CADTH

CADTH Drug Implementation Advice

Nirmatrelvir and Ritonavir (Paxlovid)

Sponsor: Pfizer Canada ULC

Indication: Treatment of mild-to-moderate COVID-19 in adults at high risk of progression to severe disease

Implementation Advice

What Is the Unmet Need for Treatment of COVID-19?

COVID-19 is a major public health burden associated with substantial numbers of infections, deaths, and hospitalizations. Vaccination is recognized as a highly efficacious measure in protecting against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, symptomatic COVID-19 illness, and COVID-19–related hospitalization and death. However, some individuals remain unvaccinated and certain risk groups may have reduced protection, such as immunocompromised individuals. The waning effectiveness of vaccines may also lead to breakthrough infections in those who are vaccinated. The most significant risk factors for breakthrough infections that have resulted in hospitalization or death are advanced age, being immunocompromised, and medical comorbidities. The greatest risk factor for progression to severe COVID-19 is advanced age.

What Is Paxlovid?

Paxlovid (nirmatrelvir; ritonavir) is an orally administered protease inhibitor antiviral drug. The recommended dosage is 300 mg nirmatrelvir (150 mg tablet × 2) with 100 mg ritonavir (100 mg tablet) with all 3 tablets taken together orally twice daily for 5 days. Results from the manufacturer-sponsored, multicentre, phase II/III, double-blind, randomized controlled trial (EPIC-HR) demonstrated that the use of nirmatrelvir in combination with ritonavir was associated with a statistically significant reduction in the incidence of COVID-19–related hospitalization or death from any cause through day 28 compared with placebo in adult symptomatic outpatients with mild-to-moderate COVID-19 who were considered at high risk for progression to severe disease, including hospitalization or death.

How Did CADTH Approach This Review?

The aim of this CADTH review was to inform decision-making on the optimal use of nirmatrelvir and ritonavir (Paxlovid) for mild-to-moderate COVID-19 in adult patients with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death. CADTH convened an implementation advice panel (the “panel”) that spanned various disciplines and clinical settings with geographical representation across Canada. The panel captured expert advice through consensus and prioritized patient populations that were most likely to benefit from treatment in a tiered risk group approach.

What Is the Implementation Advice?

The panel suggests prioritizing adult patients with symptoms of COVID-19 with confirmed SARS-CoV-2 infection into 3 groups based on those with the highest risk of progressing to severe COVID-19 and those who will benefit most from the drug based on availability of supply (Table 1).

What Are the Limitations of the Review?

The review is limited to evidence available at the time of the review. Important gaps in the available evidence include the lack of efficacy data of nirmatrelvir and ritonavir for patients fully vaccinated with an additional dose against SARS-CoV-2, for the Omicron variant, and comparative data versus monoclonal antibody treatments. There is also a scarcity of safety data in a large patient population.

Table 1: Prioritization of Treating Patients With COVID-19 With Nirmatrelvir and Ritonavir (Paxlovid) Based on a Tiered Risk Group Approach

Tier	Risk group
1	Immunocompromised[a] individuals not expected to mount an adequate immune response to SARS-CoV-2 infection, regardless of vaccine status Undervaccinated[b] individuals ≥ 80 years of age Undervaccinated individuals ≥ 60 years of age residing in rural or remote communities, residing in a long-term care setting, or members of the Indigenous community
2	Undervaccinated individuals ≥ 70 years of age Undervaccinated individuals ≥ 60 years of age with ≥ 2 comorbidities[c] Undervaccinated individuals ≥ 50 years of age residing in rural or remote communities, residing in a long-term care setting, or members of the Indigenous community
3	Undervaccinated individuals ≥ 60 years of age Undervaccinated individuals ≥ 50 years of age with ≥ 2 comorbidities

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Definition from Ontario COVID-19 Science Advisory Table (January 8, 2022): Examples of immunocompromised or immunosuppressed individuals include individuals with active treatment for solid tumour and hematologic malignancies, receipt of solid organ transplant and taking immunosuppressive therapy, receipt of chimeric antigen receptor (CAR) T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy), moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency, Good syndrome, hyper-IgE syndrome), advanced or untreated HIV infection, active treatment with high-dose corticosteroids (i.e., ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumour-necrosis factor blockers, and other biologic agents that are immunosuppressive or immunomodulatory.[1]

[b] Undervaccinated individuals are defined as those who have been treated with 0 to 2 doses of an approved 2-dose vaccine or 0 to 1 dose of an approved 1-dose vaccine for SARS-CoV-2 infection and are >6 months from their last dose of vaccine.

[c] Comorbidities include obesity (i.e., body mass index ≥ 30), current smoking status, chronic kidney disease, diabetes, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease (including congenital heart disease) or hypertension, chronic lung disease (including chronic obstructive pulmonary disease, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, and pulmonary hypertension), sickle cell disease, neurodevelopmental disorders (including cerebral palsy, Down syndrome), genetic or metabolic syndromes and severe congenital anomalies, injection drug use, problematic alcohol use, severe mental illness, and medical-related technological dependence not related to COVID-19 (including tracheostomy, gastrostomy, or positive pressure ventilation).[2-6]

Panel Deliberation

The panel, comprising 8 members representing infectious diseases, emergency medicine, pediatrics, geriatrics, ethics, pharmacy, and nursing from urban and rural clinical settings across Canada, met on January 11, 2022. The aim was to inform decision-making on the optimal use of nirmatrelvir and ritonavir in patients with mild-to-moderate COVID-19. Particularly, CADTH was seeking feedback from the panel regarding the prioritization of patient populations to receive treatment in situations when supply is limited. These would include the following:

- patient populations that demonstrate the greatest unmet need for a treatment to avoid progression to severe COVID-19
- patient populations that are most likely to achieve benefit from the drug and achieve treatment goals of preventing hospitalizations and/or death
- patient populations that are less likely to benefit from the drug and not achieve treatment goals due to uncertainty in efficacy and/or safety.

Considerations for special populations, as well as considerations associated with administration and treatment course (i.e., prescribing advice), were discussed.

The clinical value of nirmatrelvir used in combination with ritonavir was deliberated in the context of the ongoing public health emergency of the COVID-19 pandemic. The advice reflects the panel's consensus based on the best available evidence for the treatment of nirmatrelvir and ritonavir and based on their clinical expertise in the diagnosis and management of COVID-19. The panel also discussed ethical considerations for the judicious use of nirmatrelvir and ritonavir, particularly in scenarios of high demand for treatment. Drug costs or a health economic analysis were not considered.

Place in Therapy

Goals of Treatment

The panel concluded that the primary goal of treatment with oral antivirals is the reduction of hospitalizations and deaths in symptomatic patients at high risk for progression to severe COVID-19.

Unmet Needs

The panel members agreed that the greatest unmet needs are in immunocompromised patients, those with advanced age, undervaccinated individuals (i.e., those who have been treated with 0 to 2 doses of an approved 2-dose vaccine or 0 to 1 dose of an approved 1-dose vaccine for SARS-CoV-2 infection and are >6 months from their last dose of vaccine), and those with multiple comorbidities.

Special consideration should be given for the use of oral medications in patients who are geographically isolated and unable to access care. These include rural and remote communities with inadequate access to health care facilities for hospitalization and for treatment with sotrovimab, an intravenously administered monoclonal antibody that is indicated for the treatment of mild-to-moderate COVID-19 in adult patients who are at high risk for progression to severe COVID-19. Special consideration should also be considered for vulnerable populations that have had poor outcomes to COVID-19, such as those in long-term care and the Indigenous population. Long-term care was the only congregate care

setting prioritized by the panel because of the prevalence of advanced age in this population because age is a significant risk factor for hospitalization and death.

Precautions

Patients with contraindications should not be treated with nirmatrelvir and ritonavir because, according to the Health Canada product monograph, including special populations such as women who are pregnant or breastfeeding and patients with severe hepatic or renal impairment. Precautions should be taken regarding drug-drug interactions for specific drug classes (e.g., HIV protease inhibitors) and for medications metabolized by CYP3A4.

Prescribing Advice

As per the Health Canada product monograph, treatment with nirmatrelvir and ritonavir is to be initiated within 5 days of symptom onset.

The panel affirms that there is a need to confirm the SARS-CoV-2 infection through a diagnostic test; furthermore, there is consensus that the use of either a rapid antigen test, preferably supervised by a health care professional, or a polymerase chain reaction (PCR) test is acceptable.

Nirmatrelvir and ritonavir are indicated for use in an outpatient setting.

Background

An overview of the details for the drug under review is provided in Table 2.

Table 2: Review Details

Item	Description
Drug product	Nirmatrelvir 150 mg and ritonavir 100 mg (Paxlovid); tablets, oral
Indication	Treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death
Health Canada approval status	Authorized: NOC with Terms and Conditions
NOC date	January 17, 2022
Sponsor	Pfizer Canada ULC

NOC = Notice of Compliance; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

COVID-19

Canada has published case report data on 2,098,779 SARS-CoV-2 infections, including 96,451 hospitalizations and 30,104 deaths, since the beginning of the COVID-19 pandemic.[7] Based on the current evidence, hospitalizations and deaths appear to be directly related to age and are more common in patients with comorbidities. There was an age-dependent trend for both hospitalizations (24.3% were ≥ 80 years old, 19.0% were 70 to 79 years old, 17.8% were 60 to 69 years old) and deaths (61.3% were ≥ 80 years old, 21% were 70 to 79 years old, and 10.5% were 60 to 69 years old).[7] During the second wave of the pandemic in Canada, the most common comorbidities in hospitalized patients were hypertension (27.6%), diabetes (15.9%), asthma (7.0%), coronary artery disease (6.0%), chronic lung disease (5.2%), congestive heart failure (3.5%), active cancer (3.2%), and obesity (1.9%).[8]

Throughout the pandemic, various domestic and international groups have examined risk factors for hospitalization and death related to COVID-19. Risk factors for hospitalizations included age and comorbidities (including asthma, cancer, chronic kidney disease, diabetes, hypertension, immunosuppression, intellectual and developmental disability, injection drug use, alcohol use, and schizophrenia and psychotic disorders) as shown in Figure 1.[4] A Canadian study found that significant predictors for mortality included solid organ transplant (hazard ratio [HR] = 3.06; 95% confidence interval [CI], 2.03 to 4.63), dementia (HR = 1.46; 95% CI, 1.35 to 1.58), chronic kidney disease (HR = 1.45; 95% CI, 1.34 to 1.57), severe mental illness (HR = 1.42; 95% CI, 1.12 to 1.80), cardiovascular disease (HR = 1.22; 95% CI, 1.15 to 1.30), diabetes (HR = 1.19; 95% CI, 1.12 to 1.26), chronic obstructive pulmonary disease (HR = 1.19; 95% CI, 1.12 to 1.26), cancer (HR = 1.17; 95% CI, 1.09 to 1.27), and hypertension (HR = 1.16; 95% CI, 1.07 to 1.26).[6] A US study found the strongest risk factors for death were obesity (adjusted risk ratio [aRR] = 1.30; 95% CI, 1.27 to 1.33), anxiety and fear-related disorders (aRR = 1.28; 95% CI, 1.25 to 1.31), and diabetes with complications (aRR = 1.26; 95% CI, 1.24 to 1.28), as well as the total number of conditions, with aRRs of death ranging from 1.53 (95% CI, 1.41 to 1.67) for patients with 1 condition to 2.55 (95% CI, 2.32 to 2.80) for patients with 2 to 5 conditions (compared with patients who had no conditions).[5] Certain populations may also be at increased risk of worse outcomes, including those in long-term care settings[9] and Indigenous populations.[10]

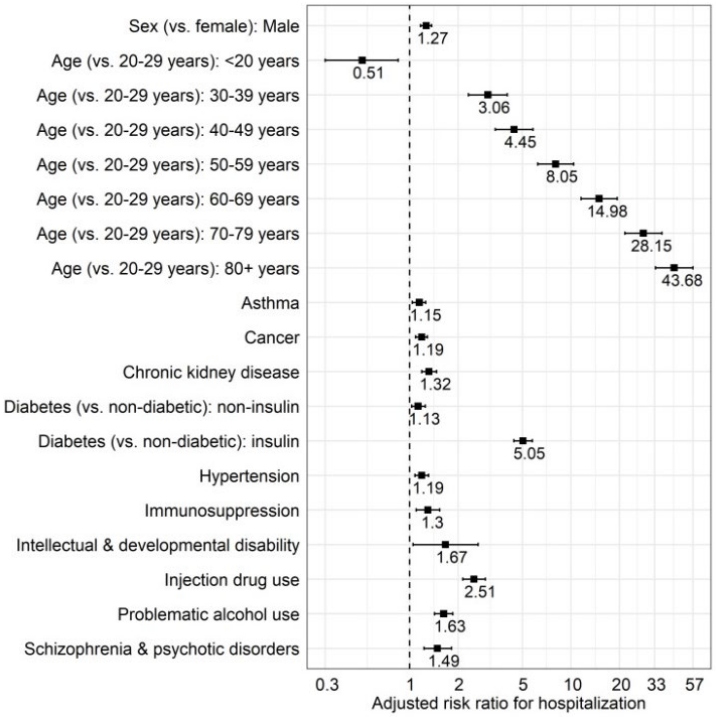
More than 31 million Canadians have had at least 1 dose of vaccine.[11] Despite this, there have been more than 140,000 patients diagnosed with a breakthrough infection while

partially or fully vaccinated (from patients with case-level–reported vaccination status between December 2020 to December 2021).[7] Despite the existence of breakthrough infections, hospitalizations and deaths have been mostly attributed to unvaccinated patients (40,287 [80.1%] and 7,917 [76.0%], respectively) between December 14, 2020 and December 4, 2021.[7] The literature suggests that most breakthrough infections that result in hospitalization or death occurred in patients with advanced age, being immunocompromised, and/or with medical comorbidities (e.g., diabetes, hypertension).[12,13]

As of December 19, 2021, the 2 main SARS-CoV-2 variants of concern in Canada with active cases were Delta (28%) and Omicron (72%), with the Omicron variant as the currently dominant variant.[7] In Ontario, a matched cohort analysis comparing Delta with Omicron variants found that although the Omicron variant was more transmissible, it was associated with 54% lower risk of hospitalization or death compared to the Delta variant.[14] The Omicron variant is believed to have spread in the UK before its emergence in Canada[15]; therefore, monitoring epidemiology data from there may be helpful to understand its impact domestically. In England, there have been 649,834 confirmed, probable, or possible cases of infection with the Omicron variant as of December 29, 2021, and 851 hospitalizations (median age = 45.5 years) and 57 deaths (age range = 41 to 99 years) associated with it.[16]

On December 3, 2021, Public Services and Procurement Canada announced signed agreements for access to a novel protease inhibitor antiviral treatment (1 million courses of nirmatrelvir and ritonavir).[17] In preparation of the regulatory approval, CADTH developed interim procedures to review therapeutics related to drugs for COVID-19 to help identify patient populations that may gain the most benefit from these treatments.[18]

Figure 1: Risk Factors for Hospitalization With COVID-19



Source: Velásquez et al. (2021). Copyright 2021 MDPI. Reprinted in accordance with CC BY 4.0.[4]

Nirmatrelvir and Ritonavir (Paxlovid)

Nirmatrelvir is an orally administered medication for the treatment of COVID-19. It is a peptidomimetic inhibitor of SARS-CoV-2 3C-like (3CL) protease. The use of nirmatrelvir renders the virus incapable of processing polyprotein precursors, thus preventing viral replication.[3] Nirmatrelvir is administered in combination with ritonavir, which is not active against SARS-CoV-2. The role of ritonavir is to inhibit the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir.[3]

The approved indication for nirmatrelvir in combination with ritonavir is for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death. The recommended dosage is 300 mg nirmatrelvir (150 mg tablets × 2) with 100 mg ritonavir (100 mg tablet) with all 3 tablets taken together orally twice daily for 5 days.

The Health Canada product monograph states that the following medical conditions or other factors place patients at high risk for progression to severe COVID-19: older age (i.e., 60 years of age and older), obesity or being overweight (i.e., body mass index > 25 kg/m^2), current smoker, chronic kidney disease, diabetes, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease (including congenital heart disease) or hypertension, chronic lung disease (i.e., chronic obstructive pulmonary disease, asthma [moderate to severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension), sickle cell disease, neurodevelopmental disorders (i.e., cerebral palsy, Down syndrome) or other conditions that confer medical complexity (i.e., genetic or metabolic syndromes and severe congenital anomalies), active cancer, and medical-related technological dependence not related to COVID-19 (i.e., tracheostomy, gastrostomy, or positive pressure ventilation). The product monograph states that other medical conditions or factors (i.e., race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19; however, no further description of these characteristics is reported in the product monograph.[3]

Nirmatrelvir in combination with ritonavir has been authorized for emergency use in the US for mild-to-moderate COVID-19 in adults at high risk for progression to severe disease[19]. The combination of nirmatrelvir and ritonavir has not yet been authorized for use by the European Medicines Agency (EMA), although the agency, under Article 5(3), did endorse use before a formal authorization is issued.[20]

Summary of Evidence

Description of Studies

One manufacturer-sponsored, multicentre, phase II/III, double-blind, randomized controlled trial was the primary source of evidence for the efficacy and safety of nirmatrelvir and ritonavir. The EPIC-HR trial (N = 2,246)[21] evaluated the superiority of the combination of nirmatrelvir and ritonavir compared with placebo for the treatment of adult symptomatic outpatients with mild-to-moderate COVID-19 who were considered at high risk for progression to severe disease and/or hospitalization. Risk factors for disease progression included diabetes, overweight, chronic lung disease including asthma, chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically related technological dependence, or age 60 years or older regardless of comorbidities. Medications were administered at the dosage recommended in the product monograph (300 mg of nirmatrelvir and 100 mg of ritonavir orally twice daily for 5 days). The primary outcome of the EPIC-HR trial was a combined outcome of the proportion of patients with COVID-19–related hospitalization or who died from any cause through day 28 (efficacy assessment). The study's safety follow-up period was through day 34.[21]

Patients were eligible for the trial if they were at least 18 years old with a confirmed SARS-CoV-2 infection and symptom onset within 5 days before randomization. Patients needed to have at least 1 characteristic or underlying medical condition associated with an increased risk of developing severe illness from COVID-19. Patients included in the EPIC-HR trial were not vaccinated against COVID-19 and did not have a prior or current disease episode or any past confirmed SARS-CoV-2 infection. Key exclusion criteria included pregnancy, breastfeeding, oxygen saturation level less than 92%, medical history of active liver disease, moderate-to-severe renal impairment, and use of any medications or substances that are highly dependent on CYP3A4 for clearance or are strong inducers of CYP3A4.[21] Subgroup analyses were reported for some populations of patients, which were stratified by time from symptom onset, baseline demographics, selected comorbidities, baseline antibody status, and baseline viral load.

Overall, 2,246 patients were randomized; of these, 94% of patients completed the safety follow-up period of 34 days at the time of data cut-off (December 11, 2021). The proportions of patients who discontinued the study were similar between treatment groups. The most frequent reason for discontinuation was withdrawal by patient. Baseline characteristics were generally comparable between treatment groups (Table 3). Among patients included in the trial, 87% were between the ages of 18 years and 65 years. Most of the trial population was from the US (41%) or Europe (30%). The most common comorbidities and risk factors for severe illness from COVID-19 included cigarette smoker (39%), obesity (37%), age older than 60 years (22%), hypertension (33%) and diabetes mellitus (12%). Patients in the study were not vaccinated for COVID-19; however, 51% were found to have a positive SARS-CoV-2 baseline antibody status. The primary variant across both treatment arms was Delta (98%), including clades 21J, 21A, and 21I.[3]

The primary analysis was conducted in the modified intent-to treat (mITT) analysis set, consisting of all treated patients with onset of symptoms within the previous 3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment. Secondary analyses were also conducted in the mITT1 analysis set, consisting of all treated patients with onset of symptoms within the previous 5 days who at

baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment, and in the mITT2 analysis set, consisting of all treated patients with onset of symptoms within the previous 5 days.

Table 3: Summary of Baseline Characteristics of Patients in the EPIC-HR Trial

Patient characteristic	Nirmatrelvir and ritonavir (n = 1,120)	Placebo (n = 1,126)
Age (years), mean (SD)	45.3 (15.40)	46.3 (15.51)
Age category (years), n (%)		
18 to 44	556 (49.6)	517 (45.9)
45 to 59	338 (30.2)	349 (31.0)
60 to 64	86 (7.7)	112 (9.9)
65 to 74	104 (9.3)	117 (10.4)
≥ 75	36 (3.2)	31 (2.8)
Sex, n (%)		
Male	566 (50.5)	582 (51.7)
Female	554 (49.5)	544 (48.3)
Geographic location, n (%)		
US	463 (41.3)	465 (41.3)
Europe	334 (29.8)	335 (29.8)
India	95 (8.5)	98 (8.7)
Rest of world	228 (20.4)	228 (20.2)
BMI (kg/m^2), n (%)		
< 25	220 (19.6)	217 (19.3)
25 to < 30	492 (43.9)	489 (43.4)
30 to < 35	276 (24.6)	268 (23.8)
35 to < 40	78 (7.0)	88 (7.8)
≥ 40	53 (4.7)	63 (5.6)
Time since first symptom (days), n (%)		
≤ 3	754 (67.3)	735 (65.3)
> 3	366 (32.7)	391 (34.7)
Comorbidities or risk factors, n (%)		
Cardiovascular disorder	42 (3.8)	50 (4.4)
Chronic kidney disease	6 (0.5)	8 (0.7)
Chronic lung disease	62 (5.5)	41 (3.6)
Cigarette smoker	428 (38.2)	448 (39.8)
Diabetes mellitus	135 (12.1)	138 (12.3)
Hypertension	359 (32.1)	380 (33.7)
Immunosuppression	6 (0.5)	7 (0.6)
Cancer	5 (0.4)	6 (0.5)
Neurodevelopmental disorder	2 (0.2)	1 (<0.1)
Sickle cell disease	0	0
HIV infection	0	1 (<0.1)

Patient characteristic	Nirmatrelvir and ritonavir (n = 1,120)	Placebo (n = 1,126)
Device dependence	4 (0.4)	3 (0.3)
COVID-19 mAb treatment, n (%)		
Received or expected to receive	70 (6.3)	70 (6.2)
Not received or not expected to receive	1,050 (93.8)	1,056 (93.8)
Risk factors of interest, n (%)		
0	2 (0.2)	0
1	449 (40.1)	425 (37.7)
2	393 (35.1)	408 (36.2)
3	183 (16.3)	192 (17.1)
4	77 (6.9)	75 (6.7)
> 4	16 (1.4)	26 (2.3)
SARS-CoV-2 baseline antibody, n (%)		
Positive	581 (51.9)	568 (50.4)
Negative	518 (46.3)	537 (47.7)
Unknown	21 (1.9)	21 (1.9)

BMI = body mass index; mAb = monoclonal antibody; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation.

Source: Topline Results Report.[21]

Efficacy Results

The use of nirmatrelvir in combination with ritonavir was associated with a statistically significant reduction in the incidence of COVID-19–related hospitalization or death from any cause through day 28 compared with placebo (difference from placebo of –5.8%; 95% CI, –7.8 to –3.8; P < 0.0001). Results for the secondary analyses performed in these populations were consistent with those obtained from the primary analysis and are presented in Table 4.[21]

Table 4: Summary of Key Efficacy Outcomes in the EPIC-HR Trial

COVID-19 related hospitalization or death from any cause through day 28	Nirmatrelvir and ritonavir	Placebo
mITT population (primary analysis in the trial)[a]		
Patients contributing to the analysis, n	**697**	**682**
Any events, n (%)	**5 (0.7)**	**44 (6.5)**
Difference from placebo (95% CI);[b]	**–5.8 (–7.8 to –3.8)**	
P value	**< 0.0001**	
Events, n (%)		
Hospitalization	5 (0.7)	44 (6.5)
Death	0	9 (1.3)
mITT1 population (secondary analysis in the trial)[c]		
Patients contributing to the analysis, n	**1,039**	**1,046**
Any events, n (%)	**8 (0.8)**	**66 (6.3)**
Difference from placebo (95% CI);[b]	**–5.6 (–7.2 to –4.0)**	
P value	**< 0.0001**	

COVID-19 related hospitalization or death from any cause through day 28	Nirmatrelvir and ritonavir	Placebo
Events, n (%)		
Hospitalization	8 (0.8)	65 (6.2)
Death	0	12 (1.1)
mITT2 population (secondary analysis in the trial)[d]		
Patients contributing to the analysis, n	**1,109**	**1,115**
Any events, n (%)	**9 (0.8)**	**68 (6.1)**
Difference from placebo (95% CI);[b]	**–5.4 (–6.9 to –3.8)**	
P value	**< 0.0001**	
Events, n (%)		
Hospitalization	9 (0.8)	67 (6.0)
Death	0	12 (1.1)

CI = confidence interval; mITT = modified intention-to-treat.

[a] mITT: all treated patients with onset of symptoms ≤ 3 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment.

[b] The estimated cumulative proportion of participants hospitalized or death by day 28 was calculated for each treatment group using the Kaplan-Meier method, in which patients without hospitalization and death status through day 28 were censored at the time of study discontinuation.

[c] mITT1: all treated patients with onset of symptoms ≤ 5 days who at baseline did not receive nor were expected to receive COVID-19 therapeutic monoclonal antibody treatment.

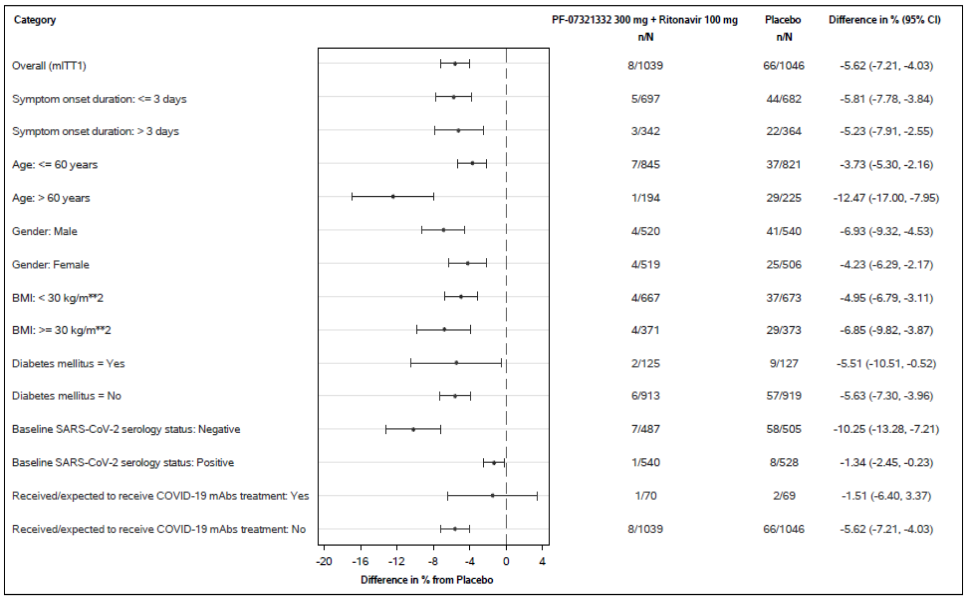
[d] mITT2: all treated patients with onset of symptoms ≤ 5 days.

Source: Topline Results Report.[21]

Selected subgroup analyses were reported in the product monograph for the mITT1 population (all treated patients with onset of symptoms ≤ 5 days and without COVID-19 therapeutic monoclonal antibody treatment) and results are presented in Figure 2. Limited conclusions can be drawn from subgroup analyses because the study was not adequately designed for such analyses.

Results for the analyses performed in these subpopulations were consistent with those obtained from the analyses performed in the overall population; among these are a few subgroups of particular interest of the CADTH review. The results of the subgroup analyses suggest that the magnitude of the difference between groups may be higher in patients older than 60 years of age as well as in patients with a negative baseline SARS-CoV-2 serology status. However, inconclusive results were observed in patients who received or were expected to receive COVID-19 monoclonal antibody treatment because the CI included the null. These results should be interpreted in light of the limitations mentioned previously.

Figure 2: Primary Efficacy Outcomes in the EPIC-HR Trial — Subgroup Results for mITT1 Population Through Day 28



BMI = body mass index; CI = confidence interval; mAb = monoclonal antibody; PF-07321332 = nirmatrelvir; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: All categories are based on mITT1 population except for COVID-19 mAb which is based on mITT2 population.

Source: Product monograph.[3]

Harms Results

A total of 23% of patients experienced adverse events (AEs) throughout the trial duration. The most common AEs reported included dysgeusia, diarrhea, and various investigations. AEs (all grades regardless of causality) in the nirmatrelvir and ritonavir group (≥ 1%) that occurred at a greater frequency (≥ 5 patient difference) than in the placebo group were dysgeusia (6% and < 1%, respectively), diarrhea (3% and 2%), hypertension (1% and < 1%), and myalgia (1% and < 1%).[3] The proportions of patients experiencing serious adverse events (SAEs) were small and were lower with nirmatrelvir and ritonavir than with placebo (2% with active treatment and 7% with placebo). Discontinuations due to AEs were low. No descriptions of the SAEs or the withdrawals due to AEs were reported. There were no deaths in the nirmatrelvir and ritonavir group during the study period whereas 13 patients died in the placebo arm. The causes of death were not individually reported; however, deaths were representative of any cause, not only COVID-19–related causes (patients were at high risk and presented with comorbidities) (Table 5).

Table 5: Summary of Key Harms Outcomes

Harm	Nirmatrelvir and ritonavir (n = 1,109)	Placebo (n = 1,115)
Patients with ≥ 1 AE		
AEs, n (%)	**251 (22.6)**	**266 (23.9)**
Most common events, n (%)		
Dysgeusia	62 (5.6)	3 (0.3)
Diarrhea	34 (3.1)	18 (1.6)
Fibrin D-dimer increased	21 (1.9)	31 (2.8)
Alanine aminotransferase increased	17 (1.5)	27 (2.4)
Headache	15 (1.4)	14 (1.3)
Nausea	16 (1.4)	19 (1.7)
Creatinine renal clearance decreased	16 (1.4)	18 (1.6)
Vomiting	12 (1.1)	9 (0.8)
Patients with ≥ 1 SAE		
SAEs, n (%)	**18 (1.6)**	**74 (6.6)**
Patients who discontinued study drug due to AEs		
WDAEs, n (%)	**23 (2.1)**	**47 (4.2)**
Mortality		
Deaths, n (%)	**0**	**13 (1.2)**

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: Topline Results Report.[21]

Critical Appraisal

Overall, the EPIC-HR trial was methodologically rigorous. Some issues have been identified regarding mainly the generalizability of the findings, especially to the current Canadian setting.

Internal Validity

At the time of the CADTH review, the results available from the EPIC-HR trial were incompletely reported, and only limited subgroup data were available to inform on the optimal use of nirmatrelvir and ritonavir. Therefore, a comprehensive critical appraisal was not possible.

Findings from the trial are based on a relatively small sample size of 2,246 patients, considering the interindividual variations observed in the COVID-19 disease progression and response to treatment as well as the anticipated widespread use of the drug. Detailed calculations for sample size were not reported and it is unclear whether interindividual variability was considered. Although results of the subgroup analyses were generally aligned with those of the total population, the study was not adequately designed for such analyses. The sample size calculation only included subgroups by age analysis (age < 65 years versus ≥ 65 years), serology status, and baseline viral load. Randomization was stratified by geographic region and by treatment with COVID-19 therapeutic monoclonal antibodies, but not by any other relevant interindividual variables. It is also unknown whether testing was adjusted for multiplicity and whether interaction tests were done. Therefore, the true

treatment effect in specific populations remains uncertain. The drug was well-tolerated in the study population with few patients discontinuing the treatment. Exposure and follow-up in larger patient populations may be required to fully characterize the safety profile.

Generalizability

A wide range of interindividual variations have been observed in COVID-19 disease characteristics, disease progression, and response to treatment.[22] These include individual risk factors for disease progressions, rapid apparition of several mutations in coronavirus genotypes (variants), as well as characteristics inherent to the geographical location and to the nature of health care systems in each country. For example, the criteria for hospitalizing patients may vary across health care systems worldwide and hospitalization may be delayed in countries where health care carries an out-of-pocket expense.[23]

Patients included in the EPIC-HR trial were relatively young, 87% being between the ages of 18 years and 65 years. This limits conclusions on the efficacy and safety of nirmatrelvir and ritonavir in an elderly population, which is important given the significant mortality risk in this population.[6] Patients presented with various risk factors for severe illness from COVID-19, as seen in the routine clinical setting. Half of the patients were found to have a positive SARS-CoV-2 baseline antibody status, which raises questions about how such a high level of positivity could occur considering prior infection or vaccination was prohibited and why this seems to be higher than reported in other trials,.[24,25] The primary variant observed in the trial population was Delta; however, the sponsor anticipates that nirmatrelvir and ritonavir will likely have sustained activity against the Omicron variant due to its intracellular mechanism of action that is independent of mutations in the region of the spike protein.[26] No data are available regarding the activity of nirmatrelvir against the SARS-CoV-2 Omicron variant in cell culture; however, an in vitro biochemical assay suggested that the 3CL protease P132H substitution found in the Omicron variant did not reduce nirmatrelvir activity.[3]

Some safety considerations should guide the use of nirmatrelvir and ritonavir, which is associated with CYP3A inhibition, resulting in a number of drug-drug interactions. The combination of nirmatrelvir and ritonavir is also not recommended in patients with severe renal or hepatic impairment.

As a result, the real-world effectiveness of nirmatrelvir and ritonavir in Canadian patients may vary from what was observed in the EPIC-HR study. Important gaps in the available evidence include the lack of data in patients fully vaccinated with an additional booster dose against SARS-CoV-2, clinical data regarding the efficacy of nirmatrelvir and ritonavir against the Omicron variant, comparative data versus monoclonal antibody treatments, and exposure and follow-up data in larger patient populations to fully characterize the safety profile.

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