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SYNOPSIS

Study Title: An Interventional Efficacy and Safety, Phase 2/3, Double-Blind, 2-Arm Study to Investigate Orally Administered PF-07321332/Ritonavir Compared With Placebo in Nonhospitalized Symptomatic Adult Participants With COVID-19 Who are at Low Risk of Progressing to Severe Illness

Study Number: C4671002

Regulatory Agency or Public Disclosure Identifier Number:

EudraCT Number: 2021-002857-28

NCT ID: NCT05011513

Study Phase: 2/3

Name of Study Intervention: PF-07321332 (nirmatrelvir)

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: Final CSR (Last Participant Last Visit) Version 1.0; 09 March 2023

Number of Study Center(s) and Investigator(s):

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications: None

Study Period:

Study initiation date (First Participant First Visit): 25 August 2021

Last Participant Last Visit: 25 July 2022

This study was terminated early.

Rationale:

The purpose of this Phase 2/3 double-blind, 2-arm, interventional study was to evaluate the efficacy, safety, and tolerability of nirmatrelvir/ritonavir for the treatment of nonhospitalized, symptomatic, adult participants with coronavirus disease 2019 (COVID-19) who are at low risk of progression to severe illness.

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Objectives, Endpoints, and Statistical Methods:

Table S1. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
Primary			
Efficacy	To compare the efficacy of nirmatrelvir/ritonavir to placebo for the treatment of symptomatic COVID-19 in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.	• Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.	The difference in median time (days) to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28 between nirmatrelvir/ritonavir and placebo in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease at baseline and were treated ≤5 days after COVID-19 symptom onset. This was estimated irrespective of adherence to randomized treatment.
Secondary			
Safety	To describe the safety and tolerability of nirmatrelvir/ritonavir relative to placebo in the treatment of nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progression to severe disease.	• Incidence of treatment-emergent adverse events (TEAEs). • Incidence of serious adverse events (SAEs) and adverse events (AEs) leading to discontinuations.	Not Applicable.
Efficacy	To compare nirmatrelvir/ritonavir versus placebo for COVID-19 related hospitalization and all-cause mortality in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.	• Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28. • Proportion of participants with death (all cause) through Week 24.	• The difference in proportion of patients experiencing COVID-19 related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease and were treated ≤5 days after COVID-19 symptom onset. This was estimated without regard to adherence to randomized treatment. • Not Applicable.

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Table S1. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
Efficacy	To compare nirmatrelvir/ritonavir versus placebo for COVID-19 related medical visits in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease	• Number of COVID-19 related medical visits through Day 28.	• The difference in the estimated rate of the number of COVID-19-related medical visits through Day 28 in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease and were treated ≤5 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.
		• Number of days in hospital and intensive care unit (ICU) stay in participants with COVID-19-related hospitalization through Day 28.	• The difference in the estimated rate of number of days in hospital and ICU stay in patients with COVID-19-related hospitalization through Day 28 in nonhospitalized adult patients with COVID-19 who are at low risk of progression to severe disease and were treated ≤5 days after COVID-19 symptom onset. This will be estimated without regard to adherence to randomized treatment.

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Table S1. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
Efficacy	To compare nirmatrelvir/ritonavir to placebo for the duration and severity of signs and symptoms in nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progression to severe disease.	• Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28. • Time (days) to sustained resolution of all targeted COVID-19 signs/symptom through Day 28. • Duration of each targeted COVID-19 sign/symptom. • Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28. • Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	Not Applicable.
PK	To determine the pharmacokinetics (PK) of nirmatrelvir in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.	Nirmatrelvir PK in plasma and whole blood (if feasible).	Not Applicable.
Efficacy	To describe the viral load in nasal samples over time in nonhospitalized adult participants with COVID-19 who are at low risk of progression to severe disease.	Viral titers measured via reverse transcription polymerase chain reaction (RT-PCR) in nasal swabs over time.	Not Applicable.

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Table S2. Summary of Efficacy Analyses (Modified Intention-to-Treat 1 [mITT1])

Endpoint	Analysis Type	Analysis Model
Time (days) to sustained alleviation of all targeted COVID-19 signs/symptoms through Day 28.	Primary Efficacy Analysis	Kaplan-Meier & Log rank test
Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28.	Key secondary analysis	Kaplan-Meier method
Proportion of participants with death (all cause) through Week 24.	Secondary analysis	Logistic Regression
Number of COVID-19-related medical visits through Day 28.	Secondary analysis	Descriptive statistics (based on negative Binomial Model)
Number of days in hospital and ICU stay in participants with COVID-19-related hospitalization through Day 28.	Secondary analysis	Descriptive statistics
Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28.[a]	Secondary Efficacy Analysis	Logistic regression model
Time (days) to sustained resolution of all targeted COVID-19 signs/symptom through Day 28.	Secondary analysis	Kaplan-Meier & Log rank test
Duration of each targeted COVID-19 sign/symptom.	Secondary analysis	Kaplan-Meier estimate, Descriptive statistics (median, quartiles)
Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28.[b]	Secondary analysis	Logistic regression model
Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	Secondary analysis	Breslow-Day test for Homogeneity of the Odds Ratios
Viral titers measured via RT-PCR in nasal swabs over time.	Secondary analysis	Mixed model for repeated measures analysis

a. Definition for severity of signs and symptoms included case report form (CRF) data (hospitalization due to COVID-19 and death of any cause) that was considered as having severe signs and symptoms.
b. Definition for worsening of signs and symptoms was expanded to include hospitalization due to COVID-19 and death of any cause based on CRF data. Participants with hospitalization due to COVID-19 and death of any cause were considered as having worsening of signs and symptoms.

Table S3. Analysis Sets

Population	Description
Full analysis set (FAS)	All participants randomly assigned to study intervention regardless of whether or not study intervention was administered.
Safety analysis set (SAS)	All participants who received at least 1 dose of study intervention. Participants were analyzed according to the intervention they actually received. A randomized but not treated participant was excluded from the safety analyses.
Modified intention-to-treat (mITT)	All participants randomly assigned to study intervention who took at least 1 dose of study intervention and with at least 1 postbaseline visit through Day 28 who were treated ≤3 days after COVID-19 symptom onset. Participants were analyzed according to the study intervention to which they were randomized.
mITT1	All participants randomly assigned to study intervention, who took at least 1 dose of study intervention. Participants were analyzed according to the study intervention they were randomized.
Per protocol (PP)	All participants in the mITT1 set without important protocol deviations considered to impact the interpretation of the primary efficacy endpoint. Protocol deviations were reviewed to generate the list of participants with significant deviations to be excluded from the PP analysis set. The PP exclusion criteria were finalized prior to breaking the blind.

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Methodology:

This Phase 2/3, randomized, double-blind, placebo-controlled study in nonhospitalized symptomatic adult participants with COVID-19 who are at low risk of progressing to severe illness evaluated the efficacy, safety, and tolerability of nirmatrelvir/ritonavir compared with placebo. Eligible participants with a confirmed diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were randomized (1:1) to receive nirmatrelvir/ritonavir or placebo orally every 12 hours (q12h) for 5 days (10 doses total). Randomization was stratified by geographic region, by vaccination status, and by COVID-19 symptom onset (≤3 days vs >3 to 5 days).

Due to a very low rate of hospitalization or death observed in the standard-risk patient population, the decision was made to cease enrollment and terminate the study as of 15 June 2022. An interim clinical study report (CSR) presented the results of participants enrolled through Protocol Amendment 4 who completed the Day 34 assessments (data cutoff 19 December 2021).

This final (last participant last visit [LPLV]) CSR presents all data as of LPLV.

Number of Participants (planned and analyzed):

Approximately 1980 participants were to be randomly assigned to study intervention. Based on the 4 site exclusions: 1288 participants were assigned to treatment. The number of participants analyzed per analysis population was: FAS, 1296; SAS, 1288; mITT1, 1288; mITT, 929; and PP analysis set, 1218.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Nonhospitalized, symptomatic adult participants with COVID-19 who were at low risk of progression to severe illness were enrolled in this study.

Participants ≥18 years of age (or the minimum country specific age of consent if >18) at the time of the Screening Visit with a confirmed SARS-CoV-2 infection as determined by RT-PCR in any specimen collected within 5 days prior to randomization and initial onset of signs/symptoms attributable to COVID-19 within 5 days prior to the day of randomization and at least 1 of the specified signs/symptoms attributable to COVID-19 present on the day of randomization were enrolled in this study.

Eligibility criteria for vaccination status changed based on regulatory feedback and eligibility to receive Paxlovid™.

- Prior to Protocol Amendment 5 (21 January 2022), participants with underlying medical conditions associated with an increased risk of developing severe illness from COVID-19 and who were fully vaccinated and met the other eligibility criteria were eligible to participate in the study.

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- Participants without underlying medical conditions associated with an increased risk of developing severe illness from COVID-19 and were either not vaccinated (before Protocol Amendment 5) or were vaccinated more than 12 months before screening (for participants enrolled under Protocol Amendment 5 [21 January 2022]) and met the other eligibility criteria were permitted to participate in the study.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

Participants were randomly assigned to 1 of 2 treatment groups in the study:

- Two tablets of nirmatrelvir 150 mg and 1 capsule of ritonavir 100 mg every 12 hours (q12h) orally (PO) for 5 days.

- Two tablets of placebo for nirmatrelvir and 1 capsule of placebo for ritonavir q12h PO for 5 days

Participants in either treatment group were permitted to receive standard of care (SoC) therapy so long as it was not prohibited.

Table S4. Investigational Product Description, Vendor Lot Number, Pfizer Lot Number, Strength/Potency, and Dosage Form

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
PF-07321332 150 mg Tablet (Croscarmellose Sodium)	FG9946	21-DP-00680	150 mg	TABLET
PF-07321332 150 mg Tablet (Croscarmellose Sodium)	Not applicable	21-DP-00651	150 mg	TABLET
Placebo for PF-07321332 Tablet (Pink Oval)	Not applicable	21-DP-00601	0 mg	TABLET
Placebo for PF-07321332 Tablet (Pink Oval)	Not applicable	21-DP-00720	0 mg	TABLET
Placebo for Ritonavir 100 mg Size AAA Swedish Orange Capsule	74132.1	21-DP-00588	0 mg	CAPSULE
Placebo for Ritonavir 100 mg Size AAA Swedish Orange Capsule	74132.3	21-DP-00682	0 mg	CAPSULE
Placebo for Ritonavir 100 mg Size AAA Swedish Orange Capsule	74132.7	21-DP-00726	0 mg	CAPSULE
Ritonavir 100 mg Size AAA Swedish Orange Capsule	74132.13	21-DP-00825	100 mg	CAPSULE
Ritonavir 100 mg Size AAA Swedish Orange Capsule	74132.2	21-DP-00591	100 mg	CAPSULE
Ritonavir 100 mg Size AAA Swedish Orange Capsule	74132.4	21-DP-00681	100 mg	CAPSULE

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Duration of Study Intervention:

The planned treatment duration was 5 days (10 doses total).

Summary of Results:

Demographic and Other Baseline Characteristics:

Demographic characteristics for the mITT1 analysis set were similar between the nirmatrelvir/ritonavir and placebo groups.

- Over half of participants were female and the majority were White. Approximately 41% of participants were Hispanic or Latino.

- The median age was 41.00 (18.00, 87.00) years and nearly 90% of participants were under 60 years of age at the time of randomization. The mean (standard deviation [SD]) body mass index (BMI) was 26.26 (5.15) kg/m^2, and approximately 49% of participants had a BMI $\geq$25 kg/m^2 at the time of screening.

Baseline characteristics were balanced between both treatment groups.

Exposure:

The mean duration of treatment was similar across treatment groups. Overall, most participants received study intervention for at least 5 calendar days. Participants receiving only 1 dose of treatment on Day 1 were expected to receive the last dose on Day 6 if the treatment was completed.

Efficacy Results:

Primary Efficacy Endpoint Results

The primary analysis result was not statistically significant and the primary objective of the study was not met. Treatment with nirmatrelvir/ritonavir reduced the median time to sustained alleviation of all targeted signs and symptoms through Day 28 by 1 day in the mITT1 analysis set who received treatment within 5 days of symptom onset, but the difference was not statistically significant (p=0.6027) as assessed by the log rank test (ie, no covariate adjustment).

Secondary Efficacy Endpoint Results

All further analyses used nominal p-values for reporting.

- The observed event rate of COVID-19-related hospitalization or death from any cause through Day 28 in the mITT1 analysis set was 10 of 634 (1.577%) participants in the placebo group, and 5 of 654 (0.765%) in the nirmatrelvir/ritonavir group. After accounting for premature study discontinuation (ie, to include participants discontinued from the study before Day 28 without having experienced an event) by using the

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follow-up time in the Kaplan-Meier calculation, treatment with nirmatrelvir/ritonavir showed a -0.813% (95% confidence interval [CI]: -1.999 to 0.374; p=0.1796) absolute reduction (51.215% relative risk reduction), reducing the event rate from 1.587% to 0.774%. Through Day 28, there was 1 death in the placebo group and 0 deaths in the nirmatrelvir/ritonavir group.

  - In the post hoc subgroup analysis by risk status at baseline, the risk reduction was more apparent in the subgroup of participants who were considered as high risk (ie, vaccinated with at least 1 risk factor) than in participants who were considered as standard risk (ie, participants who did not have risk factors and were either vaccinated or not vaccinated).

- In the mITT1 analysis set, there was 1 death in the placebo group (Day 6) and none in the nirmatrelvir/ritonavir group through Week 24.

- Compared with the nirmatrelvir/ritonavir group (15 participants), more participants in the placebo group (25 participants) had COVID-19-related medical visits and reported more visits (nirmatrelvir/ritonavir: 24 visits; placebo: 36 visits). After adjusting for geographic region, symptom onset duration, baseline SARS-CoV-2 serology status, vaccination status, and baseline viral load, the COVID-19-related medical visits occurred less frequently in the nirmatrelvir/ritonavir group at 50.2% of the rate in the placebo group, but the difference was not significant (p=0.0971).

- Including participants with and without hospitalizations, the nirmatrelvir/ritonavir group reported fewer days in the hospital than in the placebo group: mean (SD) 0.049 (0.591) days for nirmatrelvir/ritonavir and 0.181 (1.787) days for placebo. Similar results were observed for non-ICU visit. No participants in the nirmatrelvir/ritonavir group reported any ICU visits. For the 3 participants in the placebo group with an ICU visit, the duration of hospitalization ranged from 10 days to 21 days.

- Over the study period from Day 1 through Day 28, the proportion of participants with severe signs and symptoms was lower in the nirmatrelvir/ritonavir group (19.136%) compared with the placebo group (21.643%) (p=0.1622). Similar findings were observed at baseline (Day 1) and during treatment (Days 2 to 6), but the difference was not significant (p=0.2494 and p=0.0783, respectively). However, after treatment and during the follow-up period (Day 7 to Day 28), the proportion of participants with severe signs and symptoms was lower in the nirmatrelvir/ritonavir group compared with placebo (p=0.0280).

- Treatment with nirmatrelvir/ritonavir reduced the median time to sustained resolution of all targeted COVID-19-related signs and symptoms through Day 28 by 1 day compared with placebo (15 days vs 16 days, respectively), but the mean difference was not significant (15.598 days vs 16.285 days, respectively; p=0.4298).

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- Reductions in the median time to sustained alleviation and sustained resolution of each targeted COVID-19 sign and symptom were observed with nirmatrelvir/ritonavir treatment compared with placebo by 2 days for stuffy or runny nose and 1 day for shortness of breath or difficulty breathing; cough; feeling hot or feverish; and sore throat (sustained alleviation) and by 2 days for headache and sore throat and by 1 day for muscle or body aches; shortness of breath or difficulty breathing; chills or shivering; cough; feeling hot or feverish; and stuffy or runny nose (sustained resolution).

- Participants in the nirmatrelvir/ritonavir group were less likely to progress to a worsening status (ie, increased severity for any targeted symptom) through Day 28 compared with the placebo group, but the treatment difference was not significant (odds ratio versus placebo 0.802, p=0.1086).

- Among participants with resting peripheral oxygen saturation ≥95% at baseline (Day 1), twice as many participants in the placebo group than in the nirmatrelvir group had an oxygen saturation <95% (12 vs 6 participants, respectively). Participants who had a resting peripheral oxygen saturation ≥95% at baseline (Day 1) were more likely to maintain those levels at Day 5 than those with a resting peripheral oxygen saturation <95% at baseline, but the treatment difference was not significant (p=0.3262).

- On-treatment reduction in viral load (ie, change from baseline in viral load ribonucleic acid [RNA] concentration) was significantly (p<0.0001) larger in the nirmatrelvir/ritonavir treatment group than in the placebo group.

    - Mean baseline (Day 1) (SD) $\log_{10}$ viral load was 6.045 (1.862) $\log_{10}$ copies/mL in the placebo group and 6.214 (1.794) $\log_{10}$ copies/mL in the nirmatrelvir/ritonavir group. After accounting for treatment, geographic region, baseline SARS-CoV-2 serology status, symptom onset duration, vaccination status, and baseline viral load, the change from baseline to Day 5 adjusted mean (standard error [SE]) reduction in $\log_{10}$ viral load was -2.551 (0.088) $\log_{10}$ copies/mL in the placebo group and -3.419 (0.084) $\log_{10}$ copies/mL in the nirmatrelvir/ritonavir group, reflecting an additional average reduction (95% CI) of -0.868 (-1.073 to -0.663), p<0.0001) $\log_{10}$ copies/mL

    - Among participants with detectable viral load at baseline (545 for nirmatrelvir/ritonavir; 517 for placebo), overall reductions in viral load over time (ie, change from baseline in viral RNA concentration through Day 14) occurred more rapidly in the nirmatrelvir/ritonavir group than in the placebo group with the difference between both groups most apparent at Day 5: Least squares mean difference (SE) $\log_{10}$ copies/mL: -0.736 (0.120) at Day 3; -0.834 (0.106) at Day 5; -0.231 (0.100) at Day 10; and -0.215 (0.077) at Day 14.

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Safety Results:

- The proportion of participants with all-causality TEAEs that started on or prior to the Day 34 visit was comparable between the nirmatrelvir/ritonavir (25.8%) and placebo (24.1%) groups.

- Most of the all-causality TEAEs experienced by participants in both treatment groups were mild (Grade 1) to moderate (Grade 2) in severity. The proportion of participants with all-causality severe (Grade 3) or potentially life threatening (Grade 4) TEAEs was comparable between the nirmatrelvir/ritonavir (3.7%) and placebo (3.9%) groups.

- Of the most frequently reported all-causality TEAEs (≥1%), the following were reported at a higher frequency (≥3 participant difference) in the nirmatrelvir/ritonavir group compared with the placebo group: Dysgeusia (6.7% vs 0.5%%, respectively), Diarrhoea (4.0% vs 3.0%, respectively), Dyspepsia (1.2% vs 0.3%, respectively), Nausea (3.1% vs 2.7%, respectively), Alanine aminotransferase (ALT) increased (2.1% vs 1.3%, respectively), and Aspartate aminotransferase (AST) increased (1.4% vs 0.6%, respectively).

    - In the nirmatrelvir/ritonavir group, these TEAEs were nonserious and mostly mild (Grade 1) or moderate (Grade 2) in severity.

    - Of these TEAEs, discontinuation of nirmatrelvir/ritonavir occurred in 3 participants for Dysgeusia, 2 participants each for Diarrhoea and Dyspepsia, and 1 participant for Nausea.

- The proportion of participants with all-causality treatment-emergent SAEs was low and comparable between the nirmatrelvir/ritonavir (1.2%) and placebo (1.9%) groups. The most frequently reported all-causality SAEs (≥2 participants) in the nirmatrelvir/ritonavir and placebo groups were COVID-19 pneumonia (0.5% and 1.3%, respectively) and Pneumonia (0.2% and 0.3%, respectively). No SAEs were considered treatment-related by the investigator.

- Hemodynamic and inflammatory adverse events of special interest (AESIs) reported at a greater frequency (≥2 participant difference) in the nirmatrelvir/ritonavir group compared with the placebo group were: Syncope (3 [0.5%] vs 0 participants, respectively), Hypotension (2 [0.3%] vs 0 participants, respectively), and Prothrombin time prolonged (3 [0.5%] vs 1 [0.2%] participants, respectively). No thyroid-related AESIs were reported at a greater frequency (≥2 participant difference) in the nirmatrelvir/ritonavir group compared with the placebo group. AESIs reported at a greater frequency (≥2 participant difference) in the placebo group compared with the nirmatrelvir/ritonavir group were: Tachycardia (3 [0.5%] vs 1 [0.2%] participants, respectively), Activated partial thromboplastin time prolonged (12 [1.9%] vs 7 [1.1%] participants, respectively), and Blood thyroid stimulating hormone increased (7 [1.1%] vs 3 [0.5%] participants, respectively).

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- In the nirmatrelvir/ritonavir group, 16 (2.4%) participants discontinued study intervention due to at least 1 AE and continued the study compared with 5 (0.8%) participants in the placebo group. Of the 21 participants who discontinued study intervention in both groups, 13 participants had at least 1 TEAE that was considered by the investigator to be related to study intervention.

- No participants in the nirmatrelvir/ritonavir group experienced an AE resulting in death (Grade 5), compared to 1 participant in the placebo group who experienced an SAE of COVID-19 pneumonia that resulted in death.

- No clinically meaningful differences were observed between the nirmatrelvir/ritonavir and placebo groups with respect to hematology and clinical chemistry laboratory test results.

- One participant in the nirmatrelvir/ritonavir group met laboratory criteria as a potential Hy's Law case at baseline; however, this was not a case of drug-induced liver injury because the liver laboratory abnormalities occurred prior to exposure of study intervention. The participant completed study intervention and no longer met the protocol definition of potential Hy's law by Day 7; liver laboratory values improved over time with ALT and AST returning to normal levels by Day 37.

- No clinically meaningful findings in vital sign measurements were observed in this study. The incidence of participants with diastolic blood pressure >90 mmHg or systolic blood pressure >140 mmHg was comparable between the nirmatrelvir/ritonavir (9.1% and 9.6%, respectively) and placebo (11.6% and 11.0%, respectively) groups.

Pharmacokinetic Results:

Geometric mean (coefficient of variation % [CV%]) nirmatrelvir concentrations, representative of maximum observed concentration (C_{max}) on Day 1 (30 to 90 minutes postdose) and predose concentration (C_{trough}) on Day 5 (preferably up to 2 hours predose) were 1521 (74%) ng/mL and 2566 (71%) ng/mL, respectively.

Conclusions:

- The primary analysis result was not statistically significant and the primary objective of the study was not met. Treatment with nirmatrelvir/ritonavir reduced the median time to sustained alleviation of all targeted signs and symptoms through Day 28, but the difference was not statistically significant.

- Treatment with nirmatrelvir/ritonavir reduced the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 compared with placebo; the event rate was reduced from 1.587% to 0.774% with a -0.813% absolute reduction or a 51.215% relative reduction. There was 1 death in the placebo group and none in the nirmatrelvir/ritonavir group.

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- COVID-19-related medical visits were less frequent in the nirmatrelvir/ritonavir group than in the placebo group, but the difference was not statistically significant. The nirmatrelvir/ritonavir group reported fewer days in the hospital compared with the placebo group. No participants in the nirmatrelvir/ritonavir group reported any ICU visits compared with the 3 participants in the placebo group.

- Treatment with nirmatrelvir/ritonavir showed consistent improvements in COVID-19-related signs and symptoms compared with placebo, although not all mean differences were statistically significant.

- Participants in the nirmatrelvir/ritonavir group were less likely to progress to a worsening status (ie, increasing severity for any targeted symptom) through Day 28 compared with the placebo group, but the treatment difference was not statistically significant.

- Participants who had a resting peripheral oxygen saturation ≥95% at baseline (Day 1) were more likely to maintain those levels at Day 5 than those with a resting peripheral oxygen saturation <95% at baseline, but the treatment difference was not statistically significant.

- The antiviral effect of nirmatrelvir/ritonavir was demonstrated by a significant reduction of SARS-CoV-2 viral load compared with placebo at Day 5.

- The geometric mean trough concentration of nirmatrelvir on Day 5 was consistent with the predicted concentrations via a population PK model and were similar to exposures (C_{trough}) associated with the administration of nirmatrelvir/ritonavir 300 mg/100 mg.

- Treatment with nirmatrelvir/ritonavir was safe and well tolerated.

    - The incidence of all-causality TEAEs was comparable for both treatment groups. Most all-causality TEAEs in both treatment groups were mild (Grade 1) to moderate (Grade 2) in severity. The proportion of participants with all-causality severe (Grade 3) or potentially life-threatening (Grade 4) TEAEs was comparable between treatment groups.

    - The proportion of participants with all-causality treatment-emergent SAEs was low and comparable between treatment groups.

    - No participants in the nirmatrelvir/ritonavir group discontinued the study due to an all-causality AE compared with 1 participant in the placebo group. In total, 16 (2.4%) participants in the nirmatrelvir/ritonavir group discontinued study intervention due to at least 1 AE and continued the study compared with 5 (0.8%) participants in the placebo group.

    - The incidence of participants with hemodynamic, inflammatory, or thyroid-related AESIs was comparable between treatment groups, except for Syncope, Hypotension,

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and Prothrombin time prolonged which occurred at a greater frequency in the nirmatrelvir/ritonavir group; and Tachycardia, Activated partial thromboplastin time prolonged, and Blood thyroid stimulating hormone increased which occurred at a greater frequency in the placebo group.

- Treatment with nirmatrelvir/ritonavir was not associated with clinically meaningful changes in laboratory values or vital signs.
    - One participant in the nirmatrelvir/ritonavir group met laboratory criteria as a potential Hy's law case at baseline, which was not a drug-induced liver injury since the laboratory abnormalities occurred prior to exposure of study intervention; liver laboratory values improved over time with ALT and AST returning to normal levels by Day 37.