CLINICAL STUDY REPORT SYNOPSIS

SYNOPSIS

Study Title: A Phase 2/3, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Study to Evaluate the Safety And Efficacy of 2 Regimens of Orally Administered PF-07321332/Ritonavir in Preventing Symptomatic SARS-CoV-2 Infection in Adult Household Contacts of an Individual with Symptomatic COVID-19

Study Number: C4671006

Regulatory Agency or Public Disclosure Identifier Number:

EudraCT Number: 2021-002894-24

ClinicalTrials.gov identification (ID): NCT05047601

Study Phase: 2/3

Name of Study Intervention: PF-07321332 (nirmatrelvir)

Name of Sponsor/Company: Pfizer Inc.

Clinical Study Report (CSR) Version and Report Date: Final CSR Last Participant Last Visit (LPLV) (Amendment to 27 May 2022) Version 2.0; 07 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:

Not Applicable.

Study Period:

Study Initiation Date (First Participant First Visit): 09 September 2021

Study Completion (LPLV Date): 12 April 2022

This study was neither discontinued nor interrupted.

Rationale:

The purpose of this study is to evaluate the efficacy and safety of nirmatrelvir/ritonavir as postexposure prophylaxis for adult household contacts of an individual with symptomatic coronavirus disease 2019 (COVID-19).

CLINICAL STUDY REPORT SYNOPSIS

Objectives, Endpoints, and Statistical Methods:

Table S1. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
Primary:			
Efficacy	• To compare the efficacy of 5-day and 10-day regimens of nirmatrelvir/ritonavir versus placebo in preventing symptomatic reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen test (RAT)-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants who develop a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14.	• The risk reduction between 5-day and 10-day regimens of nirmatrelvir/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline and are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.
Secondary:			
Safety	• To describe the safety and tolerability of 5-day and 10-day regimens of nirmatrelvir/ritonavir relative to placebo in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	• Incidence of treatment emergent adverse events (TEAEs) • Incidence of serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation.	• Not applicable.
Efficacy	• To compare the efficacy of 5-day and 10-day regimens of nirmatrelvir/ritonavir versus placebo in preventing symptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection	Of the participants who have a negative RT-PCR result at baseline and who are at increased risk of severe COVID-19 illness: • Proportion of participants with symptomatic, RT-PCR or RAT-confirmed SARS-	• The risk reduction between 5-day and 10-day regimens of nirmatrelvir/ritonavir versus placebo in the proportion of individuals who develop symptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 in adults who have a negative RT-PCR result at baseline,

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
	in adult participants who have a negative RT-PCR result at baseline, who are at increased risk of severe COVID-19 illness, and who are household contacts of an individual with symptomatic COVID-19.	CoV-2 infection through Day 14. • Proportion of participants with COVID-19 related hospitalization or death from any cause by Day 28.	who are at increased risk of severe COVID-19 illness, and who are household contacts of an individual with symptomatic COVID-19. This will be estimated without regard to adherence to randomized treatment.
Efficacy	• To compare the efficacy of 5-day and 10-day regimens of nirmatrelvir/ritonavir versus placebo in preventing SARS-CoV-2 infection in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with asymptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14. • Time to RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14. Of the participants who have a positive RT-PCR result at baseline: • Proportion of participants with symptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14. Of the participants who have a negative or positive RT-PCR result at baseline: • Proportion of participants with symptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14.	• Not applicable.
Efficacy	• To compare the efficacy of 5-day and 10-day regimens of nirmatrelvir/ritonavir versus placebo in the duration and severity of COVID-19 related signs and symptoms in adult participants who have a negative RT-PCR result at baseline and who are	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with no, mild, moderate, or severe signs and symptoms attributed to COVID-19 through Day 28. • Number of days of symptomatic SARS-CoV-2 infection through Day 28.	• Not applicable.

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
	household contacts of an individual with symptomatic COVID-19.		
Pharmacokinetics	• To determine the pharmacokinetics (PK) of nirmatrelvir in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	• Nirmatrelvir PK in plasma and whole blood (if feasible).	• Not applicable.
Efficacy	• To describe all-cause mortality in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Proportion of participants with death (all-cause) through Day 38.	• Not applicable.
Efficacy	• To describe the viral load in nasal samples over time in adult participants who have a negative or positive RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Viral titers measured via RT-PCR in nasal swabs over time. Of the participants who have a positive RT-PCR result at baseline: • Viral titers measured via RT-PCR in nasal swabs over time.	• Not applicable.
Efficacy	• To describe hospitalizations in adult participants who have a negative RT-PCR result at baseline and who are household contacts of an individual with symptomatic COVID-19.	Of the participants who have a negative RT-PCR result at baseline: • Number of days of hospital and intensive care unit (ICU) stay in participants with COVID-19-related hospitalization through Day 28.	• Not applicable.
Efficacy	• To describe COVID-19 related medical visits in adult participants who have a negative RT-PCR result at	Of the participants who have a negative RT-PCR result at baseline:	• Not applicable.

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
	baseline and who are household contacts of an individual with symptomatic COVID-19.	• Number of COVID-19 related medical visits through Day 28.	

Table S2. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Analysis Model
Proportion of participants who developed a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 for participants who had a negative RT-PCR result at baseline.	Primary Efficacy analysis	modified Intent-to-Treat (mITT)	Generalized estimating equation (GEE)/Generalized linear model Descriptive statistics
Proportion of participants who developed a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 who had a negative RT-PCR result at baseline.	Sensitivity analysis for primary endpoint	Per Protocol (PP)	GEE/Generalized linear model
Proportion of participants who developed a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 who had a negative RT-PCR result at baseline.	Sensitivity analysis for primary endpoint	mITT excluding Site 1483	GEE/Generalized linear model
Proportion of participants who developed a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 who had a negative RT-PCR result at baseline.[a]	Sensitivity analysis for primary endpoint	mITT	GEE/Generalized linear model
Proportion of participants who developed a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 who had a negative RT-PCR result at baseline.[b]	Sensitivity analysis for primary endpoint	mITT	GEE/Generalized linear model
Proportion of participants who developed a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 who had a negative RT-PCR result at baseline.	Sensitivity analysis for primary endpoint	mITT regardless of data cleaning level	GEE/Generalized linear model

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Analysis Model
Proportion of participants who developed a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 who had a negative RT-PCR result at baseline.	Sensitivity analysis for primary endpoint	mITT by considering all randomized participants as independent participants	GEE/Generalized linear model
Proportion of participants who developed a symptomatic, RT-PCR confirmed SARS-CoV-2 infection through Day 14 who had a negative RT-PCR result at baseline.	Sensitivity analysis for primary endpoint	mITT	GEE/Generalized linear model
Proportion of participants who developed a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 who had a negative RT-PCR result at baseline.[c]	Sensitivity analysis for primary endpoint	mITT	GEE/Generalized linear model
Proportion of participants who developed a symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 who had a negative RT-PCR result at baseline.[d]	Subgroup analyses for the primary endpoint	mITT	GEE/Generalized linear model
Proportion of participants with symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 for participants who had a negative RT-PCR result at baseline and who were at increased risk of severe COVID-19 illness.	Secondary analysis	mITT2	GEE/Generalized linear model
Proportion of participants with symptomatic, RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 for participants who had a negative RT-PCR result at baseline and who were at increased risk of severe COVID-19 illness.	Sensitivity analysis for secondary endpoint	mITT2 considering all randomized participants as independent participants	GEE/Generalized linear model
Proportion of participants with COVID-19 related hospitalization or death from any cause by Day 28 for participants who had a negative RT-PCR result at baseline and who were at increased risk of severe COVID-19 illness.	Secondary analysis	mITT2	Descriptive statistics Logistic regression model if applicable
Proportion of participants with asymptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 for participants who had a negative RT-PCR result at baseline.	Secondary analysis	mITT	GEE/Generalized linear model

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Analysis Model
Time to RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 for participants who had a negative RT-PCR result at baseline.	Secondary analysis	mITT	Kaplan-Meier plot; Cox proportional hazard model as needed
Proportion of participants with symptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 in participants who had a positive RT-PCR result at baseline.	Secondary analysis	mITT1	GEE/Generalized linear model
Proportion of participants with symptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 in participants who had a positive RT-PCR result at baseline.	Sensitivity analysis for secondary endpoint	mITT1 by considering all randomized participants as independent participants	GEE/Generalized linear model
Proportion of participants with symptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 in participants who had a positive RT-PCR result at baseline.	Subgroup analyses on pre- or post-emergence of the omicron variant for secondary endpoint	mITT1	GEE/Generalized linear model
Proportion of participants with symptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 in participants who had a negative or positive RT-PCR result at baseline.	Secondary analysis	mITT3	GEE/Generalized linear model
Proportion of participants with symptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 in participants who had a negative or positive RT-PCR result at baseline.	Sensitivity analysis for secondary endpoint	mITT3 by considering all randomized participants as independent participants	GEE/Generalized linear model
Proportion of participants with symptomatic RT-PCR or RAT-confirmed SARS-CoV-2 infection through Day 14 in participants who had a negative or positive RT-PCR result at baseline.	Subgroup analyses on pre- or post-emergence of the omicron variant for secondary endpoint	mITT3	GEE/Generalized linear model

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Analysis Model
Proportion of participants with no, mild, moderate, or severe signs and symptoms attributed to COVID-19 through Day 28 for participants who had a negative RT-PCR result at baseline.	Secondary analysis	mITT	Descriptive statistics Logistic regression model
Number of days of symptomatic SARS-CoV-2 infection through Day 28 for participants who had a negative RT-PCR result at baseline.	Secondary analysis	mITT	Descriptive statistics
Proportion of participants with death (all-cause) through Day 38 for participants who had a negative RT-PCR result at baseline.	Secondary analysis	mITT	Descriptive statistics Logistic regression model if applicable
Viral titers measured via RT-PCR in nasal swabs over time for participants who had a negative RT-PCR result at baseline.	Secondary analysis	mITT	Descriptive statistics
Viral titers measured via RT-PCR in nasal swabs over time for participants who had a positive RT-PCR result at baseline.	Secondary analysis	mITT1	Descriptive statistics
Number of days of hospital and ICU stay in participants with COVID-19 related hospitalization through Day 28 for participants who had a negative RT-PCR result at baseline.	Secondary analysis	mITT	Descriptive statistics
Number of COVID-19 related medical visits through Day 28 for participants who had a negative RT-PCR result at baseline.	Secondary analysis	mITT	Descriptive statistics and negative binomial model

a. If a participant received therapeutic monoclonal antibody or other treatment approved under EUA for SARS CoV-2 and had a positive RT-PCR or RAT through Day 14, the participant was considered to have achieved the primary endpoint.
b. If a participant had SARS-CoV-2 Symptom on or before Day 14 and all RT-PCR or RAT were missing on or after the symptom day through Day 14, the participant was considered to have achieved the primary endpoint.
c. A participant was considered to have achieved the primary endpoint if 1 of the following criteria were met:

- Reported symptoms consistent with COVID-19 by Day 14 and was missing infection status for ≥4 days through Day 14.
- Had a positive RT-PCR or RAT test result by Day 14 and missing ≥4 daily symptom diary entries through Day 14.
- Lost to follow-up through Day 14.

d. Subgroup analyses included by age group, sex, race, geographic regions, presence of risk factors associated with severe COVID-19 illness, pre- or post-emergence of the omicron variant, baseline serology status.

CLINICAL STUDY REPORT SYNOPSIS

Methodology:

This Phase 2/3, randomized, double-blind, double-dummy, placebo-controlled study in approximately 2880 participants who had a negative screening SARS-CoV-2 RAT result and who were asymptomatic household contacts of individuals who were symptomatic and recently tested positive for SARS-CoV-2 (index case: defined as patient with symptomatic COVID-19) compared the efficacy of 2 regimens of nirmatrelvir/ritonavir versus placebo. Index cases may have been participants in Phase 2/3 safety and efficacy studies of nirmatrelvir/ritonavir (C4671002 and C4671005), but this was not required. Eligible participants for this study were randomly assigned (1:1:1) within 96 hours after collection of the index case's first positive SARS-CoV-2 test to treatment in 1 of 3 intervention groups. The total duration of the study was up to 42 days.

Number of Participants (planned and analyzed):

Approximately 2880 participants were to be randomized to study intervention. The number of participants analyzed per analysis set was: Full Analysis Set, 2957; Safety Analysis Set, 2942; mITT, 2721; mITT1, 116; mITT2, 2017; mITT3, 2858; and PP, 2361.

Based on the exclusion of 2 sites from the reanalysis, the number of participants analyzed per analysis set was: Full Analysis Set, 2736; Safety Analysis Set, 2721; mITT, 2514; mITT1, 115; mITT2, 1838; mITT3, 2649; and PP, 2167.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were participants who had a negative screening SARS-CoV-2 RAT result and who were asymptomatic household contacts of individuals who were symptomatic and recently tested positive for SARS-CoV-2 (index case: defined as patient with symptomatic COVID-19).

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

Eligible participants for this study were randomly assigned (1:1:1) within 96 hours after collection of the index case's first positive SARS-CoV-2 test to receive:

- Nirmatrelvir/ritonavir every 12 hours (q12h) for 5 days followed by matching placebo q12h for 5 days; or
- Nirmatrelvir/ritonavir q12h for 10 days; or
- Matching placebo for nirmatrelvir/ritonavir q12h for 10 days.

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 Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
PF-07321332 150 mg Tablet (Croscarmellose Sodium)	FG9131	21-DP-00654	150 mg	TABLET
PF-07321332 150 mg Tablet (Croscarmellose Sodium)	FG9946	21-DP-00680	150 mg	TABLET
PF-07321332 150 mg Tablet (Croscarmellose Sodium)	FJ1399	21-DP-00677	150 mg	TABLET
PF-07321332 150 mg Tablet (Croscarmellose Sodium)	FK0781	21-DP-00808	150 mg	TABLET
PF-07321332 150 mg Tablet (Croscarmellose Sodium)	N/A	21-DP-00651	150 mg	TABLET
Placebo for PF-07321332 Tablet (Pink Oval)	N/A	21-DP-00601	0 mg	TABLET
Placebo for PF-07321332 Tablet (Pink Oval)	N/A	21-DP-00720	0 mg	TABLET
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	74132.5	21-DP-00704	0 mg	CAPSULE
Ritonavir 100 mg Size AAA Swedish Orange Capsule	74132.10	21-DP-00727	100 mg	CAPSULE
Ritonavir 100 mg Size AAA Swedish Orange Capsule	74132.4	21-DP-00681	100 mg	CAPSULE

Duration of Study Intervention:

The planned treatment duration is 10 days or 11 days depending if 2 doses or 1 dose of study intervention were administered on Day 1, respectively.

Summary of Results:

Demographic and Other Baseline Characteristics:

Baseline characteristics, including risk factors for progression to severe COVID-19 were balanced across treatment groups:

- The mean (SD) age of participants was 43.06 (14.77) years with similar proportion of Males (46.8%) and Females (53.2%).
- At Baseline, most participants (94.7%) had a negative RT-PCR confirmed SARS-CoV-2 result .
- At Baseline, most participants had a positive serology antibody test (90.7%).

CLINICAL STUDY REPORT SYNOPSIS

- Most participants (72.6%) had at least 1 protocol-defined risk factor for progression to severe COVID-19
- Most participants (87.0%) had not received a COVID-19 vaccine.
- Most participants (69.5%) were in the United States.

Participants in this study were household contacts of individuals who were symptomatic and had recently tested positive for SARS-CoV-2 (ie, index cases).

Exposure:

Overall, most participants received study intervention for 10 days (ie, 2 doses of study intervention were administered on Day 1) or 11 days (ie, 1 dose of study intervention was administered on Day 1).

Efficacy Results:

Primary Endpoint Results

The study was powered to detect a 70% risk reduction of developing symptomatic, RT-PCR or RAT confirmed SARS-CoV-2 infection through Day 14 relative to placebo. Among participants who had a negative RT-PCR result at baseline (ie, mITT), the proportion of participants who developed symptomatic RT-PCR or RAT confirmed SARS-CoV-2 infection through Day 14 was 2.6% (n=22) for the nirmatrelvir/ritonavir 5-day regimen, 2.4% (n=20) for the nirmatrelvir/ritonavir 10-day regimen, both lower than the 3.9% (n=33) for placebo. The risk reduction vs placebo was 29.8% (p=0.1722) and 35.5% (p=0.1163) for the 5-day and 10-day regimens, respectively.

Primary Endpoint by Subgroup Results

Results of subgroup analyses by participant age, sex, race, geographic region, and pre- or post-emergence of the omicron variant were generally consistent with the primary analysis except for presence of risk factors and baseline serology antibody status. In participants with or without risk factors for severe COVID-19 illness, a numerically greater risk reduction of developing symptomatic RT-PCR or RAT confirmed SARS-CoV-2 infection through Day 14 was observed for nirmatrelvir/ritonavir 5-day (64%) and 10-day (65%) regimens vs placebo for participants who did not have risk factors for severe COVID-19 than for participants who had risk factors. In participants with or without antibodies to SARS-CoV-2 at baseline, a numerically greater risk reduction of developing symptomatic RT-PCR or RAT confirmed SARS-CoV-2 infection through Day 14 was observed in participants for the 5-day (41%) and 10-day (43%) regimens vs placebo who were sero-positive at baseline than in participants who were sero-negative at baseline.

Key Secondary Endpoint Results

CLINICAL STUDY REPORT SYNOPSIS

Among participants who had a negative RT-PCR result at baseline and were at increased risk of severe COVID-19 illness (ie, mITT2), the proportion of participants with symptomatic SARS-CoV-2 infection through Day 14 was 2.9% (n=18) and 2.6% (n=16) for the nirmatrelvir/ritonavir 5-day and 10-day regimens, respectively, and 3.5% (n=21) in placebo. The risk reduction vs placebo was 12.0% (p=0.6766) and 19.1% (p=0.5070) for the 5-day and 10-day regimens, respectively.

Secondary Endpoint Results

The following efficacy results were reported for participants who had a negative RT-PCR result at baseline (ie, mITT):

- The risk reduction of asymptomatic RT-PCR or RAT confirmed SARS-CoV-2 infection through Day 14 for the nirmatrelvir/ritonavir 5-day and 10-day regimens vs placebo was similar to that observed for the primary endpoint; the risk reduction vs placebo was 32.8% (p=0.1869) and 36.7% (p=0.1221), respectively.

- RT-PCR or RAT confirmed SARS-CoV-2 infection through Day 14, regardless of the presence or absence of symptoms, was reported for 39 (4.621%) and 36 (4.337%) participants in the nirmatrelvir/ritonavir 5-day and 10-day groups, respectively, fewer than the 58 (6.905%) participants in the placebo group. Statistically significant differences in the time to RT-PCR or RAT confirmed SARS-CoV-2 infection were observed between the 5-day (p=0.0368) and 10-day (p=0.0186) regimens vs placebo.

- Among participants who had a positive SARS-CoV-2 RT-PCR or RAT result during the study, the proportion of participants who reported having no symptoms or having mild, moderate, or severe signs and symptoms consistent with COVID-19 through Day 28 was generally similar between treatment groups. Among participants who had a negative SARS-CoV-2 RT-PCR or RAT result, severity of symptoms was generally similar between treatment groups.

- The number of days participants had symptomatic RT-PCR or RAT confirmed SARS-CoV-2 infection through Day 28 varied from 1-2 days to 1-2 weeks or more and no consistent differences between treatment groups were observed.

- No deaths from any cause occurred through Day 38.

- No hospitalizations or ICU stays were reported for participants in the nirmatrelvir/ritonavir 5-day or 10-day groups. One participant in the placebo group had hospitalization ≥1 day.

- A similar proportion of participants across treatment groups reported COVID-19 medical visits through Day 28: 15.4% participants in the nirmatrelvir/ritonavir 5-day group had 145 medical visits; 12.4% participants in the nirmatrelvir/ritonavir 10-day group had 124 medical visits, and 15.5% participants in the placebo groups had 152 visits.

CLINICAL STUDY REPORT SYNOPSIS

Among participants who had a positive RT-PCR result at baseline (ie, mITT1), the risk reduction of symptomatic RT-PCR or RAT confirmed SARS-CoV-2 infection through Day 14 was not notably different between the treatment groups: risk reduction vs placebo was 25.0% (p=0.4126) and -24.4% (p=0.4273) for the nirmatrelvir/ritonavir 5-day and 10-day regimens, respectively. However, analysis of this endpoint was constrained by the small sample size of the analysis set (n=115 participants).

Among participants who had a negative, positive, or missing RT-PCR result at baseline (ie, mITT3), there was a trend towards risk reduction of symptomatic RT-PCR or RAT confirmed SARS-CoV-2 infection through Day 14 for the nirmatrelvir/ritonavir 5-day and 10-day regimens vs placebo: risk reduction was 27.4% (p=0.1333) and 4.7% (p=0.8088), respectively.

Among participants who had a negative SARS-CoV-2 RT-PCR result at baseline and were at increased risk of severe COVID-19 illness (ie, mITT2), no COVID-19-related hospitalizations or deaths from any cause by Day 28 were reported for participants in the nirmatrelvir/ritonavir 5-day or 10-day groups. In the placebo group, there were no deaths and 1 participant had a COVID-19-related hospitalization.

Among participants who had a negative SARS-CoV-2 RT-PCR result at baseline (ie, mITT) and had viral titers above the limit of detection, mean viral loads were lower for the nirmatrelvir/ritonavir 5-day and 10-day regimens vs placebo and persisted through Day 14, with the largest differences observed on Day 5, Day 6, and Day 7. Peak mean viral load was approximately 0.5 $\log_{10}$ copies/mL lower for the 5-day and 10-day regimens vs placebo.

Among participants who had a positive RT-PCR result at baseline (ie, mITT1), mean viral loads decreased over time for all treatment groups; however, decreases in viral load occurred earlier for the 5-day and 10-day regimens vs placebo, with the largest differences observed on Day 5 and Day 6.

- Mean viral loads on Day 5 were 1.470 $\log_{10}$ copies/mL (SD=2.057) and 1.413 $\log_{10}$ copies/mL (SD=1.745) for the 5-day and 10-day regimens, respectively, and 2.994 $\log_{10}$ copies/mL (SD=2.677) for placebo.

- Mean viral loads on Day 6 were 1.065 $\log_{10}$ copies/mL (SD=1.656) and 0.997 $\log_{10}$ copies/mL (SD=1.696) for the 5-day and 10-day regimens, respectively, and 2.466 $\log_{10}$ copies/mL (SD=2.561) for placebo.

Safety Results:

The overall incidence of all-causality TEAEs was generally similar across the treatment groups. These AEs were mostly mild (Grade 1) or moderate (Grade 2) in severity, except for 1 severe (Grade 3) event of Dysgeusia and 1 severe (Grade 3) event Fibrin D dimer increased in the 5-day regimen and 1 severe (Grade 3) event of Dysgeusia in the 10-day regimen. There

CLINICAL STUDY REPORT SYNOPSIS

were no deaths related to an AE in any treatment group. There were no discontinuations from the study due to AEs.

The proportion of participants with all-causality SAEs was low and similar across treatment groups. All of the SAEs were severe (Grade 3) except for COVID-19 Pneumonia in the 10-day regimen which was potentially life-threatening (Grade 4). None of these SAEs were considered related to the study intervention.

The proportion of participants in the nirmatrelvir/ritonavir 5-day and 10-day regimens (1.1% and 1.2%, respectively) and in placebo (1.6%) who discontinued study intervention due to an AE and continued in the study, was low and generally similar.

Few (≤0.5%) events leading to discontinuation of study intervention in any treatment group were considered by the investigator to be related to study intervention.

- The majority of these AEs that led to discontinuations in nirmatrelvir/ritonavir 5-day and 10-day regimens were mild (Grade 1) or moderate (Grade 2). There were no events that were potentially life-threatening (Grade 4).

Overall, the incidence of participants with hemodynamic, inflammatory, or thyroid-related AESIs was low and comparable between treatment groups.

No clinically meaningful differences were observed between the 5-day and 10-day nirmatrelvir/ritonavir regimens and placebo with respect to hematology and clinical chemistry laboratory test results.

No potential Hy's Law cases were identified in any treatment group for participants with baseline AST, ALT, and total bilirubin values within the normal range or above the normal range.

No clinically meaningful findings in vital sign measurements were observed in this study. The assessments and observations were comparable across treatment groups.

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 predose) were 1332 (100%) ng/mL and 1808 (124%) ng/mL, respectively, for the nirmatrelvir/ritonavir 5-day group; and 1363 (101%) ng/mL and 1761 (125%) ng/mL, respectively, for the nirmatrelvir/ritonavir 10-day group.

Conclusions:

- Treatment with the 5-day and 10-day regimens of nirmatrelvir/ritonavir vs placebo showed a risk reduction of 29.8% (p=0.1722) and 35.5% (p=0.1163), respectively, for developing symptomatic RT-PCR or RAT confirmed SARS-CoV-2 infection through

CLINICAL STUDY REPORT SYNOPSIS

Day 14 in participants who had a negative RT-PCR result at baseline and were household contacts of an individual with symptomatic COVID-19. The proportion of participants who had events was 2.6% (n=22) and 2.4% (n=20) for the 5-day and 10-day regimens, respectively, and 3.9% (n=33) for placebo.

- Similar trends towards risk reduction with the 5-day and 10-day regimens vs placebo were observed regardless of age, sex, race, geographic region, and pre/post emergence of the omicron variant. A numerically greater risk reduction was observed in the 5-day and 10-day regimens in participants without risk factors for severe COVID-19 illness and in participants who were sero-positive at baseline.

- Treatment with the 5-day and 10-day regimens of nirmatrelvir/ritonavir vs placebo showed a risk reduction of 32.8% and 36.7%, respectively, for asymptomatic infection through Day 14 in participants who had a negative RT-PCR result at baseline.

- In participants who had a positive RT-PCR result at baseline, the antiviral effect of the 5-day and 10-day regimens of nirmatrelvir/ritonavir was demonstrated by a quicker decrease in mean viral loads compared to placebo, with the largest differences observed on Day 5 and Day 6 where viral load was approximately 1.5 $\log_{10}$ copies/mL lower.

  - In participants who had a negative RT-PCR result at baseline, the antiviral effect of the 5-day and 10-day regimens of nirmatrelvir/ritonavir was demonstrated by a statistically significant difference in the time to RT-PCR or RAT confirmed SARS-CoV-2 infection relative to placebo, as well as an approximately 0.5 $\log_{10}$ copies/mL reduction in peak viral load level among the subset of participants who had a viral titer result above the limit of detection.

- The mean exposures of nirmatrelvir on Day 5 were consistent with the profile predicted in a preliminary population PK model and were confirmed by exposures (C_{trough}) previously associated with nirmatrelvir/ritonavir 300 mg/100 mg.

- Treatment with the 5-day and 10-day regimens of nirmatrelvir/ritonavir was safe and well-tolerated.

  - The incidence of all-causality TEAEs was low and generally similar across treatment groups. Most all-causality TEAEs in all treatment groups were mild (Grade 1) to moderate (Grade 2) in severity. No participants in any treatment group experienced an AE resulting in death.

  - No participants discontinued study due to an AE. The incidence of discontinuation of study intervention due to an AE was low and generally similar across the treatment groups.

  - Overall, the incidence of participants with hemodynamic, inflammatory, or thyroid-related AESIs was low and comparable between treatment groups.

CLINICAL STUDY REPORT SYNOPSIS

- Treatment with the nirmatrelvir/ritonavir 5-day and 10-day regimens was not associated with clinically meaningful changes in laboratory values or vital signs.