Clinical trial results:
An Interventional Efficacy And Safety, Phase 2/3, Double-Blind, 2-Arm Study To Investigate Orally Administered PF-07321332/Ritonavir Compared With Placebo In Nonhospitalised Symptomatic Adult Subjects With Covid-19 Who Are At Low Risk Of Progressing To Severe Illness

Summary

EudraCT number	2021-002857-28
Trial protocol	ES HU BG CZ SK
Global end of trial date	25 July 2022

Results information

Result version number	v1 (current)
This version publication date	11 August 2023
First version publication date	11 August 2023

Trial information

Trial identification

Sponsor protocol code	C4671002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05011513
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 July 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

An Interventional Efficacy And Safety, Phase 2/3, Double-Blind, 2-Arm Study To Investigate Orally Administered Pf-07321332/Ritonavir Compared With Placebo In Nonhospitalised Symptomatic Adult Subjects With Covid-19 Who Are At Low Risk Of Progressing To Severe Illness

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 August 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 47
Country: Number of subjects enrolled	Brazil: 32
Country: Number of subjects enrolled	Bulgaria: 260
Country: Number of subjects enrolled	Colombia: 13
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 5
Country: Number of subjects enrolled	Malaysia: 19
Country: Number of subjects enrolled	Mexico: 113
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Puerto Rico: 6
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Slovakia: 25
Country: Number of subjects enrolled	South Africa: 24
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Thailand: 94

Country: Number of subjects enrolled	Turkey: 75
Country: Number of subjects enrolled	Ukraine: 88
Country: Number of subjects enrolled	United States: 413
Worldwide total number of subjects	1288
EEA total number of subjects	346

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1223
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who had confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as determined by reverse transcription polymerase chain reaction (RT-PCR) within 5 days prior to randomization were included in the study.

Pre-assignment

Screening details:

A total of 1440 subjects signed informed consent form and were randomised. Out of which, 1288 subjects received study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg

Arm description:

Subjects were randomised to receive nirmatrelvir 300 mg and ritonavir 100 mg orally every 12 hours from Day 1 to 5

Arm type	Experimental
Investigational medicinal product name	Ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ritonavir 100 mg every 12 hours

Investigational medicinal product name	Nirmatrelvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Nirmatrelvir 300 mg every 12 hours

Arm title	Placebo

Arm description:

Subjects were randomised to receive placebo matched to nirmatrelvir/ritonavir every 12 hours for 10 doses from Day 1 through Day 5.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo every 12 hours

Number of subjects in period 1	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo
Started	654	634
Completed	519	507
Not completed	135	127
Adverse event, serious fatal	-	1
Consent withdrawn by subject	17	18
Study terminated by sponsor	108	105
Unspecified	1	-
Lost to follow-up	9	3

Baseline characteristics

Reporting groups	
Reporting group title	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg
Reporting group description:	
Subjects were randomised to receive nirmatrelvir 300 mg and ritonavir 100 mg orally every 12 hours from Day 1 to 5	
Reporting group title	Placebo
Reporting group description:	
Subjects were randomised to receive placebo matched to nirmatrelvir/ritonavir every 12 hours for 10 doses from Day 1 through Day 5.	

Reporting group values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo	Total
Number of subjects	654	634	1288
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	618	605	1223
From 65-84 years	36	29	65
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	41.76	42.63	
standard deviation	± 13.47	± 13.13	-
Sex: Female, Male Units: Subjects			
Female	344	352	696
Male	310	282	592
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	39	32	71
Asian	69	72	141
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	28	23	51
White	512	498	1010
More than one race	0	0	0
Unknown or Not Reported	6	9	15
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	272	261	533
Not Hispanic or Latino	378	367	745

Unknown or Not Reported	4	6	10

End points

End points reporting groups

Reporting group title	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg
Reporting group description:	
Subjects were randomised to receive nirmatrelvir 300 mg and ritonavir 100 mg orally every 12 hours from Day 1 to 5	
Reporting group title	Placebo
Reporting group description:	
Subjects were randomised to receive placebo matched to nirmatrelvir/ritonavir every 12 hours for 10 doses from Day 1 through Day 5.	

Primary: Time to Sustained Alleviation of Overall COVID-19 Signs and Symptoms Through Day 28

End point title	Time to Sustained Alleviation of Overall COVID-19 Signs and Symptoms Through Day 28
End point description:	
Sustained alleviation of targeted COVID-19 signs/symptoms was defined as the event occurring on the first 4 consecutive days when all symptoms scored as moderate or severe at the time of enrollment were scored as mild or absent and those scored mild or absent at the time of enrollment were scored as absent. Missing severity at baseline was considered as mild. Time to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28, was calculated as time (days) from start of study intervention or placebo (Day 1) until sustained alleviation of all targeted COVID-19 associated signs and symptoms. In this end point, time to sustained alleviation is reported consolidated for overall COVID-19 signs and symptoms. mITT1 population included all subjects randomly assigned to study intervention, who received at least 1 dose of study intervention. Subjects were analysed according to the study intervention they were randomised.	
End point type	Primary
End point timeframe:	
From Day 1 to Day 28	

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	654	634		
Units: Days				
median (confidence interval 95%)	12.000 (11.000 to 13.000)	13.000 (12.000 to 14.000)		

Statistical analyses

Statistical analysis title	Nirmatrelvir 300 mg + Ritonavir 100 mg, Placebo
Comparison groups	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg v Placebo

Number of subjects included in analysis	1288
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6027
Method	Logrank

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious AEs and AEs Leading to Study and Study Drug Discontinuation

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious AEs and AEs Leading to Study and Study Drug Discontinuation

End point description:

AE=any untoward medical occurrence in a subject or clinical study subject temporally associated with use of study intervention, whether or not considered related to study intervention.SAE=any untoward medical occurrence at any dose that resulted in any of following outcomes: death; life-threatening; required inpatient hospitalisation or prolongation of existing hospitalisation; persistent or significant disability/incapacity; congenital anomaly/birth defect; or that was considered as an important medical event. TEAEs=events started on or after study medication start date and time. AEs included serious and non-serious adverse events. AEs that led to study discontinuation and AEs that led to discontinuation of study intervention and then continued study were also reported. Safety analysis set=subjects who received at least 1 dose of study intervention; analyzed according to intervention they actually received. A randomised but not treated subjects was excluded from safety analyses.

End point type	Secondary

End point timeframe:

From start of study intervention (Day 1) up to Day 34

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	654	634		
Units: Subjects				
TEAEs	169	153		
SAEs	8	13		
AEs led to discontinuation of study	0	1		
AEs led to discontinue study drug;continued study	16	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With COVID-19 Related Hospitalization or Death From any Cause Through Day 28

End point title	Percentage of Subjects With COVID-19 Related Hospitalization or Death From any Cause Through Day 28

End point description:

Percentage of subjects with COVID-19 related hospitalisation or death from any cause during the first 28 days of the study was estimated using the Kaplan-Meier (KM) method. mITT1 population included all subjects randomly assigned to study intervention, who received at least 1 dose of study intervention. Subjects were analysed according to the study intervention they were randomised.

End point type	Secondary

End point timeframe:

From Day 1 to Day 28

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	654	634		
Units: Percentage of subjects				
number (not applicable)				
COVID-19 hospitalization	0.765	1.577		
Death	0	0.158		

Statistical analyses

Statistical analysis title	Nirmatrelvir 300 mg + Ritonavir 100 mg, Placebo
Comparison groups	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg v Placebo
Number of subjects included in analysis	1288
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1796 [1]
Method	Normal approximation

Notes:

[1] - P-value reported for COVID-19 hospitalization and death due to any cause.

Secondary: Percentage of Subjects With Death Through Week 24

End point title	Percentage of Subjects With Death Through Week 24

End point description:

Percentage of subjects with death (all-cause) event were reported in this end point. mITT1 population included all subjects randomly assigned to study intervention, who received at least 1 dose of study intervention. Subjects were analysed according to the study intervention they were randomised.

End point type	Secondary

End point timeframe:

From Day 1 to Week 24

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	654	634		
Units: Percentage of subjects				
number (not applicable)	0	0.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hospitalisation and Intensive Care Unit (ICU) Stay Through Day 28

End point title	Duration of Hospitalisation and Intensive Care Unit (ICU) Stay Through Day 28

End point description:

mITT1 population included all subjects randomly assigned to study intervention, who received at least 1 dose of study intervention. Subjects were analysed according to the study intervention they were randomised.

End point type	Secondary

End point timeframe:

From Day 1 to Day 28

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	654	634		
Units: Days				
arithmetic mean (standard deviation)				
Hospitalization	0.049 (± 0.591)	0.181 (± 1.787)		
ICU	0.000 (± 0.000)	0.065 (± 1.004)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of COVID-19 Related Medical Visits per Day Through Day 28

End point title	Number of COVID-19 Related Medical Visits per Day Through Day 28

End point description:

Number of COVID-19 related medical visits per day were reported in this endpoint. mITT1 population included all subjects randomly assigned to study intervention, who received at least 1 dose of study intervention. Subjects were analysed according to the study intervention they were randomised.

End point type	Secondary

End point timeframe:

From Day 1 to Day 28

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	654	634		
Units: Medical visits per day				
least squares mean (confidence interval 95%)	0.0010 (0.0005 to 0.0019)	0.0020 (0.0010 to 0.0038)		

Statistical analyses

Statistical analysis title	Nirmatrelvir 300 mg + Ritonavir 100 mg, Placebo
Comparison groups	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg v Placebo
Number of subjects included in analysis	1288
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0971
Method	Negative binomial

Secondary: Percentage of Subjects With Severe Signs and Symptoms of COVID-19 Through Day 28

End point title	Percentage of Subjects With Severe Signs and Symptoms of COVID-19 Through Day 28

End point description:

Subjects recorded a daily severity rating of their symptom severity over past 24 hours based on a 4-point scale in which 0 was reported if no symptoms were present; 1 if mild; 2 if moderate; and 3 if severe. A subject with severe score for any targeted symptoms post-baseline was counted as severe. Vomiting and diarrhea each was rated on a 4-point frequency scale where 0 was reported for no occurrence, 1 for 1 to 2 times, 2 for 3 to 4 times, and 3 for 5 or greater. Sense of smell and sense of taste each be rated on a 3-point Likert scale where 0 was reported if the sense of smell/taste was the same as usual, 1 if the sense of smell/taste was less than usual, and 2 for no sense of smell/taste. mITT1 population included all subjects randomly assigned to study intervention, who received at least 1 dose of study intervention. Subjects were analysed according to the study intervention they were randomised. Here, 'Number of Subjects Analysed' signifies subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

From Day 1 to Day 28

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	648	633		
Units: Percentage of subjects				
number (not applicable)	19.136	21.643		

Statistical analyses

Statistical analysis title	Nirmatrelvir 300 mg + Ritonavir 100 mg, Placebo
Statistical analysis description:	
Main effects of treatment, geographic region, baseline SARS-CoV-2 serology status and baseline viral load (< 4 log10 copies/mL, >= 4 log10 copies/mL).	
Comparison groups	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg v Placebo
Number of subjects included in analysis	1281
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1622
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.819
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.618
upper limit	1.084

Secondary: Time to Sustained Resolution of Overall COVID-19 Signs and Symptoms Through Day 28

End point title	Time to Sustained Resolution of Overall COVID-19 Signs and Symptoms Through Day 28
End point description:	
Sustained resolution was defined as when targeted symptoms are scored as absent for 4 consecutive days. The first day of the 4 consecutive-day period was considered the first event date. mITT1 population included all subjects randomly assigned to study intervention, who received at least 1 dose of study intervention. Subjects were analysed according to the study intervention they were randomised. Here, ''Number of Subjects Analysed'' signifies subjects evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
From Day 1 to Day 28	

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	425		
Units: Days				
median (confidence interval 95%)	15.000 (14.000 to 16.000)	16.000 (15.000 to 17.000)		

Statistical analyses

Statistical analysis title	Nirmatrelvir 300 mg + Ritonavir 100 mg, Placebo
Comparison groups	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg v Placebo
Number of subjects included in analysis	853
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4298
Method	Logrank

Secondary: Time to Sustained Resolution of Each COVID-19 Signs and Symptoms Through Day 28

End point title	Time to Sustained Resolution of Each COVID-19 Signs and Symptoms Through Day 28

End point description:

Sustained resolution was defined as when targeted symptoms are scored as absent for 4 consecutive days. The first day of the 4 consecutive-day period was considered the first event date. In this endpoint time to sustained alleviation is reported for each COVID-19 signs and symptoms. mITT1 population included all subjects randomly assigned to study intervention, who received at least 1 dose of study intervention. Subjects were analysed according to the study intervention they were randomised. Here ''Number of Subjects Analysed''=subjects evaluable for this end point and ''number analysed''= subjects evaluable at specified time points.

End point type	Secondary

End point timeframe:

From Day 1 to Day 28

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	654	634		
Units: Days				
median (confidence interval 95%)				
Muscle or body aches (n=466,449)	8.000 (7.000 to 9.000)	9.000 (7.000 to 10.000)		
Short of breath or difficult breathing(n=222,205)	7.000 (5.000 to 7.000)	8.000 (7.000 to 11.000)		
Chills or shivering(n=318,319)	4.000 (3.000 to 5.000)	5.000 (4.000 to 6.000)		
Cough(n=512,502)	11.000 (10.000 to 12.000)	12.000 (11.000 to 13.000)		
Diarrhea(n=143,117)	6.000 (6.000 to 8.000)	5.000 (4.000 to 6.000)		
Feeling hot or feverish(n=356,350)	4.000 (3.000 to 5.000)	5.000 (5.000 to 6.000)		
Headache(n=429,424)	7.000 (7.000 to 9.000)	9.000 (8.000 to 10.000)		
Nausea(n=180,165)	6.000 (4.000 to 7.000)	5.000 (4.000 to 7.000)		
Stuffy or runny nose(n=491,484)	9.000 (7.000 to 10.000)	10.000 (9.000 to 11.000)		
Sore throat(n=371,381)	6.000 (6.000 to 7.000)	8.000 (7.000 to 8.000)		
Vomit(n=52,43)	3.000 (2.000 to 4.000)	3.000 (2.000 to 7.000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Sustained Alleviation of Each COVID-19 Signs and Symptoms Through Day 28

End point title	Time to Sustained Alleviation of Each COVID-19 Signs and Symptoms Through Day 28

End point description:

Sustained alleviation of targeted COVID-19 signs/symptoms = event occurring on first 4 consecutive days when all symptoms scored as moderate or severe at time of enrollment were scored as mild or absent and those scored mild or absent at time of enrollment were scored absent. Missing severity at baseline was treated as mild.Time to sustained alleviation of all targeted COVID-19 signs and symptoms through Day 28, was calculated as time (days) from start of study intervention or placebo(Day 1)until sustained alleviation of all targeted COVID-19 associated signs and symptoms. In this endpoint time to sustained resolution is reported consolidated for each COVID-19 signs and symptoms. mITT1 population analysed. 99999=due to variability of data, number of subjects with events available was not sufficient for calculation of limits using Kaplan-Meier method. Subjects analysed according to study intervention they were randomised.''Number of Subjects Analysed''=subjects evaluable for endpoint.

End point type	Secondary

End point timeframe:

From Day 1 to Day 28

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	654	634		
Units: Days				
median (confidence interval 95%)				
Muscle or body aches(n=466, 449)	5.000 (4.000 to 6.000)	5.000 (4.000 to 6.000)		
Short of breath or difficulty breathing(n=222,205)	5.000 (4.000 to 6.000)	6.000 (5.000 to 7.000)		
Chills or shivering(n=318,319)	3.000 (3.000 to 4.000)	3.000 (3.000 to 4.000)		
Cough(n=512,502)	7.000 (6.000 to 8.000)	8.000 (7.000 to 9.000)		
Diarrhea(n=143,117)	6.000 (5.000 to 9.000)	4.000 (3.000 to 6.000)		
Feeling hot or feverish(n=356,350)	3.000 (-99999 to 99999)	4.000 (3.000 to 4.000)		
Headache(n=429,424)	5.000 (4.000 to 5.000)	5.000 (5.000 to 6.000)		
Nausea(n=180,165)	4.000 (3.000 to 5.000)	4.000 (3.000 to 5.000)		
Stuffy or runny nose(n=491,484)	5.000 (4.000 to 6.000)	7.000 (6.000 to 7.000)		
Sore throat(n=371,381)	4.000 (4.000 to 5.000)	5.000 (4.000 to 6.000)		
Vomit(n=52,43)	3.000 (2.000 to 4.000)	3.000 (2.000 to 7.000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Progression to Worsening Status of COVID-19 Signs and Symptoms

End point title	Percentage of Subjects With Progression to Worsening Status of COVID-19 Signs and Symptoms

End point description:

Subjects recorded a daily severity rating of their symptom severity over the past 24 hours based on a 4-point scale in which 0 was reported if no symptoms were present; 1 if mild; 2 if moderate; and 3 if severe. Vomiting and diarrhea was rated on a 4-point frequency scale where 0 is reported for no occurrence, 1 (mild) for 1 to 2 times, 2 (moderate) for 3 to 4 times, and 3 (severe) for 5 or greater. Progression to a worsening status for any targeted symptom was based up on increasing severity (i.e. the first time any targeted symptoms worsened after treatment relative to baseline). mITT1 population included all subjects randomly assigned to study intervention, who received at least 1 dose of study intervention. Subjects were analysed according to the study intervention they were randomised.

End point type	Secondary

End point timeframe:

From Day 1 to Day 28

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	648	633		
Units: Percentage of subjects				
number (not applicable)	75.463	78.515		

Statistical analyses

Statistical analysis title	Nirmatrelvir 300 mg + Ritonavir 100 mg, Placebo

Statistical analysis description:

Main effects of treatment, geographic region, symptom onset duration (<=3, >3), baseline SARS-CoV-2 serology status (positive/negative), vaccination status (complete/not vaccinated) and baseline viral load (<4 log10 copies/mL, >=4 log10 copies/mL).

Comparison groups	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg v Placebo
Number of subjects included in analysis	1281
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1086
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.802
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.613
upper limit	1.05

Secondary: Plasma Concentration Versus Time Summary of PF-07321332

End point title	Plasma Concentration Versus Time Summary of PF-07321332[2]

End point description:

Safety analysis set included all subjects who received at least 1 dose of study intervention. Subjects were analyzed according to the intervention they actually received. A randomised but not treated subjects was excluded from the safety analyses. Here ' Number of Subjects Analysed'=subjects evaluable for this end point and 'number analysed'= subjects evaluable at specified time points.

End point type	Secondary

End point timeframe:

Day 1: 1 hour post dose; Day 5: 0 minutes pre-dose

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg			
Subject group type	Reporting group			
Number of subjects analysed	287			
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)				
Day 1 (1 hour post-dose) (n=104) Day 5 (0 minutes pre-dose) (n=287)	2437 (± 1791.3) 3468 (± 2454.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Resting Peripheral Oxygen Saturation Greater Than or Equal to (>=) 95% at Day 1 and Day 5

End point title	Percentage of Subjects With Resting Peripheral Oxygen Saturation Greater Than or Equal to (>=) 95% at Day 1 and Day 5

End point description:

Percentage of subjects with a resting peripheral oxygen saturation >=95% were reported in this endpoint.mITT1 population included all subjects randomly assigned to study intervention, who received at least 1 dose of study intervention. Subjects were analysed according to the study intervention they were randomised.

End point type	Secondary

End point timeframe:

Day 1 and Day 5

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	638	604		
Units: Percentage of subjects				
number (not applicable)				
Day 1(n=16,28) Day 5(n=638,604)	62.500 94.671	67.857 93.212		

Statistical analyses

Statistical analysis title	Nirmatrelvir 300 mg + Ritonavir 100 mg, Placebo
Comparison groups	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg v Placebo

Number of subjects included in analysis	1242
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3262
Method	Breslow-Day Test
Parameter estimate	Odds ratio (OR)
Point estimate	50.333
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.163
upper limit	192.472

Secondary: Change From Baseline in Logarithm to Base10 (Log10) Transformed Viral Load at Days 3, 5, 10 and 14

End point title	Change From Baseline in Logarithm to Base10 (Log10) Transformed Viral Load at Days 3, 5, 10 and 14

End point description:

Nasal samples were collected to estimate the viral load in subjects in terms of logarithm to base 10 (log10) copies per milliliter. mITT1 population included all subjects randomly assigned to study intervention, who received at least 1 dose of study intervention. Subjects were analysed according to the study intervention they were randomised. Here, ''Number of Subjects Analysed'' signifies subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Days 3, 5, 10 and 14

End point values	Nirmatrelvir 300 milligram (mg) + Ritonavir 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	515	493		
Units: Log 10 copies per milliliter				
least squares mean (standard error)				
Day 3 (n=515, 493)	-2.302 (± 0.096)	-1.565 (± 0.098)		
Day 5 (n=505, 480)	-3.669 (± 0.090)	-2.835 (± 0.093)		
Day 10 (n=489, 478)	-4.873 (± 0.081)	-4.642 (± 0.082)		
Day 14 (n=508, 484)	-5.464 (± 0.072)	-5.249 (± 0.075)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and Non-SAEs: From Day 1 to Week 24; All-cause mortality: till Week 24

Adverse event reporting additional description:

Same event may appear as both SAE and non-SAE but are distinct events. An event may be categorised as serious in 1 subject and non-serious in another, or a subject may have experienced both SAE and non-SAE. Safety population comprised of all subjects who received at least 1 dose of study intervention during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects were randomised to receive placebo matched to nirmatrelvir/ritonavir every 12 hours for 10 doses from Day 1 through Day 5.

Reporting group title	Nirmatrelvir 300 mg + Ritonavir 100 mg

Reporting group description:

Subjects were randomised to receive nirmatrelvir 300 mg and ritonavir 100 mg orally every 12 hours from Day 1 to 5.

Serious adverse events	Placebo	Nirmatrelvir 300 mg + Ritonavir 100 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 634 (2.05%)	8 / 654 (1.22%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 634 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 634 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer metastatic			

subjects affected / exposed	0 / 634 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	1 / 634 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osmotic demyelination syndrome			
subjects affected / exposed	0 / 634 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	0 / 634 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	8 / 634 (1.26%)	3 / 654 (0.46%)	
occurrences causally related to treatment / all	0 / 9	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
COVID-19			
subjects affected / exposed	1 / 634 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 634 (0.32%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 634 (0.16%)	0 / 654 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia aspiration			
subjects affected / exposed	0 / 634 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	0 / 634 (0.00%)	1 / 654 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Placebo	Nirmatrelvir 300 mg + Ritonavir 100 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 634 (11.20%)	120 / 654 (18.35%)	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	12 / 634 (1.89%)	7 / 654 (1.07%)	
occurrences (all)	12	8	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 634 (0.63%)	9 / 654 (1.38%)	
occurrences (all)	4	11	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	7 / 634 (1.10%)	4 / 654 (0.61%)	
occurrences (all)	7	4	
Fibrin D dimer increased			
subjects affected / exposed	9 / 634 (1.42%)	8 / 654 (1.22%)	
occurrences (all)	10	8	
Alanine aminotransferase increased			
subjects affected / exposed	8 / 634 (1.26%)	14 / 654 (2.14%)	
occurrences (all)	10	18	
Nervous system disorders			
Headache			

subjects affected / exposed	9 / 634 (1.42%)	6 / 654 (0.92%)	
occurrences (all)	9	6	
Dysgeusia			
subjects affected / exposed	3 / 634 (0.47%)	44 / 654 (6.73%)	
occurrences (all)	3	44	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	19 / 634 (3.00%)	26 / 654 (3.98%)	
occurrences (all)	20	30	
Dyspepsia			
subjects affected / exposed	2 / 634 (0.32%)	8 / 654 (1.22%)	
occurrences (all)	2	8	
Nausea			
subjects affected / exposed	17 / 634 (2.68%)	21 / 654 (3.21%)	
occurrences (all)	18	24	
Vomiting			
subjects affected / exposed	11 / 634 (1.74%)	11 / 654 (1.68%)	
occurrences (all)	14	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2021	Amendment 1: Changed endpoint to include, instead of exclude hospitalisation: Number of COVID-19 related medical visits including hospitalisation through Day 28. Confirmed SARS-CoV-2 infection requirement updated from 72 hours to 5 days.
19 July 2021	Amendment 2: Vaccination criteria was updated from partially to fully vaccinated and the risk factor of =60 years of age was added.
03 August 2021	Amendment 3: Vaccination criteria was updated to clarify that subjects without underlying medical conditions associated with an increased risk of developing severe illness from COVID-19 are not eligible if they have been vaccinated. It is only fully vaccinated subjects with underlying medical conditions that are eligible. Primary estimand changed to specify inclusion of participants who were randomised <=3 days after symptom onset.
23 November 2021	Amendment 4: Secondary endpoints and estimands updated to reflect new hypothesis testing hierarchy. Language was added to provide additional information about the study unblinding plan.
21 January 2022	Amendment 5: The secondary endpoint of incidence of COVID-19-associated hospitalisations or death from any cause will be analyzed to provide a point estimate and 95% CI to measure associated variability. Other clinically relevant secondary endpoints (COVID-19 related medical visits) will also be analysed. Extend study enrollment to assess potential benefit to subjects at low risk of progression to severe COVID-19 in the clinically relevant endpoint of hospitalisation or death.
09 June 2022	Amendment 6: Added hypertension as a potential risk and removed hemodynamic and inflammatory effects, and TSH and T4 (free) elevations as potential risks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In subject disposition, there was discontinuations due to AE, which was captured under "Death" as reason for discontinuation. Adverse event was COVID-19 pneumonia and the subject died due to that event and discontinued study.

Notes: