Clinical trial results:
An Interventional, Efficacy and Safety, Phase 2, Randomized, Double-Blind, 2-arm Study to Investigate a Repeat 5-day Course of Nirmatrelvir/Ritonavir Compared to Placebo/Ritonavir in Participants at Least 12 Years of age with Rebound of COVID-19 Symptoms and Rapid Antigen Test Positivity

Summary

EudraCT number	2022-002827-36
Trial protocol	DE GR IT
Global end of trial date	09 February 2024

Results information

Result version number	v1 (current)
This version publication date	02 August 2024
First version publication date	02 August 2024

Trial information

Trial identification

Sponsor protocol code	C4671042

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05567952
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	66 Hudson Boulevard Est, New York, United States, NY 10001
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of nirmatrelvir/ritonavir to placebo/ritonavir on viral ribonucleic acid (RNA) level in nasopharyngeal (NP) swabs in participants with mild-to-moderate coronavirus disease 2019 (COVID-19).

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 Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 October 2022
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
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	Canada: 2
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	United States: 426
Worldwide total number of subjects	436
EEA total number of subjects	1

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)	1
Adults (18-64 years)	313
From 65 to 84 years	116
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 436 participants were randomized and treated in this study to evaluate the efficacy and safety of a repeat 5-day treatment course of nirmatrelvir/ritonavir or placebo/ritonavir for the treatment of mild-to moderate COVID-19.

Period 1

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

Arms

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

Arm description:

Participants received nirmatrelvir 300 milligrams (mg) (participants with estimated glomerular filtration rate [eGFR] greater than or equal to [>=] 30 to less than [<] 60 millilitre per minute [mL/min]/1.73 meters squared [m^2] [or estimated creatinine clearance [CrCl] >=30 to <60 mL/min] received 150 mg every 12 hours [q12h] for 5 days at screening) and ritonavir 100 mg, orally for 5 days q12h from Day 1 to Day 5.

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

Dosage and administration details:

Participants received Nirmatrelvir 300 mg q12h for 5 days, as oral dose.

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

Dosage and administration details:

Participants received Ritonavir 100 mg q12h for 5 days, as oral dose.

Arm title	Placebo + Ritonavir 100 mg

Arm description:

Participants received placebo matched to nirmatrelvir followed by ritonavir 100 mg orally, for 5 days q12h from Day 1 to Day 5.

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

Dosage and administration details:

Participants received Ritonavir 100 mg q12h for 5 days, as oral dose.

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

Dosage and administration details:

Participants received placebo q12h for 5 days, as oral dose.

Number of subjects in period 1	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo + Ritonavir 100 mg
Started	292	144
Completed	280	138
Not completed	12	6
Consent withdrawn by subject	6	3
Unspecified	3	1
Lost to follow-up	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Nirmatrelvir 300 mg + Ritonavir 100 mg
Reporting group description:	
Participants received nirmatrelvir 300 milligrams (mg) (participants with estimated glomerular filtration rate [eGFR] greater than or equal to [>=] 30 to less than [<] 60 millilitre per minute [mL/min]/1.73 meters squared [m^2] [or estimated creatinine clearance [CrCl] >=30 to <60 mL/min] received 150 mg every 12 hours [q12h] for 5 days at screening) and ritonavir 100 mg, orally for 5 days q12h from Day 1 to Day 5.	
Reporting group title	Placebo + Ritonavir 100 mg
Reporting group description:	
Participants received placebo matched to nirmatrelvir followed by ritonavir 100 mg orally, for 5 days q12h from Day 1 to Day 5.	

Reporting group values	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo + Ritonavir 100 mg	Total
Number of subjects	292	144	436
Age Categorical Units: Participants			
Adolescents (12-17 years)	1	0	1
Adults (18-64 years)	209	104	313
From 65-84 years	77	39	116
85 years and over	5	1	6
Age Continuous Units: years			
arithmetic mean	53.5	53.5	
standard deviation	± 16.52	± 16.43	-
Gender Categorical Units: Participants			
Female	167	80	247
Male	125	64	189
Race Units: Subjects			
White	264	132	396
Black or African American	12	8	20
Asian	13	2	15
American Indian or Alaska Native	0	1	1
Multiracial	1	0	1
Not reported	2	1	3
Ethnicity Units: Subjects			
Hispanic or Latino	159	72	231
Not Hispanic or Latino	131	72	203
Not reported	2	0	2

End points

End points reporting groups

Reporting group title	Nirmatrelvir 300 mg + Ritonavir 100 mg

Reporting group description:

Participants received nirmatrelvir 300 milligrams (mg) (participants with estimated glomerular filtration rate [eGFR] greater than or equal to [>=] 30 to less than [<] 60 millilitre per minute [mL/min]/1.73 meters squared [m^2] [or estimated creatinine clearance [CrCl] >=30 to <60 mL/min] received 150 mg every 12 hours [q12h] for 5 days at screening) and ritonavir 100 mg, orally for 5 days q12h from Day 1 to Day 5.

Reporting group title	Placebo + Ritonavir 100 mg

Reporting group description:

Participants received placebo matched to nirmatrelvir followed by ritonavir 100 mg orally, for 5 days q12h from Day 1 to Day 5.

Primary: Change From Baseline to Day 5 in Viral Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA Level in NP Swabs - mITT Population

End point title	Change From Baseline to Day 5 in Viral Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA Level in NP Swabs - mITT Population

End point description:

Baseline was defined as the latest measurement between Day -1 and Day 1, but post-dose samples that are collected within 1 hour post start of dosing were treated as baseline. Samples with result "less than (<) lower limit of quantification (LLOQ)" are imputed as 1.7 log10 copies/milliliter (mL), and samples with result "Not Detected" are imputed as 0.0 log10 copies/mL. Modified intent-to-treat (mITT) analysis population included all participants randomly assigned to study intervention who took at least 1 dose of study intervention and who had a positive viral RNA NP swab test result (>= 2.0 log10 copies per mL) at baseline. Here, 'Number of Subjects Analysed (N)' signifies participants evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Day 5

End point values	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo + Ritonavir 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	113		
Units: Log10 copies/mL				
least squares mean (standard error)	-3.871 (± 0.129)	-3.166 (± 0.171)		

Statistical analyses

Statistical analysis title	Nirmatrelvir300+Ritonavir100/Placebo+Ritonavir100

Statistical analysis description:

Mixed model for repeated measures (MMRM) included fixed effects of treatment, geographic region, baseline SARS-CoV-2 RNA level, visit, and treatment-by-visit interaction; an unstructured (co) variance structure was used.

Comparison groups	Nirmatrelvir 300 mg + Ritonavir 100 mg v Placebo + Ritonavir 100 mg
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	MMRM
Parameter estimate	Least square (LS) mean difference
Point estimate	-0.705
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.093
upper limit	-0.316

Secondary: Time to Two Consecutive Negative Rapid Antigen Test (RAT) Results At Least 24 Hours (hrs) Apart Through Day 28- mITT Population

End point title	Time to Two Consecutive Negative Rapid Antigen Test (RAT) Results At Least 24 Hours (hrs) Apart Through Day 28- mITT Population

End point description:

The event of 2 consecutive negative RAT results obtained at least 24 (-2) hrs apart through Day 28 was defined as achieving 2 consecutive non-missing RATs with negative results through Day 28, where the 2 tests are at least 22 hours and at most 7 days apart. For the event of 2 consecutive negative RAT results obtained at least 24 hrs apart through Day 28, the date of the first negative RAT result was considered the first event date. Time to 2 consecutives negative RAT results obtained at least 24 hrs apart defined as: for participant achieving event, time to event = (first event date) -(first dose date) + 1. For participant not achieving event (censored), censoring date was at last date of RAT measurement, time = (censoring date)-(first dose date) + 1 or Day 27 whichever occurred first (Day 27 was last possible day to achieve 2 consecutive negative RAT results obtained at least 24 hrs apart through Day 28). mITT analysis set evaluated. 'N'= participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Day 1 of dosing maximum up to Day 28

End point values	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo + Ritonavir 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	115		
Units: Days				
median (confidence interval 95%)	4.000 (4.000 to 5.000)	5.000 (5.000 to 6.000)		

Statistical analyses

Statistical analysis title	Nirmatrelvir300+Ritonavir100/Placebo+Ritonavir100

Statistical analysis description:

Analysis was based on Cox proportional hazard (PH) model which included treatment, geographic region, baseline SARS-CoV-2 RNA level (< 4 log10 copies/mL or >= 4 log10 copies/mL) and time since the last vaccination (less than or equal to [<=6] months, > 6 months or unvaccinated) as appropriate.

Comparison groups	Nirmatrelvir 300 mg + Ritonavir 100 mg v Placebo + Ritonavir 100 mg
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0697
Method	COX proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.235
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.983
upper limit	1.551

Secondary: Time to Sustained Alleviation of All Targeted Signs and Symptoms Through Day 28- mITT Population

End point title	Time to Sustained Alleviation of All Targeted Signs and Symptoms Through Day 28- mITT Population

End point description:

Sustained alleviation of all targeted COVID-19 signs/symptoms was defined as the event occurring on the first of 2 consecutive days when all symptoms scored as moderate or severe at study entry are scored as mild or absent and all symptoms scored mild or absent at study entry are scored as absent. The first day of the 2 consecutive-day period was considered the first event date. The time to sustained symptom alleviation was defined as for a participant with sustained symptom alleviation, time to event was calculated as (First Event Date) – (First Dose Date) +1. For a participant that either completed Day 28 of the study or discontinued from the study before Day 28 without sustained symptom alleviation (censored), censoring date was at the last date on which symptom alleviation was assessed, and time was calculated as (Censoring Date) – (First Dose Date) +1 or Day 27 whichever occurred first. mITT analysis set evaluated. 'N'=participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Day 1 of dosing maximum up to Day 28

End point values	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo + Ritonavir 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	99		
Units: Days				
median (confidence interval 95%)	8.000 (7.000 to 10.000)	9.000 (8.000 to 11.000)		

Statistical analyses

Statistical analysis title	Nirmatrelvir300+Ritonavir100/Placebo+Ritonavir100

Statistical analysis description:

Analysis was based on Cox proportional hazard (PH) model which included treatment, geographic region, baseline SARS-CoV-2 RNA level (< 4 log10 copies/mL or >= 4 log10 copies/mL) and time since the last vaccination (<=6 months, > 6 months or unvaccinated) as appropriate.

Comparison groups	Nirmatrelvir 300 mg + Ritonavir 100 mg v Placebo + Ritonavir 100 mg
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5202
Method	COX proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.848
upper limit	1.385

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

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

End point description:

An AE was any untoward medical occurrence in a participant temporally associated with the use of study intervention, whether or not considered related to the study intervention. SAE was any untoward medical occurrence at any dose that: resulted in death, was life threatening (risk of death), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions), resulted in congenital anomaly/birth defect, was a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic. TEAEs were defined as AE that started on or after study medication on Day 1 up to Week 24 follow-up. AEs included both SAEs and all non-SAEs. Safety population included all participants randomly assigned to study intervention and who took at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

Day 1 of dosing maximum up to Week 24 follow-up

End point values	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo + Ritonavir 100 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	144		
Units: Participants				
AEs	148	55		
SAEs	3	1		
AEs leading to discontinuation from study	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 of dosing maximum up to Week 24 follow-up

Adverse event reporting additional description:

An event may be categorized as serious in 1 participant and non-serious in other, or a participant may experience both serious and non-serious event. Safety population: all participants randomly assigned to study intervention, who took at least 1 dose of study intervention.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v26.1

Reporting groups

Reporting group title	Nirmatrelvir 300 mg + Ritonavir 100 mg

Reporting group description:

Enter Description here

Reporting group title	Placebo + Ritonavir 100 mg

Reporting group description:

Enter Description here

Serious adverse events	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo + Ritonavir 100 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 289 (1.04%)	1 / 144 (0.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 289 (0.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 289 (0.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			

subjects affected / exposed	1 / 289 (0.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised anxiety disorder			
subjects affected / exposed	1 / 289 (0.35%)	0 / 144 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypovolaemia			
subjects affected / exposed	0 / 289 (0.00%)	1 / 144 (0.69%)	
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: 5 %

Non-serious adverse events	Nirmatrelvir 300 mg + Ritonavir 100 mg	Placebo + Ritonavir 100 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 289 (10.03%)	2 / 144 (1.39%)	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	29 / 289 (10.03%)	2 / 144 (1.39%)	
occurrences (all)	29	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2022	The population in the estimands and the primary analysis population was updated with the requirement of a positive rapid antigen test at baseline to align with the inclusion/exclusion criteria. Endpoint of: 'Proportion of participants with SARS-CoV-2 RNA in NP swabs below the LLOQ (defined as <2.0 log10 copies/mL) on both Days 5 and 10'. Removed as a secondary endpoint and added as a tertiary/exploratory endpoint. New secondary endpoint/estimand of: 'Time to 2 consecutive negative rapid antigen test results.' Added. The corresponding analysis for secondary endpoints were updated /added with more details. Updated sample size assumptions and the corresponding calculation to reflect the change in the primary analysis population. Amended to add self-administered daily rapid antigen tests for all study days between scheduled visits until 2 consecutive negative rapid antigen test results are obtained at which point, rapid antigen testing will be performed only at remaining scheduled visits. Text describing Tables 4 and 5 was revised to clarify DDI table content. Tables were updated with information from the Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid (August 2022).
12 May 2023	Primary and secondary estimands and the mITT analysis set description have been updated to include that participants must have a positive viral RNA NP swab test result at baseline. Sample size calculation updated.
29 June 2023	Additional secondary analyses for primary and secondary efficacy endpoints using the new analysis set (mITT1). Update the multiplicity adjustment accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported