the proportion of subjects below the limit of detection for infectious SARS-CoV-2 on day 3 of treatment by infection virus assay from mid-turbinate swabs. Begun in September 2022, the study is anticipated to complete in July 2023.

Additional *Cortellis RI* Resources Briefing Information

Event Materials (IDRAC 361596)

***AdComm Bulletin* and *FDA Workshop Bulletin* Coverage**

Click here for:
Drugs and Biologics FDA Advisory Committees (IDRAC 23827)
Medical Devices and IVDs FDA Advisory Committees (IDRAC 289859)
and
Drugs and Biologics FDA Workshops (IDRAC 40156)*
Medical Devices and IVDs FDA Workshops (IDRAC 268264)*

**FDA Workshop Bulletins* are added directly to Cortellis.

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