EU RISK MANAGEMENT PLAN FOR PAXLOVID (NIRMATRELVIR/RITONAVIR)

RMP version to be assessed as part of this application:

RMP Version number: 4.2

Data lock point for this RMP: 07 June 2024 (Clinical Trial exposure); 30 September 2024 (Post-Marketing exposure)

Date of final sign off: 04 August 2025

Rationale for submitting an updated RMP: The MAH is submitting this EU RMP to support the variation extending indication to paediatric patients 6 years of age and older, weighing at least 20 kg. This RMP also covers the changes following completion of study C4671039 in the Pharmacovigilance Plan (A multiple dose, pharmacokinetic and safety study in healthy lactating adult women), and updates the status and milestones of PASSs C4671037 (in pregnant women) and C4671047 (in patients with moderate to severe hepatic impairment).

Summary of significant changes in this RMP:

RMP PART/Module	Major Change(s)
PART I. PRODUCT(S) OVERVIEW	Proposed indication extended to paediatric patients 6 years of age and older, weighing at least 20 kg, has been added. Details of the new pack size (containing 5 daily blister cards with 2 nirmatrelvir tablets and 2 ritonavir tables, divided for morning and evening doses) have been added; the new pack is intended for - patients with moderate renal impairment - paediatric patients ≥6 years of age weighing ≥20 to <40 kg.
PART II. SAFETY SPECIFICATION	
Module SI. Epidemiology of the Indication(s) and Target Populations	Indication and Epidemiology data (including Incidence, Prevalence and Existing treatment options) updated.
Module SII. Non-Clinical Part of the Safety Specification	Non-clinical Part updated, including the latest nonclinical virology data.
Module SIII. Clinical Trial Exposure	Exposure data in paediatric population (from study C4671026 – EPIC-PEDS; with cut-off date 07 June 2024) have been added.
Module SIV. Populations Not Studied in Clinical Trials	Updates made in Section SIV.1 and Section SIV.3 as per available data in paediatric population.
Module SV. Post-Authorisation Experience	Post-authorisation data up to cut-off date of 30 September 2024 included.
Module SVI. Additional EU Requirements for the Safety Specification	No changes made.
Module SVII. Identified and Potential Risks	No major changes made, apart from the removal of reference to the completed pharmacokinetic and safety study in healthy lactating women (C4671039).
Module SVIII. Summary of the Safety Concerns	No changes made.

RMP PART/Module	Major Change(s)
PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	Updated text regarding specific adverse reaction follow-up questionnaires. Exposure during Pregnancy follow-up questionnaire for non-study cases has been updated; the follow-up questionnaires (Data Capture Aids - DCAs) for safety during use in lactation and for lack of efficacy have been reviewed to minimise burden on reporters, remove duplicative questions (already asked as part of Company's standard follow-up questionnaires), and simplify the language (with no significant changes in the information captured). The new follow-up questionnaires are included in Annex 4. DCA for hypertension has been removed. Removal of the study C4671039 (completed). Updated status and milestones of PASSs C4671037 and C4671047.
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 the updates in PART III.
PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN	Changes made based on the updates in PART III.
PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	Annex 2: Changes made based on updates in PART III of this RMP (study C4671039 moved from ongoing studies to completed; status and milestones of PASSs C4671037 and C4671047 updated). Annex 4: Updated form listing specific questions for Exposure during Pregnancy cases for non-study cases. Updated DCAs for safety during use in lactation, and for lack of efficacy. Removal of DCA for hypertension. Annex 8: Summary of changes reflecting the above updates is included. No changes to the other Annexes.

Other RMP versions under evaluation: None

Details of the currently approved RMP:

RMP Version number: 3.1

Approved with procedure: EMEA/H/C/005973/II/0057/G

Date of approval (opinion date): 27 March 2025

QPPV name: 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.

LIST OF ABBREVIATIONS

Abbreviation	Definition
3CL	3C-like
$3CL^{pro}$	3C-like protease
AA	African American
ACE2	Angiotensin-converting enzyme 2
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
AI/AN	American Indian/Alaska Native
AKI	Acute Kidney Injury
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
C_{max}	Maximum concentration recorded
CHMP	Committee for Medicinal Products for Human Use
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMA	Conditional Marketing Authorisation
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus disease 2019
COVID-NET	COVID-19-Associated Hospitalization Surveillance Network
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
EDP	Exposure During Pregnancy

Abbreviation	Definition
EEA	European Economic Area
EFD	Embryo-foetal development
eGFR	Estimated Glomerular Filtration Rate
EHR	Electronic Health Records
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPIC	Evaluation of Protease Inhibition for COVID-19
EPIC-HR	Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (study C4671005)
EPIC-PEDS	Evaluation of Protease Inhibition for COVID-19 in Pediatrics (Study ID C4671026)
EPIC-PEP	Evaluation of Protease Inhibition for COVID-19 in Post-Exposure Prophylaxis (Study ID C4671006)
EPIC-SR	Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients (Study ID C4671002)
ERVISS	European Respiratory Virus Surveillance Summary
EU	European Union
EUA	Emergency Use Authorisation
F	Female
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
LV +dP/dt max	Maximum positive slope of the left ventricular pressure wave; an index of cardiac contractility
M	Male
MAA	Marketing Authorisation Applicant

Abbreviation	Definition
MAH	Marketing Authorisation Holder
MERS	Middle east respiratory syndrome
M/O	Multiple/Other
M^{pro}	Main Protease (also referred to as 3CL protease)
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
NOAEL	No-observed-adverse-effect-level
NPA	National Prescription Audit
OCS	Oral corticosteroids
PASC	Post-Acute clinical Sequalae of COVID-19
PASS	Post-Authorisation Safety Study
PCR	Polymerase Chain Reaction
PEDSnet	Pediatric Learning Health System Clinical Research Network
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PL	Product Label
PPND	Pre- and Post-Natal Development
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
Unk	Unknown
US	United States
UV-Vis	Ultraviolet-visible spectroscopy
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 88 nM (range: 39-146 nM) against the Omicron sub-variants, reflecting EC_{50} value fold-changes ≤1.8 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.

<table>
<tr><td></td><td>Proposed: Treatment of coronavirus disease 2019 (COVID-19) in adults and paediatric patients 6 years of age and older weighing at least 20 kg who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19.</td></tr>
<tr><td>Dosage in the EEA</td><td>Adults
Current: The recommended dose in adults 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.

Paediatric population (6 years of age and older)
Proposed:<table><tr><td>Paediatric patients ≥6 years of age, weighing ≥ 40 kg</td><td>The recommended dose 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.</td></tr><tr><td>Paediatric patients ≥6 years of age, weighing ≥ 20 kg to <40 kg</td><td>The recommended dose is 150 mg nirmatrelvir (one 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) taken together orally every 12 hours for 5 days.</td></tr></table>
Refer to the SmPC for dosing information on special populations.</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>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, for twice daily dose. Each daily blister card contains 4 nirmatrelvir tablets and 2 ritonavir tablets (divided for morning and evening doses).

For paediatric patients ≥6 years of age weighing ≥20 to <40 kg each daily blister card contains 2 nirmatrelvir tablets and 2 ritonavir tablets (divided for morning and evening doses).

For patients with moderate renal impairment, each daily blister card contains 2 nirmatrelvir tablets and 2 ritonavir tablets (divided for morning and evening doses).

Daily blister card specific for patients with severe renal impairment contains 2 nirmatrelvir tablets and 1 ritonavir tablet for administration once on Day 1, and 1 nirmatrelvir tablet and 1 ritonavir tablet for administration once daily on Days 2 to 5.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>Yes</td></tr>
</table>

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 and paediatric patients 6 years of age and older weighing at least 20 kg 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 13 April 2024, the overall number of people who had been infected with SARS-CoV-2 was over 704 million worldwide.[4]

Table 1 shows the incidence and prevalence as of 13 April 2024 for the US, and EU-27 countries. In the EU, as of 13 April 2024 the total number of confirmed cases had accumulated about 212 million people, or 413,283 per 1,000,000 people. Across 27 countries in the EU, Romania and Poland reported the lowest incidence rates while France, Slovenia, and Austria reported the highest.[4]

Table 1. Incidence, Prevalence, and Mortality of COVID-19 as of 13 April 2024

	Total Cases	Incidence: Total Cases/ 1,000,000	Active Cases	Prevalence: Active Cases/ 1,000,000	Total Deaths	Mortality: Deaths / 1,000,000	Population
Global	704,753,890	90,413	22,123,398	2,711	7,010,681	899.4	8,161,972,572[a]
EU-27	187,384,280	420,917	682,765	1,534	1,263,437	2,838	445,181,267
UK	24,910,387	363,666	0	0	232,112	3,389	68,497,907
EU-27 + UK	212,294,667	413,283	682,765	1,329	1,495,549	2,911	513,679,174
US	111,820,082	333,985	786,167	2,348	1,219,487	3,642	334,805,269
EU-27 Countries							
Austria	6,081,287	670,727	3,811	420	22,542	2,486	9,066,710
Belgium	4,861,695	416,659	521	45	34,376	2,946	11,668,278
Bulgaria	1,339,851	195,753	8,159	1,192	38,748	5,661	6,844,597
Croatia	1,309,728	322,650	32,609	8,033	18,687	4,604	4,059,286
Cyprus	681,110	556,741	0	0	1,365	1,116	1,223,387
Czech Republic	4,759,041	443,246	318	30	43,517	4,053	10,736,784
Denmark	3,183,756	545,636	0	0	8,814	1,511	5,834,950
Estonia	628,070	475,123	N/A	N/A	3,001	2,270	1,321,910

Table 1. Incidence, Prevalence, and Mortality of COVID-19 as of 13 April 2024

	Total Cases	Incidence: Total Cases/ 1,000,000	Active Cases	Prevalence: Active Cases/ 1,000,000	Total Deaths	Mortality: Deaths / 1,000,000	Population
Finland	1,516,117	272,930	170	31	11,958	2,153	5,554,960
France	40,138,560	612,013	0	0	167,642	2,556	65,584,518
Germany	38,828,995	462,891	405,368	4833	183,027	2,182	83,883,596
Greece	6,101,379	591,412	N/A	N/A	37,869	3,671	10,316,637
Hungary	2,230,232	232,164	29,029	3022	49,048	5,106	9,606,259
Ireland	1,734,582	345,521	170	34	9,491	1,891	5,020,199
Italy	26,723,249	443,445	165,544	2747	196,487	3,261	60,262,770
Latvia	982,505	531,418	4,384	2371	6,715	3,632	1,848,837
Lithuania	1,397,806	525,154	431	162	9,897	3,718	2,661,708
Luxembourg	391,232	609,044	N/A	N/A	1,232	1,918	642,371
Malta	121,420	273,448	386	869	885	1,993	444,033
Netherlands	8,635,786	501,747	195	11	22,992	1,336	17,211,447
Poland	6,661,991	176,524	N/A	N/A	120,598	3,196	37,739,785
Portugal	5,643,062	556,484	127	13	28,126	2,774	10,140,570
Romania	3,529,735	185,470	657	35	68,929	3,622	19,031,335
Slovakia	1,877,605	343,872	0	0	21,224	3,887	5,460,193
Slovenia	1,356,546	652,803	22	11	7,100	3,417	2,078,034
Spain	13,914,811	297,840	30,634	656	121,760	2,606	46,719,142
Sweden	2,754,129	269,511	230	23	27,407	2,682	10,218,971

a. "World population based on https://www.worldometers.info/world-population/world-population-by-year/. accessed on 15 August 2024"

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]

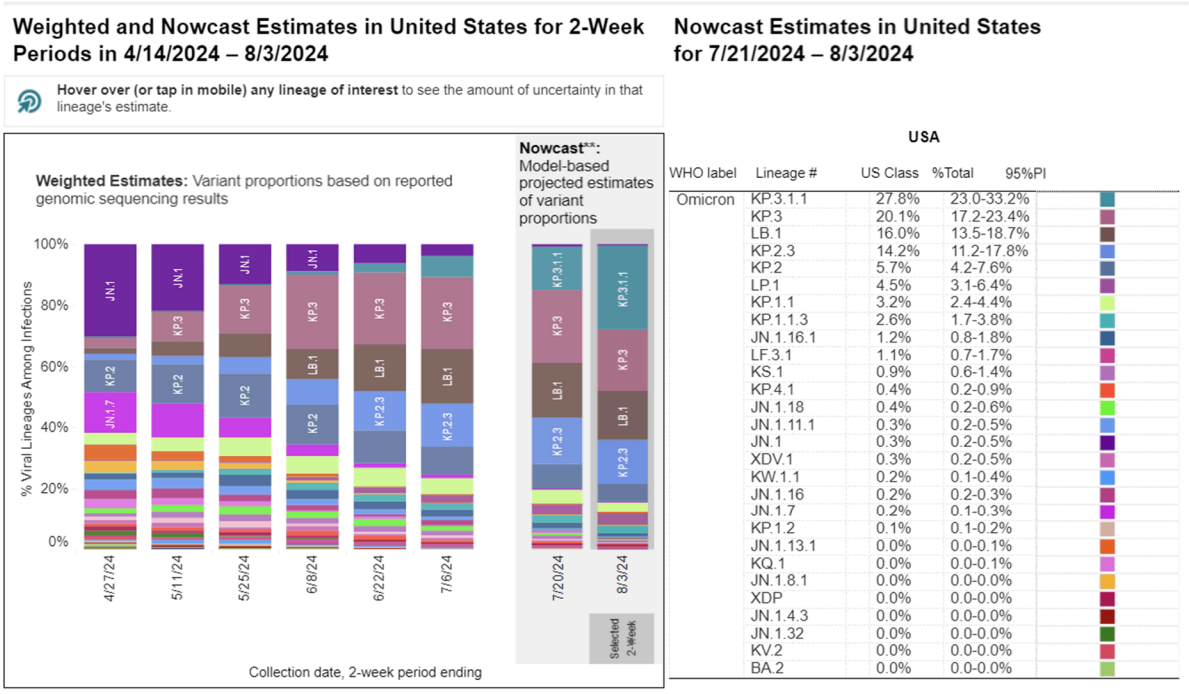
Prevalence:

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 13 April 2024, the overall prevalence estimates for the EU and UK were 1,534 active cases per 100,000.[4] The range of reported prevalence for EU-27 was 0 to 8,033 per 100,000, although this wide range may reflect a difference in reporting quality across countries. Cyprus, Denmark, France, and Slovakia reported the lowest prevalence while, Croatia, Germany, and Hungary reported the highest. It should be noted that Cyprus, Denmark, France, and Slovakia reported 0 active cases on 13 April 2024, leading to a prevalence estimate of 0 per 100,000 population (Table 1).

Variant-specific data

Since the end of 2021, nearly all SARS-CoV-2 infections have been caused by descendant strains of the Omicron variant. Before the 2023-2024 season, the Omicron XBB.1.5 variant dominated globally.[8] In early 2024, the Omicron JN.1 variant emerged as the most prevalent. Currently as of 21 July 2024, the most common variants globally as estimated by the World Health Organization were KP.3 (29.4%) and JN.1 (25.7%).[9] Based on data from the European Respiratory Virus Surveillance Summary (ERVISS), as of spring 2024, the SARS-CoV-2 variant BA.2.86 and its subvariants, including KP.3, continue to dominate in EU.[10] In the US, the most common variant as of 03 August 2024 was the KP.3.1.1 lineage, accounting for 27.8% of SARS-CoV-2 specimens sequenced. The variants from all SARS-CoV-2 specimens sequenced by the US CDC during the week ending 03 August 2024 can be found in Figure 1, along with the variant proportions identified from the week of 14 April 2024 through the week of 03 August 2024.[11]

Figure 1. Variant proportions for all SARS-CoV-2 specimens sequenced by the CDC during the week of 14 April 2024 through 03 August 2024

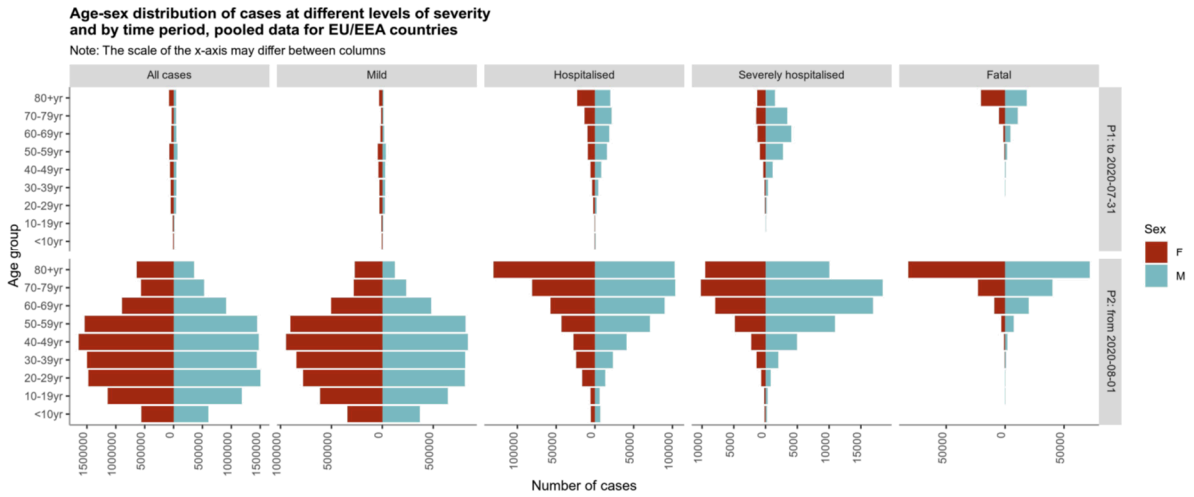


** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
# Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one 2-week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all 2-week periods displayed. While all lineage are tracked by CDC, those named lineages not enumerated in this graphic are aggregated with their parent lineages, based on Pango lineage definitions, described in more detail here: https://web.archive.org/web/20240116214031/https://www.pango.network/the-pango-nomenclature-system/statement-of-nomenclature-rules.

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

Data on the age and sex distributions of COVID-19 cases in Europe by severity of symptoms as posted on 04 November 2021 are shown in Figure 2[12], which captures over 80% of the official number of cases reported by ECDC epidemic intelligence.[13]

Figure 2. 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[12].

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.[14] Only cases and deaths with information reported to the CDC were included in these summaries. Similar to the data in Europe, the US data highlight that individuals of all ages, sexes, and races were diagnosed with COVID-19, but the proportion of deaths is highest among individuals aged 50 years and older.

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]

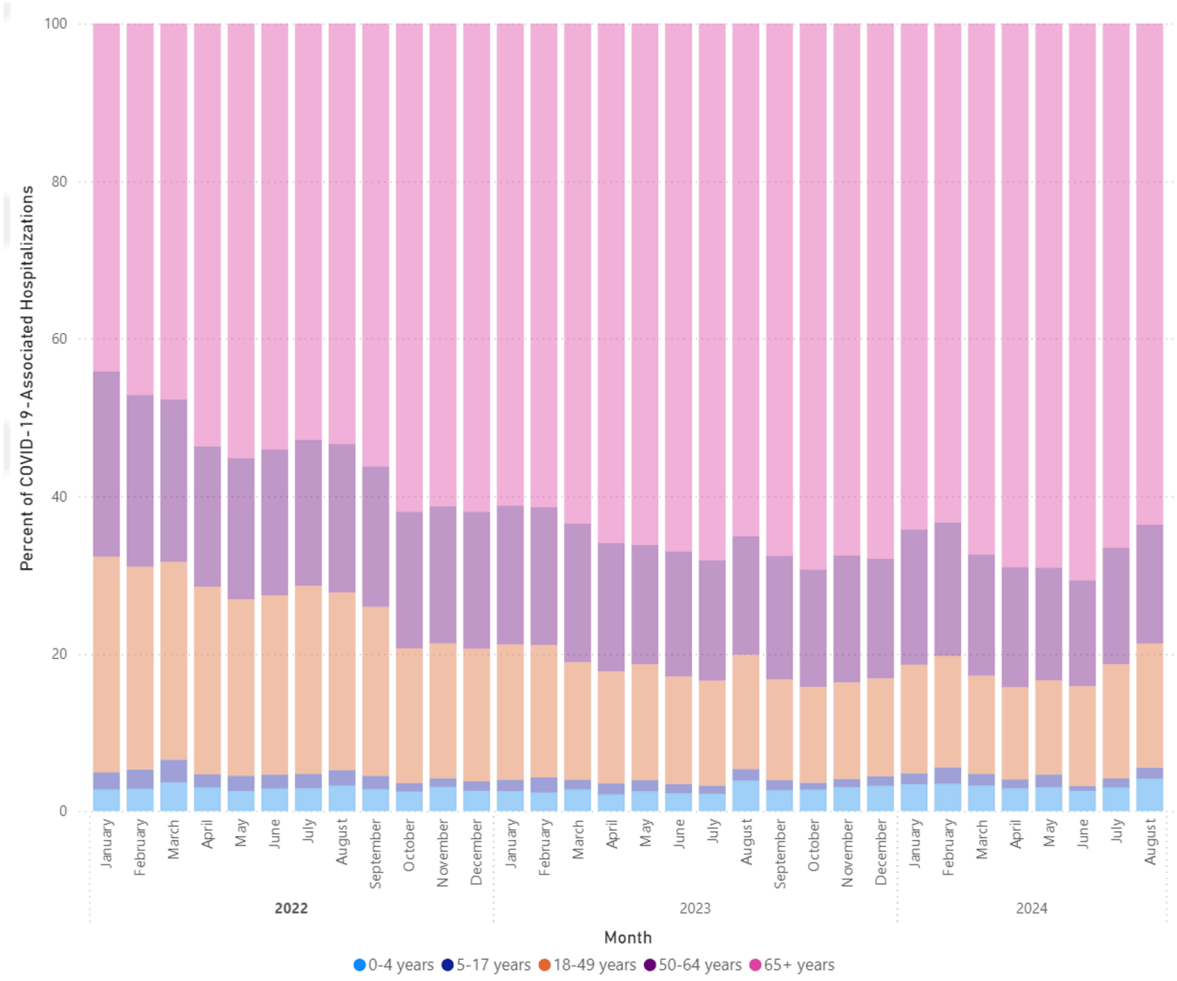
Event	Age Group	Age %	Sex	Sex %	Race[b]	Race %	Age Group	Males %	Females %
Deaths	**0-4**	0.1	**Males**	55	**H/L**	17.1	**0-4**	53.6	46.4
	5-11	0.1	**Females**	45	**AI/AN**	0.9	**5-11**	56.2	43.8
	12-15	0.1	**Other**	<0.1	**Asian**	3.2	**12-15**	48.1	51.9
	16-17	<0.1			**Black**	13.2	**16-17**	61.7	38.3
	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.

By August 2024, the most common variants were descendant strains of the Omicron variant, such as KP.3 and JN.1. In 2024, most hospitalizations due to COVID-19 continue to be among individuals aged 65 years and older. Figure 3 displays the CDC's estimated percent of hospitalizations stratified by age group in the US. Additionally, the CDC estimates that the distribution of COVID-19 hospitalizations by sex and race/ethnicity have not varied substantially since the onset of Omicron in 2022.[15]

Figure 3. CDC Estimated Percent of COVID-19 Hospitalizations by Age Group in the US from 01 January 2022 to 01 August 2024



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.[16]

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.[17]

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.[18]

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.[19] 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.[20-24]

African American COVID-19 patients have been reported to have an increased risk of hospitalisation,[21,25] and mortality,[26] 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.[27] 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.[28] 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.[29]

Paediatric-specific data

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.[30] 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.[30] 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.[31]

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.[32] 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. Other US paediatric data are generally consistent with the CDC findings.

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)

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.[33] 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			

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)
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)
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.[34]

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%.[35]

Risk Factors

Human-to-human transmission of SARS-CoV-2 occurs primarily through respiratory droplets and direct contact.[36] Thus the risk of initial infection increases through spending time in close physical proximity to others, especially in indoor spaces with poor ventilation.[37] 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.[37,38] Among children, the primary source of infection is an infected adult living in the same household.[39]

According to the CDC, some ethnic minority groups have a higher risk of infection (Table 6).[40] Male sex is also a significant risk factor for severe disease and mortality due to COVID-19.[41] 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.[42,43] 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.[44,45]

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.[29,40-42,46-53] Among adults, these risks increase for every 10-year age group above age 39 (Table 6).[29,40,46-51,54] 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.[55] 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.[56]

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.[29,47,54,36,52,57,58] 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.[59]

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.[29,47,48,52,54,60-74]

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.[54]

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)

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
	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)
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.

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

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).[16] 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.[16]

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.[75]

The presence of one or more underlying medical conditions also increases risk of severe or fatal disease among children aged 5-17.[76-79] In particular, childhood obesity has been consistently associated with two to three times the risk of severe disease or hospitalisation[76,79-81] and among hospitalised children with COVID-19 diabetes has been shown to increase the risk of death two-fold compared with those without diabetes.[82] 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.[83] 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.[39,77]

The main existing treatment options:

As of October 2024, EMA has authorised 8 treatments for COVID-19.[84]

Veklury (remdesivir) was granted conditional marketing authorization on 03 July 2020. A marketing authorization was granted on 08 August 2022. Veklury is an antiviral medicine used to treat COVID-19 in adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at the start of treatment) and in adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of developing severe COVID-19.
On 12 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.

Also on 12 November 2021, another monoclonal antibody Regkirona (regdanvimab) was granted marketing authorisation. Regkirona is a medicine used for treating COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of their disease becoming severe.

Another monoclonal antibody, RoActemra (tocilizumab) received on 07 December 2021 an authorization to treat different symptoms and diseases. RoActemra can also be used for the treatment of adults with COVID-19 who are receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation (breathing assisted by a machine).

On 17 December 2021, Kineret (anakinra) received marketing authorization to treat COVID-19 (in addition to other symptoms and diseases) in adults with pneumonia requiring supplemental oxygen (low or high flow oxygen) and who are at risk of developing severe respiratory failure. Also, Xevudy (sotrovimab) granted authorization that same day for the

treatment of 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 the disease becoming severe.

On 16 December 2021, CHMP issued advice on the use of Paxlovid (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.

Evusheld (tixagevimab/cilgavimab) was approved on 25 March 2022 to prevent COVID-19 in adults and adolescents (from 12 years of age weighing at least 40 kilograms). It is also used to treat COVID-19 in adults and adolescents who do not require supplemental oxygen and who are at increased risk of the disease becoming severe. Evidence suggests that it is highly uncertain that tixagevimab plus cilgavimab is effective against Omicron variants of COVID 19. Because of this, it is not recommended.

NICE recommends the use of nirmatrelvir plus ritonavir and sotrovimab as options for treating COVID 19 for people who do not need supplemental oxygen and have an increased risk for progression to severe COVID 19, as defined in the independent advisory group report

- Nirmatrelvir plus ritonavir is recommended in adults.
- Sotrovimab is recommended in adults and young people aged 12 years and over and weighing at least 40 kg, only if nirmatrelvir plus ritonavir is contraindicated or unsuitable.[85]

NICE does not recommend tixagevimab plus cilgavimab, within its marketing authorisation, for treating COVID-19 in adults who do not need supplemental oxygen and who have an increased risk of progression to severe COVID-19. This recommendation is from NICE's technology appraisal guidance on remdesivir and tixagevimab plus cilgavimab for treating COVID-19.[86,87]

NICE has restarted its evaluation of molnupiravir for treating COVID-19 to address appeal points raised in the multiple technology appraisal TA878 [ID6340].[88]

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.[89-92] The most common symptoms for symptomatic infected persons are fever, dry cough, and fatigue; upper respiratory tract symptoms can include pharyngalgia, headaches, and myalgia.[36] 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.[36] In addition, 10–20% of COVID-19-infected persons experience persistent or new symptoms for periods of weeks to years.[36]

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.[92] The most common symptoms of COVID-19 are fever, cough, and shortness of breath for both children and adults

(Table 8).[93,94] 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.[95]

A recent meta-analysis has estimated that 46.7% of infections in children are asymptomatic[92], 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%.[96] 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%.[97]

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.[98,99] 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[99] 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.[98,100]

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.[101] 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.[102]

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.[101]

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.[98] 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.[102] 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.[90]

A study of 82 cases (aged 0 to 21 year-old) 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.[103]

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[16,29,41,50,52,53,60,104] • Older age [16,29,50,52,60,78,104] • Ethnic minorities[16,52,54,60,78] • Lower socioeconomic status[52,60] • Obesity[29,36,50,52,60,62,63,65,67,70,78] • Smoking[50,52,57,58,60,69,78] • Blood group type A[44,45]	• Disability/clinical frailty/worse scores on health/comorbidity scales[52,78,105] • Cardiovascular disease[36,50,52,60,70,78,104,106] • Hypertension[36,50,52,60,64-66,69,104,106] • Dyslipidemia[50,65,70] • Chronic lung diseases / asthma[16,50,52,60,69,70,78,104,106] • Diabetes / higher hemoglobin A1c level[16,36,50,52,60,65,69,70,78,104,106] • Cancer[29,50,60,69,78,106] • Liver disease[60,68,70,78,106] • Neurological diseases (e.g., stroke or dementia)[50,52,60,70,78,106] • Chronic kidney disease or failure / elevated baseline creatinine[16,36,50,52,60,69,70,78,106]	• Cardiac injury/elevated troponin[16,50,104,106] • Arryhthmia[106] • Shock[106] • Pulmonary embolism[61] • Respiratory failure/hypoxia[50,106] • GI bleeding[106] • Anemia[106] • Disseminated intravascular coagulation[106] • Rhabdomyolosis[106] • Bacterial infection/sepsis[106] • Higher neutrophil-to-lymphocyte ratio[108] • Electrolyte disturbance[106] • Elevated glycated hemoglobin[109] • Neutrophilia[50,108] • Lymphopenia[16,50,69] • Thrombocytopenia[16,50,106,108]

Table 9. Factors Associated with Severe Disease or Death in those with COVID-19

Demographic Characteristics	Comorbid Conditions	Complications of COVID-19
	• Autoimmune disease[52,60,70,106] • Immunosuppression/immune compromised[52,60,74,78] • Organ transplant[60,69,78] • Mycotic infection[72] • HIV[78] • Sickle cell disease[78] • Vitamin D deficiency[62,73] • Certain genetic polymorphisms[42,43,107]	• High circulating histone levels[110] • Lower serum iron or total iron banding capacity[111] • Higher serum ferritin levels[111] • Presence of infiltrate by chest imaging[16] • High SARS-CoV2 viral load[16]

Mortality

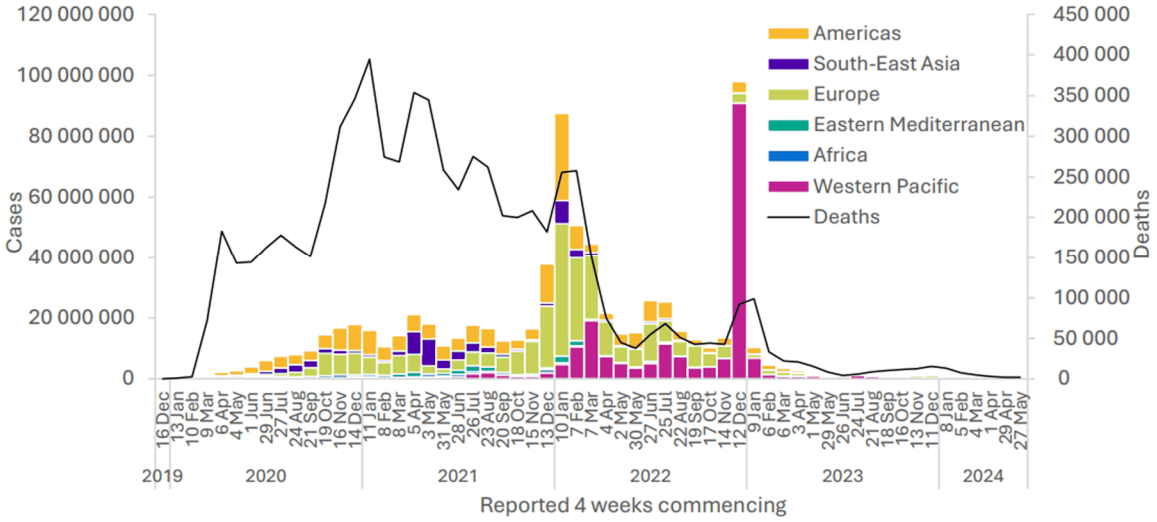
Mortality data are presented from Worldometer, an independent organisation that publishes current, reliable COVID-19 statistics online.[3] The mortality of SARS-CoV-2 infection is defined as the cumulative number of deaths among detected cases.

Mortality data of COVID-19 is presented in Table 1. As of 13 April 2024, there were 1,495,549 deaths or 2,911 deaths per 1,000,000 in the EU-27+UK.[4] Reported mortality among EU countries ranged from 1,116 to 5,661 deaths per 1,000,000 (Table 1). Cyprus and Netherlands reported the lowest mortality; Croatia, Hungary, and Bulgaria reported the highest.[4]

Mortality rates are declining over time, presumably due to an improved understanding of COVID-19 and its management (Figure 4).[112] Deaths involving COVID-19 vary by age with an increase among people aged 25 to 44 years, a decrease for those aged 45 to 54 years and those aged 75 to 84 years, but deaths remain similar for all other age groups. Overall, deaths involving COVID-19 are low for age groups aged under 55 years and high for those aged 85 years and over. This has been consistent throughout the coronavirus pandemic and reflects the highest overall hospital admission rates in the oldest age groups.[113]

The number of COVID-19 deaths reported by World Health Organization as of 23 June 2024 are shown in Figure 4[114]

Figure 4. COVID-19 cases and global deaths reported by World Health Organization as of 23 June 2024



Complications of COVID-19 and Long-COVID

Complications of COVID-19 include impaired function of the heart/cardiovascular system[115-118], brain/neurological system[119,120], lung, gastrointestinal/hepatobiliary system[121], kidney[122,123], metabolic / endocrine systems[124], and coagulation system[125,126,20,23,127] 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.[128]

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.[115,116]. 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%.[117] 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.[118] 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.[116]

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).[119] 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.[120]

A systematic review by Sourani A et al.[129] reported that 71.4% of patients from seven datasets, presented with spinal epidural hematoma. Of them, three patients were treated conservatively, while four received neurosurgical intervention. Also, patients with pain and sensorimotor deficits responded fully to the given treatment (100%). However, no response was observed by the sphincter to the given treatment (0%). Long-term follow-up resulted in a good recovery in 71% of patients. SARS-CoV-2-associated spontaneous spinal haemorrhage is a rare complication of infection, with an often insidious presentation that requires high clinical suspicion.

Another rare infection in COVID-19 patients included mucormycosis.[130] The overall mortality rate in COVID-19–associated mucormycosis patients was found to be 38.9%.

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%).[131] 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.[132]

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).[121]

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.[122] 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.[123]

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.[124]
Other complications of COVID-19 include hemolytic anemia[133], endocrine disorders (including the thyroid, pancreas, adrenal, neuroendocrine, gonadal, and parathyroid glands)[134,135], musculoskeletal disorders including persisting or new-onset fatigue, myalgia, arthralgia, arthritis, muscle weakness[136], opportunistic infections[74], and adverse pregnancy outcomes including preterm labor and cesarean delivery without any intrauterine infection, and severe neonatal asphyxia.[137]
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.[126]

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.[128]

Complications of Long-Covid

COVID-19 symptoms can persist weeks or months beyond the acute infection.[138,139] 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).[140]

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%).[141]

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.[142]

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.[117] 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.[143]

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.[115-117]

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.[144]

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%.[145] 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.[132]

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.[136]

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.[16,21-23,36,52,62-70,104,106,146-148] 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.[149]

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

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.[29] 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

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) %
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%).[33] 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.[30] 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%).[30] 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.[150]

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%.[52]

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%).[104]

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%).[151]

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%.[16]

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%).[152]

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.[153] SARS-CoV-2 infects cells through the ACE2 receptors with the lung and bronchial epithelial cells as the primary sites of infection.[154] Like other coronaviruses, SARS-CoV-2 encodes a main protease (M^{pro}), also referred to as 3C-like protease ($3CL^{pro}$),[155,156] which is a virally encoded enzyme essential for viral replication.[157] 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.[158] No close human analogs of the coronavirus M^{pro} are known.[159] 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.[160]

Nirmatrelvir is a peptidomimetic inhibitor of SARS-CoV-2 M^{pro}. 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.[161]

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, XBB.1.5, EG.5, and JN.1 was assessed in Vero E6-TMPRSS2 cells in the presence of a P-gp inhibitor. Nirmatrelvir had a median EC_{50} value of 88 nM (range: 39-146 nM) against the Omicron sub-variants, reflecting EC_{50} value fold-changes ≤1.8 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[162] as well as the COVID 19 Guidance on Developing Drug and

Biological Product[163]. Different in vitro approaches were undertaken to evaluate potential nirmatrelvir resistance pathways, specifically:

1. Evaluation of nirmatrelvir potency against a panel of SARS-CoV-2 M^{pro} mutant enzymes.
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.[164,165] Resistance studies have also provided evidence for cross resistance to nirmatrelvir by other M^{pro} inhibitors.[165,166]
3. 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.

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

- The following 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 in cell culture (internal Pfizer laboratory data and in recent publications[164,165]) are listed in the table below with additional EC_{50}-fold changes reported in literature.[167-171]

Single Substitution (EC_{50} value fold change)	T21I (1.1-4.8), S46F (ND), L50F (1.2-4.2), P108S (ND), T135I (ND), F140L (4.1), S144A (2.2-5.3), C160F (2.1), E166A (3.3), E166V (25-288), L167F (1.9-2.5), T169I (ND), H172Y (15), A173V (0.9-2.3), V186A (ND), R188G (ND), A191V (0.7-1.5), 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 (83-250), T21I+A173V (3.1-8.9), T21I+T304I (3.0-7.9), L50F+E166V (34-175), L50F+T304I (5.9), T135I+T304I (3.8), F140L+A173V (10-17), H172Y+P252L (ND), A173V+T304I (5.8-20), T21I+L50F+A193P+S301P (29), T21I+S144A+T304I (11-28), T21I+C160F+A173V+V186A+T304I (28-29), T21I+A173V+T304I (15-16), and L50F+F140L+L167F+T304I (43-55).

ND = no data (mutation emerged from nirmatrelvir resistance-selection but has not been tested for EC_{50} determination in an antiviral assay). EC_{50} ranges are shown in instances where multiple data points are reported.

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.[164] 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. Through March 2024, E166V as a single M^{pro} mutation did not occur in any of the ~15 million isolates and was only found in 44 out of ~15 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.[172]

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.[173-175] 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.[175].

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 trial exposure (Safety Analysis Set) in paediatric population (N=75) from study C4671026 (with database lock date of 07 June 2024) is detailed in Table 13, Table 14 and Table 15 for each analysis set (cohort).

Clinical study exposure data (Safety Analysis Set) in participants ≥18 years are detailed from Table 16 to Table 21 for the pivotal studies C4671005 (EPIC-HR), C4671002 (EPIC-SR) and C4671006 (EPIC-PEP).

Participants ≥6 years of age (C4671026)

Table 13. Clinical Trial Exposure by Duration – Safety Analysis Set (C4671026)

Duration of Exposure[a]	Cohort 1a[b] 150 mg[e] (N=9)		Cohort 1a[b] 300 mg[e] (N=39)		Cohort 1b[c] 300 mg[e] (N=13)		Cohort 2[d] 150 mg[e] (N=14)	
	Person	Person Time (days)	Person	Person time (days)	Person	Person time (days)	Person	Person time (days)
At least ≥1 day[f]	9	9	39	39	13	13	14	14
At least ≥2 days[f]	9	9	39	39	13	13	14	14
At least ≥3 days[f]	9	9	39	39	13	13	14	14
At least ≥4 days[f]	9	9	39	39	13	13	13	13
At least ≥5 days[f]	9	12	39	47	13	17	13	16
Cumulative up to 3 days	0	-	0	-	0	-	1	3
Cumulative up to 4 days	0	-	0	-	0	-	1	3
Cumulative up to 5 days	6	30	31	155	9	45	11	53
Cumulative up to > 5 days	9	48	39	203	13	69	14	71

a. Exposure is not inclusive of any gaps or withholding of treatment.
b. Cohort 1a: ≥ 40 kg, ≥ 12 to < 18 years
c. Cohort 1b: ≥ 40 kg, ≥ 6 to < 12 years
d. Cohort 2: ≥ 20 to < 40 kg, ≥ 6 to < 18 years
e. Nirmatrelvir dosage administered; ritonavir 100 mg is also administered.
f. Person Time in each of the duration of exposure rows is incremental and unique; thus does not include the duration (days) of previous time intervals.

[redacted] SDTM Creation: 11JUN2024 (16:29) Source Data: adsl Table Generation: 09OCT2024 (11:46) (Database snapshot date: 07JUN2024) Output File: ./nda_ph23/C4671026_sNDA_RMP/cum_dur_rmp and ./nda_ph23/C4671026_sNDA_RMP/cum2_dur_rmp

Table 14. Clinical Trial Exposure by Age Group and Gender – Safety Analysis Set (C4671026)

	Cohort 1a - 150 mg (N=9)				Cohort 1a - 300 mg (N=39)				Cohort 1b - 300 mg (N=13)				Cohort 2 - 150 mg (N=14)			
	Male		Female		Male		Female		Male		Female		Male		Female	
	Person	Person Time	Person	Person Time	Person	Person Time	Person	Person Time	Person	Person Time	Person	Person Time	Person	Person Time	Person	Person Time
Age group (years)																
≥ 6 to < 12 years	0	-	0	-	0	-	0	-	7	36	6	33	5	26	7	35
≥ 12 to < 18 years	5	27	4	21	17	88	22	115	0	-	0	-	2	10	0	-

Exposure is not inclusive of any gaps or withholding of treatment.
Cohort 1a: ≥ 40 kg, ≥ 12 to < 18 years, Cohort 1b: ≥ 40 kg, ≥ 6 to < 12 years, Cohort 2: ≥ 20 to < 40 kg, ≥ 6 to < 18 years.
Person time= Days

[redacted] SDTM Creation: 11JUN2024 (16:29) Source Data: adsl Table Generation: 09OCT2024 (11:47)
(Database snapshot date : 07JUN2024) Output File: ./nda_ph23/C4671026_sNDA_RMP/age_sex_rmp

Table 15. Clinical Trial Exposure by Race, Ethnicity, Comorbidity – Safety Analysis Set (C4671026)

	Cohort 1a - 150 mg (N=9)		Cohort 1a - 300 mg (N=39)		Cohort 1b - 300 mg (N=13)		Cohort 2 - 150 mg (N=14)	
	Person	Person Time (days)	Person	Person Time (days)	Person	Person Time (days)	Person	Person Time (days)
Race								
White	5	25	19	98	9	49	11	58
Black or African American	2	11	10	53	1	5	3	13
Asian	1	6	1	6	0	-	0	-
American Indian or Alaska Native	0	-	7	35	2	10	0	-
Not reported/Unknown	1	6	2	11	1	5	0	-
Ethnicity								
Hispanic or Latino	5	25	24	123	9	48	8	42
Non-Hispanic or non-Latino	3	17	15	80	4	21	6	29
Not reported	1	6	0	-	0	-	0	-
Comorbidity								
Renal impairment	0	-	1	6	0	-	0	-
Cardiovascular disorder	0	-	1	5	0	-	1	5

Table 15. Clinical Trial Exposure by Race, Ethnicity, Comorbidity – Safety Analysis Set (C4671026)

	Cohort 1a - 150 mg (N=9)		Cohort 1a - 300 mg (N=39)		Cohort 1b - 300 mg (N=13)		Cohort 2 - 150 mg (N=14)	
	Person	Person Time (days)	Person	Person Time (days)	Person	Person Time (days)	Person	Person Time (days)
Immunosuppression	1	6	2	11	1	5	1	6
Diabetes mellitus	0	-	3	15	0	-	0	-
Chronic respiratory disease	2	11	16	81	5	28	7	38
Obesity	5	25	20	106	8	41	4	20

Exposure is not inclusive of any gaps or withholding of treatment.
Cohort 1a: ≥ 40 kg, ≥ 12 to < 18 years, Cohort 1b: ≥ 40 kg, ≥ 6 to < 12 years, Cohort 2: ≥ 20 to < 40 kg, ≥ 6 to < 18 years.

[redacted] SDTM Creation: 11JUN2024 (16:29) Source Data: adsl Table Generation: 09OCT2024 (11:48) (Database snapshot date: 07JUN2024) Output File: ./nda_ph23/C4671026_sNDA_RMP/race_rmp
[redacted] SDTM Creation: 11JUN2024 (16:29) Source Data: adsl Table Generation: 09OCT2024 (11:53) (Database snapshot date: 07JUN2024) Output File: ./nda_ph23/C4671026_sNDA_RMP/ethnic_rmp
[redacted] SDTM Creation: 11JUN2024 (15:29) Source Data: adsl Table Generation: 04NOV2024 (17:47) (Database snapshot date: 07JUN2024) Output File: ./nda_ph23/C4671026_sNDA_RMP/impair_rmp

Participants ≥18 years of age (C4671002, C4671005, C4671006)

Table 16. Clinical Trial Exposure by Duration – Safety Analysis Set (C4671005, C4671002, C4671006)

	Nirmatrelvir 300 mg + Ritonavir 100 mg					
Duration of Exposure[a]	**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 (days) 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 [redacted] and [redacted] (including those switched to [redacted]) were excluded.
d. Participants enrolled at sites [redacted] and [redacted] (including those switched to [redacted]) are excluded.
e. Participants enrolled at sites [redacted], [redacted] (including those switched to [redacted]), [redacted], and [redacted] (2022 enrolees) are excluded.

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

Table 17. Clinical Trial Exposure by Duration, Cumulative Person Time – Safety Analysis Set (C4671005 and C4671002)

	Nirmatrelvir 300 mg + Ritonavir 100 mg			
Duration of Exposure[a]	**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

a. Exposure is not inclusive of any gaps or withholding of treatment.

Table 17. Clinical Trial Exposure by Duration, Cumulative Person Time – Safety Analysis Set (C4671005 and C4671002)

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

b. Participants enrolled at sites [redacted] and [redacted] (including those switched to [redacted] are excluded.
c. Participants enrolled at sites [redacted], [redacted] (including those switched to [redacted]), [redacted], and [redacted] (2022 enrolees) are excluded.

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

Table 18. 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 [redacted] and [redacted] (including those switched to [redacted]) were excluded.
b. Exposure is not inclusive of any gaps or withholding of treatment.

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

Table 19. Clinical Trial Exposure by Age Group and Gender – Safety Analysis Set (C4671005, C4671002, C4671006)

	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 [redacted] and [redacted] (including those switched to [redacted]) 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 [redacted] and [redacted] (including those switched to [redacted]) were excluded.
c. Participants enrolled at sites [redacted], [redacted] (including those switched to [redacted]), [redacted], and [redacted] (2022 enrolees) are excluded.

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

Table 20. Clinical Trial Exposure by Race and Ethnicity – Safety Analysis Set (C4671005, C4671002, C4671006)

	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 [redacted] and [redacted] (including those switched to [redacted] 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 [redacted] and [redacted] (including those switched to [redacted]) were excluded.
c. Participants enrolled at sites [redacted], [redacted] (including those switched to [redacted]), [redacted], and [redacted] (2022 enrolees) are excluded.

Exposure is not inclusive of any gaps or withholding of treatment.
[redacted] 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
[redacted] 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
[redacted] 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 21. Clinical Trial Exposure by Special Populations – Safety Analysis Set (C4671005, C4671002, C4671006)

	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 21. Clinical Trial Exposure by Special Populations – Safety Analysis Set (C4671005, C4671002, C4671006)

	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 [redacted] and [redacted] (including those switched to [redacted]) 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 [redacted] and [redacted] (including those switched to [redacted]) were excluded.
c. Participants enrolled at sites [redacted], [redacted] (including those switched to [redacted]), [redacted], and [redacted] (2022 enrolees) are excluded.

Exposure is not inclusive of any gaps or withholding of treatment.
[redacted] SDTM Creation: 10JAN2023 (13:31) Table Generation: 13JAN2023 (10:25) (Database snapshot date: 29APR2022) Output File: ./nda/C4671005_SiteEx/impair_rmp
[redacted] SDTM Creation: 17JAN2023 (12:44) Table Generation: 06MAR2023 (14:35) (Database snapshot date: 11AUG2022) Output File: ./nda/C4671002_RMP_SiteEx/impair_rmp
[redacted] 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 from the clinical trials in this RMP, C4671005, C4671002, C4671006, C4671026 are listed in Table 22 below.

Table 22. 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 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	No	Dosage recommendations for renal impaired patients are detailed in SmPC Section 4.2 *Posology and method of administration.* Dose reductions for patients with moderate and severe impairment (including those requiring haemodialysis) have been defined.
Known HIV infection with a viral load greater than 400 copies/mL or taking prohibited medications for HIV treatment	Ritonavir may select for resistant HIV strains in patients with uncontrolled HIV infection.	No	Information on the risk of HIV 1 developing 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	Ritonavir is a strong inhibitor of CYP3A4.	No	As per Section 4.3 *Contraindications* of the SmPC, the use of

Table 22. 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)
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			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 (<6 years of age), and specific subpopulations that were excluded from the nirmatrelvir/ritonavir clinical development program.

Table 23. 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 22). 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.

Table 23. Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Breastfeeding women	Breastfeeding women were excluded from the nirmatrelvir/ritonavir pivotal studies C4671002, C4671005 and C4671006 (refer to Table 22). Data are not available to assess the effects of nirmatrelvir/ritonavir on the breastfed infant or 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 22). For available exposure of hepatic impaired participants (in the pivotal studies said above), please refer to Table 21.
• 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 21; for exposure in paediatric participants with renal impairment (in study C4671026) refer to Table 15. 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. Dosage recommendations for renal impaired patients are detailed in SmPC Section 4.2 *Posology and method of administration.* Dose reductions for patients with moderate and severe impairment, including those requiring haemodialysis, have been defined.
• 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 21; for exposure in paediatric participants with cardiovascular disease (in study C4671026) refer to Table 15.
• 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 21; for exposure in immunocompromised paediatric participants (in study C4671026) refer to Table 15.

Table 23. 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 15 and Table 20 for exposure information by ethnic origin in paediatric population from study C4671026 and in participants aged ≥18 years from the pivotal studies C4671002, C4671005 and C4671006, respectively.
Subpopulations carrying relevant genetic polymorphisms	No data available.
Paediatric population	Participants aged less than 18 years were excluded from the pivotal studies C4671002, C4671005 and C4671006. Safety in paediatric population aged 6 years and older (weighing at least 20 kg) has been assessed as part of study C4671026; for available exposure, refer to Table 13, Table 14, and Table 15.
Elderly population	Please refer to Table 19 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

In the US, the estimation of the patient's exposure was calculated using IQVIA data based on National Prescription Audit[a]. Up to the end of September 2024, the prescriptions for Paxlovid™ in the US, dispensed and sold to patients based on NPA data are 18,982,545 (assumed to be patients who took the drug).

Cumulative exposure for Non-US countries has been estimated to be 6,839,397 based on available sales data (Kg of product) provided by IQVIA Health Prescribing Insights Medical[b], up to 1st quarter of 2024 (ie, 31 March 2024). Data from 01 April 2024 through 30 September 2024 have been extrapolated considering the average value of the last 4 quarters available. To estimate the number of patients treated with nirmatrelvir/ritonavir, the following assumptions were made:

- duration of therapy = 5 days;
- each patient received 2 nirmatrelvir tablets (150 mg) and 1 ritonavir tablet (100 mg) twice daily.

SV.1.2. Exposure

With the methodology above (refer to Section SV.1.1), it has been estimated that ***25,821,942 patients*** have been exposed cumulatively to nirmatrelvir/ritonavir from the first EUA in US (on 22 December 2021) up to the end of September 2024, including approximately 18,982,545 patients in US and 6,839,397 patients in Non-US countries.

The worldwide exposure by gender and age group, for US and Non-US countries, based on available data[c] (written prescriptions) provided by IQVIA Health Prescribing Insights Medical, is reported in Table 24.

---

[a] NPA captures prescriptions that are dispensed & sold to patients out of the front door of retail, mail, and long-term care pharmacies within the US, applying projections to account for prescription volumes from non-reporting stores.

[b] IQVIA data should not be regarded as complete sales information. Some countries where nirmatrelvir/ritonavir is sold may not be covered by IQVIA. In addition, the lack of sales in some countries where Paxlovid is marketed might be attributed to the potentially limited distribution of COVID products through certain channels (eg, restricted data via government distribution), which could result in an underestimation of the values. Furthermore, IQVIA does not capture retail sales data and hospital data in all countries. Therefore, the sales volumes obtained through the use of IQVIA are likely to result in a large underestimate of the actual distributed product.

[c] Data available up to the end of the 1st quarter 2024 (ie, 31 March 2024) and from 9 countries.

Table 24. Cumulative Estimated Exposure by Gender and Age

	Sex			Age (years)				
	F	M	Unk	0-15	16-20	21-65	>65	Unk
US	11,444,061	7,538,484	-	99,023	284,164	11,229,206	7,370,152	-
Non-US	3,313,326	3,487,608	38,463	16,657	102,365	2,978,804	3,683,084	58,487

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 review of the available safety data 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" 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 and no data available yet from other studies in the drug development program. Please refer to the *Risk-Benefit impact* summarized below in Section SVII.1.2 for each safety concern.

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 25.

Table 25. 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 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

Safety in patients with renal impairment previously classified as missing information has been removed from the list of safety concerns (CHMP positive opinion adopted on 27 March 2025 with procedure EMEA/H/C/005735/II/0057/G).

It was known that when dosed with ritonavir, the primary clearance mechanism of nirmatrelvir is via renal excretion of unchanged drug. Significant increase 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 twice daily for patients with moderate renal impairment had been included in SmPC.
A further Phase 1 study in severe renal impaired population, either on hemodialysis or not on hemodialysis (Study C4671028) was conducted. Based on pharmacokinetic data simulation, dose recommendation and regimen of nirmatrelvir/ritonavir (300 mg/100 mg once on day 1, followed by 150 mg /100 mg once daily from Day 2 to 5) for patients with severe renal impairment has been also added in the SmPC.

The evaluation of the safety data collected from participants with COVID-19 and severe renal impairment across Study C4671028 and the 3 pivotal Phase 2/3 Studies[d] C4671005, C4671002, and C4671006, did not highlight changes in the already known safety profile of nirmatrelvir/ritonavir. In patients with severe renal impairment, the nirmatrelvir/ritonavir

[d] Studies C4671005, C4671002, and C4671006 had a study exclusion criterion to exclude participants with an eGFR <45 mL/min/1.73 m^2 (using the serum creatinine-based CKD-EPI eGFR equation) within 6 months of the screening visit. However, 11 adult participants with severe renal impairment from Studies C4671005 (6 participants), C4671002 (3 participants), and C4671006 (2 participants) were enrolled despite this exclusion criterion because baseline eGFR results (collected prior to the first dose of study intervention) were not always available before a participant started treatment.

safety profile remains consistent with that in patients with mild or moderate renal impairment or with normal renal function.

The product information adequately addresses the use in the renal impaired population and no further characterisation of these patients is deemed necessary. In accordance with these considerations, Safety in patients with renal impairment is no longer considered a missing information.

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 26. 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 being conducted to assess the safety in patients with moderate and severe hepatic impairment; see PART III.2.

Table 27. 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 is being conducted in pregnant and breastfeeding women; see PART III.2.

Module SVIII. Summary of the Safety Concerns

Table 28. 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 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 include 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:**

Specific follow-up questionnaires are used for cases of exposure during pregnancy. For study cases, a pregnancy follow-up questionnaire (Exposure During Pregnancy Supplemental Form for study case; refer to Annex 4) is included in the study protocols. For non-study cases, follow-up activities (through an automation process) are conducted based on the list of specific questions for EDP cases, which are included in the form in Annex 4. This form is used in combination with Company's standard follow-up questionnaires querying on relevant missing data.

Follow-up questionnaires (named "Data Capture Aids", refer to Annex 4) are also used to gather data about the safety during use in lactation and for lack of efficacy (including fields to request information on the COVID-19 variant). The content of these specific adverse reaction follow-up questionnaires is limited to the collection of additional information not addressed by other Company's standard follow-up questionnaires and questionnaires for breastfeeding and lack of effect (used for all MAH's products) which query about other relevant missing data.

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

As part of the enhanced signal detection activities, 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

C4671037 summary

Study short name and title:
Study C4671037; Safety of Paxlovid During Pregnancy.

Rationale and study objectives:
The purpose of the study is to assess the safety of nirmatrelvir/ritonavir in pregnant women. The primary study objective is to estimate the birth prevalence, prevalence ratio, and prevalence difference of the following adverse pregnancy (Spontaneous abortion, Elective termination, Stillbirth, Preterm delivery), offspring (Major congenital malformations, Intrauterine growth retardation/small for gestational age) and maternal outcomes (Gestational diabetes, Gestational hypertension, postpartum haemorrhage, Maternal death) in women with COVID-19 who are exposed to nirmatrelvir/ritonavir during pregnancy compared with those in women with COVID-19 who are exposed to molnupiravir (or other comparable medications for COVID-19), where available, during pregnancy or to women with COVID-19 unexposed to any study medications during pregnancy:

The secondary study objective is to assess maternal exploratory outcomes that will be identified based on conditions appearing in the study population after exposure to nirmatrelvir/ritonavir.

Study design:
Non-Interventional Post-Authorisation safety study.

Study population:
The target study population will be individuals with COVID 19 exposed to nirmatrelvir/ritonavir or comparator drug molnupiravir or other comparable medications and individuals unexposed to nirmatrelvir/ritonavir, molnupiravir, or other comparable medications (the unexposed comparison group), while they are pregnant.
Milestones:

Milestone	Due date
Interim report 2 submission	31 December 2025
Final report submission	31 March 2026

C4671047 Summary

Study short name and title:
C4671047; Safety of Paxlovid Among Patients with Moderate or Severe Hepatic Impairment.

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

The primary study objectives are to assess the safety of nirmatrelvir/ritonavir relative to the comparator populations prescribed molnupiravir (or other comparable medications for COVID-19), where available, and to unexposed patients with COVID-19, and to assess side

effects resulting from drug overexposure due to impaired liver function and with regard to severity and frequency compared with comparator groups.

The secondary objective is to assess all safety events included in the primary objective that require hospitalisation or emergency department visits.

Study design:
Non-Interventional Post-Authorisation safety study.

Study population:
Patients with moderate and severe hepatic impairment.

Milestones:

Milestone	**Due date**
Interim report 2 submission	31 December 2025
Final report submission	31 March 2026

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. Ongoing and Planned Additional Pharmacovigilance Activities

Table 29. 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				
Study C4671037 Safety of Paxlovid During Pregnancy *Ongoing*	To assess the safety of nirmatrelvir/ritonavir in pregnant women. The primary study objective is to estimate the birth prevalence, prevalence ratio, and prevalence difference of the following adverse pregnancy (Spontaneous abortion, Elective termination, Stillbirth, Preterm delivery), offspring (Major congenital malformations, Intrauterine growth retardation/small for gestational age) and maternal outcomes (Gestational diabetes, Gestational hypertension, postpartum haemorrhage, Maternal death) in women with COVID-19 who are exposed to nirmatrelvir/ritonavir during pregnancy compared with those in women with COVID-19 who are exposed to molnupiravir (or other comparable medications for COVID-19), where available, during pregnancy or to women with COVID-19 unexposed to any study medications during pregnancy: The secondary study objective is to assess maternal exploratory outcomes that will be identified based on conditions appearing in the study	Safety during use in pregnancy and lactation	Interim report 2 submission	31 December 2025
			Final report submission	31 March 2026

Table 29. Ongoing and Planned Additional Pharmacovigilance Activities

Study (short name and title) Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	population after exposure to nirmatrelvir/ritonavir.			
Study C4671047 Safety of Paxlovid Among Patients with Moderate or Severe Hepatic Impairment *Ongoing*	To assess the safety of nirmatrelvir/ritonavir in patients with moderate and severe hepatic impairment. The primary study objectives are to assess the safety of nirmatrelvir/ritonavir relative to the comparator populations prescribed molnupiravir (or other comparable medications for COVID-19), where available, and to unexposed patients with COVID-19, and to assess side effects resulting from drug overexposure due to impaired liver function and with regard to severity and frequency compared with comparator groups. The Secondary objective is to assess all safety events included in the primary objective that require hospitalisation or emergency department visits.	Safety in patients with hepatic impairment	Interim report 2 submission	31 December 2025
			Final report submission	31 March 2026

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 30 and Table 31 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 30. 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 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 31 below. There are no additional risk minimisations measures proposed.

Table 31. 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: Study C4671047 (Final report submission by 31 March 2026).
Safety during use in pregnancy and lactation	Routine risk minimisation measures: SmPC Section 4.6 *Fertility, pregnancy and lactation*. Pack size. Medicine's legal status. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pregnancy follow-up questionnaires and DCA for lactation to collect relevant information during follow-up activities. Additional pharmacovigilance activities: Study C4671037 (Final report submission by 31 March 2026).

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 and paediatric patients 6 years of age and older weighing at least 20 kg 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 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: Study C4671047; See PART II.C of this summary for an overview of the post-authorisation development plan.

Missing information 2: 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

Missing information 2: Safety during use in pregnancy and lactation

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study C4671037; 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

Study C4671037

Purpose of the study: To assess the safety of Paxlovid in pregnant women.

The primary study objective is to estimate the birth prevalence, prevalence ratio, and prevalence difference of the adverse pregnancy (Spontaneous abortion, Elective termination, Stillbirth, Preterm delivery), offspring (Major congenital malformations, Intrauterine growth retardation/small for gestational age) and maternal outcomes (Gestational diabetes, Gestational hypertension, postpartum haemorrhage, Maternal death) in women with COVID-19 who are exposed to nirmatrelvir/ritonavir during pregnancy compared with those in women with COVID-19 who are exposed to molnupiravir (or other comparable medications for COVID-19), where available, during pregnancy or to women with COVID-19 unexposed to any study medications during pregnancy:

The secondary study objective is to assess maternal exploratory outcomes that will be identified based on conditions appearing in the study population after exposure to nirmatrelvir/ritonavir.

Study C4671047

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

The primary study objectives are to assess the safety of nirmatrelvir/ritonavir relative to the comparator populations prescribed molnupiravir (or other comparable medications for COVID-19), where available, and to unexposed patients with COVID-19, and to assess side effects resulting from drug overexposure due to impaired liver function and with regard to severity and frequency compared with comparator groups.

The secondary objective is to assess all safety events included in the primary objective that require hospitalisation or emergency department visits.

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

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. The New England journal of medicine. 2020;382(8):727-33.
2. WHO. (2020). Coronavirus Disease 2019 (COVID-19) Situation Report – 11.
3. Worldometers. (2023). Coronavirus Updates. Available from: https://www.worldometers.info/about/. Accessed on: July 28, 2023.
4. Worldometers. (2024). Reported Cases and Deaths by Country or Territory. Available from: https://www.worldometers.info/coronavirus/#countrieshttps://www.worldometers.info/coronavirus/#countries. Accessed on: 15 January 2025.
5. Worldometers. (2023). COVID-19 Data. Available from: https://www.worldometers.info/coronavirus/about. Accessed on: 23 November 2023.
6. Thomas E, Delabat S, Carattini YL, et al. SARS-CoV-2 and Variant Diagnostic Testing Approaches in the United States. Viruses. 2021;13(12).
7. CDC. (2024). Variant Proportions. . Available from: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed on: 03 September 2024.
8. WHO. (2023). Weekly epidemiological update on COVID-19 - 25 August 2023 Updated 25 August 2023. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---30-august-2023.
9. WHO. (2024). COVID-19 epidemiological update – 13 August 2024 Updated 13 August 2024. Available from: https://www.who.int/publications/m/item/covid-19-epidemiological-update-edition-170#:~:text=From%20the%20available%20data%2C%20over,and%20new%20ICU%20admissions%2C%20respectively.
10. ERVISS. (2024). European Respiratory Virus Surveillance Summary Updated 03 September 2024. Available from: https://erviss.org/.
11. CDC. (2024). COVID Data Tracker. Department of Health and Human Services, CDC. Available from: https://covid.cdc.gov/covid-data-tracker. Accessed on: 03 September 2024.
12. ECDC. (2021). COVID-19 Surveillance report. Week 43, 2021. 04 November 2021 (b). "2 Severity. 2.2 Age-sex pyramids". Available from: https://COVID19-surveillance-report.ecdc.europa.eu. Accessed on: 26 March 2022.
13. ECDC. (2021). COVID-19 Surveillance report. Week 43, 2021. 04 November 2021. "4 TESSy data quality. 4.2 Variable completeness". Available from: https://COVID19-surveillance-report.ecdc.europa.eu. Accessed on: 26 March 2022.
14. CDC. (2023). COVID Data Tracker. Available from: https://covid.cdc.gov/covid-data-tracker/#demographics. Accessed on: 25 May 2023.
15. CDC. (2024). COVID-NET. Department of Health and Human Services, CDC. Available from: https://www.cdc.gov/covid/php/covid-net/index.html. Accessed on: 03 September 2024.
16. Ozonoff A, Schaenman J, Jayavelu ND, et al. Phenotypes of disease severity in a cohort of hospitalized COVID-19 patients: Results from the IMPACC study. EBioMedicine. 2022;83:104208.

17. Sozio E, Moore NA, Fabris M, et al. Identification of COVID-19 patients at risk of hospital admission and mortality: a European multicentre retrospective analysis of mid-regional pro-adrenomedullin. Respiratory research. 2022;23(1):221.
18. Mayor N, Meza-Torres B, Okusi C, et al. Developing a Long COVID Phenotype for Postacute COVID-19 in a National Primary Care Sentinel Cohort: Observational Retrospective Database Analysis. JMIR public health and surveillance. 2022;8(8):e36989.
19. Leidman E, Duca LM, Omura JD, et al. COVID-19 Trends Among Persons Aged 0-24 Years - United States, March 1-December 12, 2020. MMWR Morbidity and mortality weekly report. 2021;70(3):88-94.
20. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet (London, England). 2020;395(10239):1763-70.
21. Price-Haywood EG, Burton J, Fort D, et al. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. The New England journal of medicine. 2020;382(26):2534-43.
22. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ (Clinical research ed). 2020;369:m1966.
23. Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ (Clinical research ed). 2020;369:m1996.
24. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. Jama. 2020;323(20):2052-59.
25. Azar KMJ, Shen Z, Romanelli RJ, et al. Disparities In Outcomes Among COVID-19 Patients In A Large Health Care System In California. Health Aff (Millwood). 2020;39(7):1253-62.
26. Holmes L, Jr., Enwere M, Williams J, et al. Black-White Risk Differentials in COVID-19 (SARS-COV2) Transmission, Mortality and Case Fatality in the United States: Translational Epidemiologic Perspective and Challenges. International journal of environmental research and public health. 2020;17(12).
27. Gold JAW, Rossen LM, Ahmad FB, et al. Race, Ethnicity, and Age Trends in Persons Who Died from COVID-19 - United States, May-August 2020. MMWR Morbidity and mortality weekly report. 2020;69(42):1517-21.
28. Rossen LM, Branum AM, Ahmad FB, et al. Excess Deaths Associated with COVID-19, by Age and Race and Ethnicity - United States, January 26-October 3, 2020. MMWR Morbidity and mortality weekly report. 2020;69(42):1522-27.
29. Dai CL, Kornilov SA, Roper RT, et al. Characteristics and Factors Associated with COVID-19 Infection, Hospitalization, and Mortality Across Race and Ethnicity. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021;10.1093/cid/ciab154.
30. Havers FP, Whitaker M, Self JL, et al. Hospitalization of Adolescents Aged 12-17 Years with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1, 2020-April 24, 2021. MMWR Morbidity and mortality weekly report. 2021;70(23):851-57.

31. CDC. (2022). COVID-NET. COVID-NET Laboratory Confirmed COVID-19 Hospitalizations. Available from: https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html#virusTypeDiv.
32. Van Dyke ME, Mendoza MCB, Li W, et al. Racial and Ethnic Disparities in COVID-19 Incidence by Age, Sex, and Period Among Persons Aged <25 Years - 16 U.S. Jurisdictions, January 1-December 31, 2020. MMWR Morbidity and mortality weekly report. 2021;70(11):382-88.
33. Bailey LC, Razzaghi H, Burrows EK, et al. Assessment of 135 794 Pediatric Patients Tested for Severe Acute Respiratory Syndrome Coronavirus 2 Across the United States. JAMA pediatrics. 2021;175(2):176-84.
34. Preston LE, Chevinsky JR, Kompaniyets L, et al. Characteristics and Disease Severity of US Children and Adolescents Diagnosed With COVID-19. JAMA network open. 2021;4(4):e215298.
35. Sebastian T, Carlson JJ, Gaensbauer J, et al. Epidemiology and Transmission Dynamics of COVID-19 in an Urban Pediatric US Population. Public health reports (Washington, DC : 1974). 2022;137(5):1013-22.
36. Tang SGH, Hadi MHH, Arsad SR, et al. Prerequisite for COVID-19 Prediction: A Review on Factors Affecting the Infection Rate. International journal of environmental research and public health. 2022;19(20).
37. Bouffanais R, Lim SS. Cities - try to predict superspreading hotspots for COVID-19. Nature. 2020;583(7816):352-55.
38. Hawkins D. Differential occupational risk for COVID-19 and other infection exposure according to race and ethnicity. American journal of industrial medicine. 2020;63(9):817-20.
39. Siebach MK, Piedimonte G, Ley SH. COVID-19 in childhood: Transmission, clinical presentation, complications and risk factors. Pediatric pulmonology. 2021;56(6):1342-56.
40. CDC. (2022). Risk for COVID-19 Infection, Hospitalization, and Death By Race/Ethnicity. Available from: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html. Accessed on: 09 July 2022.
41. Taslem Mourosi J, Anwar S, Hosen MJ. The sex and gender dimensions of COVID-19: A narrative review of the potential underlying factors. Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases. 2022;103:105338.
42. Ishak A, Mehendale M, AlRawashdeh MM, et al. The association of COVID-19 severity and susceptibility and genetic risk factors: A systematic review of the literature. Gene. 2022;836:146674.
43. Sienko J, Marczak I, Kotowski M, et al. Association of ACE2 Gene Variants with the Severity of COVID-19 Disease-A Prospective Observational Study. International journal of environmental research and public health. 2022;19(19).
44. Pereira E, Felipe S, de Freitas R, et al. ABO blood group and link to COVID-19: A comprehensive review of the reported associations and their possible underlying mechanisms. Microbial pathogenesis. 2022;169:105658.

45. Balaouras G, Eusebi P, Kostoulas P. Systematic review and meta-analysis of the effect of ABO blood group on the risk of SARS-CoV-2 infection. PloS one. 2022;17(7):e0271451.
46. CDC. (2022). Risk for COVID-19 Infection, Hospitalization, and Death By Age Group. Available from: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html. Accessed on: 09 July 2022.
47. Izcovich A, Ragusa MA, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PloS one. 2020;15(11):e0241955.
48. Booth A, Reed AB, Ponzo S, et al. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. PloS one. 2021;16(3):e0247461.
49. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-36.
50. Patel NA. Pediatric COVID-19: Systematic review of the literature. American journal of otolaryngology. 2020;41(5):102573.
51. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta paediatrica (Oslo, Norway : 1992). 2020;109(6):1088-95.
52. Crossfield SSR, Chaddock NJM, Iles MM, et al. Interplay between demographic, clinical and polygenic risk factors for severe COVID-19. International journal of epidemiology. 2022;51(5):1384-95.
53. Twitchell DK, Christensen MB, Hackett G, et al. Examining Male Predominance of Severe COVID-19 Outcomes: A Systematic Review. Androgens: clinical research and therapeutics. 2022;3(1):41-53.
54. Bhaskaran K, Bacon S, Evans SJ, et al. Factors associated with deaths due to COVID-19 versus other causes: population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. The Lancet regional health Europe. 2021;6:100109.
55. CDC. (2022). Risk for COVID-19 Infection, Hospitalization, and Death By Race/Ethnicity. Available from: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html. Accessed on: 01 May 2022.
56. Woodruff RC, Campbell AP, Taylor CA, et al. Risk Factors for Severe COVID-19 in Children. Pediatrics. 2022;149(1).
57. He Y, He Y, Hu Q, et al. Association between smoking and COVID-19 severity: A multicentre retrospective observational study. Medicine. 2022;101(29):e29438.
58. Benowitz NL, Goniewicz ML, Halpern-Felsher B, et al. Tobacco product use and the risks of SARS-CoV-2 infection and COVID-19: current understanding and recommendations for future research. The Lancet Respiratory medicine. 2022;10(9):900-15.
59. CDC. (2021). Different Groups of People. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html. Accessed on: 16 August 2021.

60. CDC. (2021). People with Certain Medical Conditions. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed on: 16 August 2021.
61. Fu Z, Bai G, Song B, et al. Risk factors and mortality of pulmonary embolism in COVID-19 patients: Evidence based on fifty observational studies. Medicine. 2022;101(45):e29895.
62. Karampela I, Vallianou N, Magkos F, et al. Obesity, Hypovitaminosis D, and COVID-19: the Bermuda Triangle in Public Health. Current obesity reports. 2022;11(3):116-25.
63. Heubner L, Petrick PL, Güldner A, et al. Extreme obesity is a strong predictor for in-hospital mortality and the prevalence of long-COVID in severe COVID-19 patients with acute respiratory distress syndrome. Scientific reports. 2022;12(1):18418.
64. Khairy Y, Naghibi D, Moosavi A, et al. Prevalence of hypertension and associated risks in hospitalized patients with COVID-19: a meta-analysis of meta-analyses with 1468 studies and 1,281,510 patients. Systematic reviews. 2022;11(1):242.
65. Makhoul E, Aklinski JL, Miller J, et al. A Review of COVID-19 in Relation to Metabolic Syndrome: Obesity, Hypertension, Diabetes, and Dyslipidemia. Cureus. 2022;14(7):e27438.
66. Qian Z, Li Z, Peng J, et al. Association between hypertension and prognosis of patients with COVID-19: A systematic review and meta-analysis. Clinical and experimental hypertension (New York, NY : 1993). 2022;44(5):451-58.
67. Moreno-Fernandez J, Ochoa J, Ojeda ML, et al. Inflammation and oxidative stress, the links between obesity and COVID-19: a narrative review. Journal of physiology and biochemistry. 2022;78(3):581-91.
68. Luo M, Ballester MP, Soffientini U, et al. SARS-CoV-2 infection and liver involvement. Hepatology international. 2022;16(4):755-74.
69. Eyitemi J, Thomas B, Ramos Y, et al. SARS-CoV-2: Review of Conditions Associated With Severe Disease and Mortality. International journal of preventive medicine. 2022;13:109.
70. Fitero A, Bungau SG, Tit DM, et al. Comorbidities, Associated Diseases, and Risk Assessment in COVID-19-A Systematic Review. International journal of clinical practice. 2022;2022:1571826.
71. Wang Y, Nan L, Hu M, et al. Significant association between anemia and higher risk for COVID-19 mortality: A meta-analysis of adjusted effect estimates. The American journal of emergency medicine. 2022;58:281-85.
72. Liu A, Li Z, Su G, et al. Mycotic infection as a risk factor for COVID-19: A meta-analysis. Frontiers in public health. 2022;10:943234.
73. Mishra P, Parveen R, Bajpai R, et al. Vitamin D Deficiency and Comorbidities as Risk Factors of COVID-19 Infection: A Systematic Review and Meta-analysis. Journal of preventive medicine and public health = Yebang Uihakhoe chi. 2022;55(4):321-33.
74. Abdoli A, Falahi S, Kenarkoohi A. COVID-19-associated opportunistic infections: a snapshot on the current reports. Clinical and experimental medicine. 2022;22(3):327-46.
75. Tsai YT, Ku HC, Maithreepala SD, et al. Higher Risk of Acute Respiratory Distress Syndrome and Risk Factors among Patients with COVID-19: A Systematic Review,

Meta-Analysis and Meta-Regression. International journal of environmental research and public health. 2022;19(22).
76. Graff K, Smith C, Silveira L, et al. Risk Factors for Severe COVID-19 in Children. The Pediatric infectious disease journal. 2021;40(4):e137-e45.
77. Moreira A, Chorath K, Rajasekaran K, et al. Demographic predictors of hospitalization and mortality in US children with COVID-19. European journal of pediatrics. 2021;180(5):1659-63.
78. Tsankov BK, Allaire JM, Irvine MA, et al. Severe COVID-19 Infection and Pediatric Comorbidities: A Systematic Review and Meta-Analysis. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2021;103:246-56.
79. Kompaniyets L, Agathis NT, Nelson JM, et al. Underlying Medical Conditions Associated With Severe COVID-19 Illness Among Children. JAMA network open. 2021;4(6):e2111182.
80. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. JAMA pediatrics. 2020;174(10):e202430.
81. Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. BMJ (Clinical research ed). 2020;370:m3249.
82. Oliveira EA, Mak RH, Colosimo EA, et al. Risk factors for COVID-19-related mortality in hospitalized children and adolescents with diabetes mellitus: An observational retrospective cohort study. Pediatric diabetes. 2022;23(6):763-72.
83. Karavanaki K, Rodolaki K, Soldatou A, et al. Covid-19 infection in children and adolescents and its association with type 1 diabetes mellitus (T1d) presentation and management. Endocrine. 2022;10.1007/s12020-022-03266-7:1-16.
84. EMA. (2024). COVID-19 medicines. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/public-health-threats/coronavirus-disease-covid-19/covid-19-medicines. Accessed on: October 2024.
85. NICE Guidance. Nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19. 2024. Available from: https://www.nice.org.uk/guidance/ta878/informationforpublic.
86. NICE Guidance. COVID-19 rapid guideline: managing COVID-19. 2024. Available from: https://www.nice.org.uk/guidance/ng191/resources/covid19-rapid-guideline-managing-covid19-pdf-66142077109189.
87. NICE Guidance. Remdesivir and tixagevimab plus cilgavimab for treating COVID-19. 2024. Available from: https://www.nice.org.uk/guidance/ta971/chapter/1-Recommendations.
88. NICE Guidance. Molnupiravir for treating COVID-19 [ID6340]. 2024. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta11409.
89. Pollock AM, Lancaster J. Asymptomatic transmission of covid-19. BMJ (Clinical research ed). 2020;371:m4851.
90. Toba N, Gupta S, Ali AY, et al. COVID-19 under 19: A meta-analysis. Pediatric pulmonology. 2021;56(6):1332-41.

91. Oran DP, Topol EJ. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic : A Systematic Review. Annals of internal medicine. 2021;174(5):655-62.
92. Sah P, Fitzpatrick MC, Zimmer CF, et al. Asymptomatic SARS-CoV-2 infection: A systematic review and meta-analysis. Proceedings of the National Academy of Sciences of the United States of America. 2021;118(34).
93. CDC. COVID 19 Response Team - Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. MMWR Morbidity and mortality weekly report. 2020;69(14):422-26.
94. Yasuhara J, Watanabe K, Takagi H, et al. COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. Pediatric pulmonology. 2021;56(5):837-48.
95. Remelli F, Volpato S, Trevisan C. Clinical Features of SARS-CoV-2 Infection in Older Adults. Clinics in geriatric medicine. 2022;38(3):483-500.
96. Kumar B, Scheffler P. Ear, Nose, and Throat Manifestations of COVID-19 in Children. Pediatric annals. 2021;50(7):e277-e81.
97. Vosoughi F, Makuku R, Tantuoyir MM, et al. A systematic review and meta-analysis of the epidemiological characteristics of COVID-19 in children. BMC pediatrics. 2022;22(1):613.
98. CDC. (2021). Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). . Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Accessed on: 07 March 2021.
99. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. The New England journal of medicine. 2020;383(18):1757-66.
100. Khan K, Karim F, Cele S, et al. Omicron infection enhances neutralizing immunity against the Delta variant. 2021;10.1101/2021.12.27.21268439 %J medRxiv:2021.12.27.21268439.
101. CDC. (2023). COVID Data Tracker New Hospital Admissions. Available from: https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions. Accessed on: 04 January 2023.
102. ECDC. (2022). Country Overview Report: Week 50, 2022 Available from: https://www.ecdc.europa.eu/en/covid-19/country-overviews. Accessed on: 04 January 2023.
103. Rubenstein S, Grew E, Clouser K, et al. COVID-19 in Pediatric Inpatients: A Multi-Center Observational Study of Factors Associated with Negative Short-Term Outcomes. Children (Basel, Switzerland). 2021;8(11).
104. Alharbi AM, Rabbani SI, Halim Mohamed AA, et al. Analysis of potential risk factors associated with COVID-19 and hospitalization. Frontiers in public health. 2022;10:921953.
105. Mattsson G, Gonzalez Lindh M, Razmi R, et al. Clinical frailty scale as a predictor of disease severity in patients hospitalised with COVID-19 - an observational cohort study. Infectious diseases (London, England). 2022;54(8):583-90.
106. Chen Z, Peng Y, Wu X, et al. Comorbidities and complications of COVID-19 associated with disease severity, progression, and mortality in China with centralized

isolation and hospitalization: A systematic review and meta-analysis. Frontiers in public health. 2022;10:923485.
107. Gupta K, Kaur G, Pathak T, et al. Systematic review and meta-analysis of human genetic variants contributing to COVID-19 susceptibility and severity. Gene. 2022;844:146790.
108. Zinellu A, Mangoni AA. A systematic review and meta-analysis of the association between the neutrophil, lymphocyte, and platelet count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio and COVID-19 progression and mortality. Expert review of clinical immunology. 2022;18(11):1187-202.
109. Numaguchi R, Kurajoh M, Hiura Y, et al. Glycated hemoglobin level on admission associated with progression to severe disease in hospitalized patients with non-severe coronavirus disease 2019. Journal of diabetes investigation. 2022;13(10):1779-87.
110. Ligi D, Giglio RV, Henry BM, et al. What is the impact of circulating histones in COVID-19: a systematic review. Clinical chemistry and laboratory medicine. 2022;60(10):1506-17.
111. Zhou S, Li H, Li S. The Associations of Iron Related Biomarkers with Risk, Clinical Severity and Mortality in SARS-CoV-2 Patients: A Meta-Analysis. Nutrients. 2022;14(16).
112. Horwitz LI, Jones SA, Cerfolio RJ, et al. Trends in COVID-19 Risk-Adjusted Mortality Rates. Journal of hospital medicine. 2021;16(2):90-92.
113. ONS. (2023). Coronavirus (COVID-19) latest insights: Deaths Updated 28 March 2023. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19latestinsights/deaths. Accessed on: 04 September 2024.
114. WHO. (2024). COVID-19 epidemiological update – 15 July 2024 Updated 03 September 2024. Available from: https://www.who.int/publications/m/item/covid-19-epidemiological-update-edition-169. .
115. Louis DW, Saad M, Vijayakumar S, et al. The Cardiovascular Manifestations of COVID-19. Cardiology clinics. 2022;40(3):277-85.
116. Tobler DL, Pruzansky AJ, Naderi S, et al. Long-Term Cardiovascular Effects of COVID-19: Emerging Data Relevant to the Cardiovascular Clinician. Current atherosclerosis reports. 2022;24(7):563-70.
117. Henning RJ. Cardiovascular complications of COVID-19 severe acute respiratory syndrome. American journal of cardiovascular disease. 2022;12(4):170-91.
118. Salabei JK, Asnake ZT, Ismail ZH, et al. COVID-19 and the cardiovascular system: an update. The American journal of the medical sciences. 2022;364(2):139-47.
119. Dimitriadis K, Meis J, Neugebauer H, et al. Neurologic manifestations of COVID-19 in critically ill patients: results of the prospective multicenter registry PANDEMIC. Critical care (London, England). 2022;26(1):217.
120. Hussaini H, Rogers S, Kataria S, et al. COVID-19-Induced Seizures: A Meta-Analysis of Case Series and Retrospective Cohorts. Cureus. 2022;14(8):e28633.
121. Shih AR, Misdraji J. COVID-19: gastrointestinal and hepatobiliary manifestations. Human pathology. 2023;132:39-55.

122. Mallhi TH, Khan YH, Alzarea AI, et al. Incidence, risk factors and outcomes of acute kidney injury among COVID-19 patients: A systematic review of systematic reviews. Frontiers in medicine. 2022;9:973030.
123. Matsumoto K, Prowle JR. COVID-19-associated AKI. Current opinion in critical care. 2022;28(6):630-37.
124. Ssentongo P, Zhang Y, Witmer L, et al. Association of COVID-19 with diabetes: a systematic review and meta-analysis. Scientific reports. 2022;12(1):20191.
125. Cunningham RM, Johnson Moore KL, Moore JS. Coagulopathy during COVID-19 infection: a brief review. Clinical and experimental medicine. 2022;10.1007/s10238-022-00891-4:1-12.
126. Kankaria R, Sanina C, Gabr M, et al. Extracardiac Prothrombotic Effects of COVID-19. Cardiology clinics. 2022;40(3):337-44.
127. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. Jama. 2020;324(8):782-93.
128. Malas MB, Naazie IN, Elsayed N, et al. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. EClinicalMedicine. 2020;29:100639.
129. Sourani A, Vahdat N, Son C, et al. SARS-CoV-2 infection and spontaneous spinal hemorrhage: a systematic review. Neurosurgical review. 2023;46(1):300.
130. Özbek L, Topçu U, Manay M, et al. COVID-19-associated mucormycosis: a systematic review and meta-analysis of 958 cases. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2023;29(6):722-31.
131. Khraisat B, Toubasi A, AlZoubi L, et al. Meta-analysis of prevalence: the psychological sequelae among COVID-19 survivors. International journal of psychiatry in clinical practice. 2022;26(3):234-43.
132. Dangayach NS, Newcombe V, Sonnenville R. Acute Neurologic Complications of COVID-19 and Postacute Sequelae of COVID-19. Critical care clinics. 2022;38(3):553-70.
133. Al-Kuraishy HM, Al-Gareeb AI, Kaushik A, et al. Hemolytic anemia in COVID-19. Annals of hematology. 2022;101(9):1887-95.
134. Esmaeilzadeh A, Elahi R, Siahmansouri A, et al. Endocrine and metabolic complications of COVID-19: lessons learned and future prospects. Journal of molecular endocrinology. 2022;69(3):R125-r50.
135. Tian Y, Zhao J, Wang T, et al. Thyroid diseases are associated with coronavirus disease 2019 infection. Frontiers in endocrinology. 2022;13:952049.
136. Swarnakar R, Jenifa S, Wadhwa S. Musculoskeletal complications in long COVID-19: A systematic review. World journal of virology. 2022;11(6):485-95.
137. Khedmat L, Mohaghegh P, Veysizadeh M, et al. Pregnant women and infants against the infection risk of COVID-19: a review of prenatal and postnatal symptoms, clinical diagnosis, adverse maternal and neonatal outcomes, and available treatments. Archives of gynecology and obstetrics. 2022;306(2):323-35.
138. Carfì A, Bernabei R, Landi F. Persistent Symptoms in Patients After Acute COVID-19. Jama. 2020;324(6):603-05.

139. Greenhalgh T, Knight M, A'Court C, et al. Management of post-acute covid-19 in primary care. BMJ (Clinical research ed). 2020;370:m3026.
140. NICE. National Institute for Clinical Excellence Clinical Guidelines. 2021. Available from: https://www.nice.org.uk/guidance/ng188/chapter/context#post-covid-19-syndrome.
141. Willi S, Lüthold R, Hunt A, et al. COVID-19 sequelae in adults aged less than 50 years: A systematic review. Travel medicine and infectious disease. 2021;40:101995.
142. Yang T, Yan MZ, Li X, et al. Sequelae of COVID-19 among previously hospitalized patients up to 1 year after discharge: a systematic review and meta-analysis. Infection. 2022;50(5):1067-109.
143. Greer N, Bart B, Billington CJ, et al. COVID-19 postacute care major organ damage: a systematic review. BMJ open. 2022;12(8):e061245.
144. Simon M, Simmons JE. A Review of Respiratory Post-Acute Sequelae of COVID-19 (PASC) and the Potential Benefits of Pulmonary Rehabilitation. Rhode Island medical journal (2013). 2022;105(7):11-15.
145. Patel UK, Mehta N, Patel A, et al. Long-Term Neurological Sequelae Among Severe COVID-19 Patients: A Systematic Review and Meta-Analysis. Cureus. 2022;14(9):e29694.
146. Hur K, Price CPE, Gray EL, et al. Factors Associated With Intubation and Prolonged Intubation in Hospitalized Patients With COVID-19. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2020;163(1):170-78.
147. Nowak B, Szymański P, Pańkowski I, et al. Clinical characteristics and short-term outcomes of patients with coronavirus disease 2019: a retrospective single-center experience of a designated hospital in Poland. Polish archives of internal medicine. 2020;130(5):407-11.
148. Shi C, Wang L, Ye J, et al. Predictors of mortality in patients with coronavirus disease 2019: a systematic review and meta-analysis. BMC infectious diseases. 2021;21(1):663.
149. ECDC. (2021). COVID-19 Surveillance report. Week 43, 2021. 04 November 2021 (b). “3 Risk groups most affected. 3.1 Preconditions: frequency distribution by severity”. Available from: https://COVID19-surveillance-report.ecdc.europa.eu. Accessed on: 31 December 2021.
150. Choi JH, Choi SH, Yun KW. Risk Factors for Severe COVID-19 in Children: A Systematic Review and Meta-Analysis. Journal of Korean medical science. 2022;37(5):e35.
151. Reyes LF, Murthy S, Garcia-Gallo E, et al. Respiratory support in patients with severe COVID-19 in the International Severe Acute Respiratory and Emerging Infection (ISARIC) COVID-19 study: a prospective, multinational, observational study. Critical care (London, England). 2022;26(1):276.
152. Vagliano I, Schut MC, Abu-Hanna A, et al. Assess and validate predictive performance of models for in-hospital mortality in COVID-19 patients: A retrospective cohort study in the Netherlands comparing the value of registry data with high-granular electronic health records. International journal of medical informatics. 2022;167:104863.

153. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-73.
154. Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nature medicine. 2020;26(5):681-87.
155. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet (London, England). 2020;395(10224):565-74.
156. Zhang L, Lin D, Sun X, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. Science (New York, NY). 2020;368(6489):409-12.
157. Kim JC, Spence RA, Currier PF, et al. Coronavirus protein processing and RNA synthesis is inhibited by the cysteine proteinase inhibitor E64d. Virology. 1995;208(1):1-8.
158. Hegyi A, Ziebuhr J. Conservation of substrate specificities among coronavirus main proteases. The Journal of general virology. 2002;83(Pt 3):595-99.
159. Anand K, Ziebuhr J, Wadhwani P, et al. Coronavirus main proteinase (3CLpro) structure: basis for design of anti-SARS drugs. Science (New York, NY). 2003;300(5626):1763-7.
160. Pillaiyar T, Manickam M, Namasivayam V, et al. An Overview of Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV) 3CL Protease Inhibitors: Peptidomimetics and Small Molecule Chemotherapy. Journal of medicinal chemistry. 2016;59(14):6595-628.
161. Owen DR, Allerton CMN, Anderson AS, et al. An oral SARS-CoV-2 M(pro) inhibitor clinical candidate for the treatment of COVID-19. Science (New York, NY). 2021;10.1126/science.abl4784:eabl4784.
162. FDA. US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for Industry Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency. June 2006. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/antiviral-product-development-conducting-and-submitting-virology-studies-agency.
163. FDA. US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry. . February 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention.
164. Zhou Y, Gammeltoft KA, Ryberg LA, et al. Nirmatrelvir-resistant SARS-CoV-2 variants with high fitness in an infectious cell culture system. Science advances. 2022;8(51):eadd7197.
165. Iketani S, Mohri H, Culbertson B, et al. Multiple pathways for SARS-CoV-2 resistance to nirmatrelvir. Nature. 2023;613(7944):558-64.
166. Jochmans D, Liu C, Donckers K, et al. The Substitutions L50F, E166A, and L167F in SARS-CoV-2 3CLpro Are Selected by a Protease Inhibitor In Vitro and Confer Resistance To Nirmatrelvir. mBio. 2023;14(1):e0281522.

167. Takashita E, Fujisaki S, Morita H, et al. Assessment of the frequency of SARS-CoV-2 Omicron variant escape from RNA-dependent RNA polymerase inhibitors and 3C-like protease inhibitors. Antiviral research. 2023;216:105671.
168. Gammeltoft KA, Zhou Y, Ryberg LA, et al. Substitutions in SARS-CoV-2 Mpro Selected by Protease Inhibitor Boceprevir Confer Resistance to Nirmatrelvir. Viruses. 2023;15(9).
169. Heilmann E, Costacurta F, Moghadasi SA, et al. SARS-CoV-2 3CL(pro) mutations selected in a VSV-based system confer resistance to nirmatrelvir, ensitrelvir, and GC376. Sci Transl Med. 2023;15:eabq7360.
170. Hu Y, Lewandowski EM, Tan H, et al. Naturally Occurring Mutations of SARS-CoV-2 Main Protease Confer Drug Resistance to Nirmatrelvir. ACS Central Science. 2023;9(8):1658-69.
171. Amblard F, LeCher JC, De R, et al. Synthesis and biological evaluation of novel peptidomimetic inhibitors of the coronavirus 3C-like protease. Eur J Med Chem. 2024;268:116263.
172. Duveau DY, Thomas CJ. The Remarkable Selectivity of Nirmatrelvir. ACS pharmacology & translational science. 2022;5(6):445-47.
173. Childs GV, Ellison DG, Lorenzen JR, et al. Immunocytochemical studies of gonadotropin storage in developing castration cells. Endocrinology. 1982;111(4):1318-28.
174. Greaves P. Chapter 13 - Endocrine Glands. In *Histopathology of Preclinical Toxicity Studies (Fourth Edition)*. Edited by: Greaves P. Boston: Academic Press; 2012. p. 725-97.
175. Rosol T, Lellis RD, Harvey P. Endocrine System. Haschek W, Rousseau C, Wallig M. Haschek and Rousseaux's Handbook of Toxicologic Pathology. Academic Press, London, UK Vol 1. 3rd ed. 2013: p. 2391-492.

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Exposure During Pregnancy Supplemental Form (for study case)

Exposure During Pregnancy Follow-up Questionnaire (for non-study case) – to be merged with other Company's standard follow-up questionnaires as appropriate

Data Capture Aid – Lactation – to be merged with Company's standard follow-up questionnaires as appropriate

Data Capture Aid – Lack of effect – to be merged with the Company's standard follow-up questionnaires as appropriate

Exposure During Pregnancy (EDP) Supplemental Form

AER # (*insert when known*)

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*)											

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?

EDP FU Questionnaire

Exposure During Pregnancy

1. According to the information provided, exposure to a product may have occurred during pregnancy or around the time of conception. Please confirm and complete all questions to the best of your ability and knowledge.

Maternal Obstetrical History

1. Occupation
_____

2. Was the mother previously pregnant?
☐ Yes ☐ No ☐ Unknown

If Yes, how many times:_____

3. Number of other children
_____

4. Outcome of previous pregnancies (e.g., live birth, miscarriage, elective termination, late fetal death, ectopic pregnancy, molar pregnancy)
_____

5. Did the mother experience previous pregnancy complications?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

6. Did the mother experience previous fetal/neonatal abnormalities?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

7. Does the mother have a history of sub-fertility?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

8. Was the mother treated for infertility?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

9. Mother's Relevant History (i.e., risk factors including environmental or occupational exposures (e.g., AIDS, toxins)).

10. Does the mother have a family history of congenital abnormality/ genetic diseases, and/or consanguinity (or any family relation or lineage) between parents?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

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

Maternal Information

1. Ante-natal check-up (e.g., fetal ultrasound, serum markers, etc.). Please specify dates in dd-Mmm-YYYY format and check-up results for this pregnancy.
_____

2. First day of last menstrual period (dd-Mmm-yyyy)
_____

3. Number of fetuses for this pregnancy
_____

4. Estimated delivery date for this pregnancy (dd-Mmm-yyyy)
_____

5. Gestational period at time of initial suspect drug exposure
_____ ☐ Trimester ☐ Month

6. Did the mother smoke during this pregnancy?
☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

7. Did the mother drink alcohol during this pregnancy?
☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

8. Did the mother use illicit drugs during this pregnancy?
☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

9. Did the mother experience any problems before delivery?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

10. Did the mother experience any problems during delivery (including delivery complications, fetal distress, amniotic fluid abnormal, abnormal placenta)?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

11. Did the mother experience any problems after delivery?
☐ Yes ☐ No ☐ Unknown

If yes, please specify_____

12. Mode of delivery
☐ Vaginal ☐ Cesarean ☐ Unknown

13. Outcome of this pregnancy

- ☐ Full term live birth
- ☐ Premature live birth
- ☐ Post-mature live birth
- ☐ Stillbirth
- ☐ Late foetal death
- ☐ Ectopic pregnancy
- ☐ Molar pregnancy
- ☐ Spontaneous abortion/miscarriage
- ☐ Induced/elective abortion
- ☐ Unknown

14. Date of outcome of this pregnancy (dd-Mmm-yyyy)

_____

Neonatal Information

1. Sex (at birth)

☐ Male ☐ Female

2. Weight at birth (number and unit)

_____ ☐ kg ☐ lbs & oz

3. Length at birth (number and unit)

_____

4. Head circumference at birth (number and unit)

_____

5. Apgar score at 1 min

_____

6. Apgar score at 5 min

_____

7. Gestational age at birth in weeks

_____

8. Outcome of Fetus/Infant

☐ Healthy newborn
☐ Congenital malformation/anomaly (specify below)
☐ Other neonatal problem/abnormality (include dysmaturity, neonatal illness, hospitalization, drug therapies) (specify below)
☐ Intrauterine death
☐ Neonatal death
☐ Outcome pending (not born yet)
☐ Perinatal complications (specify below)
☐ Post-perinatal complications (specify below)
☐ Unknown

Please specify:

Pregnancy Information

1. In the event of an elective termination, spontaneous abortion, or late fetal death please provide the following fetal information (if available).

Reason for termination: _____
Gestational age at termination: _____
Results of physical examination (external anomalies) and pathology and any other relevant information: _____

2. Infant illnesses, hospitalizations, drug therapies, breastfeeding

_____

3. Developmental assessment

_____

4. Malformation/anomalies diagnosed

_____

Paternal Information

1. Father's Age

_____ ☐ Years ☐ Months ☐ Days

Age Group:

☐ Adolescent (12-17 Years) ☐ Adult (18-64 Years) ☐ Elderly (65 or older)

2. Occupation

_____

3. Father's Relevant History (i.e., risk factors including environmental or occupational exposures (e.g., AIDS, toxins)).

4. Were any drugs (e.g., over-the-counter, medical prescription) taken by the father during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If yes, please specify:_____

5. Did the father smoke during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

6. Did the father drink alcohol during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

7. Did the father use illicit drugs during the mother's pregnancy or around the time of conception?

☐ Yes ☐ No ☐ Unknown

If Yes, frequency:_____

8. Does the father have a family history of congenital abnormality/ genetic diseases, and/or consanguinity (or any family relation or lineage) between parents?

☐ Yes ☐ No ☐ Unknown

If yes, please specify:_____

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

The following questions are intended to capture clinical details on child exposure to Paxlovid via breastfeeding.

1. **During 5-days Paxlovid treatment, on which days did the patient also continue breastfeeding?**

   ☐ Day 1 ☐ Day 2 ☐ Day 3 ☐ Day 4 ☐ Day 5 ☐ Not applicable

2. **How was the child breastfed?**

   ☐ Exclusively with breast milk

   ☐ Mostly with breast milk with addition of other fluids

   ☐ With breast milk and other foods

3. **If breastfeeding was stopped during Paxlovid treatment, did the mother resume breastfeeding after treatment ended?**

   ☐ Yes ☐ No ☐ Unknown ☐ Not applicable

   If yes, please specify on what day relative to last dose of Paxlovid:

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

The following questions are intended to capture clinical details about the nature and severity of COVID-19 symptoms after Paxlovid treatment.

1. **Does the patient still have a positive test for SARS-CoV-2 after Paxlovid treatment was completed?**

   ☐ Yes ☐ No ☐ Unknown

   If yes, please provide test type and date:

2. **Was the SARS-CoV-2 viral sequencing performed?**

   ☐ Yes ☐ No ☐ Unknown

   If yes, which SARS-CoV-2 variant was identified?

3. **Please provide information on patient's COVID-19 symptoms at the end of Paxlovid treatment.**

   ☐ Symptoms improved ☐ Symptoms worsened ☐ No change ☐ Other

   Please provide details:

4. **Did the patient experience any <u>new</u> COVID-19 symptoms during or at the end of Paxlovid treatment?**

   ☐ Yes ☐ No ☐ Unknown

   If yes, please provide details:

5. **Did the patient require supplemental oxygen or receive mechanical ventilation after starting Paxlovid?**

   ☐ Yes ☐ No ☐ Unknown

   If yes, please provide details, e.g., date, oxygen requirements, pulse oximetry results:

6. **Has the patient received a COVID-19 vaccination?**

   ☐ Yes ☐ No ☐ Unknown

   If yes, please provide vaccination name(s) and date(s) of administration:

7. **Were any SARS-CoV-2 serological tests performed? If yes, please provide the results.**

Test	Date Performed	Results

8. Please mark whether the patient had any of the following prior to start of therapy?

☐ Diabetes	☐ Heart disease	☐ Hypertension
☐ Liver disease	☐ Kidney disease	☐ Immunosuppressive disorder
☐ Cancer	☐ Lung disease	☐ Other relevant condition
☐ Tobacco use	☐ Obesity	

Please provide details:

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not Applicable