EU RISK MANAGEMENT PLAN FOR PAXLOVID (NIRMATRELVIR/RITONAVIR)

RMP version to be assessed as part of this application:

RMP Version number: 3.0

Data lock point for this RMP: 31 December 2022

Date of final sign off: 19 April 2023

Rationale for submitting an updated RMP: The MAH is submitting this EU RMP to support the variation providing virology updates and updates to the substrate information related to CYP2B6, MATE1 and OCT1 in the SmPC. This RMP also covers the changes under assessment in the ongoing procedure EMEA/H/C/005973/II/0042, updating clinical trial exposure for pivotal studies C4671005 (EPIC-HR), C4671002(EPIC-SR) and C4671006 (EPIC-PEP).

Summary of significant changes in this RMP:

RMP PART/Module	Major Change(s)
PART I. PRODUCT(S) OVERVIEW	Name of the active substance changed from "PF-07321332" to "nirmatrelvir" (this change has been implemented through the whole RMP); Pharmacotherapeutic group and ATC code (J05AE30) included. Information on the susceptible variants included in *Summary of mode of action* has been updated.
PART II. SAFETY SPECIFICATION	
Module SI. Epidemiology of the Indication(s) and Target Populations	Epidemiology data updated.
Module SII. Non-Clinical Part of the Safety Specification	Non-clinical Part updated including the latest nonclinical virology and toxicology data.
Module SIII. Clinical Trial Exposure	Updated clinical trial exposure for study C4671005 (EPIC-HR) following the exclusion of 2 sites from the final analysis. Exposure in pivotal studies in C4671002 (EPIC-SR) and C4671006 (EPIC-PEP) added.
Module SIV. Populations Not Studied in Clinical Trials	Updates made in Section SIV.1 based on the added pivotal studies C4671002 and C4671006.
Module SV. Post-Authorisation Experience	Post-authorisation data up to cut-off date of 31 December 2022 included.
Module SVI. Additional EU Requirements for the Safety Specification	No changes made.
Module SVII. Identified and Potential Risks	Reference to the 2 added pivotal studies C4671002 (EPIC-SR) and C4671006 (EPIC-PEP) added.

RMP PART/Module	Major Change(s)
Module SVIII. Summary of the Safety Concerns	No changes made.
PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	Updated status of the phase 1 study C4671039 (additional PV activity, category 3 study).
PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES	No changes made.
PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	Information revised based on updates in PART III.
PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN	Name of the active substance changed from "PF-07321332" to "nirmatrelvir.
PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	Annex 2: Changes made based on updates in PART III of this RMP (status of study C4671039 updated to “Ongoing”). Annex 4: Updated Pregnancy follow-up questionnaire for non-study cases (including administrative updated to the privacy notice and statement in transcription certification). Annex 8: Summary of changes reflecting the above updates is included. No changes to the other Annexes.

Other RMP versions under evaluation: None

QPPV name[1]: Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu.

LIST OF ABBREVIATIONS

Abbreviation	Definition
3CL	3C-like
$3CL^{pro}$	3C-like protease
19F	fluorine-19
AA	African American
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
AI/AN	American Indian/Alaska Native
ALT	Alanine Aminotransferase
API	Asian or Pacific Islander
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC_{24}	Area Under the concentration-time Curve from time zero to 24 hours (1 day)
BID	Twice daily
BMI	Body Mass Index
BP	Blood Pressure
CAKI	COVID-Associated Acute Kidney Injury
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CL	Clearance
C_{max}	Maximum concentration recorded
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional Marketing Authorisation
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus disease 2019
CRP	C-Reactive Protein
CSR	Clinical Study Report
CYP3A	Cytochrome P450 3A
CYP3A4	Cytochrome P450 3A4
DCA	Data Capture Aid
DDI	Drug-Drug Interaction
dNHBE	Differentiated Normal Human Bronchial Epithelial Cells
+dP/dT	Cardiac contractility
EC_{50}	Drug concentration at which 50% inhibition of viral replication is observed; Concentration required for 50% effect
EC_{90}	Drug concentration at which 90% inhibition of viral replication is observed; Concentration required for 90% effect
ECDC	European Center for Disease Control
ECG	Electrocardiogram
ED	Emergency Department
EEA	European Economic Area

Abbreviation	Definition
EFD	Embryo-foetal development
eGFR	Estimated Glomerular Filtration Rate
EHR	Electronic Health Records
EMA	European Medicines Agency
EPIC	Evaluation of Protease Inhibition for COVID-19
EPIC-HR	Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (study C4671005)
EPIC-SR	Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients (Study ID C4671002)
EPIC-PEP	Evaluation of Protease Inhibition for COVID-19 in Post-Exposure Prophylaxis (Study ID C4671006)
EU	European Union
EUA	Emergency Use Authorisation
f_m	Fraction Metabolized
FOB	Functional observational battery
GI	Gastrointestinal
GISAID	Global Initiative on Sharing All Influenza Data
GLP	Good Laboratory Practice
HbA1c	Glycated haemoglobin
HCoV	Human coronavirus
hERG	Human Ether-à-go-go-Related Gene
HIV	Human immunodeficiency virus
H/L	Hispanic/Latino
Hosp	Hospitalised
HPD	Hours post-dose
HR	Heart rate
ICD	International Classification of Diseases
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
IMD	Index of Multiple Deprivation
INN	International Non-propriety Name
K_i	Inhibition constant
KTR	Kidney Transplant Recipients
LDH	Lactate Dehydrogenase
LV +dP/dt max	Maximum positive slope of the left ventricular pressure wave; an index of cardiac contractility
MAA	Marketing Authorisation Applicant
MAH	Marketing Authorisation Holder
MATE	Multidrug and toxic compound extrusion
MERS	Middle east respiratory syndrome
M/O	Multiple/Other
M^{pro}	Main Protease (also referred to as 3CL protease)
MR-proADM	Mid-Regional pro-Adrenomedullin

Abbreviation	Definition
N/A	Not Applicable
NCHS	National Center for Health Statistics
NH/PI	Native Hawaiian/Other Pacific Islander
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMTA	National Medical and Treatment Audit
NOAEL	No-observed-adverse-effect-level
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
OCS	Oral corticosteroids
OCT	Organic cation transporter
PASC	Post-Acute clinical Sequalae of COVID-19
PASS	Post-Authorisation Safety Study
PCR	Polymerase Chain Reaction
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PL	Product Label
POC	Point of Care
PPND	Pre- and Post-Natal Development
PR	Time from beginning of the P wave until the beginning of the QRS complex
PSUR	Periodic Safety Update Report
PTSD	Post-Traumatic Stress Disorder
QR	Quick Response
QT	Time from the beginning of the QRS complex to the end of the T wave in the electrocardiogram
QTc	QT interval corrected for heart rate
RMP	Risk management plan
RR	Relative risk
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TESSy	The European Surveillance System
TMPRSS2	Transmembrane protease, serine 2
UK	United Kingdom
US	United States
WBC	White Blood Cells
WHO	World Health Organisation

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PART I. PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Nirmatrelvir/ritonavir
Pharmacotherapeutic group(s) (ATC Code)	Antivirals for systemic use, protease inhibitors (J05AE30)
Marketing Authorisation Applicant	Pfizer Europe MA EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	PAXLOVID
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class Antivirals for systemic use, protease inhibitors
	Summary of mode of action Nirmatrelvir is a peptidomimetic inhibitor of the coronavirus SARS-CoV-2 main protease (M^{pro}), also referred to as 3C-like protease ($3CL^{pro}$) or nsp5 protease. Inhibition of the SARS-CoV-2 M^{pro} renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication. Nirmatrelvir was shown to be a potent inhibitor of SARS-CoV-2 M^{pro} (Ki=0.00311 µM, or IC_{50}=0.0192 µM) in a biochemical enzymatic assay. Nirmatrelvir had a median EC_{50} value of 83 nM (range: 39-146 nM) against the Omicron sub-variants, reflecting EC_{50} value fold-changes ≤1.5 relative to the USA-WA1/2020 isolate. In addition, the antiviral activity of nirmatrelvir against the SARS-CoV-2 Alpha, Beta, Gamma, Delta, Lambda, Mu, and Omicron BA.1 variants was assessed in Vero E6 P-gp knockout cells. Nirmatrelvir had a median EC_{50} value of 25 nM (range: 16-141 nM). The Beta variant was the least susceptible variant tested with an EC_{50} value fold-change of 3.7 relative to the USA-WA1/2020. The other variants had EC_{50} value fold-changes ≤1.1 relative to USA-WA1/2020. Ritonavir is not active against SARS-CoV-2 M^{pro}. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.
	Important information about its composition: N/A
Hyperlink to the Product Information:	Please refer to Module 1.3.1 of this submission.
Indication(s) in the EEA	Current: Treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

Dosage in the EEA	Current: The recommended dosage is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days. Refer to the SmPC for dosing information on special populations.
Pharmaceutical form(s) and strengths	Current ***Nirmatrelvir*** Pink, oval film-coated tablet containing 150 mg of nirmatrelvir. ***Ritonavir*** White to off white, capsule shaped tablets containing 100 mg of ritonavir. Nirmatrelvir/ritonavir is packaged in cartons containing 5 daily blister cards. Each daily blister card contains 4 nirmatrelvir tablets and 2 ritonavir tablets.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Indication:

Treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.

Incidence:

The coronavirus disease of 2019 (COVID-19) is caused by a novel coronavirus labelled as SARS-CoV-2. The disease first emerged in December 2019, when a cluster of patients with pneumonia of unknown cause was recognised in Wuhan City, Hubei Province, China.[1] The number of infected cases rapidly increased and spread beyond China throughout the world. On 30 January 2020, the WHO declared COVID-19 a Public Health Emergency of International Concern and thus a pandemic.[2]

Estimates of SARS-CoV-2 incidence change rapidly. The MAA obtained incidence and prevalence estimates using data from Worldometer, a trusted independent organisation that collects COVID-19 data from official reports and publishes current global and country-specific statistics online.[3]

As of 03 January 2023, the overall number of people who had been infected with SARS-CoV-2 was over 665 million worldwide.[4]

Table 1 shows the incidence and prevalence as of 03 January 2023 for the US, UK, and EU-27 countries. In the EU and the UK, by 03 January 2023 the total number of confirmed cases had accumulated over 204 million people, or 39,879 per 100,000 people. Across countries in the EU, the number of confirmed cases ranged from 16,877 to 63,005 cases per 100,000 people. Poland and Romania reported the lowest incidence rates while France, Slovenia, and Austria reported the highest.[4]

In the US, the number of confirmed cases had reached over 102 million cases (30,671 per 100,000 people) by 03 January 2023.[4]

Table 1. Incidence, Prevalence, and Mortality of COVID-19 as of 03 January 2023

	Total Cases	Incidence: Total Cases/ 100,000	Active Cases	Prevalence: Active Cases/ 100,000	Total Deaths	Mortality: Deaths / 100,000	Population
Global	665,769,282	8,313	21,217,028	265	6,700,127	84	8,009,090,379[a]
EU-27	180,714,298	40,593	2,976,121	669	1,191,872	268	445,181,267
UK	24,135,084	35,235	81,385	119	198,937	290	68,497,907
EU-27 + UK	204,849,382	39,879	3,057,506	595	1,390,809	271	513,679,174
US	102,688,573	30,671	1,956,378	584	1,118,484	334	334,805,269
EU-27 Countries							
Austria	5,712,491	63,005	38,146	421	21,448	237	9,066,710
Belgium	4,668,248	40,008	26,303	225	33,228	285	11,668,278
Bulgaria	1,292,224	18,879	3,872	57	38,108	557	6,844,597
Croatia	1,264,385	31,148	2,152	53	17,638	435	4,059,286

Table 1. Incidence, Prevalence, and Mortality of COVID-19 as of 03 January 2023

	Total Cases	Incidence: Total Cases/ 100,000	Active Cases	Prevalence: Active Cases/ 100,000	Total Deaths	Mortality: Deaths / 100,000	Population
Cyprus	631,111	51,587	9,010	736	1,258	103	1,223,387
Czech Republic	4,580,954	42,666	4,693	44	42,158	393	10,736,784
Denmark	3,168,542	54,303	9,229	158	7,848	134	5,834,950
Estonia	612,432	46,329	84,570	6,398	2,872	217	1,321,910
Finland	1,438,205	25,890	15,584	281	7,933	143	5,554,960
France	39,356,184	60,008	673,039	1,026	162,377	248	65,584,518
Germany	37,410,650	44,598	538,936	642	161,714	193	83,883,596
Greece	5,548,487	53,782	0	0	34,779	337	10,316,637
Hungary	2,185,816	22,754	13,571	141	48,495	505	9,606,259
Ireland	1,687,668	33,618	5,843	116	8,293	165	5,020,199
Italy	25,143,705	41,723	417,661	693	184,642	306	60,262,770
Latvia	974,046	52,684	17,562	950	6,165	333	1,848,837
Lithuania	1,289,255	48,437	7,231	272	9,488	356	2,661,708
Luxembourg	297,757	46,353	7,633	1,188	1,133	176	642,371
Malta	116,489	26,234	731	165	817	184	444,033
Netherlands	8,569,228	49,788	23,806	138	22,989	134	17,211,447
Poland	6,369,442	16,877	914,956	2,424	118,546	314	37,739,785
Portugal	5,557,941	54,809	10,304	102	25,805	254	10,140,570
Romania	3,312,085	17,403	10,423	55	67,408	354	19,031,335
Slovakia	1,859,363	34,053	1,228	22	20,827	381	5,460,193
Slovenia	1,308,470	62,967	19,459	936	7,013	337	2,078,034
Spain	13,684,258	29,290	80,480	172	117,095	251	46,719,142
Sweden	2,674,862	26,175	39,699	388	21,795	213	10,218,971

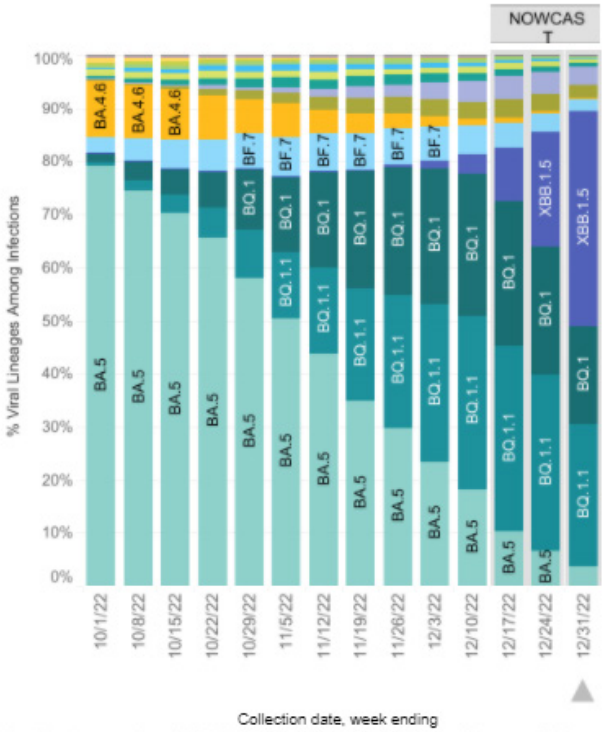
a. World population based on https://www.worldometers.info/world-population/#:~:text=7.9%20Billion%20(2022),Nations%20estimates%20elaborated%20by%20Worldometer accessed on 03 January 2023

The reported numbers refer to cases that have been tested and confirmed to be carrying the virus and sometimes, depending upon the country, also presumptive, suspect, or probable cases of detected infection. There are large geographic variations in the proportion of the population tested as well as in the quality of reporting across countries. People who carry the virus but remain asymptomatic are less likely to be tested and therefore mild cases are likely underreported.[5] Further, as at-home rapid testing kits have become more readily available[6] and formal testing resources reach capacity due to the Omicron variant, the true estimate of cases is estimated to be larger than formally reported counts. The numbers should therefore be interpreted with caution.[7] The variants from all SARS-CoV-2 specimens sequenced by the CDC during the week ending 31 December 2022 can be found in Figure 1 below, along with the variant proportions identified from the week ending 01 October through the week ending 31 December 2022.[7] Figure 2 shows the variant proportions of all EU countries from Weeks 38-49 2022[8].

Figure 1. Variant proportions for all SARS-CoV-2 specimens sequenced by the CDC during the week ending 31 December 2022 and since the week ending 01 October 2022

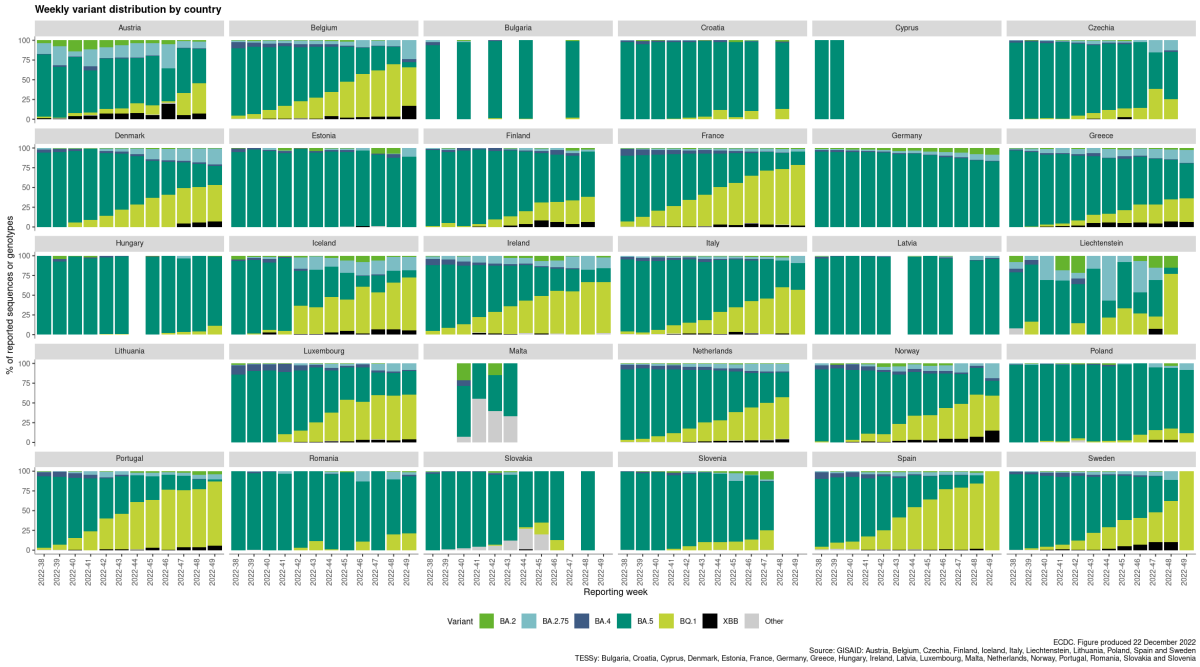
USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	XBB.1.5	VOC	40.5%	22.7-61.0%
	BQ.1.1	VOC	26.9%	18.9-36.5%
	BQ.1	VOC	18.3%	12.5-25.9%
	BA.5	VOC	3.7%	2.6-5.2%
	XBB	VOC	3.6%	2.5-5.0%
	BN.1	VOC	2.4%	1.6-3.5%
	BF.7	VOC	2.1%	1.4-3.1%
	BA.2.75	VOC	0.9%	0.5-1.4%
	BA.5.2.6	VOC	0.6%	0.4-0.9%
	BA.4.6	VOC	0.3%	0.2-0.5%
	BA.2	VOC	0.3%	0.2-0.5%
	BF.11	VOC	0.3%	0.2-0.4%
	BA.2.75.2	VOC	0.1%	0.1-0.2%
	BA.4	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%



* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
\# BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, BA.2.75.2, BN.1,XBB and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BF.11, BA.5.2.6, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. Except XBB.1.5, sublineages of XBB are aggregated to XBB. For all the lineages listed in the above table, their sublineages are aggregated to the listed parental lineages respectively. Previously, XBB.1.5 was aggregated to XBB. Lineages BA.2.75.2, XBB, XBB.1.5, BN.1, BA.4.6, BF.7, BF.11, BA.5.2.6 and BQ.1.1 contain the spike substitution R346T.

Figure 2. Weekly variant plots for the EU, Weeks 38-49 2022



Prevalence:

The prevalence of SARS-CoV-2 infection is defined as active cases per 100,000 people including confirmed cases in people who have not recovered or died. On 03 January 2023, the overall prevalence estimates for the EU and UK were 669 and 119 active cases per 100,000, respectively.[4] The range of reported prevalence for EU-27 was 0 to 6,398 per 100,000: Greece, Slovakia, and the Czech Republic reported the lowest prevalence while Luxembourg, Poland, and Estonia reported the highest (Table 1). It should be noted that Greece reported 0 active cases on 03 January 2023, leading to a prevalence estimate of 0 per 100,000 population.

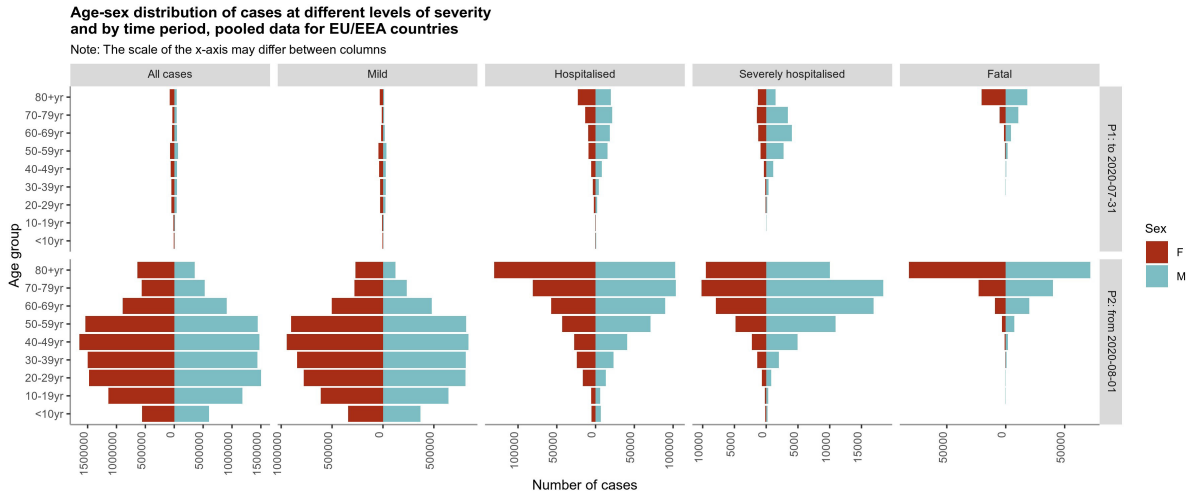
In the US, the prevalence on 03 January 2023 was 584 active cases per 100,000.[4]

Demographics of the population in the proposed indication and risk factors for the disease:

Since the beginning of the pandemic, the ECDC has collected COVID-19 information from all countries who are members of the EU/EEA. In the ECDC's TESSy database COVID-19 case-based data, including age and gender are available for over 80% of the official number of cases reported by ECDC epidemic intelligence,[9] enabling estimates of age and gender distribution representative of the European population. The ECDC website posted a notice that the 04 November 2021 edition of the COVID-19 surveillance report would be the last and that it would not be updated in that form in the future. Henceforth, surveillance data would be reported in a weekly "Country Overview Report" that provides less age-based information and no gender-based information. Relevant age- and gender-based data from the final edition of the more comprehensive COVID-19 surveillance report on 04 November 2021, as well as available age-based data from the most recent edition (23 December 2021)

of the Country Overview Report are presented. TESSy data on age and sex distributions by severity of symptoms as posted on 04 November 2021 are shown in Figure 3.[10]

Figure 3. Age-Sex Distribution of COVID-19 Cases as Different Levels of Severity, Pooled Data for EU/EEA Countries. Case-based Data from TESSy produced on 04 November 2021[a]



Note: "mild" = a case that has not been reported as hospitalized or a case that resulted in death.

a. Data from ECDC. COVID-19 Surveillance report. Week 43, 2021. 04 November 2021. "2.2 Age-sex pyramids" Accessed 26 March 2022[10].

US distributions of reported COVID cases and deaths as of 28 December 2022 are stratified by demographics and presented in Table 2 and Table 3.[11] Only cases and deaths with information reported to the CDC were included in these summaries.

Table 2. Distributions of Cases (n=94,447,829) by Age, Sex, Race, and Cross-Tabulated Age and Sex – United States as of 28 December 2022[a]

Event	Age Group	Age %	Sex	Sex %	Race[b]	Race %	Age Group	Males %	Females %
Cases	**0-4**	3.6	**Males**	46.2	**H/L**	24.7	**0-4**	52.1	47.9
	5-11	6.5	**Females**	53.8	**AI/AN**	0.9	**5-11**	51.2	48.8
	12-15	4.5	**Other**	<0.1	**Asian**	4.4	**12-15**	49.5	50.5
	16-17	2.6			**Black**	12.4	**16-17**	47.2	52.8
	18-29	20.4			**NH/PI**	0.3	**18-29**	44.6	55.4
	30-39	16.7			**White**	53.4	**30-39**	45	55
	40-49	14.2			**M/O**	3.9	**40-49**	45.1	54.8
	50-64	18.5					**50-64**	46.5	53.5
	65-74	7.3					**65-74**	47.4	52.6
	75-84	3.8					**75-84**	46.2	53.8
	85+	1.9					**85+**	37.1	62.9

a. Percentage of missing demographic data varied by types of event and demographic. Race/ethnicity available for 64% of cases, age available for 99% of cases, and sex available for 96.7% of cases.

b. Except for Hispanics/Latinos, all categories refer to non-Hispanics.

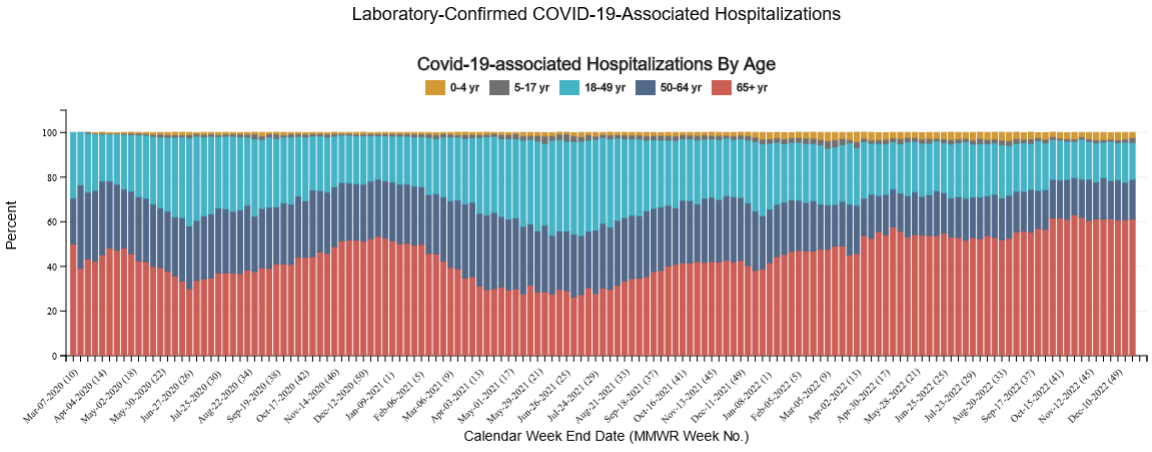
Table 3. Distributions of Deaths (n=937,757) by Age, Sex, Race, and Cross-Tabulated Age and Sex – United States as of 28 December 2022[a]

Event	Age Group	Age %	Sex	Sex %	Race[b]	Race %	Age Group	Males %	Females %
Deaths	**0-4**	0.1	**Males**	55	**H/L**	17.1	**0-4**	53.6	46.4
	5-11	0.1	**Females**	45	**AI/AN**	0.9	**5-11**	56.2	43.8
	12-15	0.1	**Other**	<0.1	**Asian**	3.2	**12-15**	48.1	51.9
	16-17	<0.1			**Black**	13.2	**16-17**	61.7	38.3
	18-29	0.7			**NH/PI**	0.2	**18-29**	60.4	39.6
	30-39	1.8			**White**	63.2	**30-39**	61	39
	40-49	4.1			**M/O**	2.2	**40-49**	62.6	37.4
	50-64	17.8					**50-64**	62	38
	65-74	22.4					**65-74**	59.4	40.6
	75-84	26					**75-84**	55.9	44.1
	85+	27					**85+**	44	56

a. Percentage of missing demographic data varied by types of event and demographic. Race/ethnicity available for 83% of deaths, age data available for 99% of deaths, and sex available for 97% of deaths.
b. Except for Hispanics/Latinos, all categories refer to non-Hispanics.

COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) performs population-based surveillance for laboratory-confirmed SARS-CoV-2-associated hospitalizations in the US. Cases are identified by reviewing hospital, laboratory, and admission database and infection control logs for patients who are hospitalized and have documented positive SARS-CoV-2 test. Based on data from COVID-NET, COVID-19 associated US hospitalizations, by age, for the period 07 March 2020 through 10 December 2022 are shown in Figure 4.[12]

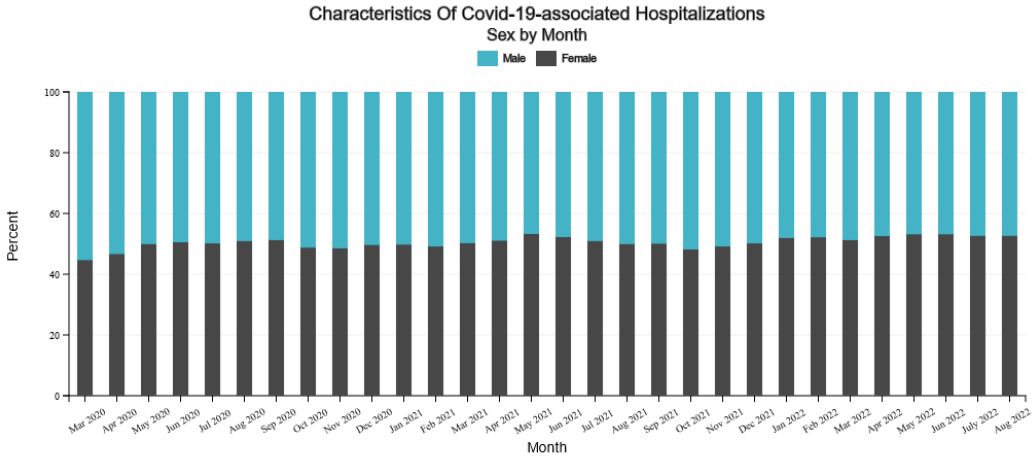
Figure 4. COVID-19-Associated US Hospital Admissions by Age, March 2020 - December 2022



The Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) hospitalization data are preliminary and subject to change as more data become available. In particular, case counts and rates for recent hospital admissions are subject to lag. Lag for COVID-NET case identification and reporting might increase around holidays or during periods of increased hospital utilization. As data are received each week, prior case counts and rates are updated accordingly.

Based on data from COVID-19 associated US hospitalizations, by sex, for the period 07 March 2020 through 31 August 2022 are shown in Figure 5[13].

Figure 5. COVID-19-Associated US Hospital Admissions by Sex, March 2020 – August 2022



1. The Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) hospitalization data are preliminary and subject to change as more data become available. In particular, case counts and rates for recent hospital admissions are subject to lag. Lag for COVID-NET case identification and reporting might increase around holidays or during periods of increased hospital utilization. As data are received each week, prior case counts and rates are updated accordingly.
2. White, Black, Asian/Pacific Islander and American Indian/Alaska Native all represent non-Hispanic ethnicity groups; Other includes persons in multiple race categories and persons for whom race is unknown.
3. All data presented, including demographics (age, sex, race and ethnicity), interventions and outcomes, underlying medical conditions, signs/symptoms at admission and discharge diagnoses are restricted to sampled and completed cases with non-missing data reported during March 1, 2020 – August 31, 2022. Due to the sampling methodology for adults aged ≥18 years, counts and unweighted percentages are only presented for demographic data. Weighted percentages are presented for intensive care unit admission, mechanical ventilation, in-hospital death, underlying medical conditions, signs/symptoms at admission, and discharge diagnoses. MD did not contribute data between December 2021 and June 2022.

Published studies have provided demographics of patients affected by COVID-19. In a study that analyzed data from 1,164 symptomatic, molecularly confirmed hospitalized (admitted between 05 May 2020 and 19 March 2021) adult COVID-19 patients from 20 different hospitals across the US, the median age was 59.0 years (intra-quartile range 20 years) and 61% of the patients were male. The racial/ethnic distribution of the patients was 48% white, 22% black, 5% Asian, 31% Hispanic and 65% non-hispanic.[14]

An observational, retrospective study examined 1,436 patients ≥18 year-old with confirmed COVID-19 presenting to the Emergency Departments of 10 hospitals in the United Kingdom, Italy, Spain and Switzerland, predominantly during the first wave of the pandemic. Those who were not admitted to hospital were a mean age of 51.6 (+/- 12.8) years old and 51.9% of them were male. Those admitted to hospital were analyzed separately according to whether they survived or not. The mean ages of those admitted were 62.5 (+/- 15.3) years and 62.6% were males for those who survived. For those who did not survive, mean age was 71.3 (+/- 12) years and 70.6% were male.[15]

Another study used data from the Primary Care Sentinel Cohort of the Oxford Royal College of General Practitioners Research and Surveillance Centre database, which is considered to be nationally representative of the English population, to identify COVID-19 cases from 01 March 2020 to 01 April 2021. Overall, the investigators identified 395,680 persons with COVID-19 among the 7,382,775 persons registered in the database. The mean (SD) age of those infected was 44.56 (21.75) years; 55.6% of them were female; the racial distribution was 65.1% white, 2.8% black, 8.7% Asian, 2.3% other and 21.1% unknown; and 57% of them were from the "most deprived" socio-economic category.[16]

An analysis of US data from 2020 showed that disease has been much less severe among ages 0-24 years compared to ages ≥25 years, with 2.5% hospitalised, 0.8% admitted to an intensive care unit, and <0.1% dying among ages 0-24, versus 16.6% hospitalised, 8.6% intensive care, and 5% dying among ages ≥25 years.[17] Early in the pandemic, approximately 90% of hospitalised cases were over 40 years old and the majority had been male, although currently there is an approximately equal distribution in sex.[18-22]

African American COVID-19 patients have been reported to have an increased risk of hospitalisation,[19,23] and mortality,[24] compared to white patients in the United States. A CDC report examined demographic trends among US COVID-19 deaths from May to August of 2020.[25] During the observation period, the percentage of US COVID-19 deaths that were Hispanic increased from 16.3% in May to 26.4% in August, the only racial or ethnic group among whom the percentage of deaths increased during that time.

An earlier CDC report on excess deaths covering 26 January 2020 through 03 October 2020 broke down excess deaths by demographics.[26] By age during that period, the largest increase in deaths compared to average expected deaths occurred among adults aged 25-44 (26.5% increase) while deaths among people <25 years was 2.0% below average during this period. By race, increases in deaths compared to expectation were largest among Hispanics (53.6% increase), Asian Americans (36.6% increase), African Americans (32.9% increase).

In a 2021 report, the CDC data on Excess Deaths Associated with COVID-19 reported that deaths in age groups 25-44, 45-64, 65-74, 75-84, and ≥85 years exceeded historical numbers from 2015-2019.[27]

While research earlier in the pandemic tended to focus on adults, more recent data have given greater attention to children and adolescents. For the period January 1-March 31 2021 across 14 states (the most recently available data), the CDC's Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) database recorded 204 adolescents aged 12-17 who were hospitalized for likely primarily COVID-19-related reasons.[28] The 204 adolescents were 47.5% male—consistent with the COVID case sex distribution across all ages—and disproportionately from minorities, with 31.4% Hispanic and 35.8% non-Hispanic African Americans.[28] For the period 07 March 2020 –24 December 2022, the CDC's COVID-NET database recorded that 6,434 children aged 0-4 had a positive COVID test proximal to hospitalization and 6,239 children aged 5-17 had a positive COVID test proximal to hospitalization.[29]

Another CDC report described demographic trends in US COVID-19 incidence among 15,068 cases aged 0-24 years across 16 jurisdictions during the period 01 January 2020 through 31 December 2020.[30] The report broke down incidence by age groups and 2020 sub-periods that are presented in Table 4. The table shows that early in 2020, 5-9 year olds were experiencing less COVID-19 than 0-4 year olds, but by the end of the year this pattern had reversed. Compared to 5-9 year olds, the age categories 10-14, 15-19, and 20-24 years old showed progressively greater incidence rates, a pattern that held throughout 2020.

Table 4. COVID-19 incidence and rate ratios, by age group among persons aged <25 years across three periods of 2020 in 16 U.S. jurisdictions

2020 Sub-Period	Age Group (years)	Number of Cases	Cases per 100,000 population (95% CI)	Rate Ratio (95% CI)
Jan 1-Apr 30	0-4	956	21 (20-23)	1.28 (1.17-1.41)
	5-9	772	17 (16-18)	Reference
	10-14	1,184	25 (23-26)	1.49 (1.36-1.63)
	15-19	3,267	67 (65-70)	4.03 (3.72-4.36)
	20-24	8,889	175 (171-178)	10.47 (9.72-11.26)
May 1-Aug 31	0-4	14,017	314 (309-319)	1.01 (0.98–1.03)
	5-9	14,406	312 (307-317)	Reference
	10-14	20,490	430 (424-436)	1.38 (1.35–1.41)
	15-19	50,210	1,034 (1,025-1,043)	3.32 (3.26–3.38)
	20-24	78,655	1,547 (1,536-1,557)	4.96 (4.88–5.05)
Sep 1-Dec 31	0-4	33,595	752 (744–760)	0.71 (0.70–0.72)
	5-9	48,824	1,056 (1,047–1,066)	Reference
	10-14	76,922	1,615 (1,604–1,627)	1.53 (1.51–1.55)
	15-19	149,660	3,083 (3,067–3,098)	2.92 (2.89–2.95)
	20-24	187,825	3,693 (3,677–3,710)	3.50 (3.46–3.53)

Other US paediatric data are generally consistent with the CDC findings. Table 5 summarizes demographic results for a retrospective cohort of 135,794 individuals under the age of 25 who were tested for COVID-19 by 08 September 2020 within the PEDSnet network of US paediatric health systems.[31] The table shows that, among the paediatric population, children age 12-17 were more frequently infected than those under age 12. African Americans and Hispanics had elevated frequencies of testing positive relative to their proportion of the cohort.

Table 5. Demographics of 135,794 US individuals under age 25 tested for COVID- 19 by 08 September 2020

Characteristic	Patients, n (%)		
	COVID-19 negative (n=130,420)	COVID-19 positive, Asymptomatic or mild illness (n=5,015)	COVID-19 positive, Severe illness (n=359)
Age, years			
<1	17,431 (13)	494 (10)	72 (20)
1-4	32,619 (25)	808 (16)	40 (11)
5-11	35,617 (27)	1,029 (21)	72 (20)
12-17	32,362 (25)	1,521 (30)	117 (33)
18-24	12,391 (10)	1,163 (23)	58 (16)
Sex			
Female	61,637 (47)	2,527 (50)	172 (48)
Male	68,701 (53)	2,485 (50)	187 (52)
Other or Unknown	82 (0.06)	3 (0.06)	0
Race/ethnicity			
Hispanic	14,156 (11)	918 (18)	108 (30)
API	4,471 (3)	151 (3)	9 (3)
Black or AA	18,646 (14)	1,424 (28)	119 (33)
White	77,540 (60)	1,988 (40)	97 (27)

Table 5. Demographics of 135,794 US individuals under age 25 tested for COVID- 19 by 08 September 2020

Characteristic	Patients, n (%)		
	COVID-19 negative (n=130,420)	COVID-19 positive, Asymptomatic or mild illness (n=5,015)	COVID-19 positive, Severe illness (n=359)
Multiple	3,883 (3)	126 (3)	5 (1)
Other or Unknown	11,724 (9)	408 (8)	21 (6)

A study of 1,945,831 individuals aged 0-18 recorded in the Premier Healthcare Database between March and October 2020 included 20,714 paediatric cases of COVID-19; the authors reported similar patterns to what is shown in Table 5 with the additional observation that COVID-19 cases aged 0-1 and 12-18 years were more likely to develop serious illness than those aged 2-11.[32]

A retrospective study of public health surveillance data in Denver, Colorado identified 9,815 children and adolescents who had COVID-19 from 1 March 2020, through 30 September 2021. The age distribution of those infected was as follows: <1 yr 4.9%, 1-4 yrs 16.3%, 5-10 yrs 29.6%, 11-13 yrs 18.4%, and 14-17 yrs 30.8%. The cases were 50% male and 50% female. The racial/ethnic distribution was Hispanic / Latino 57.3%, non-Hispanic White 29.0%, non-Hispanic Black 7.1%, and non-Hispanic other 6.5% from a base population that was Hispanic / Latino 46.2%, non-Hispanic White 36.9%, non-Hispanic Black 12.0%, and non-Hispanic other 4.9%.[33]

Risk Factors

Human-to-human transmission of SARS-CoV-2 occurs primarily through respiratory droplets and direct contact.[34] Thus the risk of initial infection increases through spending time in close physical proximity to others, especially in indoor spaces with poor ventilation.[35] People living in long-term care facilities or high-density apartment homes, or working in occupations with close proximity to others (eg, healthcare, transportation), have a higher risk of infection.[35,36] Among children, the primary source of infection is an infected adult living in the same household,[37] but age is not associated with risk of initial infection among people aged 5 and older based on current data from the CDC (Table 6).[38]

According to the CDC, some ethnic minority groups have a higher risk of infection (Table 6).[39] Male sex is also a significant risk factor for severe disease and mortality due to COVID-19.[40] In addition, there is evidence that high-risk human leukocyte antigen haplotypes, higher expression of angiotensin-converting enzyme polymorphisms, and several genes of cellular proteases increase the risk of susceptibility and severity of COVID-19.[41,42] Lastly, recent narrative reviews and meta-analyses indicate that Blood type O is associated with lower rates of SARS-CoV-2 infection; whereas type A is frequently described as a risk factor and is most often associated with COVID-19 severity and mortality.[43,44]

Table 6. Risk for COVID-19 Infection, Hospitalisation, and Death by Age Group and by Race/Ethnicity as of 28 December 2022

	Rate ratios[c]		
Age Group (years)	**Cases[d]**	**Hospitalisation[e]**	**Death[f]**
0-4	0.5	0.6	0.2
5-17	0.7	0.2	0.1
18-29[a]	Ref	Ref	Ref
30-39	1	1.5	3.5
40-49	0.9	1.9	10
50-64	0.8	3.1	25
65-74	0.6	4.8	60
75-84	0.6	8.6	140
85+	0.7	15	350
Race/Ethnicity	**Cases[g]**	**Hospitalisation[h]**	**Death[i]**
Non-Hispanic White[b]	Ref	Ref	Ref
American Indian or Alaska Native, non-Hispanic	1.5	2.5	2.1
Asian, non-Hispanic	0.8	0.7	0.8
Black or African American, non-Hispanic	1.1	2.1	1.6
Hispanic or Latino	1.5	1.9	1.7

a. Rate ratios for each age group are relative to the 18-29-year age category. This group was selected as the reference group because it has accounted for the largest cumulative number of COVID-19 cases compared to other age groups.
b. Rate ratios for each race/ethnicity group are relative to the Non-Hispanic White category.
c. Rates for age groups are expressed as whole numbers, with values less than 10 rounded to the nearest integer, two-digit numbers rounded to nearest multiple of five, and numbers greater than 100 rounded to two significant digits. Rates for race/ethnicity groups are rounded to the nearest tenth.
d. Includes all cases reported by state and territorial jurisdictions (through 06 December 2022, accessed on 13 December 2022). The denominators used to calculate rates were based on the 2019 Vintage population (https://www.census.gov/newsroom/press-releases/2019/popest-nation html).
e. Includes all hospitalizations reported through COVID-NET (from 01 March 2020 through 04 December 2022, accessed on 13 December 2022). Rates were standardized to the 2000 US standard COVID-NET catchment population.
f. Includes all deaths in National Center for Health Statistics (NCHS) provisional death counts (through 03 December 2022, accessed on 13 December 2022. The denominators used to calculate rates were based on the 2019 Vintage population.
g. Case level surveillance data from state, local and territorial public health jurisdictions (data through 7 December 2022). Numbers are ratios of age-adjusted rates standardized to the 2019 U.S. intercensal population estimate. Calculations use only the 65% of case reports that have race and ethnicity; this can result in inaccurate estimates of the relative risk among groups.
h. Includes all hospitalizations reported through COVID-NET (01 March 2020 through 03 December 2022). Numbers are ratios of age-adjusted rates standardized to the 2020 US standard COVID-NET catchment population.
i. Includes all deaths in National Center for Health Statistics Provisional Death Counts (data through 03 December 2022). Numbers are ratios of age-adjusted rates standardized to the 2019 U.S. intercensal population estimate.

Risk for severe or fatal COVID-19 disease has been shown to increase with older age, male sex, or ethnic minority status.[27,38-41,45-51] Among adults, these risks increase for every 10-year age group above age 39 (Table 6).[27,38,39,45-49,52] Table 6 also gives estimated rate ratios for COVID-19 hospitalisation and death by race/ethnicity relative to white, non-Hispanic persons in the US. Based on regularly updated data from the CDC, the highest risks of hospitalisation and death occurred in those who were American Indian or Alaska native

persons (RR = 2.5 for hospitalisation and 2.1 for death), when compared to those who were non-Hispanic white. These differences in risk among ethnic groups may be attributed to differences in underlying factors that are correlated with race/ethnicity including socioeconomic status, access to health care, and occupation-related virus exposure.[53] Children aged 5-17 typically experience a milder disease course and have lower risk of hospitalization or death. Further, among a cohort of children hospitalized with COVID-19 in the United States from March 2020 to May 2021, children 6 months – 4 years of age had a similar risk of severe disease as children ages 12 – 17 years.[54]

Risk of severe or fatal COVID-19 disease is higher among persons who are current or former smokers, have lower socioeconomic status, have no or public insurance, or live in neighbourhoods with higher rates of limited English proficiency.[27,45,52,34,50,55,56] The CDC has also recognised other socio-demographic groups who may need to take extra precautions against COVID-19 due to increased risk for severe illness: pregnant women; breastfeeding mothers; people with disabilities or those who are clinically frail; people with developmental, behavioural, or substance abuse disorders and newly resettled refugee populations.[57]

Among adults, risk for severe or fatal COVID-19 disease increases with the presence of chronic medical conditions, including obesity, chronic lung diseases (eg, COPD or asthma), cardiovascular disease, diabetes, cancer, liver disease, neurological diseases (eg, stroke or dementia), chronic kidney disease, sickle cell disease, immunosuppression, HIV, higher scores on the WHO Clinical Progression Scale and Charlson Comorbidity Index.[27,45,46,50,52,58-72] Table 7 shows the estimated hazard ratios of COVID-19 mortality associated with these chronic conditions and socio-demographics from a cohort study of 17 million adults (with 17,000 COVID-19-related deaths) in England.[52]

Table 7. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death

Characteristic	Category	COVID-19 death Hazard Ratio	
		Adjusted for age, sex, and NHS administrative region	Fully adjusted
Age	18-39	0.05 (0.04-0.06)	0.06 (0.04-0.07)
	40-49	0.32 (0.28-0.38)	0.34 (0.29-0.39)
	50-59	1.00 (ref)	1.00 (ref)
	60-69	2.93 (2.69-3.20)	2.57 (2.35-2.80)
	70-79	9.17 (8.48-9.93)	6.74 (6.21-7.31)
	80+	43.16 (40.03-46.53)	24.10 (22.23-26.13)
Sex	Female	1.00 (ref)	1.00 (ref)
	Male	1.73 (1.68-1.78)	1.55 (1.50-1.60)
BMI (kg/m^2)	Not obese	1.00 (ref)	1.00 (ref)
	30-34.9 (obese class I)	1.23 (1.18-1.28)	1.07 (1.03-1.12)
	35-39.9 (obese class II)	1.79 (1.68-1.90)	1.44 (1.36-1.54)
	40+ (obese class III)	2.76 (2.54-3.00)	2.11 (1.93-2.29)
Smoking	Never	1.00 (ref)	1.00 (ref)
	Former	1.44 (1.40-1.49)	1.26 (1.22-1.30)
	Current	1.17 (1.10-1.25)	0.97 (0.91-1.04)

Table 7. Hazard Ratios and 95% Confidence Intervals for COVID-19-related Death

Characteristic	Category	COVID-19 death Hazard Ratio	
		Adjusted for age, sex, and NHS administrative region	Fully adjusted
Ethnicity	White	1.00 (ref)	1.00 (ref)
	Mixed	1.59 (1.28-1.97)	1.43 (1.15-1.78)
	South Asian	1.97 (1.82-2.14)	1.70 (1.55-1.85)
	Black	1.82 (1.61-2.05)	1.44 (1.27-1.63)
	Other	1.38 (1.17-1.63)	1.38 (1.16-1.63)
IMD quintile[a]	1 (least deprived)	1.00 (ref)	1.00 (ref)
	2	1.17 (1.11-1.23)	1.13 (1.07-1.19)
	3	1.37 (1.30-1.44)	1.25 (1.19-1.32)
	4	1.77 (1.68-1.86)	1.53 (1.46-1.61)
	5 (most deprived)	2.11 (2.01-2.22)	1.71 (1.62-1.80)
Blood pressure	Normal	1.00 (ref)	1.00 (ref)
	High BP or diagnosed hypertension	1.09 (1.06-1.13)	0.90 (0.87-0.94)
Respiratory disease excluding asthma		1.95 (1.86–2.04)	1.66 (1.59-1.73)
Asthma (vs. none)	With no recent OCS use	1.15 (1.10-1.21)	1.00 (0.95-1.05)
	With recent OCS use	1.61 (1.47-1.75)	1.15 (1.05-1.26)
Chronic heart disease		1.57 (1.51–1.64)	
Diabetes[b] (vs. none)	With HbA1c <58 mmol/mol	1.53 (1.47-1.59)	1.20 (1.16-1.25)
	With HbA1c ≥58 mmol/mol	2.57 (2.45-2.70)	1.83 (1.74-1.93)
	With no recent HbA1c measure	2.19 (2.02-2.37)	1.71 (1.58-1.86)
Cancer (non-hematological, vs. none)	Diagnosed <1 year ago	1.47 (1.31-1.65)	1.44 (1.28-1.62)
	Diagnosed 1-4.9 years ago	1.13 (1.04-1.22)	1.11 (1.03-1.20)
	Diagnosed ≥5 years ago	0.99 (0.95-1.04)	2.41 (1.86-3.13)
Hematological malignancy (vs. none)	Diagnosed <1 year ago	2.54 (1.96-3.29)	2.80 (2.08–3.78)
	Diagnosed 1-4.9 years ago	2.28 (1.95-2.66)	2.25 (1.92-2.62)
	Diagnosed ≥5 years ago	1.71 (1.51-1.93)	1.65 (1.46-1.87)
Reduced kidney function[c] (vs. none)	eGFR 30-60	1.50 (1.45-1.55)	1.30 (1.25-1.35)
	eGFR 15-<30	2.74 (2.56-2.93)	2.52 (2.33–2.72)
	eGFR <15 or dialysis	6.40 (5.75-7.12)	4.42 (3.93-4.98)
Liver disease		2.27 (2.01-2.57)	1.75 (1.54-1.98)
Dementia		4.59 (4.33-4.87)	3.62 (3.41-3.84)
Stroke		2.03 (1.95-2.12)	1.53 (1.46-1.59)
Other neurological disease		3.15 (2.96-3.36)	2.72 (2.55-2.90)
Organ transplant		5.54 (4.51-6.81)	1.61 (1.28-2.02)
Asplenia		1.50 (1.16-1.95)	1.26 (0.97-1.64)
Rheumatoid arthritis, lupus, or psoriasis		1.30 (1.21–1.38)	1.23 (1.17-1.30)
Other immunosuppressive condition		2.75 (2.10–3.62)	2.00 (1.57-2.54)

a. Index of Multiple Deprivation (derived from the patient's postcode)
b. Classification by HbA1c is based on the most recent measurement within 15 months of baseline.
c. eGFR is measured in ml min−1 per 1.73 m2 and derived from the most recent serum creatinine measurement.
Models were adjusted for age using a four-knot cubic spline for age, except for estimation of age-group hazard ratios. Ref, reference group; 95% CI, 95% confidence interval.

A recent prospective observational study sought to better understand the association between characteristics of adult patients hospitalized with COVID-19 in the US and the risk of clinical outcomes and post-acute clinical sequalae of COVID-19 (PASC).[14] A total of 1,164 patients symptomatic patients admitted to 20 hospitals (affiliated with 15 academic institutions) across the US were enrolled. Admission-specific data elements were acquired via review of electronic medical records at 5 separate time-points over a 28-day period. The patients' disease severity was assessed at each time-point using a 7-point ordinal scale (ranging from not hospitalized/no limitations to death) based on World Health Organization and US National Institute of Allergy and Infectious Disease severity scales. Data lock on the survey data was performed on 07 April 2022. The median age was 59 years (interquartile range 20); 711 (61%) were men; the overall mortality was 14%, and 228 (20%) of the patients required invasive mechanical ventilation. The authors report that risk factors associated with prolonged hospitalization or death by day 28 included age ≥65 years, Hispanic ethnicity, elevated baseline creatinine or troponin, baseline lymphopenia, presence of infiltrate by chest imaging, and high SARS-CoV2 viral load. Survivors were prospectively surveyed for 1 year after discharge through quarterly surveys. Of these 589 completed at least one survey at follow-up. Three hundred five (52%) of those completing at least one survey had at least one symptom consistent with PASC, most commonly dyspnea. Female sex was the only associated risk factor for PASC.[14]

Another recent study by Tsai et al was conducted with the aim to estimate the global risk and risk factors associated with acute respiratory distress syndrome among patients with COVID-19. The authors performed a systematic review, meta-analysis and meta-regression of published studies from of patients in hospitals or nursing homes with ARDS after COVID-19. Study inclusion criteria were: (1) the study provided primary data on the prevalence of ARDS using validated assessment tools or coded medical report data within a population-based study after COVID-19 occurred; (2) patients were diagnosed with COVID-19; and (3) the studies were observational, such as cohort and cross-sectional studies, and were published from 2019 to 2022. A total of 12 studies, conducted in 7 countries (including the US, China, Korea, India, Germany, Poland and Greece) were included. Six studies were retrospective, three were cross-sectional, two were cohort studies, and one was a prospective study. All 12 studies were conducted with hospitalized patients. A total of 148,080 patients (50.8% male) were studied. The prevalence of ARDS among the studies ranged from 3.6% to 76.4%; the overall pooled risk was 23% (95% CI 14.3–34.7%) with significant heterogeneity within the 12 studies. Based on the meta-analysis results, significant heterogeneity was identified among the studies for the risk of ARDS. Therefore, a meta-regression analysis was conducted to identify factors affecting heterogeneity through the subgroups. Meta-regression revealed that statistically significant risk factors for ARDS included: age ≥41 to 64 years, fever, multi-lobe involvement on chest X-ray, lymphopenia, mechanical ventilation with oxygen therapy, European region, and study sample size less than or equal to 500 patients.[73]

The presence of one or more underlying medical conditions also increases risk of severe or fatal disease among children aged 5-17.[74-77] In particular, childhood obesity has been consistently associated with two to three times the risk of severe disease or hospitalisation[74,77-79] and among hospitalised children with COVID-19 diabetes has been shown to increase the risk of death two-fold compared with those without diabetes.[80] In addition, Children and adolescents with obesity, hypertension, immunodeficiencies,

malignancies, chronic respiratory diseases (cystic fibrosis, severe asthma etc.), and other chronic diseases are more susceptible to developing severe disease.[81] For many other individual comorbid conditions, pediatric sample sizes are very small and different studies produce conflicting results, so it is difficult to estimate precise risk ratios based on current literature.[37,75]

The main existing treatment options:

EMA has authorised remdesivir for the treatment of COVID-19 in adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen and in adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
Tocilizumab received an authorization for the treatment of adults with COVID-19 who are receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation.

In November 2021, Ronapreve (casirivimab/imdevimab) received EMA authorisation for treating COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) who do not require supplemental oxygen and who are at increased risk of their disease becoming severe. The medicine can also be used to prevent COVID-19 in people aged 12 years and older weighing at least 40 kilograms. Ronapreve contains two active substances, casirivimab and imdevimab.

The monoclonal antibody sotrovimab and regdanvimab and the combined tixagevimab/cilgavimab have been also authorised in EU for treating COVID-19 in patients who do not require supplemental oxygen and who are at increased risk of the disease becoming severe.

On 16 December 2021, CHMP issued advice on the use of nirmatrelvir/ritonavir for the treatment of COVID-19; on 28 January 2022, CMA was granted in EU and then switched to a full marketing authorisation on 24 February 2023.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Symptoms of COVID-19

Symptoms of COVID-19 infection can range from very mild (or no symptoms) to severe or fatal.[82-85] The most common symptoms for symptomatic infected persons are fever, dry cough, and fatigue; upper respiratory tract symptoms can include pharyngalgia, headaches, and myalgia.[34] Current data indicate that about 80% of COVID-19 patients are asymptomatic or have mild-to-moderate symptoms, while about 15% develop more severe disease requiring hospitalisation and about 5% require ventilation support.[34] In addition, 10–20% of COVID-19-infected persons experience persistent or new symptoms for periods of weeks to years.[34]

The rate of asymptomatic infection decreases with increasing age and long-term care facilities are associated with a lower rate of asymptomatic infection when compared to

household transmission or other healthcare facilities.[85] The most common symptoms of COVID-19 are fever, cough, and shortness of breath for both children and adults (Table 8).[86,87] However, it has been noted that in older people, COVID-19 clinical presentation is extremely heterogeneous and atypical signs and symptoms such as hyporexia/apyrexia, confusion, delirium, and pre-syncope / syncope are more common than in middle-aged and younger persons.[88]

A recent meta-analysis has estimated that 46.7% of infections in children are asymptomatic[85], while a recent systematic review that examined 1,140 cases of COVID-19 in children from 23 published studies found that 11% of cases were asymptomatic. Among symptoms, fever was reported in 48%, cough 37%, any nasopharyngeal symptom 22%.[89] In a more recent meta-analysis of 32 studies that provided information about COVID-19 infection in pediatric patients the proportions with specific symptoms were as follows: fever 33%, cough 25%, rhinorrhea 13%, fatigue 9%, dyspnea 9%, diarrhea 6%, headache 9%, sore throat 7% and vomiting 7%.[90]

Table 8. Signs and Symptoms among 291 Paediatric (age <18 years) and 10,944 Adult (age 18–64 years) Patients[a] with laboratory confirmed COVID-19 — United States, February 12–April 2, 2020

Sign/Symptom	No. (%) with sign/symptom	
	Paediatric	Adult
Fever, cough, or shortness of breath[b]	213 (73)	10,167 (93)
Fever[c]	163 (56)	7,794 (71)
Cough	158 (54)	8,775 (80)
Shortness of breath	39 (13)	4,674 (43)
Myalgia	66 (23)	6,713 (61)
Runny nose[d]	21 (7.2)	757 (6.9)
Sore throat	71 (24)	3,795 (35)
Headache	81 (28)	6,335 (58)
Nausea/Vomiting	31 (11)	1,746 (16)
Abdominal pain[d]	17 (5.8)	1,329 (12)
Diarrhea	37 (13)	3,353 (31)

a. Cases were included in the denominator if they had a known symptom status for fever, cough, shortness of breath, nausea/vomiting, and diarrhea. Total number of patients by age group: <18 years (N = 2,572), 18–64 years (N = 113,985).
b. Includes all cases with one or more of these symptoms.
c. Patients were included if they had information for either measured or subjective fever variables and were considered to have a fever if "yes" was indicated for either variable.
d. Runny nose and abdominal pain were less frequently completed than other symptoms; therefore, percentages with these symptoms are likely underestimates.

Progression and Timeline of Mild to Moderate Disease

Mild to moderate disease is defined as the absence of viral pneumonia and hypoxia. For those who develop symptoms, the incubation period is usually 4 to 5 days, with 97.5% experiencing symptoms within 11 days of exposure.[91,92] Those with mild COVID-19 recover at home with supportive care and guidance to self-isolate. Those with moderate disease are monitored at home and are sometimes recommended to be hospitalised if conditions worsen [92] Data on rates of re-infection are limited but variants that are not neutralized by immune antisera, such as the South African beta, delta, and omicron variants, may lead to increased risk of re-infection in the future.[91,93]

Progression and Timeline of Severe Disease Requiring Hospitalisation

Those with severe disease will require hospitalisation to manage their illness. Based on data that have been systematically collected for the US by the CDC between 01 August 2020 and 02 January 2023, there were 5,797,928 new hospital admissions for patients with confirmed COVID-19 in the US.[94] For the 50th week of 2022, 7.6 patients per 100,000 population (country range: 1.3-19.5) were hospitalised due to COVID-19 in 14 countries of the EU/EEA with available data.[95] Between 01 August 2020 and 02 January 2023, the CDC reports 175,603 total hospital admissions for patients with confirmed COVID-19 in the US for those 0-17 years of age.[94]

Studies early in the pandemic demonstrated that time from onset of illness to ARDS was 8-12 days and time from onset of illness to ICU admission was 9.5–12 days.[91] In 9 countries of the EU/EEA with available data, 0.5 patients per 100,000 population (country range 0.1-1-3) were in the ICU due to COVID-19 for the week 49 2022.[95] A recent meta-analysis found that, of patients <19 years of age, 11% went to the ICU, non-invasive ventilation was administered among 12%, and 4% required mechanical ventilation.[83] A study of 82 cases in three pediatric hospitals noted that older children and those with higher body mass index or multiple comorbidities were more likely to receive respiratory support.[96]

A large number of patient characteristics (demographic / personal, comorbid conditions, complications of COVID) have been identified as being risk factors of severe COVID or death from COVID (Table 9):

Table 9. Factors associated with severe disease or death in those with COVID-19

Demographic Characteristics	Comorbid Conditions	Complications of COVID-19
• Male gender[14,27,40,48,50,51,58,97] • Older age [14,27,48,50,58,76,97] • Ethnic minorities[14,50,52,58,76] • Lower socioeconomic status[50,58] • Obesity[27,34,48,50,58,60,61,63,65,68,76] • Smoking[48,50,55,56,58,67,76] • Blood group type A[43,44]	• Disability/clinical frailty/worse scores on health/comorbidity scales[50,76,98] • Cardiovascular disease[34,48,50,58,68,76,97,99] • Hypertension[34,48,50,58,62-64,67,97,99] • Dyslipidemia[48,63,68] • Chronic lung diseases / asthma[14,48,50,58,67,68,76,97,99] • Diabetes / higher hemoglobin a1c level[14,34,48,50,58,63,67,68,76,97,99] • Cancer[27,48,58,67,76,99] • Liver disease[58,66,68,76,99] • Neurological diseases (e.g., stroke or dementia)[48,50,58,68,76,99] • Chronic kidney disease or failure / elevated baseline creatinine[14,34,48,50,58,67,68,76,99] • Autoimmune disease[50,58,68,99] • Immunosuppression/immune compromised[50,58,72,76]	• Cardiac injury/elevated troponin[14,48,97,99] • Arryhthmia[99] • Shock[99] • Pulmonary embolism[59] • Respiratory failure/hypoxia[48,99] • GI bleeding[99] • Anemia[99] • Disseminated intravascular coagulation[99] • Rhabdomyolosis[99] • Bacterial infection/sepsis[99] • Higher neutrophil-to-lymphocyte ratio[101] • Electrolyte disturbance[99] • Elevated glycated hemoglobin[102] • Neutrophilia[48,101] • Lymphopenia[14,48,67] • Thrombocytopenia[14,48,99,101] • High circulating histone levels[103]

Table 9. Factors associated with severe disease or death in those with COVID-19

Demographic Characteristics	Comorbid Conditions	Complications of COVID-19
	• Organ transplant[58,67,76] • Mycotic infection[70] • HIV[76] • Sickle cell disease[76] • Vitamin D deficiency[60,71] • Certain genetic polymorphisms[41,42,100]	• Lower serum iron or total iron banding capacity[104] • Higher serum ferritin levels[104] • Presence of infiltrate by chest imaging[14] • High SARS-CoV2 viral load[14]

Mortality

Mortality data are presented from Worldometer, an independent organisation that publishes current, reliable COVID-19 statistics online.[3] The mortality of SARS-CoV-2 infection is defined as the cumulative number of deaths among detected cases.

As of 03 January 2023, the overall SARS-CoV-2 mortality for the EU27 + UK was 1,390,809 deaths, or 271 per 100,000 people. Reported mortality among EU countries and the UK ranged from 103 to 557 deaths per 100,000 (Table 2). Cyprus and Netherlands reported the lowest mortality; Croatia, Hungary, and Bulgaria reported the highest.[4]

In the US, as of 03 January 2023, the mortality was 1,118,484 deaths (334 per 100,000 people). Mortality in the US was higher than that of the UK (290 per 100,000).[4]

Overall reported mortality among hospitalised COVID-19 patients varies from 12.8% to 26% in the EU, UK, and US.[23,25,105,106] Mortality rates are declining over time, presumably due to an improved understanding of COVID-19 and its management.[107]

Work has been done to try and predict mortality using data from patients hospitalized with COVID-19. Two recent publications describe efforts to develop models to predict mortality. The first, by Vagliano et al, described and validated a predictive model, using data from electronic health records, for in-hospital mortality of 972 COVID-19 patients admitted between 15 February 2020 and 01 January 2021 to the intensive care units of 19 hospitals during two different waves of the pandemic. In total 322 patients (33.1 %) died during their hospital stay. Survivors were significantly younger (61.0 vs 68.2 years) and were less often males (69.8 % vs 77.6 %) than non-survivors. The strongest risk factors for mortality in the final model were older age, higher average fraction of inspired oxygen in the first 24 hours of admission, and higher maximum glucose in the first 24 hours of admission. A lower estimated glomerular filtration rate in first 24 hours of admission and higher neutrophil count in the first 24 hours of admission were other important risk factors for death.[108]

The second, by Sozio et al, was an observational, retrospective study that examined patients ≥18 years old with confirmed (by real-time reverse-transcription PCR) (COVID-19 presenting to the Emergency Departments of 10 hospitals in the United Kingdom, Italy, Spain and Switzerland, predominantly during the first wave of the pandemic. The individual probability of being discharged directly from ED or of being admitted to hospital, with or without risk of mortality due to COVID-19, was estimated with several different implementations of machine learning models based on multiclass random forest classifiers.

Analysis of Variance testing was performed according to admission and outcome status (not admitted, admitted and survived, admitted and died). Those patients who were admitted and died were older, more likely male, had higher serum creatinine levels, had lower platelet counts, had higher levels of mid-regional pro-adrenomedullin (MR-proADM; an inflammatory biomarker that improves the prognostic assessment of patients with sepsis, septic shock and organ failure), higher white blood cell counts, lower lymphocyte counts, higher LDH, Procalcitonin, CRP and D-dimer levels, and more often had comorbidities including cardiovascular disease, respiratory disease, chronic kidney disease, diabetes, hypertension, and malignancy. The most important predictors of admission and death were in order of strength: MR-proADM, age, LDH level CRP level, WBC count and platelet count. The authors presented a decision tree to facilitate interpretation of the most important interactions captured by the random forest classifier, in which age represents the predominant risk factor in determining the need for hospitalization, which is further enhanced by the patient's levels of MR-proADM and CRP.[15]

Complications of COVID-19 and Long-COVID

Complications of COVID-19 include impaired function of the heart/cardiovascular system[109-112], brain/neurological system[113,114], lung, gastrointestinal/hepatobiliary system[115], kidney[116,117], metabolic / endocrine systems[118], and coagulation system[119,120].[18,21,121]

Complications affecting the heart / cardiovascular system that have been observed include acute myocardial injury, acute coronary syndromes, venous and arterial thrombosis, cardiomyopathy, arrhythmia, myocarditis, pericarditis, heart failure, pulmonary hypertension, and right ventricular dysfunction.[109,110]. One recent review reports that the proportions of patients experiencing some of these complications are as follows: cardiac dysrhythmias in 17 to 44%, cardiac injury with increases in blood troponin in 22 to 40%, myocarditis in 2 to 7%, heart failure in 4 to 21%, and thromboembolic events in 15 to 39%.[111] Another recent review indicates that injury to the myocardium has been reported in up to 30% of hospitalized COVID-19 patients and up to 55% in those with pre-existing cardiovascular disease.[112] In addition, it has been reported that long-term follow-up of Covid-19 patients has revealed increased incidence of arrhythmia, heart failure, acute coronary syndrome, right ventricular dysfunction, and myocardial fibrosis.[110]

Neurologic complications of COVID-19 infection have also been extensively studied. Dimitriadis et al examined neurologic manifestations in critically ill COVID-19 patients in a prospective, multicenter, observational registry study of such patients admitted to 19 German ICUs between April 2020 and September 2021. During the study period, among the 15 ICUs that reported a total of 2681 admissions, 340 patients (12.7%) developed neurologic manifestations, the most common being encephalopathy (including delirium, disorder of consciousness, hypoxic encephalopathy, encephalopathy not further described), cerebrovascular disorders (including ischemic stroke, intra-cerebral hemorrhage, subarachnoid hemorrhage, posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, cerebral venous sinus thrombosis, cerebral microbleeds, subdural hematoma) and neuromuscular disorders (including polyneuropathy or myopathy, Guillain–Barré syndrome, myasthenia, myositis).[113] A meta-analysis on the incidence of seizures among COVID-19 patients by Hussaini et al included a total of 11,526 patients from 21 published articles. A total of 255 (2.2%; 95% CI 0.05-0.24, $p < 0.01$) patients presented with

seizures as the first manifestation of COVID-19. Only 71 of the 255 patients had previously been diagnosed with epilepsy.[114]

There are also psychological complications of COVID-19 infection. Khraisat et al conducted a meta-analysis to estimate the pooled prevalence of mental disorders among COVID-19 survivors. The analysis included 27 studies with a total sample size of 9605 Covid-19 survivors. The prevalence rates (95% CI) for psychological complications were as follows: overall psychological distress 36% (22–51%), post-traumatic stress disorder 20% (16–24%), anxiety 22% (18–27%), psychological distress 36% (22–51%), depression 21% (16–28%), and sleeping disorders 35% (29–41%).[122] Also, a recent narrative review of the literature on postacute neurologic sequelae of COVID-19 indicates that commonly conditions include persistent fatigue, headaches, "brain fog", depression, and anxiety.[123]

Shih et al report that patients with COVID-19 can have GI and hepatobiliary manifestations, which are often mild and transient, although they can occasionally be severe. The most common consequential GI manifestation is ischemic enterocolitis. Abnormal liver chemistries occur in 14-53% of Covid-19 patients, both at admission and during hospitalization. Typically, liver function test elevations are mild and that recover without specific treatment. Rarely patients with COVID-19 may present with acute liver failure, develop primary liver disease during their illness, or develop post- COVID-19 cholangiopathy (a form of secondary sclerosing cholangitis).[115]

Mallhi et al performed a review of 42 published systematic reviews on CAKI. They found that the incidence of CAKI ranged from 4.3% to 36.4% overall among COVID-19 patients, 36%–50% in KTRs, and up to 53% in patients with severe or critical illness.[116] Matsumoto and Prowle (2022), in their review of the literature on CAKI report that large observational studies and meta-analyses report an AKI incidence of 28--34% in all inpatients and 46--77% in patients admitted to the ICU. The majority of survivors recovered their kidney function by hospital discharge; however, they remained at increased risk of future AKI, a decline in estimated eGFR, and chronic kidney disease. Moreover, even in the absence of overt AKI a significant proportion of survivors of COVID-19 hospitalisation had reduced eGFR on follow-up.[117]

The risk of new onset diabetes mellitus was reported to be 66% (95% CI 1.38; 2.00) higher among survivors of COVID-19 compared with controls in a meta-analysis of eight studies consisting of 4,270,747 COVID-19 patients and 43,203,759 controls.[118]
Other complications of COVID-19 include hemolytic anemia[124], endocrine disorders (including the thyroid, pancreas, adrenal, neuroendocrine, gonadal, and parathyroid glands)[125,126], musculoskeletal disorders including persisting or new-onset fatigue, myalgia, arthralgia, arthritis, muscle weakness[127], opportunistic infections[72], and adverse pregnancy outcomes including preterm labor and cesarean delivery without any intrauterine infection, and severe neonatal asphyxia.[128]
A recent narrative review of coagulopathy associated with COVID-19 infection indicates thrombosis occurs as a result of the virus invading endothelial cells causing local complement activation and inflammation which leads to microvascular thrombi (both venous and arterial), which may eventually lead to widespread macrovascular thrombotic injury and in some cases end-organ failure.[120]

Based on a meta-analysis of 42 studies, the risk of thromboembolism was 21% overall and 31% in the ICU, with the pooled odds of mortality being 74% higher among those who experienced thromboembolism compared to those who did not.[129]

Complications of Long-Covid

COVID-19 symptoms can persist weeks or months beyond the acute infection.[130,131] The NICE guideline scope published on 30 October 2020 defined "Long COVID" signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more and for which signs and symptoms are not explained by an alternative diagnosis).[132]

A meta-analysis of 31 studies published until 17 September 2020 prior to the emergence of the omicron variant among patients between 18 to 49 years of age found that COVID-19 symptoms were experienced for 14 days to 3 months post-infection, including persistent fatigue (39–73%), breathlessness (39–74%), decrease in quality of life (44–69%), impaired pulmonary function, abnormal CT findings including pulmonary fibrosis (39–83%), evidence of peri-/perimyo-/myocarditis (3–26%), changes in microstructural and functional brain integrity with persistent neurological symptoms (55%), increased incidence of psychiatric diagnoses (5.8% versus 2.5–3.4% in controls), and incomplete recovery of olfactory and gustatory dysfunction (33–36%).[133]

Yang et al conducted a meta-analysis of 72 studies with a total of 88,769 patients to examine the occurrence of different symptoms up to one year of follow-up for previously hospitalised patients with COVID-19. A total of 167 sequelae related to COVID-19 were identified, the more common ones being fatigue 27.5%, somnipathy 20.1%, anxiety 18.0%, dyspnea 15.5%, PTSD 14.6%, hypomnesia 13.4%, arthralgia 12.9%, depression 12.7%, alopecia 11.2%. The prevalence of most symptoms declined after > 9 months of follow-up, but fatigue and somnipathy persisted in 26.2% and 15.1% of patients, respectively.[134]

The incidence of Long COVID is progressively greater among non-hospitalised to hospitalised to those hospitalised and treated in the ICU. It varies from 16 and 53% of patients and occurs more frequently in patients after infection with the Alpha or Delta variants in comparison with patients infected with the Omicron variant.[111] Major organ damage post-discharge among adults hospitalised for COVID-19, including incident cardiac, pulmonary, liver, acute and chronic kidney, stroke, diabetes, and coagulation disorders were consistently greater in adults hospitalised for COVID-19 compared with non-COVID-controls in a meta-analysis of nine studies with follow-up of patients ranging from 4 to 22 weeks post-discharge.[135]

Cardiovascular sequelae in post-acute COVID-19 include dyspnea, chest pain, sinus bradycardia / dysrhythmias, palpitations and/or tachycardia, cerebrovascular disorders, pericarditis, myocarditis, ischemic heart disease, heart failure, thromboembolic events, right ventricular dysfunction, myocardial fibrosis, and hypertension.[109-111]

Pulmonary symptoms and complications seen in long COVID include dyspnoea (occurring in 15% of non-hospitalized patients and up to 81% of previously hospitalised patients), cough, chest pain, or decreased exercise tolerance.[136]

A systematic review and meta-analysis assessed the long-term neurocognitive effects of COVID-19 in three studies comprised of 3,304 post-COVID-19 patients. Persistent neurological / cognitive sequelae of COVID-19 infection included headache 27.8%, fatigue 26.7%, myalgia 23.14%, anosmia 22.8%, dysgeusia 12.1%, sleep disturbance 63.1%, confusion 32.6%, difficulty concentrating 22%, and psychiatric symptoms like PTSD 31%, feeling depressed 20%, and suicidality 2%.[137] Dangayach et al. reports in a narrative review of the literature that neurologic complications in post-acute COVID-19 range from persistent fatigue, headaches, "brain fog", depression, anxiety, and postural orthostatic tachycardia even in patients with mild disease.[123]

Musculoskeletal disorders with long COVID, including persisting or new-onset fatigue, myalgia, arthralgia, arthritis, and muscle weakness, were noted in review of systematic reviews and meta-analyses that included 24 studies.[127]

Important co-morbidities:

As mentioned previously, there are a number of common comorbidities in patients with COVID-19; many of these conditions are also associated with more severe disease or progression of disease.

Important comorbidities in those with more severe disease/hospitalised COVID-19 patients include hypertension, diabetes, obesity, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease or asthma, chronic kidney disease, cancer, chronic liver disease, and autoimmune disease.[14,19-21,34,50,60-68,97,99,138-140] Prevalence of these conditions have been reported to be lower in mild cases and higher among fatal cases, as shown for EU/EEA countries in Table 10 below using TESSy data posted on 04 November 2021.[141]

Table 10. Preconditions among COVID-19 Patients in EU/EEA, by Severity of Disease. Case-based Data from TESSy Reported 04 November 2021

	EU/EEA, reported on 04 November 2021			
	Mild	**Hosp**	**Severe**	**Fatal**
Total N	2,196,678	368,145	54,504	118,934
Asplenia (%)	0	0	0	0
Asthma (%)	0.9	1.3	1.4	1.1
Cancer, malignancy (%)	3.1	8.3	9.6	10.7
Cardiac disorder, excluding hypertension (%)	9.0	24.3	23.5	31.0
Chronic lung disease, excluding asthma (%)	1.8	3.6	4.3	3.6
Current smoking (%)	0.9	0.1	0.2	0.1
Diabetes (%)	5.1	16.3	20.1	18.6
Haematological disorders (%)	0	0.2	0.1	0.1
HIV/other immune deficiency (%)	0.2	0.7	0.7	0.5
Hypertension (%)	0.8	2.9	3.2	3.7
Kidney-related condition, renal disease (%)	0.3	1.7	1.9	2.6
Liver-related condition, liver disease (%)	0.3	0.6	0.7	0.6
Neuromuscular disorder, chronic neurological (%)	0.8	1.8	1.4	2.4
Obesity (%)	0.3	0.4	1.1	0.3
Other endocrine disorder, excluding diabetes (%)	0.4	0.2	0.1	0.1
Rheumatic diseases including arthritis (%)	0.1	0.1	0.1	0
Tuberculosis (%)	0	0	0	0
None (%)	76.1	37.3	31.6	24.5

Table 10. Preconditions among COVID-19 Patients in EU/EEA, by Severity of Disease. Case-based Data from TESSy Reported 04 November 2021

	EU/EEA, reported on 04 November 2021			
	Mild	**Hosp**	**Severe**	**Fatal**

TESSy website indicated that 04 November 2021 update of these data would be the last.

Table 11 below summarises comorbidities among US COVID-19 patients in a retrospective cohort study conducted among 629,953 individuals tested for COVID-19 in a large health system in the US Northwest between 01 March and 31 December 2020.[27] The most common comorbidities were similar in the full cohort and among those who tested positive: obesity, hypertension, diabetes, and asthma. Among those hospitalised for COVID-19, a large number of comorbidities had elevated prevalence compared to the full cohort and those who tested positive: obesity, hypertension, diabetes, kidney disease, congestive heart failure, coronary artery disease, and chronic obstructive pulmonary disease.

Table 11. Comorbidities in Individuals tested for COVID-19 in the Providence St. Joseph Health System – States of California, Oregon, and Washington, 01 March–31 December 2020

Comorbidity	**Tested (N= 629,953) %**	**Positive (N= 54,645) %**	**Hospitalised (N= 8,536) %**
Hypertension	23.3	19.8	40.2
Diabetes	9.4	10.9	28.3
Weight	-	-	-
Underweight	2.1	1.7	3.1
Normal	29.0	23.9	24.3
Overweight	31.7	32.6	30.3
Class 1 Obesity	19.8	22.3	21.2
Class 2 Obesity	9.6	11.1	10.9
Class 3 Obesity	7.7	8.6	10.3
Asthma	6.5	5.3	6.7
Chronic Obstructive Pulmonary Disease	4.0	2.6	8.3
Coronary Artery Disease	5.5	3.6	9.7
Myocardial Infarction	2.2	1.6	5.5
Congestive Heart Failure	5.3	3.9	13.2
Kidney Disease	5.6	5.3	17.2
Liver Disease	3.1	2.5	4.0
Cancer	6.1	3.0	6.3

In a retrospective cohort of 135,794 individuals under the age of 25 who were tested for COVID-19 by 08 September 2020 within the PEDSnet network of US paediatric health systems, the proportion of obese individuals was similar among those who tested negative (18%) and among mild or asymptomatic COVID-19 cases (19%), but clearly elevated among severe COVID-19 cases (37%).[31] Those with severe cases of COVID-19 more commonly had chronic conditions in at least two body systems, with 25% of COVID-19 negative individuals, 17% mild or asymptomatic cases, and 38% of severe cases having multiple chronic conditions. More recent data provide insight into comorbidities among the paediatric population. For the period 01 January – 31 March 2021 across 14 states, the CDC's COVID-

NET database recorded 204 adolescents aged 12-17 who were hospitalized for likely primarily COVID-related reasons.[28] Among the 204 adolescents, 70.6% had at least one major underlying medical condition, the most common conditions being obesity (35.8%), chronic lung diseases including asthma (30.9%), and neurologic disorders (14.2%).[28] A recent systematic review and meta-analysis using published reports through August 25, 2021 revealed that prematurity in young infants (RR, 2.00; 95% CI, 1.63–2.46), obesity (RR, 1.43; 95% CI, 1.24–1.64), diabetes (RR, 2.26; 95% CI, 1.95–2.62), chronic lung disease (RR, 2.62; 95% CI, 1.71–4.00), heart disease (RR, 1.82; 95% CI, 1.58–2.09), neurologic disease (RR, 1.18; 95% CI, 1.05–1.33), and immunocompromised status (RR, 1.44; 95% CI, 1.01–2.04) were significant comorbidities associated with severe COVID-19 (intensive care unit admission, invasive mechanical ventilation, and/or death) in children.[142]

Crossfield et al performed a population-based prospective study linking individual genetic, biomarker, survey and electronic health record data from >500 000 UK participants, aged 40–69 years at recruitment (2006– 2010). The study used individual patient-level data from the UK BioBank database, linked to COVID-19 data sets from laboratories, hospitals, and death certificates. The study population included those who provided baseline assessment data, were alive at the start of the study period and had not withdrawn consent. All subjects had a COVID-19 diagnosis by a positive laboratory test result or an ICD-10 code U071 or U072 recorded in hospital or death certificate data. A cohort of 9560 patients with COVID-19 of whom 50.8% (n=4,860) were women and 7,274 (76.1%) were White European were included. The most common comorbidities of the study population included cardiovascular disease (12.8%), chronic respiratory disease (15.5%), chronic kidney disease (0.8), diabetes (7.1%), hypertension (28.6%), chronic liver disease (0.3%), and neurological disease (2.3%). The total number of comorbidities per subject was 0: 52.7%; 1: 31.7%; and ≥2: 15.6%.[50]

Alharbi et al conducted a retrospective, cross-sectional observational of patients in a COVID-19-designated specialty hospital in Saudi Arabia. Over an 11-month period from March 2020 to January 2021, corresponding to the first wave of infection in the country when therapeutic interventions had limited options and were mostly dependent on a given patient's condition. A total of 619 patients' records (non-ICU = 369 and ICU = 250 patients, 61.4% male, 6.3% age 0-20 yrs, 16.8% age 21-40, 27.9% age 41-60, and 48.9% age >60) with confirmed COVID-19 diagnosed with a real-time PCR assay for SARS-CoV-2 were included. The most common comorbidities of the study population included hypertension (59.8%), diabetes (47.2%), chronic pulmonary disease (43.1%), heart failure (13.2%), coronary artery disease (4.5%), and cancer (2.7%).[97]

A prospective observational study of hospitalised patients with confirmed SARS-CoV-2 infection by reverse transcription-polymerase chain reaction and treated with advanced respiratory support (including high-flow nasal cannula, non-invasive mechanical ventilation, or invasive mechanical ventilation) during the first two years of the pandemic was conducted by Reyes et al. Included were a total of 66,565 patients from five continents (63.5% male, 82.6% hospitalised and treated in high-income countries, 78.2% hospitalised and treated in Europe, 44.0% between 60 and 80 years old) were included. The most common comorbidities of the study population included arterial hypertension (41.3), diabetes mellitus (30.3%), chronic cardiac disease (not hypertension; 22.1%), asthma (12.2%), chronic kidney disease 11.3%), obesity (16.2%), chronic pulmonary disease (not asthma; 13.3%),

rheumatological disorder (8.1%), malignant neoplasm (7.7%), chronic neurological disorder (7.4%), and dementia 6.0%).[143]

Ozonoff et al conducted a prospective, observational study of hospitalised patients with COVID-19 from 20 hospitals (affiliated with 15 academic institutions) across the US. Symptomatic patients ≥18 with confirmed positive SARS-CoV-2 PCR were enrolled within 48 hour of hospital admission. Hospital admission data collected up to 11 November 2021 was analyzed. Between 05 May 2020 and 19 March 2021, 1,164 patients enrolled in the study and who met eligibility criteria were included in the final analysis. The median age of the study population was 59 years (interquartile range 20), 61% were men, and 32% smoked or used vaporised nicotine products. The most common comorbid conditions included hypertension 58%, diabetes 37%, chronic lung disease (not asthma) 20%, asthma 15%, chronic cardiac disease 27%, chronic kidney disease 15%, chronic liver disease 5%, chronic neurologic disorder 12%, organ transplantation 5%, malignancy 10%, drug, or alcohol abuse 8%, class 1-2 obesity (BMI=30-39.9) 41%, class 3 obesity (BMI=40+) 14%.[14]

Lastly, an observational study of all COVID-19 patients admitted to 19 Dutch ICUs participating in both the national quality registry National Intensive Care Evaluation and the EHR-based Dutch Data Warehouse as conducted by Vagliano et al. A total of 1,533 patients from the EHR and 1,563 from the registry were included. Subjects were ≥18 years old and were admitted between 15 February 2020 and 01 January 2021 with confirmed COVID-19 by positive real-time reverse transcriptase polymerase chain reaction assay for SARS-CoV-2 or, in the early phase of the pandemic, with a Computed Tomography-scan consistent with COVID-19. The authors developed multiple models on data from the first 24 hours of ICU admissions from February to June 2020 (first wave) and validated the models on prospective patients admitted to the same ICUs between July and December 2020 (second wave). The authors reported the prevalence of the following comorbidities during the first and second waves, respectively, as follows: acute renal failure (9.5% and 9.3%), chronic obstructive pulmonary disease failure (9.5% and 9.1%), chronic respiratory insufficiency (3.2% and 2.0%), diabetes (21.5% and 26.9%).[108]

Module SII. Non-Clinical Part of the Safety Specification

In December 2019, COVID-19 was identified as a new, potentially fatal, respiratory infection caused by SARS-CoV-2.[144] SARS-CoV-2 infects cells through the ACE2 receptors with the lung and bronchial epithelial cells as the primary sites of infection.[145] Like other coronaviruses, SARS-CoV-2 encodes a main protease (M^{pro}), also referred to as 3C-like protease ($3CL^{pro}$),[146,147] which is a virally encoded enzyme essential for viral replication.[148] M^{pro} digests the virus P1a and P1ab polyproteins at multiple junctions to generate a series of proteins critical for virus replication and transcription, including RdRp, the helicase, and the M^{pro} itself.[149] No close human analogs of the coronavirus M^{pro} are known.[150] The essential functional importance in virus replication together with the absence of closely related homologs in humans, identify the M^{pro} as an attractive antiviral drug target.[151]

Nirmatrelvir is a peptidomimetic inhibitor of SARS-CoV-2 M^{pro}, exhibiting a broad-spectrum activity across the Coronaviridae family of Main proteases demonstrating its potential for antiviral efficacy. The critical amino acid residues involved in enzyme-inhibitor binding interactions are particularly well conserved within this family of viruses.[152] Inhibition of the SARS-CoV-2 M^{pro} renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.

The mechanism of action of nirmatrelvir has been demonstrated by various biochemical, crystallographic, and cell-based methods. Nirmatrelvir inhibited the full-length enzyme activity of SARS-CoV-2 M^{pro} with a geomean IC_{50} of 0.0192 μM and a Ki of 0.00311 μM.

In vitro antiviral activity of nirmatrelvir has been evaluated in VeroE6 derived, A549-ACE2, MRC-5, and dNHBE cells. In all cellular systems tested, nirmatrelvir demonstrated potent antiviral activity against SARS-CoV-2 and pan-coronavirus antiviral efficacy against SARS-CoV-1, MERS-CoV, and hCoV-229E . This activity is selective to the coronavirus family. Nirmatrelvir is inactive against enterovirus 71 and human rhinovirus B.[153]

The antiviral activity of nirmatrelvir against the SARS-CoV-2 Alpha, Beta, Gamma, Delta, Lambda, Mu, and Omicron BA.1 variants was assessed in Vero E6 P-gp knockout cells. Nirmatrelvir had a median EC_{50} value of 25 nM (range: 16-141 nM). The Beta variant was the least susceptible variant tested, with an EC_{50} value fold-change of 3.7 relative to USA-WA1/2020. The other variants had EC_{50} value fold-changes ≤1.1 relative to USA-WA1/2020.
The antiviral activity of nirmatrelvir against the Omicron sub-variants BA.2, BA.2.12.1, BA.4, BA.4.6, BA.5, BF.7 (P252L+F294L), BF.7 (T243I), BQ.1.11, BQ.1, and XBB.1.5 was assessed in Vero E6-TMPRSS2 cells in the presence of a P-gp inhibitor. Nirmatrelvir had a median EC_{50} value of 83 nM (range: 39-146 nM) against the Omicron sub-variants, reflecting EC_{50} value fold-changes ≤1.5 relative to the USA-WA1/2020 isolate. Nirmatrelvir also demonstrated cell culture antiviral activity in the Vero E6 TMPRSS cells against four clinical isolates of Delta variant with EC_{50} values approximately ≤2x compared to the SARS-COV-2 USA-WA1/2020 strain.

The antiviral testing strategy for nirmatrelvir has followed the FDA Guidance on Antiviral Drug Development[154] as well as the COVID 19 Guidance on Developing Drug and Biological Product[155]. Different in vitro approaches were undertaken to evaluate potential nirmatrelvir resistance pathways, specifically:

1. Evaluation of SARS-CoV-2 M^{pro} mutant enzyme activity in the presence of nirmatrelvir
2. Virus resistance selection in Vero E6 P-gp KO and A549-ACE2 cells with the same or increasing concentrations of nirmatrelvir (internal Pfizer laboratory) or in the literature.[156,157] Resistance studies have also provided evidence for cross resistance to nirmatrelvir by other protease inhibitors.[157,158]

A limited number of the putative resistance substitutions identified from the above assays, dominant M^{pro} mutations from Variants of Concern, mutations at contact resides, mutations identified from EPIC HR, and mutations circulating in GISAID (at a residue identified in resistance assay) were then tested for susceptibility to nirmatrelvir using reverse genetics.

Viruses that had mutations in the M^{pro} gene were isolated from resistance selection under nirmatrelvir drug pressure or reverse engineered.

- Several mutant M^{pro} viruses were not viable and could not be evaluated in the reverse engineered recombinant SAR-CoV-2 assay: Y54A, F140A, F140I, F140S, S144E, S144L, S144P, S144T, E166V, H172Y, A173T, and A191V.
- SARS-CoV-2 M^{pro} Amino Acid Substitutions selected by nirmatrelvir are listed in the table below (internal Pfizer laboratory data and in recent publications[156,157])

Single Substitution (EC_{50} value fold change)	T21I (1.1-4.6), L50F (1.5-4.2), P108S (ND), T135I (ND), F140L (4.1), S144A (2.2-2.5), C160F (ND), E166A (3.3), E166V (25-288), L167F (ND), T169I (ND), H172Y (ND), A173V (0.9-1.7), V186A (ND), R188G (ND), A191V (ND), A193P (ND), P252L (5.9), S301P (ND), and T304I (1.4-5.5).
≥2 Substitutions (EC_{50} value fold change)	T21I+S144A (9.4), T21I+E166V (83), T21I+A173V (3.1), T21I+T304I (3.0-7.9), L50F+E166V (34-175), L50F+T304I (5.9), T135I+T304I (3.8), F140L+A173V (10.1), H172Y+P252L (ND), A173V+T304I (20.2), T21I+L50F+A193P+S301P (28.8), T21I+S144A+T304I (27.8), T21I+C160F+A173V+V186A+T304I (28.5), T21I+A173V+T304I (15), and L50F+F140L+L167F+T304I (54.7).

ND=no data (mutation emerged from nirmatrelvir resistance-selection but has not been tested for EC_{50} determination in an antiviral assay).

Most single M^{pro} mutations and some double mutations identified which reduced the susceptibility of SARS CoV-2 to nirmatelvir resulted in an EC_{50} shift of less than ~5-fold compared to wild type SARS-CoV-2. Virus containing E166V appears to have replication defect since it either could not be generated or had a very low virus titer.[156] In general, triple mutations and some double mutations led to EC_{50} changes of greater than 5-fold compared to that of wild type. The clinical significance of these mutations needs to be further understood particularly in the context of high nirmatrelvir clinical exposure (>5x EC_{90}). Thus far these mutations have not been identified as treatment-emergent mutations associated with

hospitalization in the EPIC clinical studies. Additionally, the sponsor has reviewed data submitted to GISAID. As of 31 December 2022, E166V as a single M^{pro} mutation did not occur in any of the ~13 million isolates and was only found in 16 out of ~13 million isolates when in combination with other M^{pro} mutations.

Nirmatrelvir showed antiviral activity in BALB/c and AG-129 mice infected with mouse-adapted SARS-CoV-2. Oral administration of nirmatrelvir at 300 mg/kg or 1,000 mg/kg twice daily initiated 4 hours post-inoculation or 1,000 mg/kg twice daily initiated 12 hours post-inoculation resulted in reduction of lung viral titers and ameliorated indicators of disease (weight loss and lung pathology) compared to vehicle-treated animals. Additionally, nirmatrelvir as a single agent (300 mg/kg BID), ritonavir as a single agent (50 mg/kg BID) and in combination (50 mg/kg ritonavir + 300 mg/kg nirmatrelvir BID) were evaluated for antiviral efficacy in the BALB/c mouse SARS-CoV-2-MA-10 model. Ritonavir alone did not demonstrate antiviral activity against in vivo virus replication and did not contribute to amelioration of disease pathology, however, the combination of ritonavir and nirmatrelvir showed improved lung tissue protection compared to nirmatrelvir or ritonavir alone. This is most likely due to the increased plasma exposure levels of nirmatrelvir due to the inhibition of CYP3A-mediated metabolism of nirmatrelvir by ritonavir.

Studies on the secondary pharmacology evaluated in vitro activity of nirmatrelvir against a wide panel of receptors, transporters, ion channels and enzyme assays, and the results indicated no significant inhibition (>50%) of functional or enzyme activity, with the exception of submicromolar activity against cathepsin K (IC_{50} = 231 nM compared to activity against SARS-CoV-2 M^{pro} IC_{50} = 4 nM) as reported in the literature from a panel of 20 cysteine proteases.[159]

Safety pharmacology studies were conducted to assess potential pharmacodynamic effects on vital organ systems (central nervous, cardiovascular, and respiratory). Oral administration of up to 1000 mg/kg of nirmatrelvir to male Wistar Han rats produced no test article-related effects on FOB parameters, but at 1000 mg/kg there were test article-related lower number of mean vertical movement counts during the first 5-minute period and a higher number of mean horizontal and vertical movement counts during the last 30-minute period of the quantitative locomotor assessment compared with vehicle control. Translatability of these findings to humans is uncertain. Administration of 1000 mg/kg also resulted in transient test article-related higher respiratory rate and minute volume compared with vehicle control. Nirmatrelvir administered at 150 (75 BID) mg/kg/day to cynomolgus monkeys produced minor and transient effects such as increased systolic, diastolic and mean BP, HR decreases, and associated RR, PR, and QT interval increases. When the QT interval was corrected for HR (QTc), there was a test article-related decrease. No arrhythmias were noted. Nirmatrelvir at 150 (75 BID) mg/kg/day also produced decreases in LV +dP/dt max. All measures returned to vehicle control levels within 24 HPD, and there was no clinically meaningful effect of nirmatrelvir on hERG, isolated guinea pig heart or isolated rat aorta assays.

The potential effects on safety pharmacology parameters were monitored in the clinic (eg, ECG) and had no correlating clinical signs or histopathological findings in the 4 repeat-dose GLP toxicity studies up to 1 month in duration in rats or monkeys. ECG data were also collected in the 15-day and 1-month GLP monkey studies and there were no test article-

related changes in ECG parameters (HR, RR-, PR-, QRS-, QT-, QTc-intervals) or ECG morphology in those studies.

The ADME profile of nirmatrelvir has been extensively studied in various in vitro and in vivo studies. In the pivotal repeat dose toxicity studies in rats and monkeys, mean systemic exposure of nirmatrelvir increased with increasing dose and there were no consistent sex-related differences.

Nirmatrelvir exhibited low passive permeability and was moderately bound to plasma proteins in rat, monkey and human and preferentially partitioned into plasma relative to red blood cells. Concentration-dependent protein binding was observed in rabbit plasma but not in rat, monkey, and human. [^{14}C]Nirmatrelvir-derived radioactivity did not cross the blood:brain barrier to a quantifiable extent in rats consistent with it being a substrate for P-gp.

CYP3A4 was the major contributor (f_m=0.99) to the oxidative metabolism of nirmatrelvir. In clinical studies, ritonavir was co-administered with nirmatrelvir to inhibit CYP3A4 and increase plasma concentrations of nirmatrelvir. In vivo, unchanged nirmatrelvir was the most prevalent drug-related entity in circulation in rat, monkey, and human plasma, with M4 (PF-07329268) as a primary circulating metabolite in monkey. In a human mass-balance study of nirmatrelvir coadministered with ritonavir, the majority of nirmatrelvir-related material was excreted as unchanged parent (55% in urine and 28% in feces).

Nirmatrelvir/ritonavir demonstrated clinical DDI as a perpetrator with substrates of CYP3A4 and P-gp, but nirmatrelvir/ritonavir had little to no incremental effect on the DDI beyond that produced by ritonavir alone. The risk of other transporter DDI is not considered significant.

The toxicity of nirmatrelvir was evaluated in 4 GLP repeat-dose toxicity studies up to 1 month in duration in Wistar Han rats and cynomolgus monkeys. There were no adverse findings in any of the studies. The NOAELs were the highest dose administered in each study and represented 13x/9x (C_{max}/AUC_{24}) and 26x/16x (C_{max}/AUC_{24}) in the 1-month rat and monkey studies, respectively, over the human total nirmatrelvir C_{max} and AUC_{24} at a dose of 300/100 mg nirmatrelvir/ritonavir BID. Nonadverse, nirmatrelvir-related clinical findings included sporadic reports of salivation and soft feces in the 1-month rat study, and sporadic occurrence of emesis with slight body weight decreases in monkeys. In rats, nonadverse, monitorable and reversible clinical pathology findings included those suggestive of low-grade inflammation or alterations in the coagulation pathways without clinical or microscopic correlates. In monkeys, nonadverse, monitorable and generally reversible clinical pathology findings included increases in ALT and/or AST and increases in fibrinogen at the high dose in the 1-month study without clinical or microscopic correlates. Changes consistent with a rat-specific response to hepatic enzyme induction resulting in increased thyroxine catabolism, raised serum thyroid stimulating hormone and thyroid follicular cell hypertrophy and anterior pituitary vacuolation were observed relative to controls in both 14-day and 1-month rat toxicity studies.[160-162] This mechanism is considered to have little to no relevance to humans mostly because of the marked differences in plasma half-life of thyroid hormones and in binding to transport proteins between rodents and humans.[162].

Nirmatrelvir had no adverse effects on male or female fertility in rats, fetal morphology or embryo-fetal viability in rats and rabbits, or PPND in rats when evaluated at doses up to 1000 mg/kg/day. The exposure margins at 1000 mg/kg/day were 5x, 9x, 11x, and 9x in the fertility, EFD rat, EFD rabbit, and PPND study, respectively, based on AUC_{24} over the total clinical exposure of nirmatrelvir. In the rat fertility and EFD studies, there were no adverse effects from nirmatrelvir. In the rabbit EFD study, there were no nirmatrelvir-related effects on fetal morphology or embryo-fetal viability, although adverse nirmatrelvir-related lower fetal body weights were observed at 1000 mg/kg/day in the presence of low magnitude effects on maternal body weight change and food consumption at this dose. In the PPND study, there were no adverse effects of nirmatrelvir on the F0 and F1 generation. Therefore, nirmatrelvir presents little risk to reproductive and developmental function of humans.

Nirmatrelvir was not mutagenic or clastogenic in in vitro genetic toxicity studies and was negative in the in vivo rat micronucleus assay incorporated into the 14-day GLP repeat-dose rat toxicity study. Nirmatrelvir does not present a photo toxicity risk based on UV-Vis absorbance evaluation.

In a 14-day impurity qualification rat study, administration of 200 mg/kg/day nirmatrelvir with increased amounts of multiple impurities (PF-07336592, PF-07801198, PF-07832587, and PF-07800841 or PF-07863403, PF-07328615, and PF-07858529) did not alter the safety profile of nirmatrelvir.

The non-clinical studies performed adequately support the oral administration of nirmatrelvir in the clinic.

In summary, the non-clinical safety findings related to nirmatrelvir primarily represent monitorable and reversible clinical pathology findings included those suggestive of low-grade inflammation or alterations in the coagulation pathways in rats, or increases in ALT, AST, and fibrinogen in monkeys. These findings didn't have clinical or microscopic correlates. The key safety findings from non-clinical studies and their relevance to human usage are presented in Table 12.

Table 12. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies[a]	Relevance to Human Usage
Toxicity • Nonadverse, monitorable and reversible clinical pathology findings including those suggestive of low-grade inflammation or alterations in the coagulation pathways in rats, or increases in ALT, AST, and fibrinogen in monkeys at the high dose in the 1-month study.	Clinical pathology parameters are monitored in the clinic. To date, there have been no reports of clinically significant treatment-emergent changes in clinical pathology parameters related to inflammation, coagulation or liver function.

Table 12. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies[a]	Relevance to Human Usage
Reproductive/developmental toxicity • No nirmatrelvir-related effect in any of the parameters in the rat EFD study up to the highest dose of 1000 mg/kg/day and no nirmatrelvir-related effect on foetal morphology or embryo-foetal viability up to the highest dose of 1000 mg/kg/day in the rabbit EFD study were observed.	The available non-clinical data indicate low risk of foetal harm in humans.
Safety pharmacology: • Nirmatrelvir administered at 150 (75 BID) mg/kg/day to cynomolgus monkeys produced minor and transient effects such as increased BP, HR decreases, and associated RR, PR, and QT interval increases. When the QT interval was corrected for HR (QTc), there was a test article-related decrease. No arrhythmias were noted. Nirmatrelvir at 150 (75 BID) mg/kg/day also produced decreases in LV +dP/dt max. There was no clinically meaningful effect of nirmatrelvir on hERG, isolated guinea pig heart or isolated rat aorta assays.	No adverse changes in ECG parameters, BP or HR have been observed in the clinical setting.

a. Carcinogenicity studies were not conducted, in accordance with ICH S1b.

Module SIII. Clinical Trial Exposure

Clinical study exposure data (Safety Analysis Set) are detailed in the below tables for the pivotal studies C4671005 (EPIC-HR), C4671002 (EPIC-SR) and C4671006 (EPIC-PEP).

Table 13. Clinical Trial Exposure by Duration – Safety Analysis Set

Duration of Exposure[a]	Nirmatrelvir 300 mg + Ritonavir 100 mg					
	C4671005 (EPIC-HR) N= 1038[d]		C4671002 (EPIC-SR) N= 654[e]		C4671006 (EPIC-PEP) N= 1823[c]	
	Persons	Person Time[b] (days)	Persons	Person Time[b] (days)	Persons	Person Time[b] (days)
At least ≥1 day	1038	1038	654	654	1823	1823
At least ≥2 days	1020	1020	644	644	1809	1809
At least ≥3 days	1012	1012	635	635	1802	1802
At least ≥4 days	996	996	632	632	1793	1793
At least ≥5 days	984	1169	628	708	1778	1778
At least ≥6 days	-	-	-	-	1018	1018
At least ≥7 days	-	-	-	-	875	875
At least ≥8 days	-	-	-	-	869	869
At least ≥9 days	-	-	-	-	863	863
At least ≥10 days	-	-	-	-	853	853
At least ≥11 days	-	-	-	-	123	123

a. Exposure is not inclusive of any gaps or withholding of treatment.
b. Person Time in each of the duration of exposure rows is incremental and unique; thus does not include the duration (years) of previous time intervals.
c. Includes 912 participants receiving 5-days nirmatrelvir/ritonavir regimen and 911 participants receiving 10-days nirmatrelvir/ritonavir regimen. Participants enrolled at sites PPD and PPD (including those switched to PPD were excluded.
d. Participants enrolled at sites PPD and PPD (including those switched to PPD are excluded.
e. Participants enrolled at sites PPD, PPD (including those switched to PPD, PPD, and PPD (2022 enrolees) are excluded.

PFIZER CONFIDENTIAL SDTM Creation: 10JAN2023 (13:31) Table Generation: 13JAN2023 (10:25) (Database snapshot date: 29APR2022) Output File: ./nda/C4671005_SiteEx/cum_dur_rmp
PFIZER CONFIDENTIAL SDTM Creation: 17JAN2023 (12:44) Table Generation: 06MAR2023 (14:35) (Database snapshot date: 11AUG2022) Output File: ./nda/C4671002_RMP_SiteEx/cum_dur_rmp
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2023 (21:51) Table Generation: 12FEB2023 (21:54) Output File:./nda/C4671006_RMP_SiteEx/cum_dur_rmp

Table 14. Clinical Trial Exposure by Duration, Cumulative Person Time – Safety Analysis Set (C4671005 and C4671002)

Duration of Exposure[a]	Nirmatrelvir 300 mg + Ritonavir 100 mg			
	C4671005 (EPIC-HR) N= 1038[b]		C4671002 (EPIC-SR) N= 654[c]	
	Persons	Person Time (days)	Persons	Person Time (days)
Cumulative up to 1 day	18	18	10	10
Cumulative up to 2 days	26	34	19	28
Cumulative up to 3 days	42	82	22	37
Cumulative up to 4 days	54	130	26	53
Cumulative up to 5 days	853	4125	574	2793
Cumulative up to > 5 days	1038	5235	654	3273

Table 14. Clinical Trial Exposure by Duration, Cumulative Person Time – Safety Analysis Set (C4671005 and C4671002)

Duration of Exposure[a]	Nirmatrelvir 300 mg + Ritonavir 100 mg			
	C4671005 (EPIC-HR) N= 1038[b]		C4671002 (EPIC-SR) N= 654[c]	
	Persons	Person Time (days)	Persons	Person Time (days)

a. Exposure is not inclusive of any gaps or withholding of treatment.
b. Participants enrolled at sites PPD and PPD (including those switched to PPD are excluded.
c. Participants enrolled at sites PPD, PPD (including those switched to PPD, PPD, and PPD (2022 enrolees) are excluded.

PFIZER CONFIDENTIAL SDTM Creation: 10JAN2023 (13:31) Table Generation: 13JAN2023 (10:25) (Database snapshot date: 29APR2022) Output File:./nda/C4671005_SiteEx/cum2_dur_rmp
PFIZER CONFIDENTIAL SDTM Creation: 17JAN2023 (12:44) Table Generation: 06MAR2023 (14:34) (Database snapshot date: 11AUG2022) Output File:./nda/C4671002_RMP_SiteEx/cum2_dur_rmp

Table 15. Clinical Trial Exposure by Duration, Cumulative Person Time – Safety Analysis Set (C4671006)[a]

Duration of Exposure[b]	Nirmatrelvir 300 mg + Ritonavir 100 mg 5 Days (N=912)		Nirmatrelvir 300 mg + Ritonavir 100 mg 10 Days (N=911)	
	Persons	Person Time (days)	Persons	Person Time (days)
Cumulative up to 1 day	7	7	7	7
Cumulative up to 2 days	11	15	10	13
Cumulative up to 3 days	14	24	16	31
Cumulative up to 4 days	25	68	20	47
Cumulative up to 5 days	768	3783	37	132
Cumulative up to 6 days	907	4617	41	156
Cumulative up to 7 days	912	4652	42	163
Cumulative up to 8 days	912	4652	48	211
Cumulative up to 9 days	912	4652	58	301
Cumulative up to 10 days	912	4652	788	7601
Cumulative up to 11 days	912	4652	911	8954
Cumulative up to >11 days	912	4652	911	8954

a. Participants enrolled at sites PPD and PPD (including those switched to PPD) were excluded.
b. Exposure is not inclusive of any gaps or withholding of treatment.

PFIZER CONFIDENTIAL SDTM Creation: 31JAN2023 (21:51) Table Generation: 12FEB2023 (21:55)
Output File: ./nda/C4671006_RMP_SiteEx/cum2_dur_rmp

Table 16. Clinical Trial Exposure by Age Group and Gender – Safety Analysis Set

	Nirmatrelvir 300 mg + Ritonavir 100 mg											
	C4671005 (EPIC-HR) N=1038[a]				C4671002 (EPIC-SR) N=654[c]				C4671006 (EPIC-PEP) N= 1823[b]			
Age Group (years)	Male (n=516)		Female (n=522)		Male (310)		Female (344)		Male (n=846)		Female (n=977)	
	Persons	Person Time (Days)	Persons	Person Time (Days)	Persons	Person Time (Days)	Persons	Person Time (Days)	Persons	Person Time (Days)	Persons	Person Time (Days)
≥18 - <60	440	2255	400	2007	281	1411	306	1524	738	5562	809	6036
≥60 - <65	30	149	39	192	15	77	16	82	39	296	75	540
≥65 - <75	37	184	59	288	12	60	18	87	48	358	60	451
≥75	9	45	24	115	2	10	4	22	21	144	33	219

a. Participants enrolled at sites PPD and PPD (including those switched to PPD are excluded.
b. Includes 912 participants receiving 5-days nirmatrelvir/ritonavir regimen and 911 participants receiving 10-days nirmatrelvir/ritonavir regimen. Participants enrolled at sites PPD and PPD (including those switched to PPD were excluded.
c. Participants enrolled at sites PPD, PPD (including those switched to PPD, PPD, and PPD (2022 enrolees) are excluded.

Exposure is not inclusive of any gaps or withholding of treatment.
PFIZER CONFIDENTIAL SDTM Creation: 10JAN2023 (13:31) Table Generation: 13JAN2023 (10:25) (Database snapshot date: 29APR2022) Output File: ./nda/C4671005_SiteEx/age_sex_rmp
PFIZER CONFIDENTIAL SDTM Creation: 17JAN2023 (12:44) Table Generation: 06MAR2023 (14:33) (Database snapshot date: 11AUG2022) Output File: ./nda/C4671002_RMP_SiteEx/age_sex_rmp
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2023 (21:51) Table Generation: 12FEB2023 (21:55) Output File: /nda/C4671006_RMP_SiteEx/age_sex_rmp

Table 17. Clinical Trial Exposure by Race and Ethnicity – Safety Analysis Set

	Nirmatrelvir 300 mg + Ritonavir 100 mg					
	C4671005 (EPIC-HR) N=1038[a]		C4671002 (EPIC-SR) N=654[c]		C4671006 (EPIC-PEP) N= 1823[b]	
Race	**Persons**	**Person Time (Days)**	**Persons**	**Person Time (Days)**	**Persons**	**Person Time (Days)**
White	728	3644	512	2562	1414	10,570
Black or African American	52	268	28	145	271	2012
Asian	153	792	69	344	23	183
American Indian or Alaska Native	95	482	39	199	110	799
Multiracial	1	6	-	-	2	16
Not reported	8	38	5	18	1	10
Unknown	1	5	1	5	2	16
Ethnicity	-	-	-	-	-	-
Hispanic or Latino	425	2187	272	1378	1295	9684
Non-Hispanic or non-Latino	608	3022	378	1875	528	3922
Not reported	5	26	4	20	-	-

a. Participants enrolled at sites PPD and PPD (including those switched to PPD are excluded.
b. Includes 912 participants receiving 5-days nirmatrelvir/ritonavir regimen and 911 participants receiving 10-days nirmatrelvir/ritonavir regimen. Participants enrolled at sites PPD and PPD (including those switched to PPD were excluded.
c. Participants enrolled at sites PPD, PPD (including those switched to PPD, PPD, and PPD (2022 enrolees) are excluded.

Exposure is not inclusive of any gaps or withholding of treatment.
PFIZER CONFIDENTIAL SDTM Creation: 10JAN2023 (13:31) Table Generation: 13JAN2023 (10:25) (Database snapshot date: 29APR2022) Output File: ./nda/C4671005_SiteEx/race_rmp and /nda/C4671005_SiteEx/ethnic_rmp
PFIZER CONFIDENTIAL SDTM Creation: 17JAN2023 (12:44) Table Generation: 06MAR2023 (14:35) (Database snapshot date: 11AUG2022) Output File: ./nda/C4671002_RMP_SiteEx/race_rmp and ./nda/C4671002_RMP_SiteEx/ethnic_rmp
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2023 (21:51) Table Generation: 12FEB2023 (21:55) Output File: /nda/C4671006_RMP_SiteEx/race_rmp and /nda/C4671006_RMP_SiteEx/ethnic_rmp

Table 18. Clinical Trial Exposure by Special Populations – Safety Analysis Set

	Nirmatrelvir 300 mg + Ritonavir 100 mg					
	C4671005 (EPIC-HR) N=1038[a]		C4671002 (EPIC-SR) N=654[c]		C4671006 (EPIC-PEP) N= 1823[b]	
Comorbidities	**Persons**	**Person Time (Days)**	**Persons**	**Person Time (Days)**	**Persons**	**Person Time (Days)**
Hepatic impairment	4	21	-	-	1	8
Renal impairment	5	22	2	7	1	9
Cardiovascular disorder	39	187	7	37	15	99
Immunosuppression	6	32	-	-	-	-
Diabetes mellitus	108	541	34	173	99	712

Table 18. Clinical Trial Exposure by Special Populations – Safety Analysis Set

	Nirmatrelvir 300 mg + Ritonavir 100 mg					
	C4671005 (EPIC-HR) N=1038[a]		C4671002 (EPIC-SR) N=654[c]		C4671006 (EPIC-PEP) N= 1823[b]	
Comorbidities	**Persons**	**Person Time (Days)**	**Persons**	**Person Time (Days)**	**Persons**	**Person Time (Days)**
Chronic respiratory disease	60	302	9	47	22	161

a. Participants enrolled at sites PPD and PPD (including those switched to PPD) are excluded.
b. Includes 912 participants receiving 5-days nirmatrelvir/ritonavir regimen and 911 participants receiving 10-days nirmatrelvir/ritonavir regimen. Participants enrolled at sites PPD and PPD (including those switched to PPD were excluded.
c. Participants enrolled at sites PPD, PPD (including those switched to PPD, PPD, and PPD (2022 enrolees) are excluded.

Exposure is not inclusive of any gaps or withholding of treatment.
PFIZER CONFIDENTIAL SDTM Creation: 10JAN2023 (13:31) Table Generation: 13JAN2023 (10:25) (Database snapshot date: 29APR2022) Output File: ./nda/C4671005_SiteEx/impair_rmp
PFIZER CONFIDENTIAL SDTM Creation: 17JAN2023 (12:44) Table Generation: 06MAR2023 (14:35) (Database snapshot date: 11AUG2022) Output File: ./nda/C4671002_RMP_SiteEx/impair_rmp
PFIZER CONFIDENTIAL SDTM Creation: 31JAN2023 (21:51) Table Generation: 12FEB2023 (21:55) Output File: ./nda/C4671006_RMP_SiteEx/impair_rmp

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion criteria in the pivotal studies C4671005, C4671002 and C4671006 are listed in Table 19 below.

Table 19. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for exclusion	Missing information (Yes/No)	Rationale (if not included as missing information)
Participants <18 years of age	Paediatric subjects (<18 years of age) appear to have milder symptoms, to be more commonly asymptomatic, and are less likely to be hospitalized when compared to adults. Separate trials in paediatric patients will be conducted.	No	Paediatric subjects are not relevant for the proposed indication. Safety in paediatric population will be assessed as part of a Paediatric Investigation Plan.
Participants whose COVID-19 related signs and symptoms began >5 days from enrollment	Effectiveness of antivirals may be reduced if not initiated early after onset of symptoms.	No	Safety is not expected to differ in this population.
History of hospitalization for the medical treatment of COVID-19	Treatment intended for use in the outpatient setting.	No	Safety in patients with a prior history of hospitalization due to COVID-19 is not expected to differ in these patients.
Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or C, or acute liver failure.	Patients with active liver diseases may require dose adjustments.	Yes	N/A
Receiving dialysis or have known moderate to severe renal impairment	When dosed with ritonavir, the primary clearance mechanism of nirmatrelvir is via renal excretion of unchanged drug. Significant increases in plasma concentrations of nirmatrelvir/ritonavir in patients who were moderately or severely impaired can occur. This requires dose adjustments	Yes	N/A
Known HIV infection with a viral load greater than 400	Ritonavir may select for resistant HIV strains in	No	Information on the risk of HIV 1 developing

Table 19. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for exclusion	Missing information (Yes/No)	Rationale (if not included as missing information)
copies/mL or taking prohibited medications for HIV treatment	patients with uncontrolled HIV infection.		resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV 1 infection is included in the SmPC.
Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events during treatment and for 4 days after the last dose of nirmatrelvir /ritonavir	Ritonavir is a strong inhibitor of CYP3A4.	No	As per Section 4.3 *Contraindications* of the SmPC, the use of nirmatrelvir/ritonavir with medicinal products that are highly dependent on CYP3A is contraindicated.
Concomitant use of any medications or substances that are strong inducers of CYP3A4 are prohibited within 28 days prior to first dose of nirmatrelvir/ritonavir and during study treatment	Nirmatrelvir is a CYP3A4 substrate and co-administration with CYP3A4 inducers could result in subtherapeutic concentrations.	No	As per Section 4.3 *Contraindications* of the SmPC, the use of nirmatrelvir /ritonavir with medicinal products that are potent CYP3A inducers is contraindicated.
Females who are pregnant and breastfeeding	To avoid exposure for vulnerable populations (foetus/infant).	Yes	N/A

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical studies in the development plan are limited in size and, therefore, unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

There has been limited/no exposure to nirmatrelvir/ritonavir in some special populations such as pregnant/lactating women, paediatric participants (<18 years of age), and specific subpopulations that were excluded from the nirmatrelvir/ritonavir clinical development program.

Table 20. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Pregnant women were excluded from the nirmatrelvir/ritonavir pivotal studies C4671002, C4671005 and C4671006 (refer to Table 19). Data from the use of nirmatrelvir/ritonavir in pregnant women are limited. SmPC warns on the use of nirmatrelvir/ritonavir in pregnant and breastfeeding women.
Breastfeeding women	Breastfeeding women were excluded from the nirmatrelvir/ritonavir pivotal studies C4671002, C4671005 and C4671006 (refer to Table 19). Data are not available to assess the effects of nirmatrelvir/ritonavir on the breastfed infant or on milk production/excretion. It is unknown whether nirmatrelvir is excreted in human or animal milk. There is no information on the effects of ritonavir on the breast-fed newborns/infants or the effects of the medicinal product on milk production. Therefore, nirmatrelvir/ritonavir is not recommended during breastfeeding.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Participants with active liver diseases or acute liver failure were excluded from the pivotal studies C4671002, C4671005 and C4671006 (refer to Table 19). For available exposure of hepatic impaired participants (in the pivotal studies said above), please refer to Table 18.
• Patients with renal impairment	Participants with moderate and severe renal impairment were excluded from the pivotal study C4671002, C4671005 and C4671006 as they require dose adjustments. For available exposure of renal impaired participants (in the pivotal studies said above), please refer to Table 18. When dosed with ritonavir, the primary clearance mechanism of nirmatrelvir is via renal excretion of unchanged drug. Significant increases in plasma concentrations of nirmatrelvir/ritonavir in patients who were moderately or severely impaired can occur.
• Patients with cardiovascular disease	Cardiovascular disease is one of the medical conditions leading to a high risk for progression to severe COVID-19 (inclusion criteria for the pivotal study C4671005). For available exposure of subjects with cardiovascular disorder (in the pivotal studies C4671002, C4671005 and C4671006), please refer to Table 18.
• Immunocompromised patients	Immunosuppressive disease or immunosuppressive treatment is one of the medical conditions leading to a high risk for progression to severe COVID-19 (inclusion criteria for the pivotal study C4671005). For available exposure of subjects with immunosuppression (in the pivotal studies C4671002, C4671005 and C4671006), please refer to Table 18.

Table 20. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
• Patients with a disease severity different from inclusion criteria in clinical trials	Hospitalized patients due to COVID-19 were excluded from the pivotal studies C4671002, C4671005 and C4671006. No exposure data available.
Population with relevant different ethnic origin	Please refer to Table 17 for exposure information by ethnic origin from the pivotal studies C4671002, C4671005 and C4671006.
Subpopulations carrying relevant genetic polymorphisms	No data available.
Paediatric population	Participants aged less than 18 years were excluded from the pivotal study C4671002, C4671005 and C4671006. Safety in paediatric population will be assessed as part of a Paediatric Investigation Plan.
Elderly population	Please refer to Table 16 for exposure information in the elderly (≥65 years) from the pivotal studies C4671002, C4671005 and C4671006.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

It is not possible to determine with certainty the number of individuals who received nirmatrelvir/ritonavir. The estimated exposure and the method used to calculate it are included in Section SV.1.2 and Section SV.1.1, respectively.

SV.1.1. Method Used to Calculate Exposure

Based on the estimated exposure in US[b], data made publicly available by Competent Authorities in some countries (ie, UK[c], Italy[d], Austria[e], Japan[f] and Thailand[g]) and the number of Company's shipped packs in the above said 6 countries, an "*Average percentage of use*" is calculated:
approximately 20.6% of the total shipped packs have been estimated to be administered to the patients from data in these 6 countries.
This percentage is applied to the shipments to the other countries worldwide.

To provide an estimation of exposure by gender and age group, available data[h] (percentage of written prescriptions) provided by IQVIA Health Prescribing Insights Medical are used.

SV.1.2. Exposure

With the methodology above (refer to Section SV.1.1)[i], it has been estimated that ***11,646,361 patients*** have been exposed cumulatively to nirmatrelvir/ritonavir from the first EUA in US (on 22 December 2021) up to 31 December 2022.

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[b] In US the estimation of the patient's exposure is calculated based on the number of packages shipped by US Wholesaler to the US POCs (approximately 10,950,698 packs up to 03 January 2023) and the number of packs still available in US POCs (based on the published data on COVID-19 Public Therapeutic Locator as of 05 January 2023: COVID-19 Public Therapeutic Locator | HealthData.gov - *Locations of publicly available COVID-19 Therapeutics*. COVID-19 Public Therapeutic Locator | HealthData.gov) and applying an estimated weekly growth percentage by US State.

[c] COVID-19 Medicines Delivery Unit: Statistics » COVID-19 Therapeutics (antivirals, neutralising monoclonal antibodies and interleukin 6 inhibitors) (england nhs.uk); data up to week ending on 01 January 2023; these data do not include treatments administered as part of clinical trials.

[d] https://www.aifa.gov.it/registri-farmaci-sottoposti-a-monitoraggio; report no. 26 – data up to 27 December 2022.

[e] Publikationen der GECKO-Kommission (bundeskanzleramt.gv.at); report dated 05 December 2022; number of treatments prescribed by hospitals until 29 November 2022; number of treatments prescribed by resident doctors until 31 October 2022; no updated report had been published yet at the time of this PSUR preparation.

[f] https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00324 html; data as of 31 December 2022.

[g] https://paxlovid.dms.go.th/app/report/dashboard.php.; data up to 31 December 2022; accessed online on 05 January 2023.

[h] Data available up to the end of the 3rd quarter 2022 (ie, 30 September 2022) and from 8 countries.

[i] The applied methodology is affected by some bias (including but not limited to):

The worldwide exposure by gender and age group, for US and extra-US countries, based on data (written prescriptions) provided by IQVIA Health Prescribing Insights Medical, is reported in Table 21 and Table 22.

Table 21. Estimated exposure by Gender and Age in US

	Gender		Age (years)[a]			
	F	M	0-15	16-20	21-65	>65
Total=**8,595,340**	5,040,933	3,554,406	45,940	122,704	5,090,484	3,336,212

a. IQVIA medical data are available from NMTA (National Medical and Treatment Audit) in the US and Puerto Rico. NMTA audit can only produce patient age information in 5 year age bands due to data privacy concerns for older age groups.

Table 22. Estimated Exposure Worldwide (excluding US) by Gender and Age

	Gender			Age (years)				
	F	M	Unknown	0-17	18-64	65-74	≥75	Unknown
Total=**3,051,021**	1,407,038	1,577,953	66,030	33,645	1,293,419	676,159	983,916	63,882

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Nirmatrelvir/ritonavir does not have characteristics that would make it attractive for use for illegal purposes; therefore, no potential for drug abuse or dependence with nirmatrelvir/ritonavir is expected.

Module SVII. Identified and Potential Risks

The safety data available indicates that nirmatrelvir/ritonavir has a favorable safety profile in the studied population. Nirmatrelvir/ritonavir was well tolerated for 5 days of dosing in high-risk individuals with COVID-19 as well as individuals with standard risk. The safety profile remained generally consistent when nirmatrelvir/ritonavir was used for either 5 or 10 days Based on this, no important risks have been determined for inclusion in the RMP.

The “Safety in patients with hepatic impairment”, “Safety in patients with renal impairment” and the “Safety during use in pregnancy and lactation” are determined to be missing information for nirmatrelvir/ritonavir due to the exclusion of these populations from the pivotal studies C4671002, C4671005 and C4671006. Please refer to the *Risk-Benefit impact* summarized below in Section SVII.1.2 for each safety concern.

- different time required to distribute packs in different countries;
- the incidence of COVID-19 infection;
- despite MAH’s shipments, in some countries the product could not be available yet on the market.

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

The safety concerns of nirmatrelvir/ritonavir in the initial RMP are listed in the following Table 23.

Table 23. Safety Concerns in the Initial RMP

Important identified risks	None
Important potential risks	None
Missing information	Safety in patients with hepatic impairment
	Safety in patients with renal impairment
	Safety during use in pregnancy and lactation

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not all potential or identified risks for nirmatrelvir/ritonavir are considered to meet the level of importance necessitating inclusion in the list of safety concerns in the RMP.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Adverse reactions with clinical consequences, even serious, but associated with longer treatment duration and/or occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Hepatotoxicity
Hypertension

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation measures in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Allergic reactions/Hypersensitivity
- Drug-drug interactions (with CYP3A substrates and CYP3A inducers)

The risks of Hypersensitivity, Hepatotoxicity and Drug-drug interactions (with CYP3A substrates and CYP3A inducers) are described in the SmPC and PL. It is anticipated that these risks can be adequately minimised by routine risk minimisation and will not require additional risk minimisation measures. These risks will also be characterised through routine pharmacovigilance activities.
To further support the risk minimisation of drug-drug interactions, a QR code and website link have been included on the PL and the outer carton. They link to the MAH product website that includes a drug interaction tool, which provides another mechanism to communicate the drug interactions listed in the SmPC, in a searchable format.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: None

Important Potential Risk: None.

Missing information 1: Safety in patients with hepatic impairment

Risk-benefit impact: Participants with known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B or C infection, primary biliary cirrhosis, Child-Pugh Class B or C, or acute liver failure, have been excluded from the pivotal studies C4671005, C4671002 and C4671006.
Characterisation of the effect of moderate hepatic impairment on the plasma and urine PK of nirmatrelvir/ritonavir has been investigated within a Phase I study (C4671010). No data are currently available in patients with severe hepatic impairment. Ritonavir is principally metabolised and eliminated by the liver, and hepatic adverse events (including hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis, and jaundice) have been reported to have occurred in patients receiving ritonavir, at higher dose and longer duration as an antiretroviral agent. An increased risk for severe and potentially fatal hepatic adverse reactions in patients with chronic hepatitis B or C and treated with combined antiretroviral therapy has been also reported for ritonavir.

Further characterisation of the effect of nirmatrelvir/ritonavir in the hepatic impaired patients is needed to identify specific higher risks of clinically negative outcomes in this population.

Missing information 2: Safety in patients with renal impairment

Risk-benefit impact: When dosed with ritonavir, the primary clearance mechanism of nirmatrelvir is via renal excretion of unchanged drug. Significant increases in plasma concentrations of nirmatrelvir/ritonavir in patients who were moderately or severely impaired can occur. Based on PK-derived analysis (from study C4671011), dosing recommendations of nirmatrelvir/ritonavir 150 mg/100 mg for patients with moderate renal impairment have been included in SmPC. No data are available yet in patients with severe renal impairment.

Further characterization of the effect of nirmatrelvir/ritonavir in the renal impaired patients is required to identify specific risks or difference in the safety profile in this patient population.

Missing information 3: Safety during use in pregnancy and lactation

Risk-benefit impact: Pregnant women are excluded from the pivotal clinical studies. Considering the serious consequences of COVID-19 in pregnant people and that pregnant people at high risk of progression to severe COVID-19 disease may need to be treated with antiviral medication based on an overall benefit-risk judgement, it is important to characterise the safety profile of nirmatrelvir/ritonavir in this population and the effect on foetal development, as well as on babies exposed via breastfeeding.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Data from pivotal studies have been used to determine the important identified risks, important potential risks, and missing information.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: None

Important Potential Risk: None

SVII.3.2. Presentation of the Missing Information

Table 24. Safety in Patients with Hepatic Impairment

Evidence source: The safety profile of nirmatrelvir/ritonavir has not been investigated in patients with active liver diseases or acute liver failure due to their exclusion from the pivotal clinical studies C4671005, C4671002 and C4671006. Population in need of further characterisation: The lack of relevant data is communicated in product labelling; a Non-Interventional Post-Authorisation study using real world evidence is planned to assess the safety in patients with moderate and severe hepatic impairment; see PART III.2.

Table 25. Safety in Patients with Renal Impairment

Evidence source: The safety profile of nirmatrelvir/ritonavir has not been investigated in patients receiving dialysis or have known moderate to severe renal impairment due to their exclusion from the pivotal clinical studies C4671005, C4671002 and C4671006. Based on PK-derived analysis (from study C4671011), dosing recommendations of nirmatrelvir/ritonavir 150 mg/100 mg for patients with moderate renal impairment have been included in SmPC. Population in need of further characterisation: The lack of clinical data is communicated in product labelling; a Non-Interventional Post-Authorisation study using real world evidence is planned to assess the safety in patients with moderate and severe renal impairment, see PART III.2

Table 26. Safety during Use in Pregnancy and Lactation

Evidence source: The safety profile of nirmatrelvir/ritonavir has not been investigated in pregnant and breastfeeding women due to their exclusion from the pivotal clinical studies C4671005 C4671002 and C4671006. Population in need of further characterisation: The lack of data is communicated in product labelling; a cohort/prevalence study will be conducted in pregnant and breastfeeding women; an additional PK and safety study is planned to support the appropriate characterisation of safety in lactation; see PART III.2.

Module SVIII. Summary of the Safety Concerns

Table 27. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	Safety in patients with hepatic impairment
	Safety in patients with renal impairment
	Safety during use in pregnancy and lactation

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance for the lifecycle of a product is a critical component to the detection, assessment, understanding and mitigation of AEs. Objectives of routine pharmacovigilance includes having processes in place to assure the ongoing and timely collection, processing, follow-up, and analysis of individual AE reports and aggregate data globally, following global safety Standard Operating Procedures and regulatory guidance. Pfizer monitors the safety profile of its products, evaluates issues potentially impacting product benefit-risk profiles in a timely manner, and ensures that appropriate communication of relevant safety information is conveyed in a timely manner to regulatory authorities and other interested parties as appropriate and in accordance with international principles and prevailing regulations.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires:**

Pregnancy follow-up questionnaires (*Exposure During Pregnancy Follow-up Questionnaire* for non-study cases and *Exposure During Pregnancy Supplemental Form* for study cases attached in Annex 4) are also utilized to collect further data on pregnancy outcome and reproductive and developmental toxicity.

A Data Capture Aid has been created to gather data about the safety during use in lactation (refer to Annex 4).

Two further DCAs, for lack of efficacy (including fields to request information on the COVID-19 variant) and for hypertension are in Annex 4.

- **Other forms of routine pharmacovigilance activities:**

As part of the enhanced signal detection activities for the duration of the COVID-19 pandemic, monitoring of data on treatment failure due to emerging variants from all available data sources, will include (not limited to):

- Spontaneous cases (using a targeted follow-up questionnaire for lack of efficacy as stated above)
- Clinical trial data
- Literature
- Studies conducted by public health authorities

If the review of the data leads to an impact on the benefit risk of the product, a benefit-risk discussion and any warranted product information updates will be submitted within 1 month from assessment via appropriate variation procedure. Additionally, the interval and cumulative data will be summarised in a dedicated section in the PSUR.

III.2. Additional Pharmacovigilance Activities

PASS in pregnant and breastfeeding women summary

Study short name and title:
PASS in pregnant and breastfeeding women; A post-authorisation safety study of nirmatrelvir/ritonavir use in pregnant and breastfeeding women.

Rationale and study objectives:
The purpose of this study is to assess use of nirmatrelvir/ritonavir during pregnancy and, if feasible, lactation.

The objectives of the study are to evaluate the safety of nirmatrelvir/ritonavir in pregnant and lactating women, including pregnancy outcomes and other safety events of interest in exposed and unexposed women. As feasible, maternal, and infant outcomes will be assessed in lactating women.

Study design:
Non-Interventional Post-Authorisation secondary database collection study.

Study population:
Pregnant and lactating women identified in claims and electronic health record data in European countries.

Milestones:

Milestone	Due date
Protocol submission	31 May 2022
Estimate study start	EMA approval of protocol and nirmatrelvir/ritonavir commercially available
Progress report submission	30 November 2022
Interim report 1 submission	30 November 2023
Interim report 2 submission	29 November 2024
Final report submission	28 November 2025

Study C4671039 summary

Study short name and title:
Study C4671039; A multiple dose, pharmacokinetic and safety study in healthy lactating adult women.

Rationale and study objectives:
The purpose of this study is to assess penetration of nirmatrelvir in human breast milk.

The objective is to measure the concentration of nirmatrelvir in breastmilk in healthy women.

Study design:
Phase 1, multiple dose, open label, single arm study.

Study population:
Healthy breastfeeding women.

Milestones:

Milestone	Due date
Estimate study start	EMA approval of protocol and nirmatrelvir/ritonavir commercially available
Final study results submission	15 September 2023

PASS in moderate and severe renal impairment

Study short name and title:

PASS in moderate and severe renal impairment; A post-authorisation safety study of nirmatrelvir/ritonavir use in moderate and severe renal impairment.

Rationale and study objectives:
The purpose and objectives of this study is to assess the safety of nirmatrelvir/ritonavir in patients with moderate and severe renal impairment.

Study design:
Non-Interventional Post-Authorisation study using real world evidence.

Study population:
Patients with moderate and severe renal impairment identified from real world evidence.

Milestones:

Milestone	Due date
Study feasibility assessment	28 February 2022
Protocol submission	31 May 2022
Estimate study start	EMA approval of protocol and nirmatrelvir/ritonavir commercially available
Progress report submission	30 November 2022
Interim report 1 submission	30 November 2023
Interim report 2 submission	29 November 2024
Final report submission	30 November 2025

PASS in moderate and severe hepatic impairment

Study short name and title:
PASS in moderate and severe hepatic impairment. A post-authorisation safety study of nirmatrelvir/ritonavir use in moderate and severe hepatic impairment.

Rationale and study objectives:
The purpose and objectives of this study is to assess the safety of nirmatrelvir/ritonavir in patients with moderate and severe hepatic impairment.

Study design:
Non-Interventional Post-Authorisation study using real world evidence.

Study population:
Patients with moderate and severe hepatic impairment identified from real world evidence.

Milestones:

Milestone	Due date
Study feasibility assessment	28 February 2022
Protocol submission	31 May 2022
Estimate study start	EMA approval of protocol and nirmatrelvir/ritonavir commercially available
Progress report submission	30 November 2022
Interim report 1 submission	30 November 2023
Interim report 2 submission	29 November 2024
Final report submission	30 November 2025

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. Ongoing and Planned Additional Pharmacovigilance Activities

Table 28. Ongoing and Planned Additional Pharmacovigilance Activities

Study (short name and title) Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
PASS in pregnant and breastfeeding women A post-authorisation safety study of nirmatrelvir/ritonavir use in pregnant and breastfeeding women *Planned*	A cohort/prevalence study using secondary data from electronic health records and/or claims in European countries to assess use of nirmatrelvir/ritonavir during pregnancy and if feasible lactation. The study will also evaluate pregnancy outcomes (eg, major congenital malformations, spontaneous abortions, stillbirths, small-for-gestational-age births) as feasible in data sources, and other safety events of interest in women exposed to nirmatrelvir/ritonavir versus not exposed to nirmatrelvir/ritonavir or another appropriate comparator. As feasible, maternal, and infant outcomes will be assessed in lactating women.	Safety during use in pregnancy and lactation	Protocol submission	31 May 2022
			Estimate study start	EMA approval of protocol and nirmatrelvir/ritonavir commercially available
			Progress report submission	30 November 2022
			Interim report 1 submission	30 November 2023
			Interim report 2 submission	29 November 2024
			Final report submission	28 November 2025
Study C4671039 A multiple dose, pharmacokinetic and safety study in healthy lactating adult women. *Ongoing*	To assess penetration of nirmatrelvir in human breast milk and to measure the concentration of nirmatrelvir in breastmilk in healthy women.	Safety during use in pregnancy and lactation	Estimate study start	EMA approval of protocol and nirmatrelvir/ritonavir commercially available
			Final study results submission	15 September 2023
PASS in moderate and severe renal impairment	To assess the safety of nirmatrelvir/ritonavir in patients with moderate and severe renal impairment.	Safety in patients with renal impairment	Study feasibility assessment	28 February 2022
			Protocol submission	31 May 2022

Table 28. Ongoing and Planned Additional Pharmacovigilance Activities

Study (short name and title) Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
A post-authorisation safety study of nirmatrelvir/ritonavir use in moderate and severe renal impairment. *Planned*			Estimate study start	EMA approval of protocol and nirmatrelvir/ritonavir commercially available
			Progress report submission	30 November 2022
			Interim report 1 submission	30 November 2023
			Interim report 2 submission	29 November 2024
			Final report submission	30 November 2025
PASS in moderate and severe hepatic impairment A post-authorisation safety study of nirmatrelvir/ritonavir use in moderate and severe hepatic impairment. *Planned*	To assess the safety of nirmatrelvir/ritonavir in patients with moderate and severe hepatic impairment.	Safety in patients with hepatic impairment	Study feasibility assessment	28 February 2022
			Protocol submission	31 May 2022
			Estimate study start	EMA approval of protocol and nirmatrelvir /ritonavir commercially available
			Progress report submission	30 November 2022
			Interim report 1 submission	30 November 2023
			Interim report 2 submission	29 November 2024
			Final report submission	30 November 2025

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

There are no plans for any additional efficacy studies following marketing authorization.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

No safety concerns have been identified for which actions other than routine risk minimisation activities are necessary.

Beyond SmPC and PL, the routine risk minimization activities for nirmatrelvir/ritonavir include the pack size and medicine's legal status.
To support the risk minimisation of drug-drug interactions beyond the label, a QR code and website link have been included on the PL and the outer carton. They link to the MAH product website that includes a drug interaction tool, which provides another mechanism to communicate the drug interactions listed in the SmPC, in a searchable format.

Table 29 and Table 30 present the planned risk minimisation activities for the missing information "Safety in patients with hepatic impairment", "Safety in patients with renal impairment" and "Safety during use in pregnancy and lactation".

Table 29. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Safety in patients with hepatic impairment	Routine risk communication: SmPC Section 4.2 *Posology and method of administration,* Section 4.4 *Special warnings and precautions for use,* and Section 5.2 *Pharmacokinetic properties.* Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Pack size; medicine's legal status.
Safety in patients with renal impairment	Routine risk communication: SmPC Section 4.2 *Posology and method of administration,* Section 4.4 *Special warnings and precautions for use* and Section 5.2 *Pharmacokinetic properties.* Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Pack size; medicine's legal status.

Table 29. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Safety during use in pregnancy and lactation	Routine risk communication: SmPC Section 4.6 *Fertility, pregnancy and lactation.* Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Pack size; medicine's legal status.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in PART V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of Risk Minimisation Measures

Routine risk minimisation actions include the use of the SmPC and PL to address the safety concerns as summarised in Table 30 below. There are no additional risk minimisations measures proposed.

Table 30. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Safety in patients with hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 *Posology and method of administration*, Section 4.4 *Special warnings and precautions for use*, and Section 5.2 *Pharmacokinetic properties*. Pack size. Medicine's legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS in moderate and severe hepatic impairment (Final report submission by 30 November 2025).
Safety in patients with renal impairment	Routine risk minimisation measures: SmPC Section 4.2 *Posology and method of administration*, Section 4.4 *Special warnings and precautions for use* and Section 5.2 *Pharmacokinetic properties*. Pack size. Medicine's legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS in moderate and severe renal impairment (Final report submission by 30 November 2025).
Safety during use in pregnancy and lactation	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pregnancy follow-up

Table 30. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	SmPC Section 4.6 *Fertility, pregnancy and lactation*. Pack size. Medicine's legal status. Additional risk minimisation measures: None.	questionnaires and DCA for lactation to collect relevant information during follow-up activities. Additional pharmacovigilance activities: PASS in pregnant and breastfeeding women (Final report submission by 28 November 2025). Study C4671039 (Final study results submission by 15 September 2023).

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Paxlovid (Nirmatrelvir/ritonavir)

This is a summary of the risk management plan (RMP) for Paxlovid. The RMP details important risks of Paxlovid, how these risks can be minimised, and how more information will be obtained about Paxlovid's risks and uncertainties (missing information).

Paxlovid's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Paxlovid should be used.

This summary of the RMP for Paxlovid should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Paxlovid's RMP.

I. The Medicine and What It Is Used For

Paxlovid is authorised for the treatment of coronavirus disease 2019 (COVID-19) in adults who do not require supplemental oxygen and who are at increased high risk for progressing to severe COVID-19 (see SmPC for full indication). It contains nirmatrelvir in combination with ritonavir as the active substances and it is given by oral route.

Further information about the evaluation of Paxlovid's benefits can be found in Paxlovid's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/paxlovid.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Paxlovid, together with measures to minimise such risks and the proposed studies for learning more about Paxlovid's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Paxlovid is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Paxlovid are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Paxlovid. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	None
Important potential risks	None
Missing information	Safety in patients with hepatic impairment
	Safety in patients with renal impairment
	Safety during use in pregnancy and lactation

II.B Summary of Important Risks

Missing information 1: Safety in patients with hepatic impairment

Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.2 *Posology and method of administration*, Section 4.4 *Special warnings and precautions for use*, and Section 5.2 *Pharmacokinetic properties*. Pack size. Medicine's legal status. Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS in moderate and severe hepatic impairment; See PART II.C of this summary for an overview of the post-authorisation development plan.

Missing information 2: Safety in patients with renal impairment

Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.2 *Posology and method of administration,* Section 4.4 *Special warnings and precautions for use* and Section 5.2 *Pharmacokinetic properties*. Pack size. Medicine's legal status. Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS in moderate and severe renal impairment; See PART II.C of this summary for an overview of the post-authorisation development plan.

Missing information 3: Safety during use in pregnancy and lactation

Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.6 *Fertility, pregnancy and lactation*. Pack size. Medicine's legal status. Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS in pregnant and breastfeeding women and Study C4671039; See PART II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies, which are conditions of the marketing authorisation or specific obligation of Paxlovid.

II.C.2 Other Studies in Post-Authorisation Development Plan

PASS in pregnant and breastfeeding women

Purpose of the study: To assess use of nirmatrelvir/ritonavir during pregnancy and, if feasible, lactation.

The objectives of the study are to evaluate the safety of nirmatrelvir/ritonavir in pregnant and lactating women, including pregnancy outcomes and other safety events of interest in exposed and unexposed women. As feasible, maternal, and infant outcomes will be assessed in lactating women.

Study C4671039

Purpose of the study: To assess penetration of nirmatrelvir in human breast milk and to measure the concentration of nirmatrelvir in breastmilk in healthy women.

PASS in moderate and severe renal impairment

Purpose of the study: To assess the safety of nirmatrelvir/ritonavir in patients with moderate and severe renal impairment.

PASS in moderate and severe hepatic impairment

Purpose of the study: To assess the safety of nirmatrelvir/ritonavir in patients with moderate and severe hepatic impairment.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 1 – EudraVigilance Interface – Not Applicable

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Exposure During Pregnancy Follow-up Questionnaire (for non-study case)

Exposure During Pregnancy Supplemental Form (for study case)

Data Capture Aid – Lactation

Data Capture Aid – Hypertension

Data Capture Aid – Lack of effect

Exposure During Pregnancy (EDP) Follow-up Questionnaire

Manufacturer Reference Number (case number)

Complete all questions and boxes to the best of your ability and knowledge. If more space is needed, please attach additional pages. Forward additional relevant information as it becomes available.

Information previously provided does not need to be repeated on this form.

****Privacy notice to be provided to reporters in applicable countries (e.g., China, United Kingdom, European Economic Area countries): Adverse event information,, your contact details and the personal information that you provided shall be processed by Pfizer in accordance with Pfizer Pharmacovigilance Privacy Policy, which is available on https://privacycenter.pfizer.com/safety***

☐ **Check if you grant permission for us to contact your healthcare professional (HCP) for additional information. If agreed, please provide contact information.**

General Information

Source of Information: ○ HCP ○ Patient ○ Other, please specify

Name, address, and contact details of the source/ reporter:

Name and contact information of gynaecologist/obstetrician:

Mother's Information - Demographics

Date of Birth (dd-Mmm-yyyy) **OR Age (years) or age group (e.g., adult):**	**Height:** ○ **cm** ○ **ft & in.**	**Weight:** ○ kgs ○ lbs

Occupation:

Mother's Information - Pregnancy

First day of last menstrual period Date (dd-Mmm-yyyy):	**Number of foetuses:**	**Estimated delivery date** (dd-Mmm-yyyy):

Gestational period at time of initial exposure: _____ **Months** _____**Trimester**

Manufacturer Reference Number (case number)

Mother Information – Exposure to Products – Pfizer Drug Details

Please complete the drug details below.

Product	Indication	Start date (dd-Mmm-yyyy)	Stop date (dd-Mmm-yyyy) + Reason for Stopping	Formulation	Dose/Frequency

Were any other drugs taken during pregnancy (e.g., prescription, over-the-counter)? ○ No ○ Yes, please complete the drug details below .

Product	Indication	Start date (dd-Mmm-yyyy)	Stop date (dd-Mmm-yyyy) + Reason for Stopping	Formulation	Dose/Frequency

Manufacturer Reference Number (case number)

Mother's Information - Recreational Drug Use During Pregnancy

Did the mother smoke during this pregnancy?	○ No	○ Yes: Number per day? _____
Did the mother drink alcohol during this pregnancy?	○ No	○ Yes: Frequency? _____
Did the mother use illicit drugs during this pregnancy	○ No	○ Yes: Frequency? _____

Mother's Information - Obstetrical History

(Check the box if not applicable) ☐ Not Applicable: No previous pregnancy

Number of previous pregnancies:	**Number of other children:**

Outcome of previous pregnancies (*live birth, miscarriage, elective termination with specification of gestational length and context, late fetal death, ectopic pregnancy, molar pregnancy*). Previous maternal pregnancy complications. Previous fetal/neonatal abnormalities and type. History of sub-fertility:

Mother's Information – Relevant History

Maternal medical history – risk factors for adverse pregnancy outcomes including environmental or occupational exposures, medical disorder (e.g., hypertension, diabetes, seizure disorder, thyroid disorder, asthma, allergic disease, heart disease, psychiatric or mental health disorders, sexual transmitted disorders, hepatitis, AIDS, and other predisposing factors for neurodevelopmental disorders). Family history of congenital abnormality/ genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

Treatment for infertility (*specify*):

Results of serology tests, (e.g., *rubella, toxoplasmosis, etc*):

Ante-natal check-up (specify dates and results) (e.g., fetal ultrasound, serum markers, etc):

Manufacturer Reference Number (case number)

Mother's Information - Delivery

Any problems before delivery?	○ No	○ Yes: please specify:
Any problems during delivery? (*including delivery complications, foetal distress, amniotic fluid abnormal, abnormal placenta*):	○ No	○ Yes: please specify:
Any problems after delivery?	○ No	○ Yes: please specify:

Mode of delivery e.g., natural birth (i.e., vaginal delivery without medication or anesthesia), cesarean section:

Outcome of Pregnancy

○ Full term live birth ○ Premature live birth ○ Stillbirth ○ Late foetal death ○ Ectopic pregnancy ○ Molar pregnancy ○ Spontaneous abortion/miscarriage

○ Induced/elective abortion ○ Unknown

Date of Outcome of Pregnancy (dd-Mmm-yyyy):	**Gestational age at birth in weeks, (if known):** _____ Weeks

Neonatal Information - Outcome of Infant

○ Normal New born Apgar Score: 1 min _____ 5 min_____

○ Congenital malformation/Anomaly (specify) :

○ Other neonatal problem/abnormality (include dysmaturity, neonatal illness, hospitalization, drug therapies) (specify)*:

○ Unknown

Manufacturer Reference Number (case number)

Neonatal Information – Infant Details

Gender (sex):	Weight at birth:	Length at birth:	Head circumference at birth:
○ Male ○ Female	○ Grams ○ lbs ozs	○ cm ○ in	○ cm ○ in

Follow-up of Infant

(Check the box if not applicable) ☐ Not Applicable

Malformation/anomalies diagnosed:
Developmental assessment:
Infant illnesses, hospitalizations, drug therapies, breastfeeding:

Fetal Information

(Check the box if not applicable) ☐ Not Applicable
(In the event of an elective termination, spontaneous abortion, late fetal death – provide details if available)

Reason for termination:
Gestational age at termination:
Results of physical examination (gender, external anomalies) and pathology:

Manufacturer Reference Number (case number)

Paternal Information (Check the box if not applicable) ☐ Not applicable

Age (years):	**Date of Birth** (dd-Mmm-yyyy):	**Occupation:**

Relevant History:
Risk factors including environmental or occupational exposures, e.g., AIDS, toxins. Family history of congenital abnormality/ genetic diseases, consanguinity (or any family relation or lineage) between parents (*specify degree*):

Paternal Information - Exposure to Products

Were any drugs (e.g., over-the-counter, medical prescription) taken by the father during the mother's pregnancy? ○ No ○ Yes: please specify

Product	Indication	Start date (dd-Mmm-yyyy)	Stop date (dd-Mmm-yyyy) + Reason for Stopping	Formulation	Dose/Frequency

Paternal Information – Exposure to Products – Recreational Drug Use

Did the father smoke during the mother's pregnancy? ○ No ○ Yes: Number per day? _____

Did the father drink alcohol during the mother's pregnancy? ○ No ○ Yes, Frequency? _____

Did the father use illicit drugs during the mother's pregnancy ○ No ○ Yes, Frequency? _____

Exposure During Pregnancy (EDP) Follow-up Questionnaire

For Internal Pfizer Use – Completion by the DSU			
AER Number	**Telephone Number**		
Person Contacted	**Pfizer Receipt Date**	**Safety Receipt Date (Date of Contact)***	
Privacy notice provided ** ○ Yes ○ No ○ Not applicable			
Transcription Certification *I hereby certify that the data transcribed into this form accurately and completely reflect the information provided. Where required by local regulations, the reporter has been made aware that their personal information will be shared with Pfizer's related parties.*			
Signature	**Date**		
Preparer of the Report			

* Date of filling in the form = Safety Receipt Date (Date of Contact).

Exposure During Pregnancy (EDP) Supplemental Form

AER # (*insert when known*)

For Pfizer internal use only	
Local #	Date Reported to Pfizer

PROTOCOL # **SUBJECT #**

Complete whenever an embryo or fetus has been exposed to study drug. Send as soon as EDP has been diagnosed, together with the SAE Report Form with the appropriate fields completed. If more space is needed, use additional copies of this page.

Pregnancy

First Day of Last Menstrual Period (DD-MMM-YYYY)

Estimated Date of Delivery (DD-MMM-YYYY)

Number of Foetuses

Gestation at time of initial exposure weeks **Or, if number of weeks unknown:** ☐ First trimester? ☐ Second trimester? ☐ Third trimester?

Relevant History/Exposure to Products

Risk factors for adverse pregnancy outcomes including environmental or occupational exposures, medical disorder e.g. hypertension, diabetes seizure disorder, thyroid disorder, asthma, allergic disease, heart disease, psychiatric or mental health disorders, sexual transmitted disorders, hepatitis, AIDS, and other predisposing factors for neurodevelopmental disorders. Any treatment for infertility (please specify).Family history of congenital abnormality/genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

1) Did the mother smoke during this pregnancy? ☐ No ☐ Yes: Number per day?

2) Did the mother drink alcohol during this pregnancy? ☐ No ☐ Yes : Frequency?

3) Did the mother use illicit drugs during this pregnancy? ☐ No ☐ Yes : Frequency?

Obstetrical History *(Check the box if not applicable)*

☐ Not Applicable: No previous pregnancy

Number of previous pregnancies Number of other children

Outcome of previous pregnancies (live birth, miscarriage, elective termination with specification of gestational length and context, late fetal death, ectopic pregnancy, molar pregnancy).

Previous maternal pregnancy complications. Previous fetal/neonatal abnormalities and type. History of sub-fertility.

OUTCOME OF PREGNANCY

Complete and send after the end of pregnancy in all cases when an embryo or fetus has been exposed to study drug

Date of outcome of pregnancy DD-MMM-YYYY

Mode of delivery (e.g., natural birth [i.e., vaginal delivery without medication or anesthesia], cesarean section): [ ]

Pregnancy outcome

Check one ☐ Full term live birth ☐ Preterm live birth ☐ Stillbirth* ☐ Spontaneous abortion/miscarriage* ☐ Induced abortion ☐ Unknown

Gestational age at birth in weeks, (if known):

Complete also the Serious Adverse Event section of the report

Infant

Check one ☐ Normal ☐ Congenital Malformation/Anomaly** ☐ Other neonatal problem** ☐ Unknown

Other neonatal problem/abnormality (include dysmaturity, neonatal illness, foetal distress, amniotic fluid abnormal, anormal placenta hospitalization, drug therapies) Specify:

Apgar Score 1min 5min

☐ Male ☐ Female Birthweight grams ***Or, if birthweight in grams unknown:*** Birthweight ☐ lb ☐ oz

Length at birth: ☐ in ☐ cm Head Circumference at birth: ☐ in ☐ cm

****Complete also the Serious Adverse Event section of the report, specifying the diagnosis as the Serious Adverse Event***

Exposure During Pregnancy (EDP) Supplemental Form

AER # (*insert when known*)

For Pfizer internal use only	
Local #	Date Reported to Pfizer

PROTOCOL # **SUBJECT #**

Paternal Information *(Check the box if not applicable)*

☐ Not Applicable

Date of Birth (dd-Mmm-yyyy) : or **Occupation**

Age (years): or

Age group (e.g., adult):

Relevant History

Risk factors including environmental or occupational exposures, e.g. AIDS, toxins. Family history of congenital abnormality/genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

Exposure to Products

Where any drugs (e.g., OTC, medical prescription) taken by the father during the mother's pregnancy? ☐ No ☐ Yes, *please specify*

Product	Indication	Start Date \ Stop Date	Reason for stopping	Dose	Formulation	Frequency
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				
		DD-MMM-YYYY DD-MMM-YYYY				

Exposure to Products - Recreational Drug Use

1) Did the father smoke during the mother's pregnancy? ☐ No ☐ Yes: Number per day?

2) Did the father drink alcohol during the mother's pregnancy? ☐ No ☐ Yes : Frequency?

3) Did the father use illicit drugs during the mother's pregnancy? ☐ No ☐ Yes : Frequency?

Paxlovid (PF-07321332 and Ritonavir) Lactation Data Capture Aid

Instructions for use:

This Data Capture Aid (DCA) is intended to capture the available clinical details on exposure via lactation following administration of Paxlovid (PF-07321332/Ritonavir).

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

AE onset date (dd-Mmm-yyyy): _____

Mother's Age (e.g., years): _____**and Date of Birth (dd-Mmm-yyyy):**_____

Exposed Neonate/Infant's Age (e.g., days/weeks/months/years): _____**and Date of Birth (dd-Mmm-yyyy):**_____

If the neonate was premature, what was the Gestational Age at time of exposure (e.g. weeks/days):_____

Reporter Information

Source of information provided on this form: *(Check one):* ☐ Pediatrician ☐ Mother ☐ Other *(please specify):*		
Name of reporter completing this form *(If other than addressee, provide contact information below):*		
Phone Number:	Fax Number:	Email Address:

Product information – Paxlovid (PF-07321332/Ritonavir)

Please specify dates (dd-Mmm-yyyy) of administration of Paxlovid (PF-07321332/Ritonavir)

Details

Please specify the prescribed dose

Details

Please specify the dose taken

Details

Please specify if all doses were completed on each treatment day

Details

Please specify Batch/Lot number

Details

Paxlovid (PF-07321332 and Ritonavir) Lactation Data Capture Aid

1. Was the mother taking Paxlovid (PF-07321332/Ritonavir) while breastfeeding?

☐ No ☐ Yes

2. Did the mother stop breastfeeding while taking Paxlovid (PF-07321332/Ritonavir)?

☐ No ☐ Yes ☐ Not applicable

If yes, on what day of Paxlovid (PF-07321332/Ritonavir) treatment did she stop?

☐ Day 1
☐ Day 2
☐ Day 3
☐ Day 4
☐ Day 5

3. What day did the monther resume breastfeeding relative to the last dose of Paxlovid (PF-07321332/Ritonavir)?

Details:

4. Is breastfeeding a supplementary or the sole source of neonate/infant's nutrition?

☐ Supplementary nutrition source ☐ Sole nutrition source

What % of the neonate/infant's nutrition is via breastfeeding?

Details:

5. For how long was the neonate/infant exposed to Paxlovid (PF-07321332/Ritonavir) treatment via breastfeeding?

Details:

6. Please describe any adverse event in the mother (including dates (dd-Mmm-yyyy), outcome and treatment received)

Details:

7. Please describe any adverse event/s in the neonate/infant (including dates (dd-Mmm-yyyy), outcome and treatment received)

Details:

8. Did the mother or infant/neonate have any concurrent illness at baseline before receiving Paxlovid (PF-07321332/ritonavir)?

Details:

9. Did the neonate/infant have any concurrent illness at baseline before receiving Paxlovid (PF-07321332/ritonavir)?

Details:

10. What concomitant medications was the mother taking while breast feeding?

Details:

11. What concomitant medications was the neonate/infant taking while breast feeding?

Details:

Paxlovid (PF-07321332 and Ritonavir) Hypertension Data Capture Aid

Instructions for use:

This Data Capture Aid (DCA) is intended to capture the available clinical details about the nature and severity of hypertension experienced by a patient following administration of Paxlovid (PF-07321332/Ritonavir).

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

AE onset date (dd-Mmm-yyyy): _____

Patient Age (e.g., 65 years): _____

Reporter Information

Name of reporter completing this form *(If other than addressee, provide contact information below)*:		
Is the reporter a health care provider? ☐ Yes ☐ No If yes, please specify:		
Phone Number:	Fax Number:	Email Address:

Product information – Paxlovid (PF-07321332/Ritonavir)

Please specify dates (dd-Mmm-yyyy) of administration of Paxlovid (PF-07321332/Ritonavir)

Details

Please specify the prescribed dose

Details

Please specify the dose taken

Details

Please specify if all doses were completed on each treatment day

Details

Please specify Batch/Lot number

Details

Hypertension Follow-up Questions

Please provide additional details on a separate page, if needed and reference the question number.

1. Is the reported hypertension a:

☐ New event

☐ Recurrence/exacerbation/aggravation of pre-existing hypertension condition *(please provide details)*

2. Please provide the name, address and phone number of any specialist to whom the patient was referred for the current event of hypertension:

Details:

Details:

3. Was the event confirmed by a health care professional?
☐ Unknown ☐ No ☐ Yes

4. Please provide information on signs/symptoms of hypertension
Details:

5. Please specify blood pressure readings (systolic, diastolic) including dates (dd-Mmm-yyyy)
Details:
- prior to starting Paxlovid (PF-07321322/Ritonavir)
- at time of onset of hypertension
- time of resolution

6. Was/Is the patient hospitalized for hypertension?
☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., duration of hospitalization)*
Details:

7. Did the event require the initiation of new medication or other treatment or procedure?
☐ Unknown ☐ No ☐ Yes → If Yes, please provide details
Details:

8. Was any other diagnostic evaluation performed for hypertension?
Details:

9. Patient's outcome:
☐ Recovering ☐ Recovered ☐ Not recovered ☐ Unknown ☐ Fatal, Date (dd-Mmm-yyyy): .....

If outcome is fatal, was an autopsy performed? ☐ Unknown ☐ No ☐ Yes → *If Yes, please* provide autopsy findings
Details:

Past Medical History Questions

Please provide additional details on a separate page if needed and reference the question number.

Paxlovid (PF-07321332 and Ritonavir) Hypertension Data Capture Aid

10. Does the patient have a history of any of the following?

☐ Hypertension
☐ Diabetes
☐ Heart Disease *(please specify)*
☐ Lung Disease *(please specify)*
☐ Liver disease *(please specify)*
☐ Kidney disease *(please specify)*
☐ Cancer *(please specify)*
☐ Immunosuppressive disorder *(please specify)*
☐ Obesity
☐ Other *(please specify)*

Details:

Does the patient have any blood relatives with a history of hypertension?

☐ Yes ☐ No ☐ Unknown → If Yes, please provide details.

Details:

11. Is the patient a smoker/former smoker?

☐ Current Smoker ☐ Former smoker ☐ No

Details:

12. What concomitant medications is the patient taking? Please list including dates (dd-Mmm-yyyy): ?

Details:

13. Was the patient's hypertension controlled prior to starting Paxlovid (PF-07321322/Ritonavir)

☐ Unknown ☐ Not applicable ☐ No ☐ Yes → *If Yes, please provide details*

Details:

14. Was the patient compliant with their hypertension medication prior to starting Paxlovid (PF-07321322/Ritonavir)

☐ Unknown ☐ Not applicable ☐ No ☐ Yes → *If Yes, please provide details*

Details:

Paxlovid (PF-07321332 and Ritonavir) Lack of Effect Data Capture Aid

Instructions for use:

This Data Capture Aid (DCA) is intended to capture the available clinical details about the nature and severity of COVID-19 illness experienced, particularly in relation to potential cases of lack of effect.

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

AE onset date (dd-Mmm-yyyy): _____

Patient Age (e.g., 65 years): _____

Reporter Information

Name of reporter completing this form *(If other than addressee, provide contact information below):*		
Is the reporter a health care provider? ☐ Yes ☐ No If yes, please specify:		
Phone Number:	Fax Number:	Email Address:

Product information – Paxlovid (PF-07321332/Ritonavir)

Please specify dates (dd-Mmm-yyyy) of administration of Paxlovid (PF-07321332/Ritonavir)

Details

Please specify the prescribed dose

Details

Please specify the dose taken

Details

Please specify if all doses were completed on each treatment day

Details

Please specify Batch/Lot number

Details

Paxlovid (PF-07321332 and Ritonavir) Lack of Effect Data Capture Aid

Follow-up Questions

Please provide additional details on a separate page if needed and reference the question number.

1. Does the patient have a positive test for SARS-CoV2?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (and indicate if this is a new infection or a recurrence)*

Details: (Please specify date (dd-Mmm-yyyy) of test and type of test – e.g., nasal swab reverse transcription–polymerase chain reaction (RT-PCR) test or nucleic acid amplification–based test (NAAT) or antigen test)

2. Did the patient's COVID-19 symptoms improve or worsen while taking Paxlovid (PF-07321332/Ritonavir)?

Did the patient's symptoms improve? ☐ Yes ☐ No

If yes, please provide date *(dd-Mmm-yyyy)*:

If symptoms did not improve, did symptoms worsen?

☐ Yes ☐ No

If yes, please provide date *(dd-Mmm-yyyy)*:

3. Was/Is the patient hospitalized due to COVID-19?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., date (dd-Mmm-yyyy) of hospitalization and date (dd-Mmm-yyyy) of discharge if applicable)*

Details:

4. Is the patient still hospitalized?

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details (e.g., duration of hospitalization)*

Details:

5. Is this event considered lack of efficacy?

☐ Yes ☐ No

If yes, please select criteria used to determine this:

☐ Progression to severe COVID-19, Date *(dd-Mmm-yyyy)*:

☐ Required oxygenation for COVID-19, Date *(dd-Mmm-yyyy)*:

☐ Required hospitalization for COVID-19, Date *(dd-Mmm-yyyy)*:

☐ Death due to COVID-19, Date *(dd-Mmm-yyyy)*:

☐ other, *please specify below and include date (dd-Mmm-yyyy)*:

Details:

6. Was supplemental oxygen required after starting Paxlovid (PF-07321332/Ritonavir)?

☐ **Yes** ☐ **No**

If Yes, please provide dates of oxygen therapy and indicate the type of therapy:

☐ supplemental oxygen (not high flow) - Dates *(dd-Mmm-yyyy)*:

☐ non-invasive ventilation or high-flow - Dates *(dd-Mmm-yyyy)*:

☐ invasive ventilation or ECMO - Dates *(dd-Mmm-yyyy)*:

7. Was the patient's serostatus assessed? ☐Yes ☐No

If Yes, please provide the date of the test and indicate how assessed:

☐ antibodies to spike protein - Date *(dd-Mmm-yyyy)*:

☐ antibodies to nucleocapsid - Date *(dd-Mmm-yyyy)*:

☐ Other, please specify name of test used and Date *(dd-Mmm-yyyy)*:

Result:

Product number of test used:

Or Product lot/batch number:

8. Was sequencing for SARS-COV2 virus variant identification performed? Yes ☐ No ☐

If Yes, please attach a copy of the report or complete the below

If more than one test was performed please append all reports or complete the below for each test separately

Was the sample collected: Before ☐ *After* ☐ Paxlovid (PF-07321332/Ritonavir)

*Date (*dd-Mmm-yyyy*) of sample collection for testing:*

Viral sequencing results obtained:

Yes ☐ *No* ☐ Viral sequencing not performed ☐

If Yes, select WHO variant of interest or variant of concern detected:
☐ *Alpha B.1.1.7 UK*
☐ *Beta B.1.351 South Africa*
☐ *Delta B.1.617.2 India*
☐ *Delta [+K417N] AY.1/AY.2 India*
☐ *Gamma P.1. Brazil*
☐ *Kappa B.1.617.1 India*
☐ *Lambda C.37 Peru*
☐ *Iota B.1.526 USA (New York)*
☐ *Mu B.1.621 Colombia*
☐ *Omicron B.1.1.529*
☐ *Other, please specify virus linea*

9. Please provide information on any new or worsened symptoms/signs during the COVID-19 illness experienced (including date (dd-Mmm-yyyy) of onset/worsening)

Respiratory ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

Cardiovascular ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

Gastrointestinal/Hepatic ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

Vascular ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

Renal ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

Neurological ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

Hematological ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

Dermatological ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

OTHER ☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*
Details:

10. What concomitant medications is the patient taking? Please list including dates (dd-Mmm-yyyy):

11. Did the event require the initiation of new medication or other treatment or procedure?
☐ Unknown ☐ No ☐ Yes → If Yes, please provide details
Details:

12. Patient's outcome with COVID-19:
☐ Recovering ☐ Recovered ☐ Not recovered ☐ Unknown ☐ Fatal, Date (dd-Mmm-yyyy): .....

If outcome is fatal, was an autopsy performed? ☐ Unknown ☐ No ☐ Yes → *If Yes, please* provide autopsy findings
Details:

13. Was any other diagnostic evaluation performed?

Past Medical History Questions

Please provide additional details on a separate page if needed and reference the question number.

14. Does the patient have a history of any of the following?
☐ Hypertension
☐ Diabetes
☐ Heart Disease *(please specify)*
☐ Lung Disease *(please specify)*
☐ Liver disease *(please specify)*
☐ Kidney disease *(please specify)*
☐ Cancer *(please specify)*
☐ Immunosuppressive disorder *(please specify)*
☐ Obesity

15. Is the patient a smoker/former smoker?
☐ Current Smoker ☐ Former smoker ☐ No
Details:

☐ Other *(please specify)* *Details:*	

16. Have any pre-existing diseases worsened during the SARS-CoV2 infection (please specify)

☐ Unknown ☐ No ☐ Yes → *If Yes, please provide details*

Details:

17. Has the patient received a COVID-19 vaccination?

☐ Unknown ☐ No ☐ Yes → If Yes, please provide details (including date (dd-Mmm-yyyy)

Details: