CLINICAL STUDY REPORT SYNOPSIS

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 Increased Risk of Progressing to Severe Illness

Study Number: C4671005

Regulatory Agency or Public Disclosure Identifier Number:

EudraCT Number: 2021-002895-38

ClinicalTrials.gov ID: NCT04960202

Study Phase: 2/3

Name of Study Intervention: PF-07321332 (nirmatrelvir)

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date:

Final CSR (Amendment to 06 June 2022), 08 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:

Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med. 2022;386(15):1397-1408.

Study Period:

Study Initiation Date (First Participant First Visit): 16 July 2021

Primary Completion Date: 09 December 2021

Study Completion (Last Participant Last Visit) Date: 26 April 2022

This study was neither discontinued nor interrupted.

CLINICAL STUDY REPORT SYNOPSIS

Rationale:

The purpose of this Phase 2/3 double-blind, 2-arm, interventional study was to evaluate the efficacy and safety of PF-07321332 (also referred to as *nirmatrelvir*)/ritonavir for the treatment of nonhospitalized, symptomatic adult participants with coronavirus disease 2019 (COVID-19) who are at increased risk of progressing to severe illness.

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 COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease, who did not receive COVID-19 therapeutic monoclonal antibody (mAb) treatment and were treated ≤3 days after COVID-19 symptom onset. This will be estimated without regard to 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 increased 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 the efficacy of nirmatrelvir/ritonavir to placebo for the treatment of COVID-19 in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	• Proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28.	The difference in proportions of patients experiencing COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized adult patients with symptomatic COVID-19 who are at increased risk of progression to severe disease and who did not receive COVID-19 therapeutic mAb treatment. This will be estimated without regard to adherence to randomized treatment.
Efficacy	To compare nirmatrelvir/ritonavir to placebo for the duration and severity of signs and symptoms in nonhospitalized	• Time (days) to sustained alleviation of all targeted signs/symptoms through Day 28.	The absolute difference in median time to sustained alleviation or resolution of symptoms for all nonhospitalized adult patients with COVID-19 who are at increased

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
	symptomatic adult participants with COVID-19 who are at increased 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 signs/symptoms 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.	risk of progression to severe disease. This will be estimated irrespective of adherence to randomized treatment.
Efficacy	To compare nirmatrelvir/ritonavir to placebo for all-cause mortality in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	Proportion of participants with death (all cause) through Week 24.	Not applicable.
Pharmacokinetics	To determine the pharmacokinetics (PK) of nirmatrelvir in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	PF-07321332 PK in plasma and whole blood (if feasible).	Not applicable.
Efficacy	To describe the viral load in nasal samples over time in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	Viral titers measured via reverse transcription polymerase chain reaction (RT-PCR) in nasal swabs over time.	Not applicable.
Efficacy	To compare PF-07321332/ritonavir to placebo for COVID-19-related medical visits in nonhospitalized symptomatic adult participants with COVID-19 who are at	Number of COVID-19 related medical visits through Day 28.	Not applicable.

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
	increased risk of progression to severe disease.		
Efficacy	To compare nirmatrelvir/ritonavir to placebo for COVID-19-related hospitalizations in nonhospitalized symptomatic adult participants with COVID-19 who are at increased risk of progression to severe disease.	Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization.	

Table S2. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Analysis Model
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Primary Efficacy analysis	mITT	Kaplan-Meier method
Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28.	Key secondary analysis	mITT1	Kaplan-Meier method
Time to sustained alleviation of all targeted signs/symptoms through Day 28.	Secondary analysis	mITT mITT1 mITT2	Cox proportional hazard model
Time to sustained resolution of all targeted signs/symptoms through Day 28.	Secondary analysis	mITT mITT1 mITT2	Cox proportional hazard model
Proportion of participants with severe signs/symptoms attributed to COVID-19 through Day 28.	Secondary analysis	mITT mITT1 mITT2	Logistic regression
Duration of each targeted COVID-19 sign/symptom.	Secondary analysis	mITT mITT1 mITT2	Descriptive statistics
Progression to a worsening status in 1 or more self-reported COVID-19-associated symptoms through Day 28.	Secondary analysis	mITT mITT1 mITT2	Logistic regression
Proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5.	Secondary analysis	mITT mITT1 mITT2	Breslow-Day test for Homogeneity of the Odds Ratios

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Analysis Model
Proportion of participants with death (all cause) through Week 24.	Secondary analysis	mITT mITT1 mITT2	Logistic regression or Fisher Exact test (if appropriate)
Viral titers measured via RT-PCR in nasal swabs over time.	Secondary analysis	mITT mITT1 mITT2	MMRM analysis
Number of COVID-19 related medical visits through Day 28.	Secondary analysis	mITT mITT1 mITT2	Descriptive statistics (based on negative Binomial Distribution)
Number of days in hospital and ICU stay in participants with COVID-19 related hospitalization.	Secondary analysis	mITT mITT1 mITT2	Descriptive statistics

mITT: All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment and were treated ≤3 days of COVID-19 onset.
mITT1: All participants randomly assigned to study intervention, who took at least 1 dose of study intervention, and who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment.
mITT2: All participants randomly assigned to study intervention, who took at least 1 dose of study intervention.

Methodology:

This Phase 2/3, randomized, double-blind, placebo-controlled study in nonhospitalized, symptomatic adult participants with COVID-19 at increased risk of progressing to severe illness determined the efficacy, safety, and tolerability of nirmatrelvir/ritonavir compared with placebo. Eligible participants with a confirmed diagnosis of SARS-CoV-2 infection were randomized (1:1) to receive nirmatrelvir/ritonavir or placebo orally q12h for 5 days (10 doses total). Randomization was stratified by geographic region and whether participants had received/were expected to receive COVID-19 therapeutic mAb treatment (yes/no) based on the site investigator's assessment at the time of randomization. The total study duration is up to 24 weeks.

An interim CSR was prepared separately to present the results of a planned interim analysis that was conducted after approximately 45% of participants in the mITT analysis set completed the Day 28 assessments and included participants randomized through 29 September 2021 (data cutoff 26 October 2021).The previous final CSR, dated 05 January 2022, included data up to the primary completion date (PCD) of 09 December 2021 (data cutoff 11 December 2021) and was generated to present the results of the primary analysis of all enrolled participants who completed the Day 34 visit. This final CSR includes all data as of last participant last visit (LPLV).

CLINICAL STUDY REPORT SYNOPSIS

Number of Participants (planned and analyzed):

Approximately 3000 participants were to be randomly assigned to study intervention. A total of 2246 participants were randomized to study intervention. The number of participants analyzed per analysis population was: Full Analysis Set (FAS: all participants randomly assigned to study intervention regardless of whether or not study intervention was administered), 2246; Safety Analysis Set (all participants who received at least 1 dose of study intervention), 2224; mITT, 1379; mITT1, 2085; and mITT2, 2224; Per-protocol set, 1319.

Based on the exclusion of 2 sites from the reanalyses, 2113 participants were randomized to study intervention. The number of participants analyzed per analysis population was: Full Analysis Set (FAS: all participants randomly assigned to study intervention regardless of whether or not study intervention was administered), 2113; Safety Analysis Set (all participants who received at least 1 dose of study intervention), 2091; mITT, 1318; mITT1, 1966; and mITT2, 2091; Per-protocol set, 1262.

Diagnosis and Main Criteria for Inclusion and Exclusion:

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

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

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

- Nirmatrelvir 300 mg (ie, 2 tablets of 150 mg, or 3 tablets of 100 mg for participants in the sentinel cohort]) and ritonavir 100 mg (ie, 1 capsule of 100 mg) every 12 hours (q12h) by mouth (PO) for 5 days.
- Placebo for nirmatrelvir (2 tablets [3 tablets for the sentinel cohort]) and placebo for ritonavir (1 capsule) q12h PO for 5 days.

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

CLINICAL STUDY REPORT SYNOPSIS

Table S3. Investigational Product Description, Vendor Lot Number, Pfizer Lot Number, Strength/Potency and Dosage Form

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/ Potency	Dosage Form
PF-07321332 100 mg Tablet (10 mm Round)	PA2103562OTH	21-DP-00508	100 mg	TABLET
PF-07321332 150 mg Tablet (Croscarmellose Sodium)	FG9131	21-DP-00654	150 mg	TABLET
PF-07321332 150 mg Tablet (Croscarmellose Sodium)	N/A	21-DP-00625	150 mg	TABLET
PF-07321332 150 mg Tablet (Croscarmellose Sodium)	N/A	21-DP-00651	150 mg	TABLET
Placebo for PF-07321332 Tablet (10 mm Round)	PA2103560OTH	21-DP-00507	0 mg	TABLET
Placebo for PF-07321332 Tablet (Pink Oval)	N/A	21-DP-00601	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	N/A	21-DP-00560	0 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
Ritonavir 100 mg Size AAA Swedish Orange Capsule	N/A	21-DP-00561	100 mg	CAPSULE

Duration of Study Intervention:

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

Summary of Results:

Demographic and Other Baseline Characteristics:

Demographic and baseline characteristics for the FAS were similar between the nirmatrelvir/ritonavir and placebo groups.

- The proportion of male and female participants was balanced and the majority were White (70.8%). Approximately 41% of the participants in each treatment group were Hispanic or Latino. The median (range) age was 45.00 (18.0, 88.0) years and

CLINICAL STUDY REPORT SYNOPSIS

263 (12.4%) participants were 65 years of age or greater at the time of randomization. The mean (SD) body mass index (BMI) was 29.05 (5.56) kg/m^2.

- All participants had a laboratory confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnosis, with most (94.9%) participants having a qualifying SARS-CoV-2 positive test collected within 3 days of first dose of study intervention. Nearly 67% of participants received their first dose of study intervention within 3 days of symptom onset. Most (94.0%) participants did not receive or were not planning to receive mAbs for the disease under study at the time of randomization.

- Across treatment groups, 48.9% of participants were SARS-CoV-2 serological negative at baseline. All but 1 participant had at least 1 risk factor for severe COVID-19 with over half having 2 or more prespecified risk factors. Most (80.1%) participants had a baseline BMI ≥25 kg/m^2. Other common comorbidities included cigarette smoker (39.1%), hypertension (31.8%), and diabetes mellitus (10.8%). In total, 61.9% participants had a baseline viral load ≥4 $\log_{10}$ copies/mL and 26.9% of participants had a baseline viral load ≥7 $\log_{10}$ copies/mL.

Exposure:

The mean duration (SD) of treatment (5.03 [0.81] days) was similar across treatment groups. Overall, approximately 94% of participants received study intervention over the duration of at least 5 calendar days.

Efficacy Results:

Primary Endpoint Results

Based on the sequential design and prespecified interim analysis specifications, the primary analysis result was statistically significant ($p<0.0001$) and the primary objective of the study was met and confirmed in the final analysis. Treatment with nirmatrelvir/ritonavir significantly reduced the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 in nonhospitalized symptomatic adult participants with COVID-19 who were at increased risk of progression to severe illness at baseline.

- The observed event rate of COVID-19-related hospitalization or death from any cause with COVID-19 symptom onset ≤3 days from first dosing and no mAb treatment was 44 of 647 (6.801%) participants in the placebo group and 5 of 671 (0.745%) participants who were treated with nirmatrelvir/ritonavir.

- After accounting for premature study discontinuation (ie, to include participants discontinued from study before Day 28 without having experienced a primary endpoint event) by using the follow-up time in the Kaplan-Meier calculation, the estimated event rate of COVID-19-related hospitalization or death from any cause over the 28-day period among those treated with placebo was 6.888%. Among those

CLINICAL STUDY REPORT SYNOPSIS

treated with nirmatrelvir/ritonavir, the event rate was 0.752%, a 6.137% absolute reduction, indicating a statistically significant improvement ($p<0.0001$).

- Based on the Continuous Mapping Theorem, nirmatrelvir/ritonavir showed an 89.1% relative reduction in primary events compared to placebo.

- Primary endpoint events were mostly COVID-19-related hospitalizations that did not result in death.

- Through Day 28, there were 9 deaths in the placebo group and none in the nirmatrelvir/ritonavir group.

First Key Secondary Efficacy Endpoint Results

The observed event rate of COVID-19-related hospitalization or death from any cause through Day 28 in the mITT1 analysis set who received treatment within 5 days of symptom onset and no mAb treatment was 64 of 989 (6.471%) participants in the placebo group, and 9 of 977 (0.921%) participants in the nirmatrelvir/ritonavir group.

Because the primary endpoint was statistically significant, the first key secondary efficacy endpoint was tested at an overall level of 5% as prespecified in the protocol and SAP. Treatment with nirmatrelvir/ritonavir reduced COVID-19-related hospitalization or death in the mITT1 population from 6.571% to 0.933% compared to placebo, showing a 5.638% (95% CI: -7.308% to -3.967%; $p<0.0001$) absolute reduction or an 85.8% relative reduction in primary endpoint events.

Through Day 28, there were 12 deaths in the placebo group and 0 deaths in the nirmatrelvir/ritonavir group.

Secondary Efficacy Endpoints Results

Secondary efficacy endpoint results are summarized below for the mITT analysis set who received treatment within 3 days of symptom onset and no mAb treatment. Results for the mITT1 analysis set, who received treatment within 5 days of symptom onset and no mAb treatment, were consistent with the mITT analysis set for all endpoints except where noted below.

- Because statistical significance was achieved in the analyses of both the primary endpoint and the first key secondary efficacy endpoint, the time to sustained alleviation in all targeted signs/symptoms through Day 28 was analyzed with an alpha level of 5% in the sequential testing procedure as specified in the protocol and SAP. Treatment with nirmatrelvir/ritonavir significantly reduced the median time to sustained alleviation of all targeted signs and symptoms through Day 28 (15 days for placebo and 12 days for nirmatrelvir/ritonavir). The hazard ratio for treatment with nirmatrelvir/ritonavir versus placebo was 1.294 days (95% CI: 1.136, 1.476, p=0.0001).

CLINICAL STUDY REPORT SYNOPSIS

- Because statistical significance was achieved in the analyses of the primary endpoint and the first and second key secondary efficacy endpoints, the time to sustained resolution in all targeted signs/symptoms through Day 28 was analyzed with an overall alpha level of 5% in a Hochberg procedure, together with the COVID-19-related medical visits through Day 28, and the proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5 as specified in the SAP. Treatment with nirmatrelvir/ritonavir reduced the median time to sustained resolution of all targeted signs and symptoms through Day 28 (18 days for placebo; 16 days for nirmatrelvir/ritonavir). The hazard ratio for treatment with nirmatrelvir/ritonavir versus placebo was 1.219 days (95% CI: 1.061, 1.401; p=0.0053).

- Because statistical significance was achieved in the analyses of the primary endpoint and the first and second key secondary efficacy endpoints, the proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5 was analyzed with an overall alpha level of 5% in a Hochberg procedure, together with the time to sustained resolution in all targeted signs/symptoms through Day 28 and the COVID-19-related medical visits through Day 28 as specified in the SAP. 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 (OR 8.948 for placebo; OR 19.400 for nirmatrelvir/ritonavir), but the treatment difference was not significant (p=0.1997).

- Including participants with and without hospitalizations, the nirmatrelvir/ritonavir group reported fewer days in the hospital than in the placebo group (0.088 days per participant versus 0.844 days per participant on average). No participants in the nirmatrelvir/ritonavir group reported any ICU visits. The placebo group spent 0.179 days/participant on average in the ICU. No participant in the nirmatrelvir/ritonavir group received mechanical ventilation.

- Over the study period from Day 1 through Day 28, the proportion of participants with severe signs and symptoms was numerically lower in the nirmatrelvir/ritonavir group compared to the placebo group (18.168% vs 20.775%, p=0.3473). Although these overall proportions were not significantly different, further examination by study period revealed that nirmatrelvir/ritonavir significantly reduced sign and symptom severity through Day 28 (Day 7 to Day 28: severe signs and symptoms in 7.207% participants in nirmatrelvir group vs 11.318% in placebo group [p=0.0287]).

- Median time to sustained alleviation and sustained resolution of each targeted COVID-19 sign and symptom was achieved 1 to 2 days earlier and 1 to 3 days earlier, respectively, with nirmatrelvir/ritonavir treatment compared with placebo except for diarrhea and vomiting, which was the same for both groups. The number of participants achieving sustained alleviation and resolution of each targeted COVID-19 sign and symptom was higher in the nirmatrelvir/ritonavir group compared with placebo, except for vomiting,

CLINICAL STUDY REPORT SYNOPSIS

which was the same for both groups. Results for the mITT1 analysis set and the mITT2 analysis set were generally consistent with the mITT analysis set.

- Participants in both treatment groups had a similar likelihood of progression to a worsening status (ie, increasing severity for any targeted symptom) through Day 28 (OR versus placebo 1.088 [95% CI: 0.836, 1.416; p=0.5293]).

- On-treatment reduction in viral load was significantly (p<0.0001) larger in the nirmatrelvir/ritonavir group than in the placebo group.

    - Baseline (Day 1) log_{10} (viral load) was 5.942 log_{10} copies/mL in the placebo group and 6.029 log_{10} copies/mL in the nirmatrelvir/ritonavir group. At Day 5, after accounting for treatment, geographic region, baseline SARS-CoV-2 serology status and baseline viral load, the adjusted mean (SE) reduction in log_{10} (viral load) was -2.405 (0.083) log_{10} copies/mL in the placebo group, and -3.311 (0.083) log_{10} copies/mL in the nirmatrelvir/ritonavir group, reflecting an additional average reduction (95% CI) of -0.905 (-1.102 to -0.709, p<0.0001) log_{10} copies/mL.

- Because statistical significance was achieved in the analyses of the primary endpoint and the first and second key secondary efficacy endpoints, the COVID-19-related medical visits through Day 28 was analyzed with an overall alpha level of 5% in a Hochberg procedure, together with the time to sustained resolution in all targeted signs/symptoms through Day 28 and the proportion of participants with a resting peripheral oxygen saturation ≥95% at Days 1 and 5 as specified in the SAP. Compared with the nirmatrelvir/ritonavir group, there were approximately 5 times as many participants in the placebo group who had COVID-19 related medical visits (52 vs 10 participants, respectively). The total number of visits was approximately 4 times as high in the placebo group (81 vs 22). After adjusting for geographic region, baseline SARS-CoV-2 serology status and baseline viral load, the COVID-19 related medical visits occurred less frequently in the nirmatrelvir/ritonavir group at approximately 27.0% of the rate in the placebo group (p=0.0002).

- In the mITT analysis set, there were 11 deaths in the placebo group and none in the nirmatrelvir/ritonavir group through Week 24: Of these, 9 deaths occurred through Day 28 and the other 2 deaths occurred during the long-term follow-up period (Day 67 and Day 96). In both the mITT1 and mITT2 analysis sets, there were 15 deaths in the placebo group and none in the nirmatrelvir/ritonavir group through Week 24.

Safety Results:

- The proportion of participants with all-causality treatment-emergent adverse events (TEAEs) that started on or prior to the Day 34 visit was comparable between the nirmatrelvir/ritonavir (22.0%) and placebo (24.3%) groups.

CLINICAL STUDY REPORT SYNOPSIS

- 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 TEAEs (Grade 4) was lower in the nirmatrelvir/ritonavir group (4.0%) compared with the placebo group (8.5%).

- Of the most frequently reported TEAEs in the nirmatrelvir/ritonavir group (≥1%), Dysgeusia (4.6%), Diarrhoea (3.0%), and Vomiting (1.2%) were reported at a higher frequency than in the placebo group (0.1%, 1.5%, and 0.9%, respectively). These AEs were nonserious and mostly mild (Grade 1) to moderate (Grade 2) in severity. In the nirmatrelvir/ritonavir group, Dysgeusia, Diarrhoea, and Vomiting led to few discontinuations from study intervention: 2 participants, 1 participant, and 4 participants, respectively.

- The overall incidence of participants with all-causality treatment-emergent serious adverse events (SAEs) that started on or prior to the Day 34 visit was lower in the nirmatrelvir/ritonavir treatment group (1.7%) compared with placebo (6.7%). The most frequently reported SAEs in the nirmatrelvir/ritonavir group (≥2 participants) were COVID-19 pneumonia and COVID-19 and were reported more frequently in the placebo group than in the nirmatrelvir/ritonavir group. COVID-19 pneumonia and COVID-19 were considered related to the disease under study; none of these SAEs were considered by the investigator to be related to study intervention.

- Fewer participants in the nirmatrelvir/ritonavir group compared to the placebo group discontinued study intervention due to an AE (2.0% and 4.3%, respectively) or discontinued the study due to an AE (0% and 1.2% [all due to death], respectively). All-causality TEAEs that led to discontinuation of study intervention in more than 1 participant in either treatment group were COVID-19 pneumonia, Nausea, Creatinine renal clearance decreased, Vomiting, COVID-19, Glomerular filtration rate decreased, Pneumonia, Pneumonitis, White blood cell count decreased, and Dysgeusia.

- No participants in the nirmatrelvir/ritonavir group experienced an AE resulting in death (Grade 5) through Day 34, compared to 13 (1.2%) in the placebo group, all of which were related to the disease under study. Two deaths in the placebo group occurred during the long-term follow-up period, of which one was related to the disease under study.

- The incidence of participants with all-causality hemodynamic, inflammatory, and thyroid-related TEAEs was generally comparable between treatment groups. Fibrin D dimer increased occurred at a greater frequency in the placebo group than in the nirmatrelvir/ritonavir group (22 [2.1%] participants for nirmatrelvir/ritonavir versus 30 [2.8%] participants for placebo).

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

CLINICAL STUDY REPORT SYNOPSIS

- No potential Hy's Law cases were identified in either treatment group through Day 34.

- No clinically meaningful findings in vital sign measurements were observed in this study, and the assessments and observations were comparable across treatment groups. Few (≤5%) participants in either treatment group had clinically significant ECG findings.

Pharmacokinetic Results:

Geometric mean (coefficient of variation [CV%]) concentrations, representative of maximum observed concentration (C_{max}) on Day 1 (30 to 90 minutes postdose) and Day 5 (preferably up to 2 hours postdose) were 1510 (97%) ng/mL and 2426 (93%) ng/mL, respectively.

Conclusions:

- Based on the sequential design and prespecified interim analysis specifications, the primary analysis result was statistically significant ($p<0.0001$) and the primary objective of the study was met and confirmed in the final analysis. Treatment with nirmatrelvir/ritonavir was efficacious in reducing the incidence of COVID-19-related hospitalization or death from any cause in nonhospitalized symptomatic adult participants with COVID-19 who were at increased risk of progression to severe disease.

    - In participants who were treated within 3 days of symptom onset and no mAb treatment, nirmatrelvir/ritonavir significantly reduced the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 by 89.1% (0.752% vs 6.888%, $p<0.0001$) compared to placebo in nonhospitalized symptomatic adult participants who were at increased risk of progression to severe illness at baseline.

    - In participants who were treated within 5 days of symptom onset and no mAb treatment, nirmatrelvir/ritonavir also significantly reduced the proportion of participants with COVID-19-related hospitalization or death from any cause through Day 28 by 85.8% (0.933% vs 6.571%, $p<0.0001$) compared to placebo.

    - Sensitivity and supplemental analyses of the primary endpoint were consistent with the primary analysis.

- Treatment with nirmatrelvir/ritonavir significantly reduced the duration and severity of COVID-19 signs and symptoms compared with placebo.

    - Treatment with nirmatrelvir/ritonavir significantly shortened the median time to sustained alleviation of all targeted COVID-related signs and symptoms from 15 days to 12 days, and shortened the median time to sustained resolution of these symptoms from 18 days to 16 days.

CLINICAL STUDY REPORT SYNOPSIS

- The nirmatrelvir/ritonavir group had significantly more participants with severe symptoms before treatment, but had significantly less participants with severe symptoms after treatment.

- A numerical nonsignificant trend in reducing the frequency of postbaseline resting peripheral oxygen <95% was observed in the nirmatrelvir/ritonavir group compared with placebo.

- COVID-19-related medical visits were significantly less frequent in the nirmatrelvir/ritonavir group occurring at approximately 27.0 % of the rate in the placebo group. The nirmatrelvir/ritonavir group on average spent 0.088 days/participant (no participants reported any ICU stays) in the hospital, compared with the 0.844 days/participant (0.179 days/participant in ICU) in the placebo group. No participants in the nirmatrelvir/ritonavir group required mechanical ventilation.

- The mean predose concentration (C_{trough}) (ie, trough or minimum observed concentration [C_{min}]) of nirmatrelvir on Day 5 were consistent with the predicted profile via a preliminary population PK model and were confirmed by exposures (C_{trough}) previously associated with nirmatrelvir/ritonavir 300 mg/100 mg.

- The antiviral effect of nirmatrelvir/ritonavir was demonstrated by significant reduction of SARS-CoV-2 viral load compared with placebo, a 0.905 $\log_{10}$ copies/mL reduction among participants treated within 3 days of COVID-19 onset and no mAb treatment (mITT), or a 0.777 $\log_{10}$ copies/mL reduction among participants treated within 5 days of symptom onset and no mAb treatment (mITT1).

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

    - The overall 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. Fewer participants in the nirmatrelvir/ritonavir group reported severe events (Grade 3) or potentially life-threatening events (Grade 4) compared with the placebo group.

    - Fewer all-causality treatment-emergent SAEs were reported in the nirmatrelvir/ritonavir group compared with placebo.

    - There were 15 deaths in the placebo group (12 in the 28-day period, 1 in the safety follow-up period, and 2 in the long-term follow-up period) and none in the nirmatrelvir/ritonavir group.

    - Discontinuation of study intervention or of the study due to an AE was lower in the nirmatrelvir/ritonavir group compared with placebo.

CLINICAL STUDY REPORT SYNOPSIS

- The incidence of participants with hemodynamic, inflammatory, and thyroid-related TEAEs was generally comparable between treatment groups. Fibrin D dimer increased was the only TEAE that occurred at a greater frequency (≥5 participant difference) in the placebo group compared with the nirmatrelvir/ritonavir group.

- Nirmatrelvir/ritonavir was not associated with clinically meaningful changes in laboratory values or vital signs. Nirmatrelvir/ritonavir was not associated with any clinically significant ECG findings.