ラゲブリオカプセルに関する費用対効果評価 [第 1.0 版]

MSD 株式会社

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【目次】

略語

略語	正式表記
AE	Adverse Events
ATS	American Thoracic Society
BMJ	British Medical Journal
CADTH	Canadian Agency for Drugs and. Technologies in Health
COVID-19	Coronavirus disease 2019
CROI	Conference on Retroviruses and Opportunistic Infections
CTRI	Clinical Trial Registry of India
DSA	Deterministic sensitivity analysis
ECCMID	European Congress of Clinical Microbiology and Infectious Diseases
ECMO	Extracorporeal Membrane Oxygenation
ED	Emergency Department
EMBASE	Excerpta Medica Database
HAS	Haute Autorité de Santé
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IDSA	US Infectious Diseases Society of America
ICTRP	International Clinical Trials Registry Platform
IQWiG	Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MAGIC	Mutant-Assisted Gene Identification and Characterization
MEDLINE	Medical Literature Analysis and Retrieval System Online
MERS	Middle East Respiratory Syndrome
MTA	Multi Technology Appraisal
MV	Mechanical ventilation
NHC	β-d-N-hydroxycytidine/N-ヒドロキシシチジン
NHC-TP	Triphosphate β-d-N-hydroxycytidine/N-ヒドロキシシチジン三リン酸
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NMA	Network meta-analysis
NR	Not reported

PBAC	Pharmaceutical Benefits Advisory Committee
PMC	NIH PubMed Central
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
QOL	Quality of Life
RCT	Randomized Controlled Trial
RdRp	RNA-dependent RNA polymerase/RNA 依存性 RNA ポリメラーゼ
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SE	Standard Error
SMC	Scottish Medicines Consortium
SMR	Standardized Mortality Ratio
UPMC	University of Pittsburgh Medical Center
WHO	World Health Organization
WTP	Willingness-to-pay

図一覧

表一覧

0. 要旨

分析対象技術名 [1.1 節]	ラゲブリオ（モルヌピラビル）
他国の医療技術評価機関 における評価結果 [1.8 節]	• イギリス（National Institute for Health and Care Excellence, NICE）： Multi Technology Appraisal（MTA）実施中 • イギリス（Scottish Medicines Consortium, SMC）：該当なし • フランス（Haute Autorité de Santé, HAS）：該当なし • ドイツ（Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG）：該当なし • カナダ（Canadian Agency for Drugs and Technologies in Health, CADTH）：該当なし • オーストラリア（Pharmaceutical Benefits Advisory Committee, PBAC）：評価中
対象とする疾患・集団 [2.1 節]	重症化リスク因子を有する SARS-CoV-2 による感染症（COVID-19）患者（18 歳以上） 但し、有効性が確立していないため、重症度*の高い COVID-19 患者を除く。 *重症度の定義は新型コロナウイルス感染症（COVID-19）診療の手引き・第 8.1 版に準ずる。
比較対照技術名 [2.2 節]	標準治療
分析の立場と費用の範囲 [2.3 節]	公的医療の立場 公的医療費のみ
使用する効果指標 [2.4 節]	質調整生存年（Quality-adjusted life-year, QALY）
設定した分析期間 [2.5 節]	生涯
割引率 [2.6 節]	費用、効果ともに年率 2%
システマティックレビューの クリニカルクエスチョン [3.1/3.3 節]	介入 • ラゲブリオ/モルヌピラビル • ロナプリーブ/カシリビマブ＋イムデビマブ

システマティックレビューの クリニカルクエスチョン [3.1/3.3 節] （続き）	対象集団 • COVID-19 患者（外来のみ） • ゼビュディ/ソトロビマブ/VIR-7831 • ベクルリー/レムデシビル/GS-5734 • パキロビッド/ニルマトレルビル+リトナビル/PF-07321332 • Levovir/Revovir/clevudine/クレブジン • Arbidol/umifenovir/ウミフェノビル • Kineret/anakinra • Lenzilumab/レンジルマブ • Bebtelovimab/ベブテロビマブ • AT-527/RO7496998 • Tixagevimab + cilgavimab/(AZD7442 or AZD8895) and AZD1061 • Bamlanivimab/LY-CoV555/バムラニビマブ • Bamlanivimab + etesevimab/LY CoV555 + LY-CoV016/バムラニビマブ ＋ エテセビマブ • パルミコート/ブデソニド • フオイパン/カモスタットメシル酸塩 • コルヒチン • Regdanvimab/CT-P59 • アビガン/ファビピラビル • ヒドロコルチゾン • メチルプレドニゾロン • Nitazoxanide/ニタゾキサニド • ペグインターフェロンラムダ-1 • プレドニゾン • ADG20 • オルミエント/バリシチニブ • Ensovibep/MP0420 • ファモチジン • フルボキサミン • MP-0423 • ゾコーバ/エンシトレルビル/S-217622 比較対照 • ラゲブリオ/モルヌピラビルを除く上述の治療 アウトカム • 有効性：外来患者の治療経過に関連するアウトカム（以下を含むが、これに限定しない。） - 悪化までの期間 - 持続的回復までの期間 - COVID-19 の徴候及び症状の持続期間 - ウイルス学的治癒/ウイルスクリアランスを達成するまでの期間及び達成した患者の割合 - ウイルス量／ウイルス排出量

システマティックレビューの クリニカルクエスチョン [3.1/3.3 節] （続き）	- （下記の測定方法による）症状の重症度及びフォローアップ時の疾患の進行度 〇Pulmonary or pulmonary + score 〇National Early Warning Score 〇WHO 11-point outcomes score - フォローアップ時の臨床的改善度（WHO 臨床的改善度カテゴリースケール、または臨床/実験データ/CT スキャン/ウイルス消失率によるもの） - 全生存（人数/割合/率） - 全死因死亡（人数/割合/率） - COVID-19 関連死亡（人数/割合/率） - 入院（人数/割合/率） - 入院までの期間 - ICU または一般病棟に入院した患者（人数/割合/率） • 安全性 - 治療に関連する有害事象 - グレード 3 および 4 の有害事象 - 重篤な有害事象 - 治療の中止（有害事象によるものなど） 研究デザイン • 第 II 相または第 III 相の無作為化比較試験 検索期間 • 英語：2020/01/01～2022/12/06 • 日本語：2020/01/01～2022/12/06
システマティックレビュー結果の概要 [3.2/3.4 節]	上述のクリニカルクエスチョンに従って、システマティックレビューを実施した。分析ガイドラインには、文献検索終了時点について「分析枠組みが決定された後から製造販売業者による分析提出までの一時点に決める」の規定に沿って、既に 2021 年 5 月から 2022 年 5 月の間に 3 回実施していたシステマティックレビューに加えて、2022 年 12 月に和文文献検索を含めたシステマティックレビューの更新を実施した。（2021 年 9 月、2022 年 5 月、2022 年 12 月までの間に 3 回更新した）。 関連する論文を特定するために、文献データベースは、Embase, Medline を使用し、第4回では医中誌を追加し文献検索を実施した。また、その他の情報源として、臨床試験のデータベースや学会抄録の検索も行った。更新を含めた計 4 回の検索で同定された文献数は下記の通りである。

<table>
<tr><td>システマティックレビュー結果の概要 [3.2/3.4 節]
（続き）</td><td><table><tr><td></td><td>件数</td></tr><tr><td>文献データベース</td><td>52</td></tr><tr><td>その他の情報源</td><td>34</td></tr><tr><td>合計</td><td>86（60 試験）</td></tr></table></td></tr>
<tr><td>間接比較の結果 [3.7 節]</td><td>該当なし</td></tr>
<tr><td>追加的有用性の有無 [3.8 節]</td><td>■ 追加的有用性あり □「追加的有用性なし」あるいは「あるとは判断できない」</td></tr>
<tr><td>費用対効果の分析方法の概要 [4.1.1 項、4.2 節等]</td><td>本分析では、COVID-19 の発症から急性期治療終了までの分析期間（30 日）に決定木モデルを用い、その後の分析期間（生涯：死亡又は 100 歳まで）には 1 サイクルを 1 年（但し、初年は急性期を除いた 11 か月）に設定したマルコフモデルを用いた。決定木モデルでは外来治療（非入院）から開始され、COVID-19 の重症化に伴い、最終的に外来から入院へ移行する可能性を想定した。また、入院中に到達しうる最高レベルのケアセッティングとして 3 レベル（一般病棟、ICU、体外式膜型人工肺（ECMO）又は人工呼吸器（MV）の使用を伴う ICU）を想定し、入院後の患者の転帰として、完全に回復するケース、長期の後遺症を伴って回復するケース、入院中に死亡するケースを想定した。入院後の生存患者では、再入院を経験することも想定した。有害事象（Adverse Events, AE）または治療上緊急を要する有害事象は、非入院 COVID-19 患者を対象とした MOVe-OUT 試験で安全性及び忍容性が良好であり、特段の安全性上の懸念が認められなかったため、本分析では想定しない。
基本分析に加えて、一次元感度分析、確率的感度分析、シナリオ分析を実施した。有効性や安全性のパラメータにはデータベース調査および自社試験結果、QOL 値には文献値および海外における調査結果の日本人換算値、費用のデータにはデータベース調査の結果を主に使用した。</td></tr>
<tr><td>結果の概要 [5.1 節]</td><td>重症化リスク因子を有する SARS-CoV-2 による感染症(COVID-19)患者において、モルヌピラビル＋標準治療に対</td></tr>
</table>

	する標準治療の（Incremental Cost-Effectiveness Ratio、ICER）は 1,930,637 円/QALY であり、「医薬品及び医療機器の費用対効果評価に係る分析結果の記載様式と手引」に記載の価格調整の閾値「500 万円以下（750 万円以下）」の区分に相当すると考える。実施した PSA において ICER が基準値の 500 万円を下回る確率は 100%、250 万円を下回る確率は 93%であり、さらに公的医療の立場でのシナリオ分析全てにおいて ICER が基準値の 500 万円を下回り、基本分析と同様の結果が示された。
ICER の所属する確率が最も高いと考える区間	□ 費用削減あるいはドミナント ■ 500 万円以下（750 万円以下） □ 500 万円超（750 万円超）かつ 750 万円以下（1125 万円以下） □ 750 万円超（1125 万円超）かつ 1000 万円以下（1500 万円以下） □ 1000 万円超（1500 万円超） □ 効果が同等（あるいは劣り）、かつ費用が高い

1. 対象となる医薬品･医療機器の性質

1.1 名称

販売名	ラゲブリオカプセル 200mg
一般名	和名：モルヌピラビル 洋名：Molnupiravir

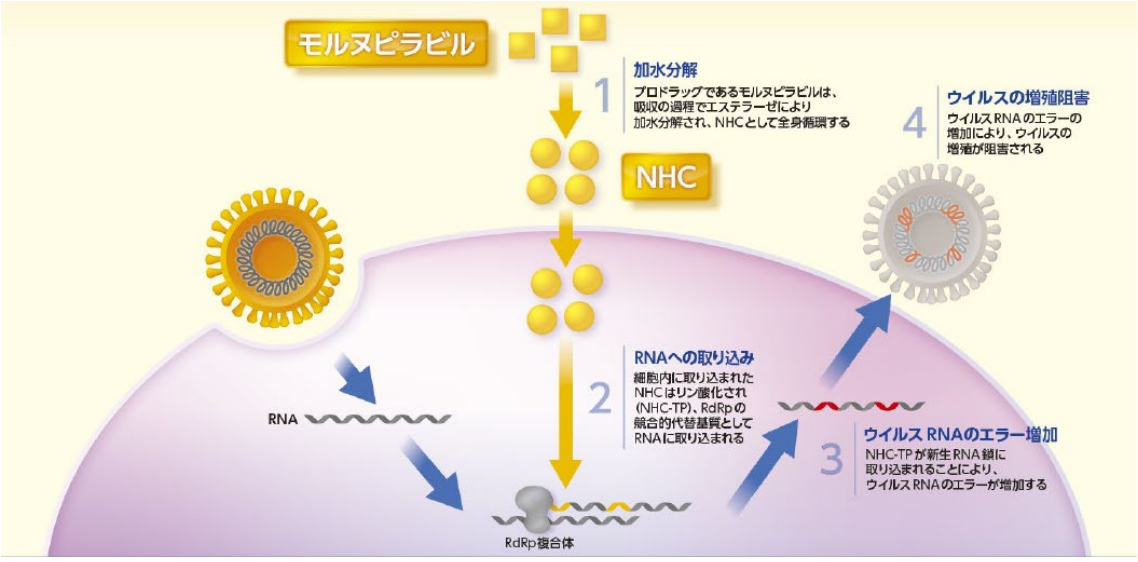
1.2 保険償還価格

薬価	200mg 1 カプセル 2,357.80 円 （2023 年 4 月時点）
算定方式	類似薬効比較方式（I）
加算率	有用性加算（II）（A＝10%）

1.3 治療効果のメカニズム

ラゲブリオ（一般名：モルヌピラビル）は、ウイルスでのエラーカタストロフの誘導により抗ウイルス作用を示す。モルヌピラビルの活性本体である N-ヒドロキシシチジン三リン酸（β-d-N-hydroxycytidine Triphosphate, NHC-TP）がウイルス由来 RNA 依存性 RNA ポリメラーゼ（RNA-dependent RNA polymerase, RdRp）によりウイルス RNA に取り込まれた結果、ウイルス RNA の複製エラーが増加し、ウイルスの増殖が阻害される（図 1）。

図 1 治療効果のメカニズム



NHC：N-ヒドロキシシチジン、NHC-TP：N-ヒドロキシシチジン三リン酸、RdRp：RNA 依存性 RNA ポリメラーゼ

出典：ラゲブリオカプセル 200mg インタビューフォーム（2023 年 4 月改訂、第 3 版）

モルヌピラビルの主要代謝物である NHC は、SARS-CoV-2 の従来株（USA-WA1/2020 株）、並びにその変異株である B.1.1.7 系統（アルファ株）、B.1.351 系統（ベータ株）、P.1 系統（ガンマ株）、B.1.617.2 系統（デルタ株）、C.37 系統（ラムダ株）、B.1.621 系統（ミュー株）および B.1.1.529/BA.1、BA1.1、BA.2、BA.4、BA.5（オミクロン株）に対して同程度の抗ウイルス作用を示した（図 2）。さらに、Kawaoka らのグループにより、より新しい BQ.1.1 系統[1]、XBB.1.5 系統[2]等に対しても同程度の抗ウイルス作用が報告されている。

図 2　NHC の SARS-CoV-2 の変異株に対する抗ウイルス作用

変異株	系統	細胞株	NHC EC_{50}値 （μM）	
			Assay 1	Assay 2
従来株（USA-WA1/2020 株）	A 系統	Vero E6	1.41	NA
		Vero E6	0.63	1.10
		Vero E6	2.0	2.26
		Vero E6	1.31	1.06
		Vero E6	2.2	2.2
		Vero E6-TMPRSS2	0.83	0.93
		Vero E6-TMPRSS2	0.65	0.67
alpha 株	B.1.1.7 系統	Vero E6	1.59	NA
beta 株	B.1.351 系統	Vero E6	1.77	NA
gamma 株	P.1 系統	Vero E6	1.32	NA
delta 株	B.1.617.2 系統	Vero E6	1.68	NA
		Vero E6	NA	1.10
lambda 株	C.37 系統	Vero E6	0.98	0.92
mu 株	B.1.621 系統	Vero E6	1.94	1.05
omicron 株	B.1.1.529/BA.1	Vero E6	1.06	1.12
	B.1.1.529/BA.1.1	Vero E6	3.35	1.86
	B.1.1.529/BA.2	Vero E6	2.5	3.4
	B.1.1.529/BA.4	Vero E6	5.2	5.5
		Vero E6	1.40	1.15
		Vero E6-TMPRSS2	0.34	0.28
	B.1.1.529/BA.5	Vero E6-TMPRSS2	0.47	0.40
		Vero E6-TMPRSS2	0.63	0.71

NA：not applicable

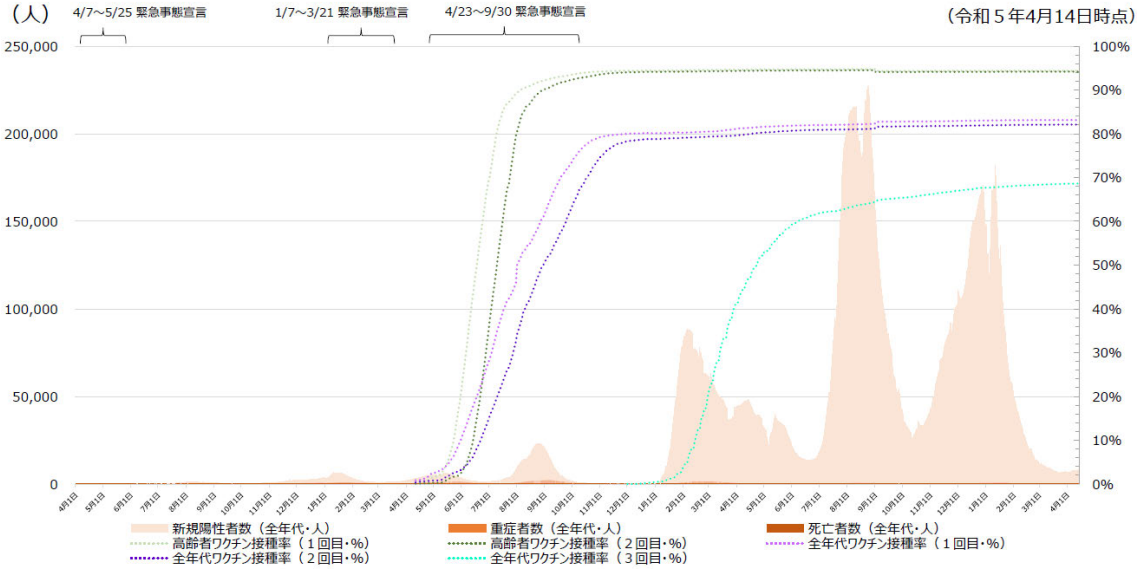
出典：ラゲブリオカプセル 200mg 添付文書（2023 年 4 月改訂、第 5 版）

1.4 対象疾患

ラゲブリオカプセルの保険適用となっている効能・効果は、「SARS-CoV-2 による感染症」（新型コロナウイルス感染症（COVID-19））である[3]。病原体である SARS-CoV-2 は、SARS や MERS の病原体と同じβコロナウイルス属に分類される動物由来コロナウイルスと判明したが宿主動物はまだ分かっていない。現在はヒト-ヒト感染によって流行が世界的に広がっている状況である。感染経路は、感染者（無症状病原体保有者を含む）から咳、くしゃみ、会話などの際に排出されるウイルスを含んだ飛沫・エアロゾル（飛沫よりさらに小さな水分を含んだ状態の粒子）の吸入が主要感染経路と考えられる。潜伏期・感染可能期間については、潜伏期は 1 ～14 日間で

あり、曝露から 5 日程度で発症することが多い。ただし、オミクロン株は潜伏期が 2～3 日、曝露から 7 日以内に発症する者が大部分であるとの報告がある。発症前から感染性があり、発症から間もない時期の感染性が高いことが市中感染の原因となっており、SARS や MERS と異なる特徴である[4]。2023 年 4 月 17 日現在、国内 COVID-19 の陽性者数は累計約 3,360 万人、累計死亡者数は約 7.4 万人である[5]。

図 3 SARS-CoV-2 による感染者数の推移



出典：厚生労働省第 121 回新型コロナウイルス感染症対策アドバイザリーボード（令和 5 年 4 月 19 日）

1.5 使用方法等

投与経路	経口
投与量・投与頻度	通常、18歳以上の患者には、モルヌピラビルとして1回800mgを 1 日 2 回、5 日間経口投与する。
効能又は効果に関連する注意	• 臨床試験における主な投与経験を踏まえ、SARS-CoV-2による感染症の重症化リスク因子を有する等、本剤の投与が必要と考えられる患者に投与すること。また、本剤の投与対象については最新のガイドライン*も参考にすること。 • 重症度の高いSARS-CoV-2による感染症患者に対する有効性は確立していない。 ＊ 新型コロナウイルス感染症（COVID-19）診療の手引き など

用法及び用量に関連する注意	SARS-CoV-2 による感染症の症状が発現してから速やかに投与を開始すること。臨床試験において、症状発現から 6 日目以降に投与を開始した患者における有効性を裏付けるデータは得られていない。
平均的な投与期間(あるいはサイクル数)	5 日間
平均投与量	1600mg/日

出典:ラゲブリオカプセル 200mg 添付文書(2023 年 4 月改訂、第 5 版)

1.6 対象疾患の治療における当該医薬品･医療機器の位置づけ

2023 年 3 月現在、国内 COVID-19 の陽性者数は累計約 3,348 万人、累計死亡者数は約 7.4 万人である[5]。COVID-19 の重症度は図 4 の通り 4 段階に分類されている[4]。

図 4 COVID-19 の重症度分類

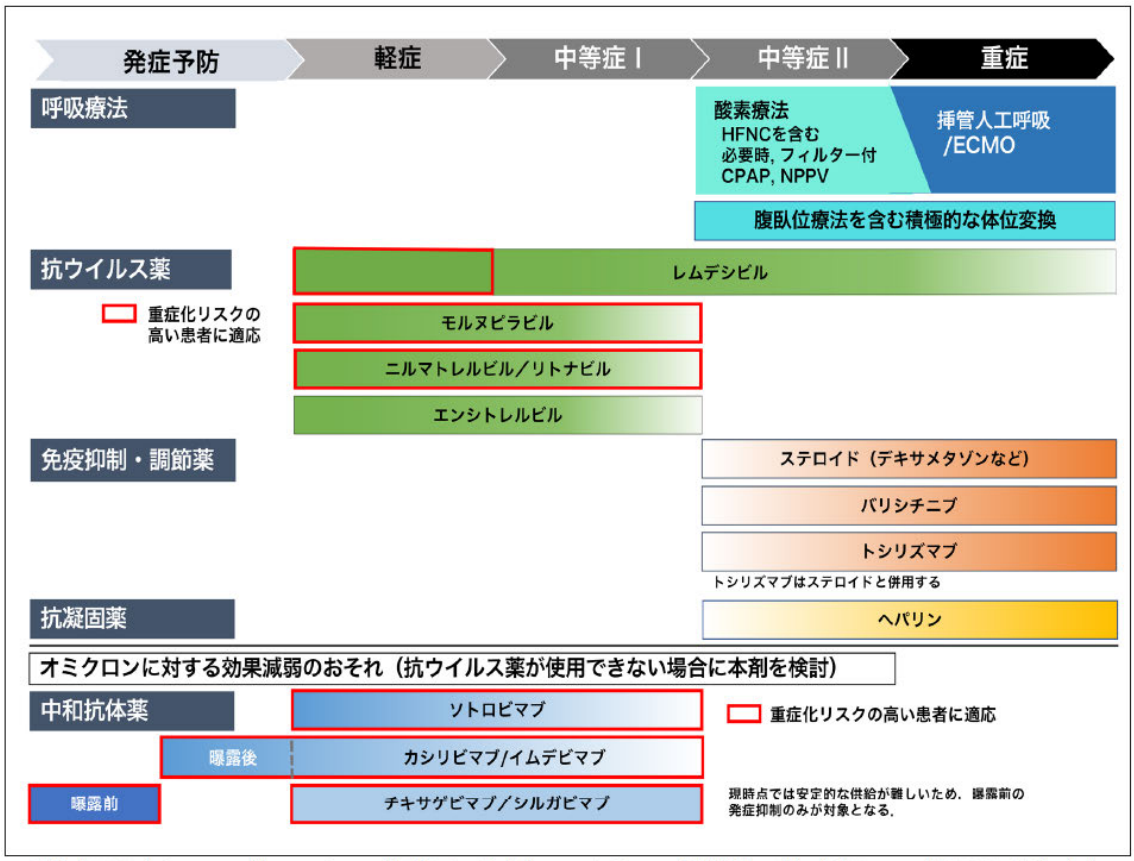
重症度	酸素飽和度	臨床状態	診療のポイント
軽　症	$SpO_2 \geq 96\%$	呼吸器症状なし or 咳のみで呼吸困難なし いずれの場合であっても肺炎所見を認めない	・多くが自然軽快するが，急速に病状が進行することもある ・高齢者では全身状態を評価して入院の適応を判断する
中等症 I 呼吸不全なし	$93\% < SpO_2 < 96\%$	呼吸困難，肺炎所見	・入院の上で慎重な観察が望ましい ・低酸素血症があっても呼吸困難を訴えないことがある
中等症 II 呼吸不全あり	$SpO_2 \leq 93\%$	酸素投与が必要	・呼吸不全の原因を推定 ・高度な医療を行える施設へ転院を検討
重　症		ICU に入室 or 人工呼吸器が必要	・人工呼吸器管理に基づく重症肺炎の 2 分類（L 型，H 型）が提唱 ・L 型：肺はやわらかく，換気量が増加 ・H 型：肺水腫で，ECMO の導入を検討 ・L 型から H 型への移行は判定が困難

・COVID-19 の死因は，呼吸不全が多いため，重症度は呼吸器症状（特に呼吸困難）と 酸素化を中心に分類した．
・SpO_2 を測定し酸素化の状態を客観的に判断することが望ましい．
・呼吸不全の定義は $PaO_2 \leq 60$ mmHg であり $SpO_2 \leq 90\%$ に相当するが，SpO_2 は 3% の誤差が予測されるので $SpO_2 \leq 93\%$ とした．
・肺炎の有無を確認するために，院内感染対策を行い，可能な範囲で胸部 CT を撮影することが望ましい．
・酸素飽和度と臨床状態で重症度に差がある場合，重症度の高い方に分類する．
・重症の定義は厚生労働省の事務連絡に従った．ここに示す重症度は中国や米国 NIH の重症度とは異なっていることに留意すること．
・この重症度分類は新型コロナウイルス感染症の肺炎の医療介入における重症度である．入院に関しては，この分類で軽症に該当する患者であっても全身状態などを考慮する必要がある（「4-5 高齢者の管理」を参照）．

出典:新型コロナウイルス感染症(COVID-19) 診療の手引き 第 9.0 版

モルヌピラビルは新型コロナウイルス感染症(COVID-19) 診療の手引き[4]の 4.重症度分類とマネジメントの中で軽症及び中等症 I の患者への投与が推奨されている(図 5)。

図 5　重症度別マネジメント



・重症度は発症からの日数，ワクチン接種歴，重症化リスク因子，合併症などを考慮して，繰り返し評価を行うことが重要である．
・個々の患者の治療は，基礎疾患や合併症，患者の意思，地域の医療体制などを加味した上で個別に判断する．
・薬物療法は COVID-19 やその合併症を適応症として日本国内で承認されている薬剤のみを記載した．詳細な使用法は，「5 薬物療法」および添付文書などを参照すること．

出典：新型コロナウイルス感染症（COVID-19）診療の手引き 第 9.0 版

1.7 主な有害事象

臨床試験において認められた主な副作用は下痢、悪心、浮動性めまい、頭痛（1%以上5%未満）であった[6]。これらの副作用について観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこととされている[3]。なお、「日本人患者へ投与時の安全性を可能な限り承認後早期に確認し、検討すること、及び有効性についても副次的に確認すること」を目的とした特定使用成績調査の中間解析（回収数：1,064例）では、副作用発現割合は72/1,061例（6.79%）であり、4例以上で発現した副作用は下痢が26例（2.45%）、発疹が6例（0.57%）、浮動性めまいが5例（0.47%）、軟便が4例（0.38%）であった。重篤な副作用の発現は4例（0.38%）であり、発疹、肝機能異常、COVID-19（増悪）、間質性肺疾患（増悪）であった[7]。

1.8 他国の医療技術評価機関における評価結果

表 1 主要国における評価の一覧表

国名	機関名	評価結果（記載例）	リスト価格 (現地通貨建)
イギリス	NICE	・推奨/非推奨/条件つき推奨(具体的に:　　) /その他（MTA 実施中） ・評価ステータス：最終ガイダンス/ドラフト/その他 (　　)	
	SMC	該当なし	
フランス	HAS	該当なし	
ドイツ	IQWiG	該当なし	
カナダ	CADTH	該当なし	
オーストラリア	PBAC	・推奨/非推奨/条件つき推奨(具体的に:　　) /その他(評価中)	

表 2 評価の有無の一覧

国名	機関名	評価結果の有無
イギリス	NICE	あり/ なし/ 評価中(ドラフトあり/なし)/不明
	SMC	あり/ なし/ 評価中/不明
フランス	HAS	あり/ なし/ 評価中/不明
カナダ	CADTH	あり/ なし/ 評価中/不明
オーストラリア	PBAC	あり/ なし/ 評価中/不明

表 3 評価結果の詳細

国名	イギリス
機関名	NICE
評価結果の URL など	https://www.nice.org.uk/guidance/indevelopment/GID-TA11297
評価対象技術	モルヌピラビル
評価結果	N/A（MTA 評価中）
条件付き推奨の場合は、その条件の詳細	N/A（MTA 評価中）

評価対象疾患	SARS-CoV-2 による感染症
使用方法（※）	通常、18 歳以上の患者には、モルヌピラビルとして 1 回 800mg を 1 日 2 回、5 日間経口投与する。
比較対照	標準治療
主要な増分費用効果比の値	N/A（MTA 評価中）

国名	オーストラリア
機関名	PBAC
評価結果の URL など	https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2022-11/covid-19-oral-treatments-outcome-nov-2022.pdf
評価対象技術	モルヌピラビル
評価結果	推奨
条件付き推奨の場合は、その条件の詳細	以下に該当する場合推奨 - 70 歳以上（無症状陽性者を含む） - 50 歳以上で複数の重症化リスク因子を有する軽症者 - 30 歳以上の先住民で複数の重症化リスク因子を有する軽症者 - 18 歳以上で中等度～重度の免疫抑制状態の軽症者
評価対象疾患	SARS-CoV-2 による感染症
使用方法（※）	通常、18 歳以上の患者には、モルヌピラビルとして 1 回 800mg を 1 日 2 回、5 日間経口投与する。
比較対照	標準治療
主要な増分費用効果比の値	N/A（評価中）

2. 費用効果分析における分析条件の設定

2.1 分析対象とする集団

重症化リスク因子を有する SARS-CoV-2 による感染症（COVID-19）患者（18 歳以上） 但し、有効性が確立していないため、重症度*の高い COVID-19 患者を除く、とする。

*重症度の定義は新型コロナウイルス感染症（COVID-19） 診療の手引き・第 8.1 版[8]に準ずる。

2.2 比較対照

ラゲブリオカプセル（以下モルヌピラビル）の保険適用となっている効能効果は「SARS-CoV-2 による感染症」であり、本剤と同様に重症化リスク因子を有する軽症又は中等症Ⅰの患者に推奨される抗ウイルス薬としてレムデシビルおよびニルマトレルビル/リトナビルも薬価収載品目として使用されている。レムデシビルは臨床専門家の意見聴取等から入院外診療において幅広くは使用されておらず、主に入院外で用いる経口薬のモルヌピラビルによっては代替されないと考えられた。一方、ニルマトレルビル/リトナビルはモルヌピラビルと同様、主に重症化リスク因子を有する入院外の軽症患者で使用される経口薬であり、治療上の位置づけが類似している（併用禁忌・併用注意薬が多い点や腎機能又は肝機能障害の患者で投与量の減量を要する点はモルヌピラビルとは異なる）。従って、本来のところニルマトレルビル/リトナビルが比較対照技術として適当と考えられるものの、ニルマトレルビル/リトナビルは分析枠組み決定の時点で薬価未収載であり薬剤価格が不明だったため、分析の実施が困難であった。

よって、その他に公的医療保険で使用が認められ代替されると想定されるものが存在しないことから、比較対照技術は、「標準治療**（評価対象技術：モルヌピラビル＋標準治療） 」として、2022 年 11 月 25 日に開催された中央社会保険医療協議会の費用対効果評価専門組織より了承を得た。**COVID-19 に対して治療の適応がある薬剤を除く、対症療法

なお、その後エンシトレルビルが薬価収載され、重症化リスク因子のない軽症例で使用されるが、当該対象患者はモルヌピラビルとは異なる。

2.3 分析の立場と費用の範囲

分析ガイドライン[9]に則り、分析の立場は「公的医療の立場」とした。また、費用の範囲は公的医療の立場において考慮すべき公的医療費（直接医療費）の範囲とした。

2.4 効果指標

分析ガイドラインに則り、評価指標は質調整生存年（QALY）とした。

2.5 分析期間

分析ガイドラインに則り、評価対象技術の費用や効果におよぼす影響を評価するのに十分に長

い分析期間を設けるため、分析期間は一生涯（死亡もしくは 100 歳のいずれか早いほう）とした。

2.6 割引率

分析ガイドラインに則り、費用および効果ともに年率 2%で現在価値に割引換算して計算した。

2.7 分析条件の設定の要約

本分析における分析条件の設定の要約を表 4 に示す。

表 4 分析条件の設定の要約

設定	項目
分析対象とする集団	重症化リスク因子を有する SARS-CoV-2 による感染症（COVID-19）患者（18 歳以上） 但し、有効性が確立していないため、重症度*の高い COVID-19 患者を除く。 *重症度の定義は新型コロナウイルス感染症（COVID-19）診療の手引き・第 8.1 版に準ずる。
比較対照	標準治療*（評価対象技術：モルヌピラビル＋標準治療） *COVID19 に対して治療の適応がある薬剤 中和抗体、その他の抗ウイルス薬等 を除く、対症療法
比較対照を選定した理由	2022 年 8 月の本剤評価品目選定時点では、臨床において抗ウイルス薬としてモルヌピラビルの他に、レムデシビルやニルマトレルビル/リトナビルが政府確保品目もしくは薬価収載後の一般流通品目として使用されている。レムデシビルは臨床専門家の意見聴取等から、入院外診療において幅広くは使用されておらず、主に入院外で用いる経口薬のモルヌピラビルによっては代替されない。一方で、ニルマトレルビル/リトナビルはモルヌピラビルと同様の経口薬であり、治療上の位置づけが類似している。したがって、本来のところニルマトレルビル/リトナビルが比較対照技術として適当と考えられるものの、ニルマトレルビル/リトナビルは薬価未収載で薬剤価格が不明なため、分析の実施が困難と考えられた。よって、その他に公的医療保険で使用が認められ代替されると想定されるものが存在しないことから、比較対照技術は標準治療（評価対象技術：モルヌピラビル＋標準治療）とすることが適当である。

分析の立場と費用の範囲	公的医療の立場 公的医療費のみ
効果指標	質調整生存年（QALY）
分析期間	生涯
割引率	費用･効果ともに年率 2%

3. 追加的有用性

3.1 クリニカルクエスチョン

対象集団における追加的有効性･安全性を検討するためのクリニカルクエスチョンを表 5 に示す。

表 5 システマティックレビューのクリニカルクエスチョン

項目	内容
対象集団	COVID-19 患者（外来のみ）
介入	以下の治療法のうちいずれかを含む • ラゲブリオ/モルヌピラビル • ロナプリーブ/カシリビマブ＋イムデビマブ • ゼビュディ/ソトロビマブ/VIR-7831 • ベクルリー/レムデシビル/GS-5734 • パキロビッド/ニルマトレルビル+リトナビル/PF-07321332 • Levovir/Revovir/clevudine/クレブジン • Arbidol/umifenovir/ウミフェノビル • Kineret/anakinra • Lenzilumab/レンジルマブ • Bebtelovimab/ベブテロビマブ • AT-527/RO7496998 • Tixagevimab + cilgavimab/(AZD7442 or AZD8895) and AZD1061 • Bamlanivimab/LY-CoV555/バムラニビマブ • Bamlanivimab + etesevimab/LY CoV555 + LY-CoV016/バムラニビマブ ＋ エテセビマブ • パルミコート/ブデソニド • フオイパン/カモスタットメシル酸塩 • コルヒチン • Regdanvimab/CT-P59 • アビガン/ファビピラビル • ヒドロコルチゾン • メチルプレドニゾロン • Nitazoxanide/ニタゾキサニド • ペグインターフェロンラムダ-1 • プレドニゾン • ADG20 • オルミエント/バリシチニブ • Ensovibep/MP0420 • ファモチジン • フルボキサミン • MP-0423 • ゾコーバ/エンシトレルビル/S-217622
比較対照	ラゲブリオ/モルヌピラビルを除く上述の治療

アウトカム	【有効性】 外来患者の治療経過に関連するアウトカム（以下を含むが、これに限定しない。） - 悪化までの期間 - 持続的回復までの期間 - COVID-19 の徴候及び症状の持続期間 - ウイルス学的治癒/ウイルスクリアランスを達成するまでの期間及び達成した患者の割合 - ウイルス量／ウイルス排出量 -（下記の測定方法による）症状の重症度及びフォローアップ時の疾患の進行度 〇Pulmonary or pulmonary+ score 〇National Early Warning Score 〇WHO 11-point outcomes score - フォローアップ時の臨床的改善度（WHO 臨床的改善度カテゴリースケール、または臨床/実験データ/CT スキャン/ウイルス消失率によるもの） - 全生存（人数/割合/率） - 全死因死亡（人数/割合/率） - COVID-19 関連死亡（人数/割合/率） - 入院（人数/割合/率） - 入院までの期間 - ICU または一般病棟に入院した患者（人数/割合/率） 【安全性】 - 治療に関連する有害事象 - グレード 3 および 4 の有害事象 - 重篤な有害事象 - 治療の中止（有害事象によるものなど）
研究デザイン	第 II 相または第 III 相の無作為化比較試験
検索対象期間	英語：2020/01/01～2022/12/06 日本語：2020/01/01～2022/12/06

3.2 システマティックレビュー

定義したクリニカルクエスチョンに基づき、システマティックレビューを実施した。詳細を下記に示す。

3.2.1 組み入れ基準と除外基準

以下に組み入れ基準と除外基準をまとめた。

表 6 臨床研究の組み入れ基準と除外基準

項目	組み入れ基準	除外基準
対象患者	COVID-19 患者*（外来のみ）**	COVID-19 患者（入院）** COVID-19 以外の患者

項目	組み入れ基準	除外基準
介入	以下の治療法のうちいずれかを含む • ラゲブリオ/モルヌピラビル • ロナプリーブ/カシリビマブ＋イムデビマブ • ゼビュディ/ソトロビマブ/VIR-7831 • ベクルリー/レムデシビル/GS-5734 • パキロビッド/ニルマトレルビル+リトナビル/PF-07321332 • Levovir/Revovir/clevudine/クレブジン • Arbidol/umifenovir/ウミフェノビル • Kineret/anakinra • Lenzilumab/レンジルマブ • Bebtelovimab/ベブテロビマブ • AT-527/RO7496998 • Tixagevimab + cilgavimab/(AZD7442 or AZD8895) and AZD1061 • Bamlanivimab/LY-CoV555/バムラニビマブ • Bamlanivimab + etesevimab/LY CoV555 + LY-CoV016/バムラニビマブ ＋ エテセビマブ • パルミコート/ブデソニド • フオイパン/カモスタットメシル酸塩 • コルヒチン • Regdanvimab/CT-P59 • アビガン/ファビピラビル • ヒドロコルチゾン • メチルプレドニゾロン • Nitazoxanide/ニタゾキサニド • ペグインターフェロンラムダ-1 • プレドニゾン • ADG20 • オルミエント/バリシチニブ • Ensovibep/MP0420 • ファモチジン • フルボキサミン • MP-0423 • ゾコーバ/エンシトレルビル/S-217622	• 組み入れ基準に記載されていない薬物的治療、および入院患者のみに使用される治療（以下を含む）。 ○ インターフェロンβ ○ クロロキン/ヒドロキシクロロキン ○ ロピナビル／リトナビル ○ アジスロマイシン • 以下のような非薬物的治療。 ○ 回復期患者血漿 ○ 漢方薬 ○ 植物性の生薬 • 予防が目的の介入
比較対照	ラゲブリオ/モルヌピラビル を除く上述の治療	介入で定義されていない治療
アウトカム ***	【有効性】 外来患者の治療経過に関連するアウトカム（以下を含むが、これに限定しない。） - 悪化までの期間 - 持続的回復までの期間	• 組み入れ基準に記載されていない臨床的な安全性または有効性のアウトカム • その他すべての非臨床試験結果

項目	組み入れ基準	除外基準
アウトカム *** （続き）	- COVID-19 の徴候及び症状の持続期間 - ウイルス学的治癒/ウイルスクリアランスを達成するまでの期間及び達成した患者の割合 - ウイルス量／ウイルス排出量 -（下記の測定方法による）症状の重症度及びフォローアップ時の疾患の進行度 〇Pulmonary or pulmonary+ score 〇National Early Warning Score 〇WHO 11-point outcomes score - フォローアップ時の臨床的改善度（WHO 臨床的改善度カテゴリースケール、または臨床/実験データ/CT スキャン/ウイルス消失率によるもの） - 全生存（人数/割合/率） - 全死因死亡（人数/割合/率） - COVID-19 関連死亡（人数/割合/率） - 入院（人数/割合/率） - 入院までの期間 - ICU または一般病棟に入院した患者（人数/割合/率） 【安全性】 - 治療に関連する有害事象 - グレード 3 および 4 の有害事象 - 重篤な有害事象 - 治療の中止（有害事象によるものなど）	
検索期間	2020 年 1 月から 2022 年 12 月まで****	2020 年 1 月より前に発表された論文
研究 デザイン	第 II 相または第 III 相の無作為化比較試験	• 無作為化試験でない試験 • 初期段階の試験（第 II 相または第 III 相試験以前） • 組み入れ患者が 20 名未満の試験*****
国・地域	制限なし	制限なし
言語	英語および日本語	左記以外の言語

*COVID-19 の確定例（PCR、診断コードなどによる）および疑い例（症状や X 線検査結果などによる）を含む。論文中で治験責任医師が「外来患者」「軽症 COVID-19 患者」（入院の記載なし）と表現した患者を含み、「入院患者」「重症／重篤 COVID-19 患者」（治験の基準に従って）と表現した患者は除外とした。検索に使用した検索式については、別添 1、別添 2、別添 3、別添 4 を参照。

**外来患者に対する有効性・安全性データが単独で提供されている場合は、入院患者及び外来患者を含む無作為化比較試験を含めることとした。外来患者については、試験中に入院した場合の解析が可能であるため、入院患者の転帰を含めることとした。

***文献から得られたアウトカムの統計的比較は本レビューの結果から行わず、記述的統計の比較のみとした。

****2022 年 5 月に実施した検索期間：2021 年 5 月～現在、新たな比較対象は 2020 年～現在（結果を網羅するため）
2022 年 12 月に実施した更新の検索期間：2022 年 5 月～現在（医中誌データベースでは 2020 年 1 月～現在）
また、重複を避けるため、オリジナルと更新の検索結果に対して、研究の重複を排除した。

***** 20 人以上の患者を含むランダム化比較試験（RCT）のサブグループ解析で 20 人未満の患者を評価した場合は対象とした。

3.2.2 使用したデータベース

上記で定義したクリニカルクエスチョンに基づき、以下のデータベースを用いて検索を行った。検索式は別添 1、別添 2、別添 3、別添 4 に記載した。

論文については下記のデータベースでの検索を実施した。

- Medical Literature Analysis and Retrieval System Online (MEDLINE)
- Excerpta Medica Database (EMBASE)
- 医中誌 web

上述の論文検索を補完するために、下記のデータベースにおいても同様に検索を実施した。

- “Living” network meta-analyses (NMAs) published by academic and government bodies:
  - The BMJ-MAGIC-WHO26 (as of 14th June 2022)
  - Cochrane-WHO27 (as of 14th June 2022)
- Guidelines on treatment of COVID-19 published by academic and government bodies:
  - The BMJ28 (as of 14th June 2022)
  - US Infectious Diseases Society of America (IDSA)29 (as of 14th June 2022)
  - US National Institutes of Health (NIH)30 (as of 14th June 2022)
- Conference proceedings:
  - American Thoracic Society (ATS) International Conference 2021, 2022
  - Conference on Retroviruses and Opportunistic Infections (CROI) 2020, 2021, and 2022
  - European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 2020, 2021, and 2022
  - Infectious Disease (ID) Week (IDSA) 2020, 2021 and 2022
- Clinical trial registries:
  - clinicaltrials.gov (as of 28th December 2022)
  - WHO International Clinical Trials Registry Platform (ICTRP) (as of 14th June 2022)
- Pre-print database:
  - NIH PubMed Central (PMC) preprints (as of 14th June 2022)

- Japanese websites:
  - KAKEN database (as of 16th December 2022)

- The Japanese Association for Infectious Diseases (日本感染症学会) (as of 16th December 2022)
- National Institute of Infectious Diseases (国立感染症研究所) (as of 16th December 2022)
- The Japanese Respiratory Society (日本呼吸器学会) (as of 16th December 2022)

3.2.3 システマティックレビューの実施

上述のクリニカルクエスチョンに従って、アブストラクトレビューおよびフルテキストレビュー、データ抽出、バイアスリスクの評価の順に実施した。すべての論文について、「3.1 クリニカルクエスチョン」で定義した基準に従って、2 名が独立してレビューを行い、Preferred Reporting Items for Systematic Reviews and Meta-Analyses（PRISMA）のフローチャートを用いて結果を示した。初回のシステマティックレビューを 2021 年 5 月に実施し（SLR 1）、以後 2022 年 12 月までの間に 3 回更新した（SLR 2: 2021 年 9 月、SLR 3: 2022 年 5 月、SLR 4: 2022 年 12 月）。SLR4 の実施時点は分析ガイドライン[9]に基づき決定した。

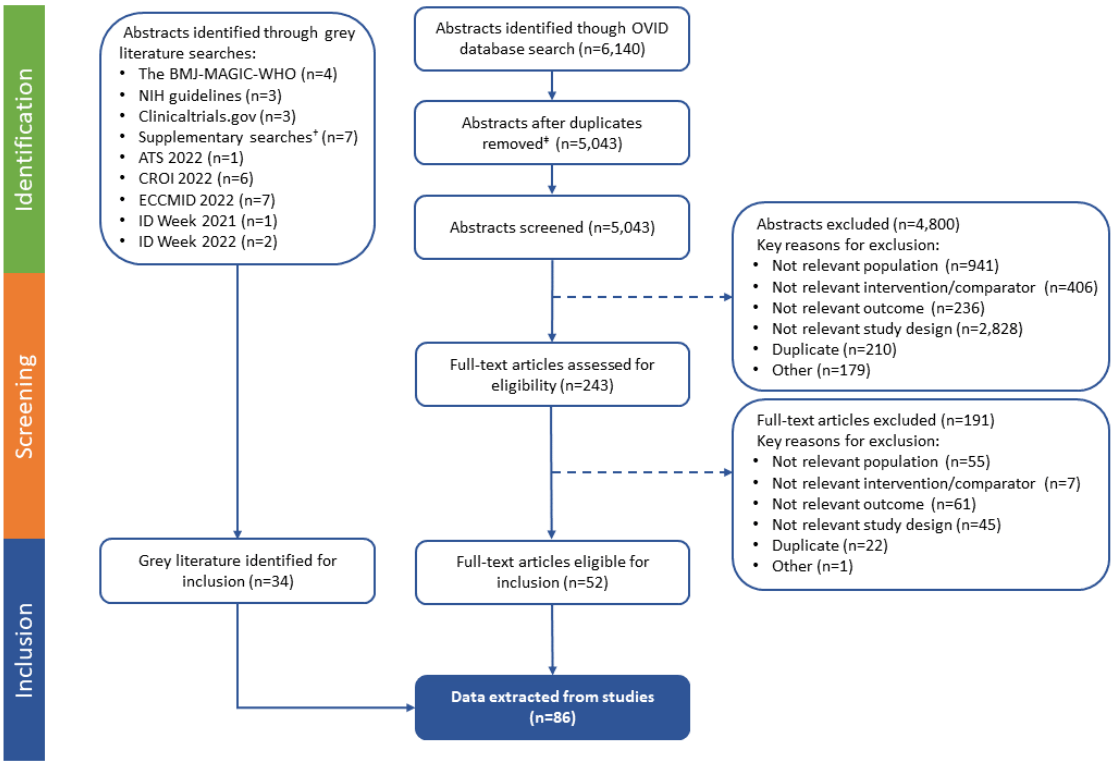
表 7 検索データベースおよび検索期間

	使用データベース	実施時期	検索対象期間
SLR 1	MEDLINE, EMBASE	2021 年 5 月	2020 年 1 月～2021 年 5 月
SLR 2	MEDLINE, EMBASE	2021 年 9 月	2020 年 1 月～2021 年 9 月
SLR 3	MEDLINE, EMBASE	2022 年 5 月	2021 年 5 月～2022 年 5 月
SLR 4	MEDLINE, EMBASE	2022 年 12 月	2022 年 5 月～2022 年 12 月
	医中誌 web	2022 年 12 月	2020 年 1 月～2022 年 12 月

3.2.4 検索結果

データベース及びその他の情報を含めて合計 6,174 件が検出され、スクリーニングの結果、86 件が同定された。図 6 に PRISMA フロー図を用いてプロセスと結果を示す。

図 6　PRISMA フロー図



*2021 年 9 月以前にイベルメクチンに関する試験報告 1 件を同定し、データを抽出した[10]。しかし、COVID-19 におけるイベルメクチンの定期的な使用は現在 WHO[11]、欧州医薬品庁[12]、米国国立衛生研究所[13]および食品医薬品局[14]によって推奨されておらず、イベルメクチン使用を裏付ける主要試験データは撤回されているため[15]、Mahmud らの試験のデータ[10]は、本報告書には含まれていない。
†補足検索として、PubMed および medRxiv のターゲット検索を行った。
‡抄録は各検索で重複を排除し、過去の検索結果（初回、1 回目の更新、2 回目の更新）と比較した。

論文およびその他の検索より、86 件（60 試験）の文献が同定された（表 8 参照、詳細は別添 5）が、その中で本剤と他剤を直接比較している臨床試験が同定されなかったこと、比較対照技術が標準治療であることから、自社試験「MOVe-OUT」のデータ（表 9 に詳細を記載）を用いて追加的有用性を検討した（3.8 追加的有用性の有無に関する評価に記載）。

表 8 同定した臨床研究(論文)の一覧表

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Antiviral therapies					
Adhikari *et al.* 2021[16]	OVID	Efficacy of Favipiravir in treatment of mild & moderate COVID-19 infection in Nepal: a multicenter, randomized, open-labelled, phase III clinical trial	Conference abstract	Adhikari *et al*. 2021 favipiravir	3
Bernal *et al.* 2022[17]	OVID	Molnupiravir for oral treatment of COVID-19 in non-hospitalized patients	Journal article	MOVe-OUT NCT04575597	3
Strizki *et al.* 2022[18]	ECCMID 2022	Virologic outcomes from MOVe-OUT, a randomized, controlled phase III trial evaluating molnupiravir for treatment of COVID-19 in non-hospitalized adults	Conference abstract		
Guan *et al.* 2022[19]	ECCMID 2022	Impact of molnupiravir treatment on patient-reported COVID-19 symptoms in the MOVe-OUT study	Conference poster		
Johnson *et al.* 2022a[20]	ECCMID 2022	Molnupiravir for treatment of COVID-19 in immunocompromised patients: efficacy, safety, and virology results from the phase III MOVe-OUT trial	Conference poster		
Johnson *et al.* 2022b[21]	OVID	Effect of Molnupiravir on Biomarkers, Respiratory Interventions, and Medical Services in COVID-19: A Randomized, Placebo-Controlled Trial	Journal article		

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Bosaeed *et al.* 2022[22]	OVID	Efficacy of favipiravir in adults with mild COVID-19: a randomized, double-blind, multicenter, placebo-controlled clinical trial	Journal article	Bosaeed *et al.* 2022 favipiravir	NR
Hammond *et al.* 2022[23]	OVID	Oral nirmatrelvir for high-Risk, non-hospitalized adults with COVID-19	Journal article	EPIC-HR NCT04960202	2/3
EPIC-SR 2022[24]	Pfizer	Pfizer Announces Additional Phase 2/3 Study Results Confirming Robust Efficacy of Novel COVID-19 Oral Antiviral Treatment Candidate in Reducing Risk of Hospitalization or Death	Press release	EPIC-SR NCT05011513	2/3
Holubar *et al.* 2022[25]	OVID	Favipiravir for treatment of outpatients with asymptomatic or uncomplicated COVID-19: a double-blind randomized, placebo-controlled, phase 2 trial	Journal article	Holubar *et al.* 2022 favipiravir NCT04346628	2
Gottlieb *et al.* 2022[26]	OVID	Early remdesivir to prevent progression to severe COVID-19 in outpatients	Journal article	PINETREE NCT04501952	3
Webb *et al.* 2022[27]	CROI 2022	Safety of remdesivir vs placebo in non-hospitalized patients with Covid-19	Conference abstract		

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Paredes *et al.* 2022[28]	ECCMID 2022	Outpatient remdesivir prevents COVID-19 progression in high-risk patients when randomized within seven days from symptom onset: sub-analyses from a phase III trial	Conference poster		
Kumarasamy *et al.* 2022[29]	CROI 2022	PHASE III trial of molnupiravir in adults with mild SARS-CoV-2 Infection in India	Conference abstract	Kumarasamy *et al*. 2022 molnupiravir	3
Painter *et al.* 2021[30]	OVID	Reduction in infectious SARS-CoV-2 in treatment study of COVID-19 with molnupiravir	Conference abstract	Painter *et al.* 2021 molnupiravir	2
Fischer *et al.* 2021[31]	clinicaltrials.gov	Molnupiravir, an Oral Antiviral Treatment for COVID-19 (pre-print)	Journal article (pre-print)	Fischer *et al.* 2021 molnupiravir [later portion of trial] NCT04405570	2a
Fischer *et al.* 2022[32]	OVID	A phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus (Published)	Journal article (published)		
Lowe *et al.* 2022a[33]	medRxiv	Favipiravir, lopinavir-ritonavir or combination therapy (FLARE): a randomized, double-blind, 2x2 factorial placebo-controlled trial of early antiviral therapy in COVID-19	Journal article (pre-print)	FLARE NCT04499677	2

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Lowe *et al.* 2022b[34]	OVID	Favipiravir, lopinavir-ritonavir or combination therapy (FLARE): a randomized, double blind, 2x2 factorial placebo-controlled trial of early antiviral therapy in COVID-19	Journal article		
MOONSONG 2021 *[author NR]*[35]	Atea Pharmaceuticals	Atea Pharmaceuticals Provides Update and Topline Results for Phase 2 MOONSONG Trial Evaluating AT-527 in the Outpatient Setting	Press release	MOONSONG	2
Ramachandran *et al.* 2022[36]	Clinical Trial Registry of India (CTRI)	Phase III, Randomized, Double-blind, Placebo-controlled trial of Efficacy, Safety and Tolerability of Antiviral drug Umifenovir vs Standard care of therapy in non-severe COVID-19 patients	Journal article	Ramachandran *et al.* 2022 umifenovir CTRI/2020/09/027535	3
Ruzhentsova *et al.* 20201, 2[37]	*The BMJ*-MAGIC-WHO	Phase 3 Trial of Coronavir (Favipiravir) in patients with mild to moderate COVID-19	Journal article (pre-print1 and publishe d2)	Ruzhentsova *et al.* 2021 favipiravir NCT04501783	3
Yotsuyanagi *et al.* 2022[38]	ECCMID 2022	Results from Ph1 and Ph2a studies of S-217622 a novel 3C-like protease inhibitor as once daily oral treatment for SARS-CoV-2 infection	Conferen ce abstract	Yotsuyanagi *et al.* 2022 S-217622	2a

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Zhao *et al.* 2021[39]	OVID	Favipiravir in the treatment of patients with SARS-CoV-2 RNA recurrent positive after discharge: A multicenter, open-label, randomized trial	Journal article	Zhao *et al*. 2021 favipiravir NCT04333589	NR
Khoo *et al.* 2022[40]	OVID	Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomized, placebo-controlled, double-blind, phase 2 trial	Journal article	AGILE CST-2 NCT04746183	2
Golan *et al.* 2022[41]	OVID	Favipiravir in patients with early mild-to-moderate COVID-19: a randomized controlled trial	Journal article	PRESECO NCT04600895	3
Zhao *et al.* 2022[42]	OVID	A trial of arbidol hydrochloride in adults with COVID-19	Journal article	Zhao *et al.* 2022 arbidol hydrochloride NCT04260594	4
McMahon *et al.* 2022[43]	OVID	Favipiravir in early symptomatic COVID-19, a randomized placebo-controlled trial	Journal article	VIRCO NCT04445467	2
Sirijatuphat *et al.* 2022[44]	OVID	Early treatment of Favipiravir in COVID-19 patients without pneumonia: a multicenter, open-labelled, randomized control study	Journal article	Sirijatuphat *et al.* 2022 favipiravir TCTR20200514001	NR

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Zou *et al.* 2022[45]	OVID	Antiviral Efficacy and Safety of Molnupiravir Against Omicron Variant Infection: A Randomized Controlled Clinical Trial	Journal article	Zou *et al.* 2022 molnupiravir ChiCTR2200056817	NR
Neutralizing antibodies (See section 3.2.21.1.1)					
Weinreich *et al.* 2020[46]	*The BMJ*-MAGIC-WHO	REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with COVID-19	Journal article	REGEN-COV NCT04425629	2
Weinreich *et al.* 2021a[47]	Identified by researchers, outside of the searches specified in section 2	REGEN-COV Antibody Cocktail Clinical Outcomes Study in COVID-19 Outpatients	Journal article (pre-print)		3
Weinreich *et al.* 2021a[47]	Identified by researchers, outside of the searches specified in section 2	REGEN-COV Antibody Cocktail Clinical Outcomes Study in COVID-19 Outpatients	Journal article (published)		
Weinreich *et al.* 2021b[48]	OVID	REGEN-COV Antibody Combination and Outcomes in Outpatients with COVID-19	Journal article (published)		
Gupta *et al.* 2021[49]	NIH guidelines	Early COVID-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab	Journal article (pre-print)	COMET-ICE NCT04545060	3

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Gupta *et al.* 2022a[50]	OVID	Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients with Mild to Moderate COVID-19	Journal article (published)		
Gupta *et al.* 2022b[51]	CROI 2022	Effect of serostatus on the efficacy of sotrovimab in preventing Covid-19 progression	Conference abstract		
Shapiro *et al.* 2022[52]	CROI 2022	Intramuscular sotrovimab is noninferior to intravenous sotrovimab for COVID-19	Conference abstract	COMET-TAIL NCT04913675	3
Gupta *et al.* 2022c[53]	December ID Week 2022	Safety, Tolerability, and Viral Pharmacodynamics of the IgG Monoclonal Antibody Sotrovimab Administered via Intramuscular Injection for the Treatment of Early Mild-to-Moderate COVID-19	Conference abstract	COMET-PEAK (Parts B and C) NCT04779879	2
Chen *et al.* 2020[54]	OVID	SARS-CoV-2 Neutralizing Antibody LY-CoV555 in outpatients with COVID-19	Journal article	BLAZE-1 NCT04427501	2
Gottlieb *et al.* 2021[55]	OVID	Effect of Bamlanivimab as Monotherapy or in Combination with Etesevimab on Viral Load in Patients with Mild to Moderate COVID-19: a Randomized Clinical Trial	Journal article		

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Dougan *et al.* 2021a[56]	OVID	Bamlanivimab + etesevimab for treatment of COVID-19 in high-risk ambulatory patients	Conference abstract		3
Dougan *et al.* 2021b[57]	OVID	Bamlanivimab plus Etesevimab in Mild or Moderate COVID-19	Journal article		
Upadhyaya *et al.* 2022[58]	CROI 2022	Bamlanivimab plus etesevimab for the treatment of Covid-19 in pediatric patients	Conference presentation		
Dougan *et al.* 2022[59]	OVID	A Randomized, Placebo-Controlled Clinical Trial of Bamlanivimab and Etesevimab Together in High-Risk Ambulatory Patients With COVID-19 and Validation of the Prognostic Value of Persistently High Viral Load	Journal article		
Chen *et al.* 2022[60]	Clinicaltrials.gov	Bamlanivimab and Etesevimab Improve Symptoms and Associated Outcomes in Ambulatory Patients at Increased Risk for Severe Coronavirus Disease 2019: Results from the Placebo-Controlled Double-Blind Phase 3 BLAZE-1 Trial	Journal article		2/3 (Results from phase 3)

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Williams *et al.* 2022[61]	ATS 2021-2022	Bebtelovimab, Alone and Together with Bamlanivimab and Etesevimab, as a Broadly Neutralizing Monoclonal Antibody Treatment and a Slow Intravenous Push Option for Ambulatory COVID-19	Conference abstract	BLAZE-4 NCT4634409	2
Davis *et al.* 2022[62]	OVID	Pharmacokinetics and pharmacodynamics of casirivimab and imdevimab in a dose-ranging study in outpatients with COVID-19	Conference abstract	Davis *et al*. 2022 casirivimab/imdevimab NCT04666441	2
Huang *et al.* 2021[63]	OVID	Effectiveness of casirivimab and imdevimab, and sotrovimab during Delta variant surge: a prospective cohort study and comparative effectiveness randomized trial	Journal article (pre-print)	UPMC Quality Improvement Review Committee Project ID 3282. University of Pittsburgh Institutional Review Board STUDY21022017 9 NCT04790786	4*
Chew *et al.* 2021[64]	OVID	Bamlanivimab reduces nasopharyngeal SARS-CoV-2 RNA levels but not symptom duration in non-hospitalized adults with COVID-19	Journal article (pre-print)	ACTIV-2/A5401 NCT04518410	2
Chew *et al.* 2022[65]	OVID	Antiviral and clinical activity of bamlanivimab in a randomized trial of non-hospitalized adults with COVID-19	Journal article		

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Boucau *et al.* 2022[66]	OVID	Monoclonal antibody treatment drives rapid culture conversion in SARS-CoV-2 infection	Journal article		2/3
Kumarasamy *et al.* 2022[67]	CROI 2022	Interim results from the randomized, controlled EMPATHY phase II/III study evaluating of casirivimab and imdevimab, a DARP in therapeutic, in patients with mild to moderate COVID-19	Conference abstract	EMPATHY NCT04828161	2/3
Streinu-Cercel *et al.* 2022[68]	OVID	Efficacy and Safety of Regdanvimab (CT-P59): A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial in Outpatients with Mild to Moderate Coronavirus Disease 2019	Journal article	CT-P59 NCT04602000	2/3 (Results from phase 2)
Montgomery *et al.* 2022a[69]	ECCMID 2022	Efficacy and safety of intramuscular administration of AZD7442 (tixagevimab/cilgavimab) for early outpatient treatment of COVID-19: the TACKLE phase III trial	Conference abstract	TACKLE NCT04723394	3
Montgomery *et al.* 2022b[70]	Clinicaltrials.gov	Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomized, double-blind, placebo-controlled trial	Journal article		

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Hobbs *et al.* 2022[71]	December ID Week 2022	Outpatient Treatment With the SARS-CoV-2–Neutralizing Antibody Combination AZD7442 (Tixagevimab/Cilgavimab) for Preventing COVID-19 Hospitalizations in the Phase 3 TACKLE Trial	Conference abstract		
STAMP 2022[72]	Adagio Therapeutics 2022	Adagio Therapeutics Announces ADG20 (adintrevimab) is the First Monoclonal Antibody to Meet Primary Endpoints with Statistical Significance Across Pre- and Post-exposure Prophylaxis and Treatment for COVID-19 and Plans to Seek US Emergency Use Authorization	Press release	STAMP	2/3
O'Brien *et al.* 2022[73]	OVID	Effect of Subcutaneous Casirivimab and Imdevimab Antibody Combination vs Placebo on Development of Symptomatic COVID-19 in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Clinical Trial	Journal article	O'Brien *et al.* 2022 casirivimab/imdevimab NCT04452318	3
Mazzaferri *et al.* 2022[74]	OVID	Exploratory data on the clinical efficacy of monoclonal antibodies against SARS-CoV-2 Omicron variant of concern	Journal article	MANTICO NCT05205759	3

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Portal-Celhay *et al.* 2022[75]	OVID	Virologic Efficacy of Casirivimab and Imdevimab COVID-19 Antibody Combination in Outpatients With SARS-CoV-2 Infection A Phase 2 Dose-Ranging Randomized Clinical Trial	Journal article	Portal-Celhay *et al.* 2022 casirivimab/imdevimab NCT04666441	2
Kim *et al.* 2022[76]	OVID	A Randomized Clinical Trial of Regdanvimab in High-Risk Patients with Mild-to-Moderate Coronavirus Disease 2019	Journal article	Kim *et al.* 2022 regdanvimab NCT04602000	3
Schilling *et al.* 2022[77]	OVID	Pharmacometric assessment of the in vivo antiviral activity of ivermectin in early symptomatic COVID-19	Journal article (pre-print)	PLATCOV NCT05041907	2
Interferon (See section 3.2.3)					
Feld *et al.* 2021[78]	*The BMJ*-MAGIC-WHO	Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomized trial	Journal article	Feld *et al*. 2021 peginterferon Lambda NCT04354259	2
Jagannathan *et al.* 2021[79]	*The BMJ*-MAGIC-WHO	Peginterferon Lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial	Journal article	Jagannathan *et al.* 2021 peginterferon Lambda-1a NCT04331899	2

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
H2 antagonist (See section 3.2.4)					
Brennan *et al.* 2022[80]	OVID	Oral famotidine versus placebo in non-hospitalized patients with COVID-19: a randomized, double-blind, data-intense, phase 2 clinical trial	Journal article	Brennan *et al.* 2022 famotidine NCT04724720	2
Steroid (See section 3.2.5)					
Ramakrishnan *et al.* 2021[81]	OVID	Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomized controlled trial	Journal article	STOIC NCT04416399	2
Yu *et al.* 2021a[82]	NIH guidelines	Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial	Journal article (pre-print)	PRINCIPLE ISRCTN86534580	NR
Yu *et al.* 2021b[83]	OVID	Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomized, controlled, open-label, adaptive platform trial	Journal article (published)		
Selective serotonin reuptake inhibitor (See section 3.2.6)					
Lenze *et al.* 2020[84]	OVID	Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients with Symptomatic COVID-19	Journal article	STOP COVID NCT04342663	2

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Seo *et al.* 2022[85]	OVID	Fluvoxamine Treatment of Patients with Symptomatic COVID-19 in a Community Treatment Center: A Preliminary Result of Randomized Controlled Trial	Journal article	Seo *et al.* 2022 fluvoxamine NCT04711863	2
Reis *et al.* 2022 3, 4[86],[87]	OVID	Effect of early treatment with fluvoxamine on risk of emergency care and hospitalization among patients with COVID-19: the TOGETHER randomized, platform clinical trial	Journal article	TOGETHER NCT04727424	3
Bramante *et al.* 2022[88]	OVID	Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19	Journal article	COVID-OUT NCT04510194	3
McCarthy *et al.* 2022[89]	OVID	Fluvoxamine for Outpatient Treatment of COVID-19: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial	Journal article (pre-print)	ACTIV-6 NCT04885530	3
Serine protease inhibitors (See section 3.2.7)					
Chupp *et al.* 2022[90]	OVID	A Phase 2 Randomized, Double-Blind, Placebo-controlled Trial of Oral Camostat Mesylate for Early Treatment of COVID-19 Outpatients Showed Shorter Illness Course and Attenuation of Loss of Smell and Taste	Journal article	Chupp *et al.* 2022 camostat mesylate NCT04724720	2

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Jilg *et al.* 2022a[91]	CROI 2022	A randomized controlled trial of camostat in outpatients with COVID-19	Conference abstract	CAMELOT NCT04583592	2
Jilg *et al.* 2022b[92]	CROI 2022	Camostat is not effective for mild-moderate COVID-19 in a phase 2 Trial of ACTIV-2	Conference abstract	ACTIV-2/A5401 NCT04518410	2
Tobback *et al.* 2022[93]	OVID	Efficacy and safety of camostat mesylate in early COVID-19 disease in an ambulatory setting: a randomized placebo-controlled phase II trial	Journal article	Tobback *et al.* 2022 camostat mesylate NCT04625114	2
Anti-inflammatory (See section 3.2.8)					
Dorward *et al.* 2022[94]	OVID	Colchicine for COVID-19 in the community (PRINCIPLE): a randomized, controlled, adaptive platform trial	Journal article	PRINCIPLE ISRCTN86534580 [trial does not appear on clinicaltrials.gov]	NR
Tardif *et al.* 2021[95]	OVID	Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomized, double-blinded, adaptive, placebo-controlled, multicenter trial	Journal article	COLCORONA NCT04322682	3
Audemard-Verger *et al.* 2022[96]	OVID	Efficacy and safety of anakinra in adults presenting deteriorating respiratory symptoms from COVID-19: A randomized controlled trial	Journal article	ANACONDA NCT04364009	3

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Antiparasitic (See section 3.2.9)					
Rocco *et al.* 2021[97]	OVID	Early use of nitazoxanide in mild COVID-19 disease: randomized, placebo-controlled trial	Journal article	Rocco *et al.* 2021 nitazoxanide NCT04552483	2
Rossignol *et al.* 2021[98]	clinicaltrials.gov	Early treatment with nitazoxanide prevents worsening of mild and moderate COVID-19 and subsequent hospitalization	Journal article (pre-print)	Rossignol *et al.* 2021 nitazoxanide NCT04486313 Rossignol *et al.* 2022 nitazoxanide NCT04486313	3
Rossignol *et al.* 2022[99]	OVID	A randomized double-blind placebo-controlled clinical trial of nitazoxanide for treatment of mild or moderate COVID-19	Journal article (published)		
Mehdat *et al.* 2022[100]	OVID	Sofosbuvir/ledipasvir in combination or nitazoxanide alone are safe and efficient treatments for COVID-19 infection: A randomized controlled trial for repurposing antivirals	Journal article	Mehdat *et al.* 2022 nitazoxanide and sofobuvir/ledipasvir NCT04498936	4

*Please note that this is described as a phase 4 (post-marketing) trial; however, patients were randomized to treatment, rather than assigned according to physician's discretion.
BMJ: British Medical Journal; CROI: Conference on Retroviruses and Opportunistic Infections; CTRI: Clinical Trial Registry of India; ECCMID: European Congress of Clinical Microbiology and Infectious Diseases; MAGIC: Mutant-Assisted Gene Identification and Characterization; NIH: National Institutes of Health; NR: not reported; RCT: randomized controlled trial; RNA: ribonucleic acid; UPMC: University of Pittsburgh Medical Center; WHO: World Health Organization.

表 9　MOVe-OUT 試験（第Ⅲ相パート）の詳細表 [17]

項目	内容
試験を実施した場所	日本、米国等 20 カ国
参加者の組入れ期間	2021 年 5 月から 10 月
対象集団	18 歳以上の非入院 COVID-19 患者
主な選択基準	1. SARS-CoV-2 陽性（無作為化前 5 日以内に採取された検体を用いた PCR 検査等により確認） 2. SARS-CoV-2 による感染症の症状 [a)] 発現が無作為化前 5 日以内であり、かつ無作為化時点において SARS-CoV-2 による感染症に関連する症状 [b)] が 1 つ以上認められる 3. 以下の定義における、軽症患者又は中等症患者 SARS-CoV-2 による感染症の重症度の判断に用いられた定義は以下のとおり。 【軽症】①及び②を満たす ①次のすべてが認められる 呼吸数が 20 回/分未満、心拍数が 90 回/分未満、SpO_2 が 93%超 [c)] ②次のいずれも認められない 安静時又は労作時の息切れ、呼吸不全 [d)]、ショック状態 [e)]、多臓器機能不全 [f)] 【中等症】①～③をすべて満たす ①　次のうち、1 つ以上が認められる 労作時の息切れ、呼吸数が 20 回/分以上 30 回/分未満、心拍数が 90 回/分以上 125 回/分未満 4. 次の SARS-CoV-2 による感染症の重症化リスク因子を少なくとも一つ有する ・ 61 歳以上 ・ 活動性のがん［免疫抑制や高い死亡率を伴わないがん（例：基底細胞がん）は除く］ ・ 慢性腎臓病 ・ 慢性閉塞性肺疾患 ・ 肥満（BMI 30 kg/m^2 以上） ・ 重篤な心疾患（心不全、冠動脈疾患又は心筋症） ・ 糖尿病

項目	内容
主な選択基準（続き）	5. 治験薬投与終了後少なくとも 4 日間避妊が可能な男性又は妊娠しておらず治験薬投与終了後少なくとも 4 日間避妊が可能な女性 a）具体的な症状の規定なし b）咳、咽頭痛、鼻閉、鼻水、労作時の息切れ又は呼吸困難、筋肉又は体の痛み、疲労、発熱（38.0℃ 超）、悪寒、頭痛、悪心、嘔吐、下痢、嗅覚消失、味覚消失 c）室内気又は SARS-CoV-2 による感染症以外の理由で酸素投与されており SARS-CoV-2 による感染症の症状発現以降に酸素量が増量されていない状態における数値 d）＜呼吸不全＞次の①～④を 1 つ以上要する場合：①気管内挿管及び人工呼吸器、②鼻カニューレを用いた高流量酸素療法（流量 20 L/min 超、酸素割合 0.5 以上）、③非侵襲的陽圧換気、④ECMO e）＜ショック状態＞昇圧剤を要する場合と定義 f）＜多臓器不全＞呼吸器、循環器、腎臓、血液、肝臓又は中枢神経系の 1 つ以上に不全又は障害が認められる急性期の患者と治験担当医師が判断した場合と定義
主な除外基準	1. 入院中又は無作為化後 48 時間以内に SARS-CoV-2 による感染症のために入院が必要となることが想定される患者 2. 透析中又は eGFR が 30 mL/min/1.73 m^2 未満 3. 直近の HIV RNA 量が 50 copies/mL 超又は過去 6 カ月において HIV の指標疾患が認められた患者 4. 好中球数 500/mm^3 未満の患者 5. HBV 又は HCV の既往を有し、肝硬変、末期肝疾患、肝細胞がん又はスクリーニング時の AST 若しくは ALT が基準値上限の 3 倍超の患者 6. 血小板数が 100,000/μL 未満又は無作為化前 5 日以内に血小板輸血を受けた患者 7. SARS-CoV-2 による感染症に対するワクチンの接種歴を有する患者 8. 本試験への組入れ理由となった今回の SARS-CoV-2 感染に対するモノクローナル抗体による治療歴を有する患者
介入方法の詳細	標準治療に加えて1回800mgを1日2回、5日間経口投与する
比較対照の詳細	プラセボ＋標準治療
試験デザイン	ランダム化比較試験
盲検化法	二重盲検法
主要評価項目	• 有効性：無作為化 29 日目までの理由を問わないすべての入院又は死亡 • 安全性：有害事象、投与中止に至った有害事象

項目	内容
主な副次評価項目	• 無作為化 29 日目までにおける特定の COVID-19 の徴候/症状（患者報告）の持続的な回復又は改善[注 1)]までの期間及び悪化[注 2)]までの期間 • 各時点における WHO11-point ordinal scale の改善のオッズ [注 1)]無作為割付け時点で症状の報告がなかった被験者は除外 [注 2)]無作為割付け時点で症状を「重度」と報告した被験者は除外
統計解析手法	• 有効性：主要評価項目である無作為化 29 日目までに入院又は死亡した被験者の割合の差（モルヌピラビル群－プラセボ群）は、SARS-CoV-2 による感染症の症状発現から無作為割付け日までの期間（3 日間以下／3 日間超）を層別因子とした層別 Miettinen and Nurminen 法により算出された調整済みリスク差及び 95%信頼区間を用いて、Cochran–Mantel–Haenszel 重み付けにより解析した。重要な副次評価項目である無作為化 29 日目までにおける特定の COVID-19 の徴候や症状（患者報告）の持続的な回復又は改善までの期間及び悪化までの期間については、モルヌピラビル群とプラセボ群の比較には層別ログランク検定を用い、ハザード比の推定には Cox 比例ハザードモデルを用いた。WHO 11-point ordinal scale スコアについては、累積ロジット関数と比例オッズモデルを用いた McCullagh の方法を用いて、群間差を評価するための共通のオッズ比を推定した。投与群に加え、層別因子もモデルに加える。WHO11-point ordinal scale は eCRF で収集した関連データに基づいて決定される。 • 安全性：群間の有害事象の割合の差について、Tier1（注目すべき事象）については P 値および 95%信頼区間、Tier2（有害事象）については 95%信頼区間を層で調整しない Miettinen and Nurminen の方法を用いて算出する。
サンプルサイズ	モルヌピラビル群：n=716、プラセボ群：n =717
フォローアップ期間	7 か月
対象者の主な背景要因	年齢：平均 43.0 歳 性別：男性 48.7%

項目	内容
主要評価項目の結果	【有効性】事前に計画された中間解析* • 無作為化 29 日目までに入院又は死亡した割合は、モルヌピラビル群 7.3%（385 例中 28 例、死亡例なし）、プラセボ群 14.1%（377 例中 53 例、うち死亡 8 例）であり、群間差は-6.8（95%信頼区間: -11.3, -2.4）、p=0.001 であった。 なお、無作為化された全例を対象とした補足的な解析で、29 日目までに入院又は死亡した被験者の割合は、モルヌピラビル群が 6.8%（709 例中 48 例）、プラセボ群が 9.7%（699 例中 68 例）でモルヌピラビル群がプラセボ群より低かった（群間差-3.0、95%信頼区間：-5.9～-0.1）。29 日目までの死亡例は、モルヌピラビル群で 1 例、プラセボ群で 9 例であった。 【安全性】全例における解析 • 本剤群の 710 例及びプラセボ群の 701 例が少なくとも 1 回の治験薬を投与され、解析対象集団に含まれた。 • 有害事象が発現した被験者の割合は、モルヌピラビル群 30.4%（710 例中 216 例）、プラセボ群 33.0%（701 例中 231 例）で両群で同程度であった。 • 有害事象による投与中止は、モルヌピラビル群 1.4%（710 例中 10 例）、プラセボ群 2.9%（701 例中 20 例）であった。 • 死亡例はモルヌピラビル群で 2 例、プラセボ群で 12 例に認められたが、いずれの事象も治験薬との因果関係は否定された。 *中間解析において早期の有効性の基準を満たしたことから、外部データモニタリング委員会により本剤の有効性が示されたとの勧告がなされ、2021 年 10 月 2 日以降の新規組入れは中止された。第Ⅲ相パート（パート 2）の予定組入れ被験者数の合計は約 1550 例であったが、早期終了となったため、第Ⅲ相パートの全体集団には、1433 例[中間解析時点の 775 例及び中間解析後に組み入れられた追加の 658 例]が含まれた。 事前に計画された中間解析において早期有効中止となったことから、本試験の成功の可否を判定する上での主たる結果は中間解析の主要評価項目の結果となる。

項目	内容
主な副次評価項目の結果	• COVID-19 の徴候及び症状（患者報告）のほとんどで、持続的な回復又は改善の可能性はプラセボの投与を受けた被験者よりもモルヌピラビル投与を受けた被験者で高かった。また、COVID-19 の徴候及び症状（患者報告）のほとんどで、進行（悪化）の可能性は、プラセボの投与を受けた被験者よりもモルヌピラビル投与を受けた被験者で低かった。 • WHO 11-point ordinal scale による不良な転帰を示す被験者の割合は、プラセボ群よりもモルヌピラビル群で低く、Day 10 及び Day 15 時の差が最も大きかった。WHO 11-point ordinal scale をカテゴリー別［0（感染していない）、1～3（歩行可能、軽
主な副次評価項目の結果（続き）	症）、4～5（入院、中等症）、6～9（入院、重症）、10（死亡）］に分類すると、Day 10 の転帰改善のオッズは、プラセボ群と比較してモルヌピラビル群で 1.58 倍高かった。
試験の限界	• COVID-19 のワクチンを接種していない被検者のみ含まれている。 • 入院の習慣や病院のキャパシティが国によって異なるため、入院に関するアウトカムに影響を与えた可能性がある。

3.3 クリニカルクエスチョン(異なる比較対照あるいは単群試験) [該当する場合のみ]

該当なし

3.4 システマティックレビュー (異なる比較対照あるいは単群試験) [該当する場合のみ]

該当なし

3.5 既存データの再解析

該当なし

3.6 メタアナリシスの詳細 [該当する場合のみ]

該当なし

3.7 間接比較やネットワークメタアナリシスの結果 [該当する場合のみ]

該当なし

3.8 追加的有用性の有無に関する評価

3.2 システマティックレビューで示した通り、本剤と他剤を直接比較している臨床試験は同定されず、プラセボ（標準治療）を対照としたランダム化比較試験（RCT）である MOVe-OUT 試験が追加的有用性の根拠として適切と考えられた。MOVe-OUT 試験第Ⅲ相パートの主要な解析である中間解析で、主要評価項目である無作為化 29 日目までの理由を問わないすべての入院又は死亡した被験者の割合において、モルヌピラビル群で 7.3%（385 例中 28 例）及びプラセボ群で 14.1%（377 例中 53 例）、割合の群間差は-6.8%（95%信頼区間：-11.3, -2.4）であり、プラセボ群に対するモルヌピラビル群の優越性が検証された。また、少なくとも 1 つの有害事象が発生した患者の割合は、モルヌピラビル群とプラセボ群で、それぞれ 30.4%（710 例中 216 例）、33.0%（701 例中 231 例）と両群で同程度であった。有害事象による投与中止は、モルヌピラビル群 1.4%（710 例中 10 例）、プラセボ群 2.9%（701 例中 20 例）であった。

3.2 システマティックレビューの終了後、英国のリアルワールドにおけるモルヌピラビルの有効性・安全性の検証を目的とした非盲検ランダム化プラグマティック試験である PANORAMIC 試験に関する論文が新たに発表された[101]。本試験では、ワクチン接種が進展しオミクロン株を主体とした変異株が流行していた 2021 年 12 月～2022 年 4 月に患者組み入れが行われた（適格 25,708 例中 SARS-CoV-2 ワクチン 3 回以上接種済 94%）。主要評価項目であるランダム化後 28 日以内の理由を問わないすべての非待機的入院又は死亡した被験者の割合は、モルヌピラビル＋標準治療群で 1%（12,529 例中 105 例）及び標準治療群でも 1%（12,525 例中 98 例）といずれも低く、両群間の差が見られなかった。一方、副次的評価項目に関しては、標準治療群に比べモルヌピラビル＋標準治療群で症状改善までの日数が有意に短い、非緊急医療電話相談（NHS111）や在宅急性期治療プログラム（Hospital at home for COVID-19）の利用割合が低い、プライマリ医受診割合が有意に低いなどの結果が報告された。

MOVe-OUT 試験と PANORAMIC 試験における入院又は死亡に関するアウトカムが異なった原因に関し、対象集団の重症化リスク保有割合が後者において明らかに低かったことが大きく影響した可能性が指摘されている（1 つ以上の重症化リスク因子を有する患者の割合：99% vs. 69%）。そのほか、ワクチン接種の有無、主たる変異株の病原性の違い（デルタ株 vs. オミクロン株）、実施時期や地域の違いに起因する標準治療（ガイドライン等）の違いなども影響した可能性が考えられる。また、その他の重要な相違点として PANORAMIC 試験では入院又は死亡のリスクが著しく高い患者において中和抗体（使用割合 1%未満）やレムデシビル（使用割合不明）の使用が許容されていた点なども挙げられる。これらに代表される両試験間の相違を背景に、PANORAMIC 試験の Day28 における標準治療群の死亡率（0.04%）及び入院率（1%）は、MOVe-OUT 試験第Ⅲ相パートの Day29 における標準治療群の死亡率（2.1%）及び入院率（13.8%）に比べ顕著に低く、入院又は死亡リスクに関して標準治療に対するモルヌピラビルの

優越性を示すことは著しく困難であったと考えられる。

重症化リスクを有する患者の入院又は死亡に対する有効性の検証を主要目的としたモルヌピラビルの RCT が MOVe-OUT 試験と PANORAMIC 試験の 2 試験に限られること、加えて両者の明示的かつ著しい異質性や例数の偏りも考慮すれば、これら 2 試験のアウトカムをランダム効果モデル等で統合する手法によってモルヌピラビルの追加的有用性を推定することは科学的妥当性の面から適切でないと考えられた。よって、本分析では追加的有用性のパラメータとして単一 RCT のデータを用いることとし、その選択にあたっては当該パラメータがリアルワールドにおける観察研究のアウトカムによっても支持される必要があると考えた。観察研究を対象とした追加的な PubMed 文献検索（2023 年 3 月実施）を行った結果、モルヌピラビルの COVID-19 関連入院又は死亡に対する有効性を支持する複数の観察研究が同定されたが[102],[103]、1 つ以上の重症化リスク因子を有する外来患者のみを対象とした観察研究としては、米国退役軍人保険の医療情報データベースを用いた Target Trial Emulation 法による COVID-19 外来患者におけるモルヌピラビルの有効性評価に関する論文（Xie, et al. 2023、表 10）が唯一同定された[104]。同研究における傾向スコアマッチング後の主要評価項目（基準日+30 日目までの入院又は死亡）の発現割合はモルヌピラビル使用患者で 2.7%、無治療患者で 3.8%であり、無治療群に対するモルヌピラビル群の相対リスクは 0.72（95%CI：0.64, 0.79）と、MOVe-OUT 試験の主要評価項目に関する time-to-event 解析で示されたハザード比 0.69（95%CI：0.48, 1.01）[17]と数値的に近く、オミクロン株流行下（2022 年 1 月～2022 年 9 月）のリアルワールドにおいてもモルヌピラビルの使用が入院又は死亡リスクの低減と関連することが示された。また、本研究の対象集団は 1 つ以上の重症化リスクを有する非入院の COVID-19 患者であり、2.1 分析対象とする集団に示す分析対象集団との類似性を有する。また対照群が無治療であることは、我が国の外来標準治療において中和抗体薬、ステロイド、レムデシビル等の使用が基本的に想定されないことや、2.2 比較対照に示す比較対象技術「標準治療（COVID-19 に対して治療の適応がある薬剤を除く、対症療法）」で想定する標準治療との共通性がある。

以上より、MOVe-OUT 試験における有効性と安全性のデータを対象集団における追加的有用性の根拠とすることは現時点で利用可能なエビデンスの選択として最も妥当と考えられ、無作為化 29 日目までの理由を問わないすべての入院又は死亡した被験者の割合を指標とした標準治療との比較に基づきモルヌピラビルの追加的有用性ありと判断した（表 11）

表 10　追加的有用性の有無に関する主な報告の概要

	Xie et al. [104]	**PANORAMIC trial** [101]	**MOVe-OUT trial** [17]
Study population	People eligible for molnupiravir	People eligible for molnupiravir but did not receive outpatient COVID-19 treatment (including molnupiravir, monoclonal antibodies, remdesivir or nirmatrelvir) from COVID-19 clinic which may have resulted in removal of highest risk population	COVID-19 non-institutionalized patients aged 18 years and older within 5 days of onset
Intervention in treatment group	Received molnupiravir as the only outpatient COVID-19 treatment	Received molnupiravir while other outpatient COVID-19 treatment (including monoclonal antibodies, remdesivir or nirmatrelvir) was also allowed	Received molnupiravir as the only outpatient COVID-19 treatment
Intervention in control group	No outpatient COVID-19 treatment	Outpatient COVID-19 treatment, including molnupiravir, was also allowed	Received standard of care
Hospitalization or death rate in control group	3.8% at 30 days	1% at 28 days	14.1% at 29 days
Death rate in control group	0.8% at 30 days	0.04% at 28 days	1.3% at 29 days
Age (years)	67.7	56.7	43.0
Baseline cardiovascular disease	40.6%	8%	11.7%
Baseline diabetes	40.8%	12%	15.9%

表 11　SARS-CoV-2 による感染症（COVID-19）患者における追加的有用性

対象集団	重症化リスク因子を有する SARS-CoV-2 による感染症（COVID-19）患者（18 歳以上） 但し、有効性が確立していないため、重症度*の高い COVID-19 患者を除く。 *重症度の定義は新型コロナウイルス感染症（COVID-19）診療の手引き・第 8.1 版に準ずる。
介入	モルヌピラビル
比較対照	プラセボ（標準治療）
アウトカム	有効性（無作為化 29 日目までの理由を問わないすべての入院又は死亡した被験者の割合）、安全性（有害事象）
追加的有用性の有無	■ 追加的有用性あり　□「追加的有用性なし」あるいは「ありとは判断できない」
判断の根拠となったデータ	□　RCT のメタアナリシス　■ 単一の RCT（MOVe-OUT 試験） □　前向きの比較観察研究　□ RCT の間接比較 □　単群試験の比較　□ 臨床データなし
追加的有用性の有無を判断した理由	• MOVe-OUT 試験第Ⅲ相パートの主要な解析である中間解析において、主要評価項目である無作為化 29 日目までの理由を問わないすべての入院又は死亡した被験者の割合において、優越性が検証された。 • MOVe-OUT 試験第Ⅲ相パートにおいて、安全性が比較対照と同程度であった。

4. 分析方法の詳細

4.1 分析方法

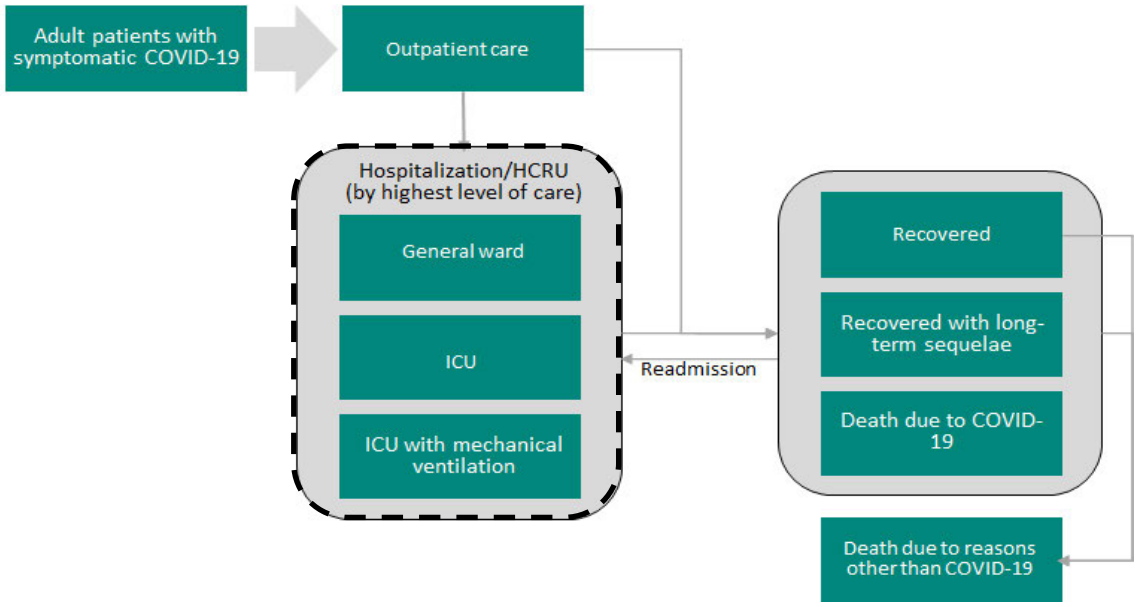
4.1.1 費用対効果の算出方法

本分析では、COVID-19 の発症から急性期治療終了までの分析期間（30 日）に決定木モデルを用い、その後の分析期間（生涯：死亡又は 100 歳まで）には 1 サイクルを 1 年（但し、初年は急性期を除いた 11 か月）に設定したマルコフモデルを用いた。

決定木モデルにおいては、COVID-19 の重症化イベントとして、COVID-19 の外来（非入院）患者における入院治療への移行、及び入院治療におけるより高度なケアセッティング［ICU、又は体外式膜型人工肺（ECMO）又は人工呼吸器（MV）の使用を伴う ICU（ICU+MV/ECMO）］への移行を想定した。

なお、モルヌピラビルは主に外来治療で用いる経口薬であることから、モデルでは入院期間や入院後の症状の持続時間の短縮は考慮していない。分析モデルの構造を図 7 に示す。

図 7 分析モデルの構造



*図中の点線部分が決定木分析に該当

分析モデルは、COVID-19 の外来治療から開始された成人患者を対象とし、COVID-19 の重症化に伴い、外来から入院へ移行する可能性を想定した。また、重症度として入院中に到達しうる 3 レベルのケアセッティング（一般病棟、ICU、ICU+MV/ECMO）を想定し、入院後の患者の転帰として、完全に回復するケース、長期の後遺症を伴って回復するケース[105], [106]、入院中に死亡するケースを想定した。さらに、入院後の生存患者では、再入院を経験することも想定した[107]。

有害事象（Adverse Events, AE）または治療上緊急を要する有害事象は、非入院 COVID-19 患者を対象とした MOVe-OUT 試験で明らかな安全性の懸念がなかったため、本分析では想定しなかった[108]。

基本分析に加えて以下の感度分析を行った。

- 一元感度分析
  特定の入力パラメータの変動が及ぼす分析結果への影響を検討するために、すべてのパラメータを組み込んで実施した。

- 確率的感度分析
  基本分析に対して全パラメータを同時に変化させて実施した。各パラメータの分布を、Briggs et al (2011)[109]に従って、以下の通り選択した。
  - 割合（二項）：ベータ分布
  - 相対リスク（有効性エンドポイントの場合）：対数正規分布
  - 費用：ガンマ分布
  - QOL 値：ベータ分布
  - その他のパラメータ：正規分布

- シナリオ分析
  新たな高病原性変異株（デルタ株相当）の流行やワクチンが無効化に向かうことを想定した悲観的条件として、MOVe-OUT 試験第Ⅲ相パートの ad hoc 解析における患者特性および疾患特性のデータ（詳細は 4.2　分析で使用したパラメータ参照）を使用して、シナリオ分析 1-3 を実施した。また、COVID-19 関連入院による短期的な労働生産性損失を踏まえ、社会の立場のシナリオ分析 4 も実施した。
  1. MOVe-OUT 試験の（全集団）の患者特性および疾患特性による分析
  2. MOVe-OUT 試験（軽症患者サブ集団*）の患者特性および疾患特性による分析
     ＊息切れなし、かつ SpO_2>93%など
  3. MOVe-OUT 試験の（60 歳以下サブ集団）の患者特性および疾患特性による分析
  4. 基本分析の設定における社会の立場での分析：入院による短期的な労働生産性損失を考慮

4.1.2 モデルで使用した仮定

本分析で使用した仮定を以下に示す。

- 分析対象集団における入院割合として、厚生労働省公表データ「新型コロナウイルス感染症患者の療養状況等及び入院患者受入病床数等に関する調査結果」[110]における 2022 年

各週の療養者数と入院者数から算出した入院割合（%）の平均値を仮定した。

- 入院における重症度を 3 レベルのケアセッティング（一般病棟、ICU、ICU+MV/ECMO）で定義し、到達した最も高い重症度により患者区分を設定した。
- モルヌピラビルは主に外来治療で用いられる薬剤であることから、入院後の治療効果及び症状の持続時間の短縮を考慮していない。
- 有害事象（AE）または治療上緊急を要する有害事象は含めていない。
- 再入院時の入院期間は 7 日間[111]と仮定した。
- 外来の COVID-19 による死亡率を 0%と仮定した。
- 100 歳以降の死亡確率は 100%に設定した。
- 再入院の健康状態に対する QOL 値は一般病棟の健康状態と同じと仮定した。
- 標準誤差（SE）は、入手できない場合、平均値の 5%（表 13）又は 10%（表 14）とした。

4.2 分析で使用したパラメータ

ベースラインの患者特性（年齢、女性比率、死亡時年齢など、但し入院割合を除く）および疾患特性（入院の内訳、入院日数）について、メディカル・データ・ビジョン（MDV）社が提供する診療データベース EBM Provider による調査（MDV データベース調査）で得られたデータを用いた。
調査の概要を表 12 に示す。本調査では、集計対象患者の組み入れ基準及び除外基準に基づき適格な [redacted] 例（ユニーク識別子ベース）が同定され、その集計結果をパラメータとして用いた。

表 12 MDV データベース調査の概要

データソース	EBM Provider®
対象期間	データ抽出期間を 2019 年 7 月*～2022 年 6 月とし、集計対象期間は 2020 年 1 月～2022 年 6 月に設定 * 併存疾患データ取得のため集計期間前 6 か月を含む
組み入れ基準	集計対象期間に、COVID-19 の初回確定診断日がある患者 COVID-19 の定義は、ICD10 コード U071（コロナウイルス感染症 2019、ウイルスが同定されたもの）
除外基準	下記のいずれかに該当する患者は集計対象から除外 • COVID-19 での受診と同月にレムデシビルの処方がある患者 • 様式 1 で妊娠の情報がある患者 • COVID-19 の初回確定診断日の該当月の 1 日時点で 18 歳未満の患者

主な患者特性の定義	COVID-19 の初回診断確定日から最終受診日までを患者区分判定期間（1 コース）とし、入院に至った場合はこれを「基準入院」と定義した。なお、初回確定診断日より後に COVID-19 後遺症の診断日データがある場合は、その前日を最終受診日とし、それまでの期間を 1 コースとした。 ■ 年齢 COVID-19 の初回確定診断日と同月の 1 日時点の年齢 ■ 患者区分（外来患者） 外来診療のみで治療を終えた患者 ■ 患者区分（入院患者） 基準入院における重症度に基づき、患者区分を定義した。 ・ 一般病棟： 基準入院期間に ICU の算定なし、かつ MV 又は ECMO の算定なしの患者 ・ ICU： 基準入院期間に ICU の算定あり、かつ MV 又は ECMO の算定なしの患者 ・ ICU+MV/ECMO： 基準入院期間に ICU の算定あり、かつ MV 又は ECMO 算定ありの患者 ■ 再入院ありの患者 基準入院期間の最終日から 60 日以内の COVID-19 を主要傷病名とする入院がある患者 ■ 後遺症ありの患者 COVID-19 の初回確定診断日後に COVID-19 後遺症の確定診断日がある患者。なお、COVID-19 後遺症の定義は、ICD10 コードで U09（コロナウイルス感染症 2019 後の病態）又は U099（コロナウイルス感染症 2019 後の病態、詳細不明）とした。 ■ 死亡例 基準入院の転帰が死亡退院である
主な治療実態関連項目の定義	■ 外来受診回数・治療期間 ・ 外来受診回数： 1 コース内の受診日数をカウント（但し、救急医療関連のデータがある場合は救急受診回数にカウント） ・ 外来治療期間： 1 コースの日数、症状の持続期間とする。 ・ 救急受診回数： 1 コース内の救急受診日数をカウント ■ 入院期間 基準入院の初日から退院日までの日数（但し、死亡による退院症例は集計から除外） ■ 再入院期間 COVID-19 主要傷病名とする再入院から退院までの日数

またシナリオ分析には、MOVe-OUT 試験の ad hoc 解析のデータを用いた（表 13）。MOVe-OUT 試験から十分なデータが得られなかったその他のパラメータ（外来での症状の持続時間、外来受診回数、救急科受診回数、救急科受診患者の割合、長期の後遺症と再入院の割合、但し再入院時の入院期間を除く）についても、MDV データベース調査で得られたデータを使用した（表

14）。また、上記いずれのデータソースからも得られない項目（入院割合、再入院時の入院期間、ICU+MV/ECMO の後遺症罹患割合）については、厚生労働省から公開されている情報[110]と文献値を使用した[111],[112]（表 13 および表 14）。

表 13　ベースラインの患者特性および疾患特性

パラメータ	MDV データベース調査または報告値（基本分析）	MOVe-OUT 試験の ad hoc 解析（シナリオ分析）
患者特性		
年齢、歳（SE）	[redacted]	45.3 (0.57)
死亡時年齢、歳（SE）	[redacted]	61 (5.86)
女性、%（SE）	[redacted]	49 (0.02)
入院割合、%（SE）	[redacted]*[110](N/A)	9.2 (0.01)
入院の内訳（患者区分別）		
一般病棟、%（SE）	[redacted]	70 (0.06)
ICU、%（SE）	[redacted]	17 (0.05)
ICU+MV/ECMO、%（SE）	[redacted]	13 (0.04)
入院日数（患者区分別）		
一般病棟、日（SE）	[redacted]	10 (0.82)
ICU、日（SE）	[redacted]	14 (1.13)
ICU+MV/ECMO、日（SE）	[redacted]	14 (1.33)

標準誤差（SE）は、入手できない場合、平均値の 5%とした。*厚生労働省公表データ「新型コロナウイルス感染症患者の療養状況等及び入院患者受入病床数等に関する調査結果」：2022 年における療養者数と入院者数（毎週発表）から算出した全ての週次入院割合（%）の平均値

表 14　その他のパラメータ

パラメータ	MDV データベース調査 または文献値
外来および救急科受診関連	
症状の持続期間（外来治療期間）、日（SE）	[redacted]
外来受診回数、回/コース（SE）	[redacted]
1 患者あたり救急科受診回数、回（SE）	[redacted]
救急科受診割合、%	[redacted]
生存患者における長期の後遺症罹患割合（患者区分別）	
外来、%	[redacted]
一般病棟、%	[redacted]
ICU、%	[redacted]
ICU+MV/ECMO、%	[redacted] [112]
COVID-19 により再入院した患者の割合（患者区分別）	
一般病棟、%	[redacted]
ICU、%	[redacted]
ICU+MV/ECMO、%	[redacted] #
再入院時の入院期間、日	[redacted] [111]

再入院例がなかったため、モデルでは ICU と同値を仮定；標準誤差（SE）は、入手できない場合、平均値の 10%とした。

4.2.1 有効性･安全性等のパラメータの詳細

モルヌピラビルの入院に対する影響のパラメータには、MOVe-OUT 試験第Ⅲ相パート（3.2.4 検索結果）の post hoc 解析における COVID-19 関連入院の相対リスクを用い、入院後の重症化に対する影響のパラメータには、ランダム化後 29 日目までに COVID-19 に関連する理由で入院した被験者（モルヌピラビル 800mg 投与群 45 例、プラセボ投与群 64 例）についての post hoc 解析における相対リスクを用いた（表 15）。

表 15　MOVe-OUT 試験第Ⅲ相パートに基づくモルヌピラビルの有効性[17]

治療効果	MOVe-OUT 試験 post hoc 解析 [95%信頼区間]
COVID-19 関連入院への進行、RR	0.69 [0.47 – 0.98]
Score 6（ICU）への進行、RR	0.83 [0.27 – 1.97]
Score 7-9（人工呼吸器の使用）への進行、RR	0.76 [0.18 - 2.17]
COVID-19 関連死亡、RRR	0.84 [0.75 – 0.92]

注：推定値は、29 日目までの MOVe-OUT 試験第Ⅲ相パートの事後解析から得られたデータ。死亡率に対するモデルの効果は、WHO clinical Progression Scale（11 点）の最高スコアに依存する。WHO score 4～5 は一般病棟、WHO score 6 は ICU、WHO score 7～9 は人工呼吸器の使用を想定した。RR: Risk ratio, RRR: Relative risk reduction

また分析モデルでは、上述したモルヌピラビルによる COVID-19 関連入院および重症化の回避を介した効果として COVID-19 による死亡リスクが低減することを想定した。標準治療における COVID-19 による死亡率としては MDV データベース調査で算出された死亡率（基本分析）と MOVe-OUT 試験の ad hoc 解析におけるデータ（シナリオ分析）を使用し、それぞれ患者区分別に異なる死亡率を想定した（表 16）。なお、外来患者の死亡情報は同調査で取得できなかったため、外来患者の COVID-19 による死亡率は 0 と仮定した。

表 16　COVID-19 による死亡率

患者区分	MDV データベース調査 （基本分析）	MOVe-OUT 試験 ad hoc 解析（シナリオ分析）
一般病棟、% (SE)	[redacted]	2.2 (0.022)
ICU、% (SE)	[redacted]	27.3 (0.134)
ICU+MV/ECMO、% (SE)	[redacted]	62.5 (0.171)

標準誤差（SE）は、入手できない場合、平均値の 10%とした。

モデルの急性期後の生存患者には、日本人の一般集団の死亡確率を第 23 回生命表から取得し適用した[113]。なお、このモデルは 100 歳まで患者を追跡するため、100 歳以降の死亡率は 100%に設定した。

- 併存疾患が死亡率に与える影響（MOVe-OUT 試験第Ⅲ相パートのパラメータを用いたシナリオ分析）について
  パンデミック初期の報告では、基礎疾患を持つ COVID-19 入院患者は、COVID-19 の重症化および死亡のリスクが高いことが示されている[114], [115], [116], [117]。このモデルは、COVID-19 の入院患者において、年齢に関係なく[118]、多くの基礎疾患が死亡のリスク上昇をもたらす可能性があることを示す文献に基づいて、入院患者と非入院患者の死亡率上昇を区別して捉えた。本モデルでは、標準化死亡比（Standardized Mortality Ratio、SMR）として、既往の併存疾患（すなわち、重度の心臓疾患、心血管障害、糖尿病）を有する患者（患者割合 [redacted]%：MOVe-OUT 試験における糖尿病、高血圧、重篤な心疾患（心不全、冠動脈疾患、心筋症）を有する患者割合）に [redacted] を適用し、急性期後の生存患者については入院患者と非入院患者の両方に既往の併存疾患の影響を考慮した[119]。この SMR は、MOVe-OUT 試験のパラメータを用いたシナリオ分析に適用された。

4.2.2 QOL 値の詳細

分析対象集団におけるベースラインの QOL 値として日本人の一般集団における EQ-5D-5L 標準値[120]を用いた。一方、日本人の COVID-19 患者の急性期治療中および治療後の健康状態

を反映した EQ-5D-5L の QOL 値の報告はない。そこで、本分析に必要な COVID-19 関連の健康状態における QOL 値として、海外の QOL 調査で得られた EQ-5D-5L データ[119]に対する日本人換算値を用いることとした。当該 QOL 調査は英国の一般人 500 人を対象に行われ、vignette で説明される 8 つの健康状態に関する EQ-5D-5L 質問票への回答が収集された（別添 6 参照）。次いで、上記 QOL 調査で得られた 5 項目 5 水準の回答から、池田ら[121]によるバリューセットを用いて日本人換算の QOL 値を算出し、その後本分析で定義する 6 つの健康状態における QOL 値に要約した（表 17）。なお、再入院の健康状態に対する QOL 値[redacted]した。

表 17　COVID-19 患者における QOL 値

健康状態	QOL 値（SE）*
軽症・中等症	[redacted]
一般病棟	[redacted]
ICU	[redacted]
ICU+MV/ECMO	[redacted]
長期の後遺症	[redacted]
長期の後遺症なしの回復	[redacted]
再入院	[redacted]

*英国 QOL 調査における Outpatient (mild), Outpatient (moderate)をプールしたデータに基づく日本人 QOL 換算値

4.2.3 費用のパラメータの詳細

本分析では MDV データベース調査により分析に必要な費用項目を推計し、費用パラメータとして使用した。推計方法の詳細を表 18 に示す。なお、同データベース調査では集計実施時点の最新の診療報酬（2022 年 4 月改定）及び最新薬価に換算した費用集計も行ったが、すべての入院区分（一般病棟、ICU、ICU＋MV/ECMO、COVID-19 関連再入院、すべての再入院）において 1 入院あたり医療費の集計値が実施時点薬価に基づく集計値を大きく上回ったため、本分析では保守的なアプローチとして標準治療の経済的負担を低めに想定することを選択し、治療実施時点の最新の単価に基づく費用を使用した（但し、著しく乖離が大きかった ICU＋MV/ECMO については文献値を利用）。

モルヌピラビルの 1 コースの薬剤費については、分析実施時点の薬価（2,357.8 円）[122]に基づき、94,312 円（1 コース：4 カプセル×2 回×5 日）とした。

表 18　治療費用の推計方法

項目	内容
費用の推計方法	集計対象患者に実施された診療行為及び薬剤、医療機器の使用を含むすべての医療行為のうち、下記の定義に該当する項目の合計費用を治療実施時の最新の診療報酬点数に基づいて推計した。
外来治療の費用	外来治療期間中の医療費と薬剤費の合計。なお、救急外来の費用は受診 1 回あたりの費用として別途集計した。 費用の集計範囲を以下に示す。 • 診療区分 A～L、N に該当する全ての診療報酬（但し、入院関連及び明らかに COVID-19 の治療と関係のない悪性腫瘍の治療などを除く） • 全ての薬剤費（但し、明らかに COVID-19 の治療と関係のない抗腫瘍剤などを除く）
入院の費用	入院期間について、期間内に退院日データがある場合は入院日から退院日まで、退院日データが無い場合は最終受診日までとした。退院以外の打ち切り症例（死亡入院、退院先が転院の入院、基準入院（かつ 1 コース内）の一部データが欠測している入院）は、全ての医療費集計から除外した。 費用の集計範囲を以下に示す。 • 診療区分 A～L、N に該当する全ての診療報酬（但し、外来診療関連及び明らかに COVID-19 の治療と関係のない悪性腫瘍や、人工関節置換術や骨折等に伴う比較的高頻度かつ高額な整形外科関連手術などを除く） • 全ての薬剤費（但し、明らかに COVID-19 の治療と関係のない抗腫瘍剤などを除く） 基準入院における治療費用： 基準入院期間中における 1 患者 1 入院あたりの医療費の合計。但し、基準入院の転帰が死亡、退院先が転院の入院や集計対象期間中に未退院の症例、入院期間中に欠損データがある症例は集計の対象から除外した。 再入院における治療費用： 再入院期間中における 1 患者 1 入院あたりの医療費の合計。但し、基準入院の場合と同じく、入院期間中に欠測データがある症例は集計対象から除外した。入院後の発症病名のみの入院は含まない。
後遺症治療費用	COVID-19 後遺症治療期間における 1 患者 1 か月あたりの医療費の合計

基本分析では、COVID-19 の外来や入院に伴う治療費用、長期の後遺症及び COVID-19 による再入院費用に MDV データベース調査で得られたデータを使用した（表 19）。

表 19　治療の費用

パラメータ	1 患者あたりの平均費用
外来受診費、円/コース	[redacted]
救急科受診費、円/回	[redacted]
COVID-19 入院費用（患者区分別）	
一般病棟、円/コース	[redacted]
ICU、円/コース	[redacted]
ICU+MV/ECMO、円/コース	[redacted][123]
再入院、円/コース	[redacted]*
後遺症治療費用、円/月	[redacted]#

* COVID-19 を主傷病名とする再入院における費用、#後遺症治療は外来・入院を問わない総費用/月の平均値

労働生産性については、15 歳以上の労働力人口において 2021 年労働力調査[124]より男女別就業率、年間の平均就業日数、及び国税庁による民間給与実態統計調査[125]（令和 4 年 9 月）に基づき 5 歳階級別の年間の平均給与額を用い 1 日あたりの平均賃金を算出した（表 20）。これらを入院による生じる労働生産性損失を考慮した社会の立場でのシナリオ分析に用いた。

表 20　年齢階級別 1 日あたりの平均賃金

年齢階級	1 日あたり平均賃金（円）
<=19	8,125
20-24	12,665
25-29	15,465
30-34	17,208
35-39	18,747
40-44	20,017
45-49	21,009
50-54	21,776
55-59	22,208
60-64	18,225
65-69	15,634
>=70	13,876

5. 分析結果

5.1 基本分析(費用対効果評価専門組織で決定された分析枠組みによる分析)の結果

下記の通り費用効果分析を実施した。

■ 費用効果分析（増分費用効果比を算出する）
□ 費用最小化分析（効果は同等として費用を比較する）

5.1.1 基本分析の増分費用、増分効果、増分費用効果比

基本分析の結果を表 21 に、費用の内訳を表 22 に示す。評価対象集団における比較対照の標準治療に対するモルヌピラビル+標準治療の 1 患者あたりの増分費用は 84,391 円、増分 QALY は 0.044QALY であった。従って、増分費用効果比（ICER）は 1,930,637 円/QALY であった。

表 21 基本分析の結果

	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER (円/QALY)
モルヌピラビル +標準治療	25.596	0.044	175,291	84,391	1,930,637
標準治療	25.552		90,900		

QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio

表 22 費用の内訳

項目	モルヌピラビル+標準治療 （円）	標準治療 （円）
1 患者あたり医療費合計	175,291	90,900
内訳		
薬剤	[redacted]	[redacted]
外来受診	[redacted]	[redacted]
救急科受診	[redacted]	[redacted]
入院	[redacted]	[redacted]
区分別：一般病床	[redacted]	[redacted]
区分別：ICU	[redacted]	[redacted]
区分別：ICU+MV/ECMO	[redacted]	[redacted]
再入院	[redacted]	[redacted]
後遺症治療	[redacted]	[redacted]

5.1.2 感度分析

5.1.2.1 一次元感度分析（Deterministic sensitivity analysis、DSA）

主要パラメータについて結果への影響を検討するため一元感度分析を実施した。パラメータを変動させる範囲は、4.1.1 費用対効果の算出方法に記載の通り各パラメータの分布特性を考慮し算出した 95%信頼区間を、割引率については分析ガイドライン[9]に基づき上限を 4%、下限を 0%と設定した。パラメータの設定の詳細を表 23 に示す。

表 23 パラメータの設定

Parameter	Base case analysis	DSA and PSA			
	Input value	Inclusion for DSA	Inclusion for PSA	SE	Distribution
Discount rate	2.0%	Yes	Yes	-	0-4%
Patient characteristics					
Age at model start	[redacted]	Yes	Yes	[redacted]	Normal
Age at death	[redacted]	Yes	Yes	[redacted]	Normal
Female	[redacted]%	Yes	Yes	[redacted]	Beta
Disease parameters					
Hospitalization rate	[redacted]%	Yes	Yes	[redacted]*	Beta
Proportion in general ward	[redacted]%	Yes	Yes	[redacted]*	Dirichlet
Proportion in intensive care unit	[redacted]%	Yes	Yes	[redacted]*	
Proportion in mechanical ventilation	[redacted]%	Yes	Yes	[redacted]*	
Length of stay in general ward, days	[redacted]	Yes	Yes	[redacted]	Normal
Length of stay in intensive care unit, days	[redacted]	Yes	Yes	[redacted]	Normal
Length of stay in mechanical ventilation	[redacted]	Yes	Yes	[redacted]	Normal
Symptom duration	[redacted]	Yes	Yes	[redacted]*	Normal
Mortality rate in general ward	[redacted]%	Yes	Yes	[redacted]*	Beta
Mortality in intensive care unit	[redacted]%	Yes	Yes	[redacted]*	Beta
Mortality rate in mechanical ventilation	[redacted]%	Yes	Yes	[redacted]*	Beta

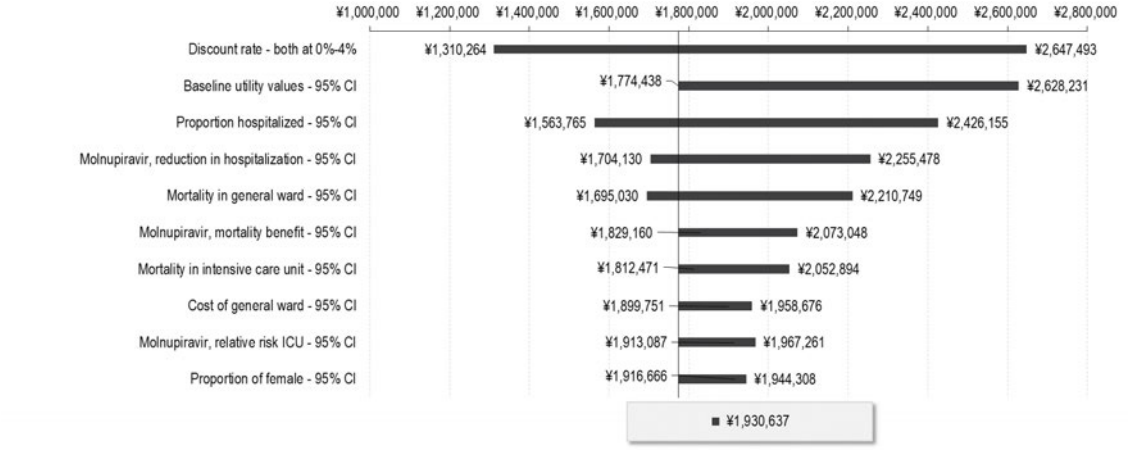
Parameter	Base case analysis	DSA and PSA			
	Input value	Inclusion for DSA	Inclusion for PSA	SE	Distribution
Number of outpatient visit	[redacted]	Yes	Yes	[redacted]	Normal
Number of emergency department visit	[redacted]	Yes	Yes	[redacted]	Normal
Proportion with emergency department visit	[redacted]%	Yes	Yes	[redacted]*	Beta
Proportion with increased mortality	[redacted]%	Yes	Yes	[redacted]*	Beta
Proportion with long-term sequelae, outpatient	[redacted]%	Yes	Yes	[redacted]*	Beta
Proportion with long-term sequelae, general ward	[redacted]%	Yes	Yes	[redacted]*	Beta
Proportion with long-term sequelae, intensive care unit	[redacted]%	Yes	Yes	[redacted]*	Beta
Proportion with long-term sequelae, mechanical ventilation	[redacted]%	Yes	Yes	[redacted]*	Beta
Readmission, from general ward	[redacted]%	Yes	Yes	[redacted]*	Beta
Readmission, from intensive care unit	[redacted]%	Yes	Yes	[redacted]*	Beta
Readmission, from mechanical ventilation	[redacted]%	Yes	Yes	[redacted]*	Beta
Readmission, length of stay	[redacted]	Yes	Yes	[redacted]*	Normal
Costs					
Cost of outpatient visit	[redacted]	Yes	Yes	[redacted]*	Gamma
Cost of emergency visit	[redacted]	Yes	Yes	[redacted]*	Gamma

Parameter	Base case analysis	DSA and PSA			
	Input value	Inclusion for DSA	Inclusion for PSA	SE	Distribution
Cost of general ward	[redacted]	Yes	Yes	[redacted]*	Gamma
Cost of intensive care unit	[redacted]	Yes	Yes	[redacted]*	Gamma
Cost of mechanical ventilation	[redacted]	Yes	Yes	[redacted]*	Gamma
Cost of long-term sequelae	[redacted]	Yes	Yes	[redacted]*	Gamma
Cost of readmission	[redacted]	Yes	Yes	[redacted]*	Gamma
Quality of life					
Mild/moderate symptomatic	[redacted]	Yes	Yes	[redacted]	Beta
General ward	[redacted]	Yes	Yes	[redacted]	Beta
Intensive care unit	[redacted]	Yes	Yes	[redacted]	Beta
Mechanical ventilation	[redacted]	Yes	Yes	[redacted]	Beta
Long-term sequelae	[redacted]	Yes	Yes	[redacted]	Beta
Recovered (no long-term sequelae)	[redacted]	Yes	Yes	[redacted]	Beta
SMR	[redacted]	Yes	Yes	[redacted]*	Normal
Effect estimates for molnupiravir					
Relative risk reduction, hospitalization	0.69	Yes	Yes	0.13	Log-normal
Relative risk, intensive care unit	0.83	Yes	Yes	0.45	Log-normal
Relative risk, mechanical ventilation	0.76	Yes	Yes	0.54	Log-normal
Relative risk reduction, mortality benefit	0.8402	Yes	Yes	0.04	Beta

*SE was assumed to be 5% of mean for these parameters.
#Assumed same as general ward
DSA: deterministic sensitivity analysis; PSA: probabilistic sensitivity analysis; SE: standard error; SMR: standardized mortality ratio

図 8 に示す通り、モルヌピラビル＋標準療法の標準療法に対する ICER に影響が大きい上位 5 つのパラメータは、割引率、入院割合、ベースライン QOL 値、モルヌピラビルの有効性（相対入院リスク）、及び一般病棟での死亡率であった。

図 8　一次元感度分析



5.1.2.2 確率的感度分析（Probabilistic sensitivity analysis、PSA）

4.1.1 費用対効果の算出方法に記載の通り、基本分析の全パラメータを 1,000 回のモンテカルロシミュレーションにより確率的感度分析を実施した。各パラメータの変動範囲は表 23 の通りである。確率感度分析の結果として、費用効果平面上の散布図（図 9）および費用効果受容曲線（図 10）を示す。モルヌピラビルが費用対効果良好となる確率は、1QALY あたり基準値（支払意思額）を 500 万円とした場合に 100%であり、費用対効果が優れている確率が高いことが示された。

図 9　費用効果平面上の散布図

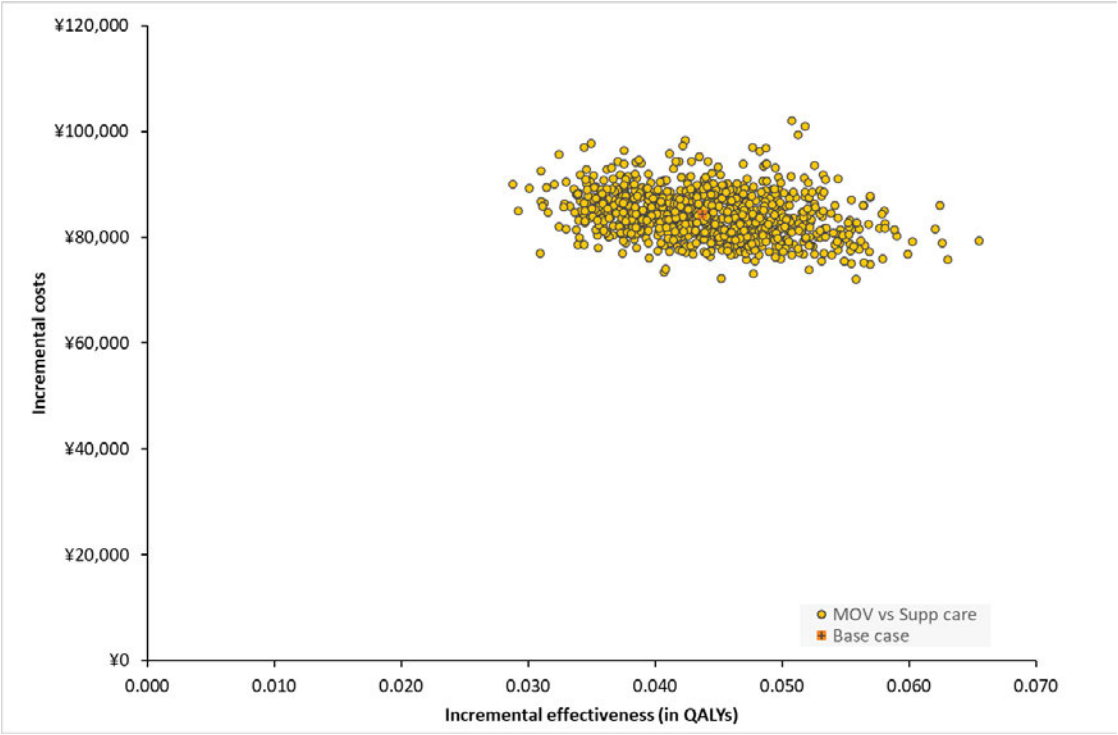
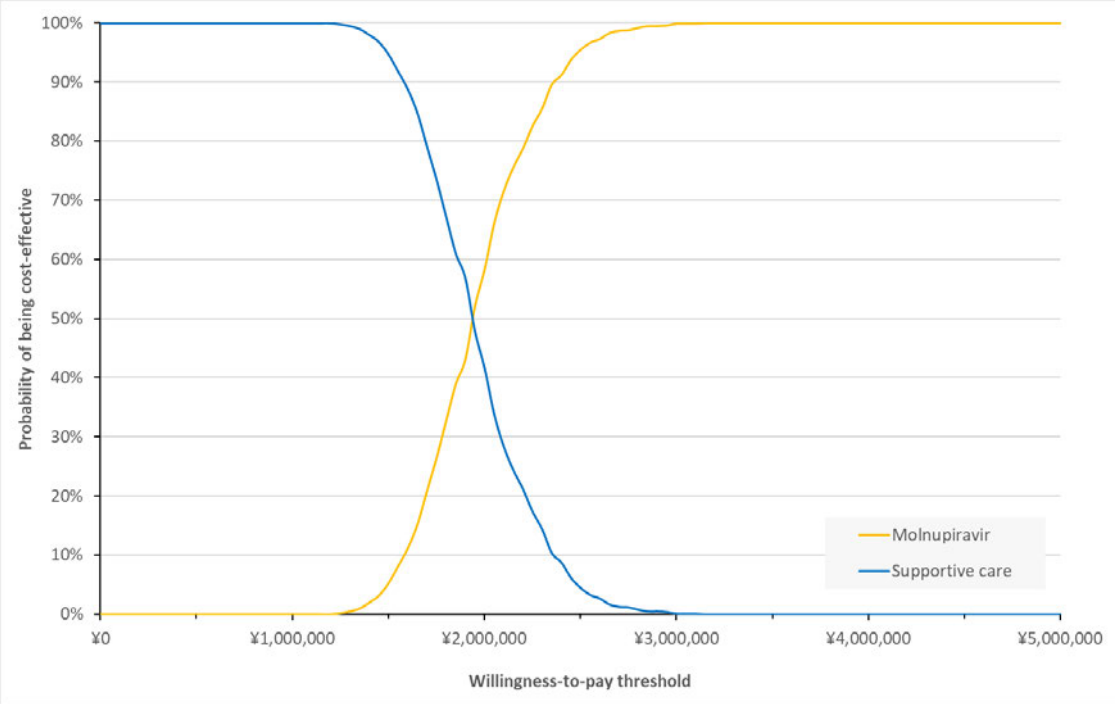


図 10　費用効果受容曲線



5.1.2.3 シナリオ分析

4.1.1 費用対効果の算出方法および 4.2 分析で使用したパラメータにおいて述べた 4 つのシナリオについて分析を実施した。

シナリオ 1：MOVe-OUT 試験（全集団）の患者特性および疾患特性による分析

患者背景およびベースラインでのリスクに MOVe-OUT 試験の全集団のデータを使用したシナリオ分析の結果を表 24 に示す。モルヌピラビル＋標準治療の標準治療に対する ICER は [redacted] 円/QALY で費用対効果は良好であった。

表 24　MOVe-OUT 試験（全集団）の患者特性および疾患特性による分析

治療	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER (円/QALY)
モルヌピラビル＋標準治療	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
標準治療	[redacted]		[redacted]		

シナリオ 2：MOVe-OUT 試験（軽症患者サブ集団）の患者特性および疾患特性による分析

本分析では、MOVe-OUT 試験の軽症患者集団とその患者背景のデータを用いた。表 25 に示す通り、モルヌピラビル+標準治療の標準治療に対する ICER は [redacted] 円/QALY で費用対効果は良好であった。

表 25　MOVe-OUT 試験（軽症患者サブ集団）の患者特性および疾患特性による分析

治療	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER (円/QALY)
モルヌピラビル +標準治療	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
標準治療	[redacted]		[redacted]		

シナリオ 3：MOVe-OUT 試験（60 歳以下サブ集団）の患者特性および疾患特性による分析

MOVe-OUT 試験の 60 歳以下の患者集団とその患者背景のデータを用いた分析の結果を表 26 に示す。モルヌピラビル+標準治療の標準治療に対する ICER は [redacted] 円/QALY で費用対効果は良好であった。

表 26　MOVe-OUT 試験（60 歳以下サブ集団）の患者特性および疾患特性による分析

治療	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER (円/QALY)
モルヌピラビル +標準治療	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
標準治療	[redacted]		[redacted]		

シナリオ 4：基本分析の設定における社会の立場での分析

基本分析について、入院患者の入院日数による短期的な労働生産性損失を考慮した社会の立場での分析を実施した。表 27 に示す通り、モルヌピラビル+標準治療の標準治療に対する ICER は [redacted] 円/QALY で費用対効果は良好であった。

表 27　基本分析の設定における社会の立場での分析

治療	効果 (QALY)	増分効果 (QALY)	費用 (円)	増分費用 (円)	ICER (円/QALY)
モルヌピラビル +標準治療	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
標準治療	[redacted]		[redacted]		

5.1.3 分析の妥当性の検討

重症化リスク因子を有する 18 歳以上の COVID-19 患者（但し、重症度の高い COVID-19 患者を除く）を分析対象集団とし、公的医療の立場に立った基本分析において、評価対象技術（モル

ヌピラビル＋標準治療）の比較対照技術（標準治療）に対する ICER の点推定値は基準値（500 万円/QALY）を下回り、費用対効果が良好である結果が示された。また PSA にて、ICER が基準値 500 万円/QALY を下回る確率は 100%、また 250 万円/QALY を下回る確率は 93%であり、モデルに用いた全てのパラメータの不確実性によりこの結果が覆される確率は想定したパラメータの変動範囲内においては低く、基本分析の頑健性が支持された。さらに、公的医療の立場でのシナリオ分析（MOVe-OUT の全集団、60 歳以下又は軽症患者サブ集団のベースラインデータを使用）の全てにおいても基本分析と同じく ICER が基準値を大きく下回ったことから、例えばオミクロン株以降に出現する SARS-Cov2 変異株がデルタ株と同等の病原性を獲得、あるいはワクチンの有効性低下といった今後の感染状況や重症化率を左右しうる主な要因について、十分に悲観的なシナリオを仮定した場合にも基本分析と同様に費用対効果が良好と考えられた。

これまでに行われた海外の HTA 機関によるモルヌピラビルの費用対効果分析の事例として英国 NICE における Multiple Technology Assessment がある。その中では、入院患者と非入院患者に対する各種 COVID-19 治療薬の臨床的および経済的評価が行われ、主として経済的評価の結果に基づき、NICE は重症化リスクを有する非入院の患者にモルヌピラビルを推奨しないとの暫定ガイダンスを発出するに至った[126]。しかし、この暫定ガイダンスには以下に示すいくつかの懸念がある。例えば、当該評価における重症化リスク因子の定義（McInnes report[127]に基づく）には年齢や複数の慢性疾患を含む COVID-19 重症化に関連する重要なリスク因子が含まれないこと、臨床的有効性のエビデンスとして重視された PANORAMIC 試験[101]では著者ら自身が認める通り全体として重症化リスクを有する患者の割合が少なかったこと、システマティックレビューとメタアナリシスに採用された個別試験の間には広範な臨床的異質性が認められたこと、それにも関わらずそういった異質性や分析の限界を評価するために通常取られるべき手法に従っていなかったことなどが指摘できる。また、経済的評価の手法は NICE のマニュアルからは逸脱した簡易化されたものであったため、少なくとも評価手順の観点からはその妥当性に懸念がある。さらに PSA が行われない代わりとして、臨床的有効性の推定値として平均値と上下両信頼限界を設定したシナリオ分析が行われたのみであり、主要パラメータの分布の不確実性を考慮に入れた評価が行われていないことから、決定エラーの起こりやすさが十分に評価されていない。なお、上記暫定ガイダンス以後、3 社の COVID-19 治療薬開発企業による NICE に対する不服申し立ての手続きが継続されており 2023 年 5 月 2 日の時点では最終的な結論に至っていない。

本分析結果については以下の強みが挙げられる。まず、本分析で用いた費用対効果分析の基本（グローバル）モデルに関して、MOVe-OUT 試験結果と予測モデルとの比較による内的妥当性の検証が行われた結果、良好な再現性が確認されている。また、海外のリアルワールドデータを用いた急性期アウトカムに関する外的妥当性の検証も実施され、良好な予測性が示されている

（データの不足のため長期アウトカムは含まず）。今回我々が評価に用いた基本モデルは NICE の経済的評価モデルとは異なり、感度分析や種々のシナリオ分析によりパラメータの不確実性に起因する決定エラーの懸念が小さいことが示されていることから、現時点で利用可能なエビデンスを用いたモデルの妥当性と不確実性への対応に関して言えば、NICE で行われた手法と比べて方法論上の妥当性がより高いと考えられる。

上記の基本モデルをベースに、以下のアプローチにより日本の治療実態を反映するパラメータを組み入れた分析モデルを構築した。モデルの構築に先立ち、国内 COVID-19 治療に関する MDV データベース調査（データ期間：2020 年 1 月～2022 年 6 月、N=[redacted]）を行い、重症度別 COVID-19 患者割合、医療資源利用、直接医療費、急性期治療のアウトカム等に関するデータを収集し、それらに由来する数値をモデルパラメータとして使用した。また、COVID-19 関連の QOL 値としては英国で実施された vignette を用いた EQ-5D-5L の被験者レベル調査データを日本人バリューセットによりマッピングした値を用い、分析ガイドライン [9] で推奨される効果指標の要件に対応させた。臨床的有効性のパラメータには、2022 年に最高峰の医学誌である The New England Journal of Medicine 誌に掲載された MOVe-OUT 試験第Ⅲ相パートの有効性アウトカムを使用した [17]。本試験に組み入れられた患者は重症化リスクを有する非入院の COVID-19 患者であり、分析前協議において合意された分析対象患者集団の定義と一致する。また、3.8 追加的有用性の有無に関する評価で述べたとおり最新の大規模観察研究で類似のアウトカムが示されている。以上のように、本分析では分析ガイドライン並びに事前に分析前協議で了承された分析枠組みに沿って、パラメータとして日本人のリアルワールドデータ並びに QOL 値を組み入れた分析モデルを構築するとともに、エビデンスレベルの高い臨床的有効性のデータが用いられたことから、全体として妥当な分析結果を示しているといえる。

一方、本分析については以下の限界があると考えられる。まず、COVID-19 発症者の入院割合に関しては、感染者数、主たる変異株の病原性、病床逼迫度、ワクチン接種率、入院基準/集計方法等の影響を受けやすく、不確実性が高い。そこで、本分析では 2022 年の状況（オミクロン株と同等の病原性とワクチン接種率維持）が継続することを想定し、入院割合として 2022 年通年の平均値[110]である[redacted]%を用いた（表 13）。但し、この値は国内療養者全体（重症化リスク因子を持たない患者を含む）に対する入院割合としては妥当なものと考えられるが、本分析の対象集団である重症化リスク保有患者に限定した場合の入院割合はこれより高いものである可能性が否定できない（参考：MDV データベース調査における 2022 年 1-6 月に基準日に持つ患者の入院割合は[redacted]%）。一方、入院以降の重症度別患者割合（表 13）、後遺症罹患割合及び COVID-19 による再入院割合（表 14）、死亡率（表 16）等に関しては MDV データベース調査で得られた全データ期間の平均値を用いており、ワクチン接種の進展や変異株の出現等に伴う変化を精密には反映していないため不確実性が高い。これらの指標に関してはデータ期間別（6

か月ごと集計値）の変動が入院割合ほどには顕著でなかったことに加え、一元感度分析の結果からも分析結果への影響は限定的と考えられた（図 8）。また、新たな変異株の出現により COVID-19 の疾患特性自体が変化する可能性も重要な不確実性として挙げられる。この点を考慮して、入院あるいは重症化割合の上昇につながる可能性のある新たな高病原性変異株の流行やワクチンが無効化に向かうことを想定した悲観的条件（MOVe-OUT 試験実施時相当）に設定したシナリオ分析を実施し、いずれのシナリオにおいても基本分析の結果が覆らないことを確認した（表 24～表 26）。

さらに、利用可能なデータの不足に起因する限界も挙げられる。具体的には、本モデルで想定するモルヌピラビルの有効性は MOVe-OUT 試験第Ⅲ相パートの主要アウトカムに基づき入院又は院内死亡率の減少によるものに限定しており、COVID-19 罹患に伴うその他の疾病負荷（非入院患者の死亡率、入院期間、症状の持続期間、後遺症（罹患後症状）の重症度や持続期間等）とこれらに対する治療の影響を考慮していない。また、社会の立場でのシナリオ分析（表 27）では入院期間の労働生産性損失のみを考慮しているため、自宅待機中や療養後の休業期間の労働生産性損失、罹患後症状による労働生産性損失、介護における COVID-19 関連費用、その他一般的な社会経済活動への影響等、リアルワールドでは少なからず発生したと考えられる社会的損失とこれらに対する治療の影響を考慮しておらず、主に外来患者で使用されるモルヌピラビルがこれらの損失の回避に少なくとも部分的には寄与する可能性が考えられることから、社会の立場の分析としては極めて保守的なアプローチであるといえる。

5.1.4 分析結果の解釈

表 28 分析結果の解釈

対象集団	重症化リスク因子を有する SARS-CoV-2 による感染症（COVID-19）患者（18 歳以上） 但し、有効性が確立していないため、重症度*の高い COVID-19 患者を除く。 *重症度の定義は新型コロナウイルス感染症（COVID-19）診療の手引き・第 8.1 版に準ずる。
比較対照	標準治療
ICER の基準値	■ 通常の品目 □ 配慮が必要な品目

ICER の所属する確率が最も高いと考える区間	□ 費用削減あるいはドミナント ■ 500 万円以下（750 万円以下） □ 500 万円超（750 万円超)かつ 750 万円以下（1125 万円以下） □ 750 万円超（1125 万円超)かつ 1000 万円以下（1500 万円以下） □ 1000 万円超（1500 万円超） □ 効果が同等（あるいは劣り）、かつ費用が高い
そのように判断した理由	重症化リスク因子を有する SARS-CoV-2 による感染症（COVID-19）患者におけるモルヌピラビル＋標準治療の標準治療に対する Incremental Cost-Effectiveness Ratio (ICER) は 1,930,637 円/QALY であり、500 万円以下の区分に該当すると考えられたため。また、実施した PSA では ICER が基準値の 500 万円を下回る確率は 100%であり、さらに公的医療の立場でのシナリオ分析全てにおいて ICER が 500 万円以下となり、基本分析と同様の結果が示されたため。

5.1.5 価格調整率の重み [該当する場合のみ]

該当なし

5.1.6 価格の引き上げ [該当する場合のみ]

該当なし

5.2 公的介護費用や生産性損失を含めた分析 [該当する場合のみ]

該当なし

5.3 その他の分析 [該当する場合のみ]

該当なし

6. 再分析用のデータ

使用したソフトウェア	バージョン	ファイル名	提出メディア
Microsoft Excel for Microsoft 365 MSO	2208	[redacted]	電子メール 添付ファイル

7. 実施体制

記載事項なし

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Appendix

別添 1：SLR1 に用いた検索式

SLR 1: May 2021 (original search)

MEDLINE (Ovid MEDLINE Daily Update and OVID MEDLINE In-Process, In-Data-Review & Other Non-Indexed Citations) search strategy*, optimized with MeSH terms applicable to EMBASE, used in May 2021 (original search)

Search line	**Search syntax**
Population	
1	exp Coronavirinae/
2	(coronavirus or covid or covid19 or sars-cov-2 or sarscov2 or Sars-coronavirus-2 or Severe Acute Respiratory Syndrome Coronavirus 20 or 2019-nCoV).mp.
3	1 or 2
Interventions/comparators	
4	(Remdesivir or Veklury or GS-5734).mp.
5	(Prednisone or Deltasone or Prednicot or Rayos or Sterapred or Orasone or A07EA03).mp.
6	(Hydrocortisone or Cortef or Plenadren or NSC*10483 or).mp
7	(Methylprednisolone or Medrol).mp.
8	(Favipiravir or Favivir or Favir or Avigan or T-705).mp.
9	(Budesonide or Pulmicort).mp.
10	(AT-527 or RO7496998).mp.

Search line	Search syntax
11	(REGEN-COV or REGN-COV or Regeneron).mp.
12	(casirivimab and imdevimab) or (REGN10933 and REGN10987).mp.
13	(VIR-7831 or sotrovimab or GSK4182136).mp.
14	Camostat mes*late.mp.
15	(Nitazoxanide or Alinia).mp.
16	(Colchicine or Colcrys or Mitigare).mp.
17	(Molnupiravir or MK-4482 or EIDD-2801).mp.
18	Bamlanivimab.mp.
19	(bamlanivimab and etesevimab).mp.
20	LY-CoV555.mp.
21	(LY-CoV555 and LYCoV016).mp.
22	((AZD7442 or AZD8895) and AZD1061).mp.
23	(Regdanvimab or Regkirona or CT-P59).mp.
24	Peginterferon Lambda-1.mp.
25	(Baricitinib or Olumiant).mp.
26	(doxycycline and ivermectin) or (Doxteric or Stromectol).mp.
27	(Famotidine or Pepcid).mp.
28	(Fluvoxamine or Floxyfral or Luvox).mp.
29	PF-07321332.mp.

Search line	Search syntax
30	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
Included study design	
32	Randomized Controlled Trials as Topic/
33	randomized controlled trial/
34	Random Allocation/
35	Double Blind Method/
36	Single Blind Method/
37	clinical trial/
38	clinical trial, phase i.pt
39	clinical trial, phase ii.pt
40	clinical trial, phase iii.pt
41	clinical trial, phase iv.pt
42	controlled clinical trial.pt
43	randomized controlled trial.pt
44	multicenter study.pt
45	clinical trial.pt
46	exp Clinical Trials as topic/
47	32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48	(clinical adj trial$).tw

Search line	Search syntax
49	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw
50	PLACEBOS/
51	placebo$.tw
52	randomly allocated.tw
53	(allocated adj2 random$).tw
54	48 or 49 or 50 or 51 or 52 or 53
55	47 or 54
Excluded study designs	
56	case report.tw
57	letter/
58	historical article/
59	56 or 57 or 58
60	55 not 59
61	3 and 30 and 60
Total hits	
62	limit 61 to yr="2020 -Current"

*For further details of the search terms and fields used in MEDLINE please see the OVID Database guide: https://ospguides.ovid.com/OSPguides/medline.htm#advanced. Search strategy designed to be compatible with EMBASE indexing system - however, all search strategies were searched in the same 5 key databases (EMBASE, MEDLINE Daily Update, MEDLINE In-Process, In-Data-Review & Other Non-Indexed Citations, APA PsychInfo, Econlit), for completeness..
mp: multi-purpose (i.e. mp after a search term will search for references where this term appears across several fields including the title, abstract, subject heading and author keywords); pt: publication type; tw: text word (i.e. tw after a search term will search for reference where the word appears in the title or abstract only).

EMBASE (1974 to 2021) search strategy*, optimized with MeSH terms applicable to EMBASE, used in May 2021 (original search)

Search line	Search syntax
Population	
1	exp Coronavirinae/
2	(coronavirus or covid or covid19 or sars-cov-2 or sarscov2 or Sars-coronavirus-2 or Severe Acute Respiratory Syndrome Coronavirus 20 or 2019-nCoV).mp.
3	1 or 2
Interventions/comparators	
4	(Remdesivir or Veklury or GS-5734).mp.
5	(Prednisone or Deltasone or Prednicot or Rayos or Sterapred or Orasone or A07EA03).mp.
6	(Hydrocortisone or Cortef or Plenadren or NSC*10483 or).mp
7	(Methylprednisolone or Medrol).mp.
8	(Favipiravir or Favivir or Favir or Avigan or T-705).mp.
9	(Budesonide or Pulmicort).mp.
10	(AT-527 or RO7496998).mp.
11	(REGEN-COV or REGN-COV or Regeneron).mp.
12	(casirivimab and imdevimab) or (REGN10933 and REGN10987).mp.
13	(VIR-7831 or sotrovimab or GSK4182136).mp.
14	Camostat mes*late.mp.

Search line	Search syntax
15	(Nitazoxanide or Alinia).mp.
16	(Colchicine or Colcrys or Mitigare).mp.
17	(Molnupiravir or MK-4482 or EIDD-2801).mp.
18	Bamlanivimab.mp.
19	(bamlanivimab and etesevimab).mp.
20	LY-CoV555.mp.
21	(LY-CoV555 and LYCoV016).mp.
22	((AZD7442 or AZD8895) and AZD1061).mp.
23	(Regdanvimab or Regkirona or CT-P59).mp.
24	Peginterferon Lambda-1.mp.
25	(Baricitinib or Olumiant).mp.
26	(doxycycline and ivermectin) or (Doxteric or Stromectol).mp.
27	(Famotidine or Pepcid).mp.
28	(Fluvoxamine or Floxyfral or Luvox).mp.
29	PF-07321332.mp.
30	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
Included study designs	
31	Clinical Trial/
32	Randomized Controlled Trial/

Search line	Search syntax
33	controlled clinical trial/
34	multicenter study/
35	Phase 3 clinical trial/
36	Phase 4 clinical trial/
37	RANDOMIZATION/
38	Single Blind Procedure/
39	Double Blind Procedure/
40	Crossover Procedure/
41	PLACEBO/
42	randomi?ed controlled trial$.tw.
43	rct.tw.
44	(random$ adj2 allocat$).tw.
45	single blind$.tw.
46	double blind$.tw.
47	((treble or triple) adj blind$).tw.
48	Placebo$.tw.
49	Prospective Study/
50	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
Excluded study designs	

Search line	Search syntax
51	Case Study/
52	case report.tw.
53	abstract report/ or letter/
54	editorial/
55	letter/
56	note/
57	51 or 52 or 53 or 54 or 55 or 56
58	50 not 58
59	3 and 30 and 58
Total hits	
60	limit 59 to yr="2020 -Current"

*For further details of the search terms and fields used in EMBASE please see the OVID Database guide: https://ospguides.ovid.com/OSPguides/embase.htm.
Search strategy designed to be compatible with EMBASE indexing system - however, all search strategies were searched in the same 5 key databases (EMBASE, MEDLINE Daily Update, MEDLINE In-Process, In-Data-Review & Other Non-Indexed Citations, APA PsychInfo, Econlit), for completeness.
mp: multi-purpose (i.e. mp after a search term will search for references where this term appears across several fields including the title, abstract, subject heading and author keywords); tw: text word (i.e. tw after a search term will search for reference where the word appears in the title or abstract only).

別添 2：SLR2 に用いた検索式

SLR2: September 2021 (first update search)

Medline (Ovid MEDLINE Daily Update and OVID MEDLINE In-Process, In-Data-Review & Other Non-Indexed Citations) search strategy*, optimized with MeSH terms applicable to EMBASE, used in September 2021 (first update search)

Search line	**Search syntax**
Population	
1	exp Coronavirinae/
2	(coronavirus or covid or covid19 or sars-cov-2 or sarscov2 or Sars-coronavirus-2 or Severe Acute Respiratory Syndrome Coronavirus 20 or 2019-nCoV).mp.
3	1 or 2
Intervention/comparators	
4	Baricitinib.mp.
5	(doxycycline and ivermectin).mp.
6	Famotidine.mp.
7	Fluvoxamine.mp.
8	PF-07321332.mp.
9	sotrovimab.mp.
10	S-217622.mp.

Search line	Search syntax
11	MP-0420.mp.
12	ensovibep.mp.
13	ADG20.mp.
14	MP-0423.mp.
15	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
Included study designs	
16	Randomized Controlled Trials as Topic/
17	randomized controlled trial/
18	Random Allocation/
19	Double Blind Method/
20	Single Blind Method/
21	clinical trial/
22	clinical trial, phase i.pt.
23	clinical trial, phase ii.pt.
24	clinical trial, phase iii.pt.
25	clinical trial, phase iv.pt.
26	controlled clinical trial.pt.
27	randomized controlled trial.pt.
28	multicenter study.pt.

Search line	Search syntax
29	clinical trial.pt.
30	exp Clinical Trials as topic/
31	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	(clinical adj trial$).tw.
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
34	PLACEBOS/
35	placebo$.tw.
36	randomly allocated.tw.
37	(allocated adj2 random$).tw.
38	32 or 33 or 34 or 35 or 36 or 37
39	31 or 38
Excluded study designs	
40	case report.tw.
41	letter/
42	historical article/
43	40 or 41 or 42
44	39 not 43
45	3 and 15 and 44
46	limit 45 to yr="2020 -Current"

Search line	Search syntax
47	limit 46 to yr="2021 -Current"
Total hits	
48	remove duplicates from 47

*For further details of the search terms and fields used in MEDLINE please see the OVID Database guide: https://ospguides.ovid.com/OSPguides/medline.htm#advanced. Search strategy designed to be compatible with EMBASE indexing system - however, all search strategies were searched in the same 5 key databases (EMBASE, MEDLINE Daily Update, MEDLINE In-Process, In-Data-Review & Other Non-Indexed Citations, APA PsychInfo, Econlit), for completeness.
mp: multi-purpose (i.e. mp after a search term will search for references where this term appears across several fields including the title, abstract, subject heading and author keywords); pt: publication type; tw: text word (i.e. tw after a search term will search for reference where the word appears in the title or abstract only).

EMBASE (1974 to 2021) search strategy*, optimized with MeSH terms applicable to EMBASE, used in September 2021 (first update search)

Search line	Search syntax
Population	
1	exp Coronavirinae/
2	(coronavirus or covid or covid19 or sars-cov-2 or sarscov2 or Sars-coronavirus-2 or Severe Acute Respiratory Syndrome Coronavirus 20 or 2019-nCoV).mp.
3	1 or 2
Intervention/comparators	
4	Baricitinib.mp.
5	(doxycycline and ivermectin).mp.

Search line	Search syntax
6	Famotidine.mp.
7	Fluvoxamine.mp.
8	PF-07321332.mp.
9	sotrovimab.mp.
10	S-217622.mp.
11	MP-0420.mp.
12	ensovibep.mp.
13	MP-0423.mp.
14	ADG20.mp.
15	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
Included study designs	
16	Clinical Trial/
17	Randomized Controlled Trial/
18	controlled clinical trial/
19	multicenter study/
20	Phase 3 clinical trial/
21	Phase 4 clinical trial/
22	RANDOMIZATION/
23	Single Blind Procedure/

Search line	Search syntax
24	Double Blind Procedure/
25	Crossover Procedure/
26	PLACEBO/
27	randomi?ed controlled trial$.tw.
28	rct.tw.
29	(random$ adj2 allocat$).tw.
30	single blind$.tw.
31	double blind$.tw.
32	((treble or triple) adj blind$).tw.
33	Placebo$.tw.
34	Prospective Study/
35	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 32 or 34
Excluded study designs	
36	Case Study/
37	case report.tw.
38	abstract report/ or letter/
39	editorial/
40	letter/

Search line	Search syntax
41	note/
42	36 or 37 or 38 or 39 or 40 or 41
43	35 not 42
44	3 and 15 and 43
Total hits	
45	limit 44 to yr="2020 -Current"

*For further details of the search terms and fields used in EMBASE please see the OVID Database guide: https://ospguides.ovid.com/OSPguides/embase.htm.
Search strategy designed to be compatible with EMBASE indexing system - however, all search strategies were searched in the same 5 key databases (EMBASE, MEDLINE Daily Update, MEDLINE In-Process, In-Data-Review & Other Non-Indexed Citations, APA PsychInfo, Econlit), for completeness.
mp: multi-purpose (i.e. mp after a search term will search for references where this term appears across several fields including the title, abstract, subject heading and author keywords); tw: text word (i.e. tw after a search term will search for reference where the word appears in the title or abstract only).

別添 3：SLR3 に用いた検索式

SLR3：May 2022 (updated search)

Medline (Ovid MEDLINE Daily Update and OVID MEDLINE In-Process, In-Data-Review & Other Non-Indexed Citations) search strategy*, optimized with MeSH terms applicable to EMBASE, used in May 2022 (updated search)

Search line	Search syntax
Population	
1	exp Coronavirinae/
2	(coronavirus or covid or covid19 or sars-cov-2 or sarscov2 or Sars-coronavirus-2 or Severe Acute Respiratory Syndrome Coronavirus 20 or 2019-nCoV).mp.
3	1 or 2
Intervention/comparators	
4	(Remdesivir or Veklury or GS-5734).mp.
5	(Prednisone or Deltasone or Prednicot or Rayos or Sterapred or Orasone or A07EA03).mp.
6	(Hydrocortisone or Cortef or Plenadren or NSC*10483).mp
7	(Methylprednisolone or Medrol).mp.
8	(Favipiravir or Favivir or Favir or Avigan or T-705).mp.
9	(Budesonide or Pulmicort).mp.
10	(AT-527 or RO7496998).mp.
11	(REGEN-COV or REGN-COV or Regeneron).mp.

Search line	Search syntax
12	(casirivimab and imdevimab) or (REGN10933 and REGN10987).mp.
13	(VIR-7831 or sotrovimab or GSK4182136 or Xevudy).mp.
14	Camostat mes*late.mp.
15	(Nitazoxanide or Alinia).mp.
16	(Colchicine or Colcrys or Mitigare).mp.
17	(Molnupiravir or MK-4482 or EIDD-2801).mp.
18	Bamlanivimab.mp.
19	(bamlanivimab and etesevimab).mp.
20	LY-CoV555.mp.
21	(LY-CoV555 and LYCoV016).mp.
22	((AZD7442 or AZD8895) and AZD1061).mp.
23	(Regdanvimab or Regkirona or CT-P59).mp.
24	Peginterferon Lambda-1.mp.
25	(Baricitinib or Olumiant).mp.
26	(doxycycline and ivermectin) or (Doxteric or Stromectol).mp.
27	(Famotidine or Pepcid).mp.
28	(Fluvoxamine or Floxyfral or Luvox).mp.
29	(Paxlovid or (nirmatrelvir and ritonavir) or PF-07321332).mp.
30	(Ensitrelvir or Xocova or S-217622).mp.
31	MP-0420.mp.
32	Ensovibep.mp.

Search line	Search syntax
33	ADG20.mp.
34	MP-0423.mp.
35	(Kineret or anakinra).mp.
36	Lenzilumab.mp.
37	(Bebtelovimab or LY-CoV1404 or LY3853113)
38	(Umifenovir or Arbidol)
39	(Clevudine or Levovir or Revovir)
40	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
Included study designs	
41	Randomized Controlled Trials as Topic/
42	randomized controlled trial/
43	Random Allocation/
44	Double Blind Method/
45	Single Blind Method/
46	clinical trial/
47	clinical trial, phase i.pt
48	clinical trial, phase ii.pt
49	clinical trial, phase iii.pt
50	clinical trial, phase iv.pt
51	controlled clinical trial.pt

Search line	Search syntax
52	randomized controlled trial.pt
53	multicenter study.pt
54	clinical trial.pt
55	exp Clinical Trials as topic/
56	41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55
57	(clinical adj trial$).tw
58	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw
59	PLACEBOS/
60	placebo$.tw
61	randomly allocated.tw
62	(allocated adj2 random$).tw
63	57 or 58 or 59 or 60 or 61 or 62
64	56 or 63
Excluded study designs	
65	case report.tw
66	letter/
67	historical article/
68	65 or 66 or 67
69	64 not 68
70	3 and 40 and 69
Total hits	

Search line	Search syntax
71	limit 70 to yr="2021-Current" and deduplicate

*For further details of the search terms and fields used in MEDLINE please see the OVID Database guide: https://ospguides.ovid.com/OSPguides/medline.htm#advanced
mp: multi-purpose (i.e. mp after a search term will search for references where this term appears across several fields including the title, abstract, subject heading and author keywords); pt: publication type; tw: text word (i.e. tw after a search term will search for reference where the word appears in the title or abstract only).

EMBASE (1974 to 2021) search strategy*, optimized with MeSH terms applicable to EMBASE, used in September 2021 (first update search)

Search line	Search syntax
Population	
1	exp Coronavirinae/d
2	(coronavirus or covid or covid19 or sars-cov-2 or sarscov2 or Sars-coronavirus-2 or Severe Acute Respiratory Syndrome Coronavirus 20 or 2019-nCoV).mp.
3	1 or 2
Intervention/comparators	
4	(Remdesivir or Veklury or GS-5734).mp.
5	(Prednisone or Deltasone or Prednicot or Rayos or Sterapred or Orasone or A07EA03).mp.
6	(Hydrocortisone or Cortef or Plenadren or NSC*10483).mp
7	(Methylprednisolone or Medrol).mp.
8	(Favipiravir or Favivir or Favir or Avigan or T-705).mp.
9	(Budesonide or Pulmicort).mp.
10	(AT-527 or RO7496998).mp.

Search line	Search syntax
11	(REGEN-COV or REGN-COV or Regeneron).mp.
12	(casirivimab and imdevimab) or (REGN10933 and REGN10987).mp.
13	(VIR-7831 or sotrovimab or GSK4182136 or Xevudy).mp.
14	Camostat mes*late.mp.
15	(Nitazoxanide or Alinia).mp.
16	(Colchicine or Colcrys or Mitigare).mp.
17	(Molnupiravir or MK-4482 or EIDD-2801).mp.
18	Bamlanivimab.mp.
19	(bamlanivimab and etesevimab).mp.
20	LY-CoV555.mp.
21	(LY-CoV555 and LYCoV016).mp.
22	((AZD7442 or AZD8895) and AZD1061).mp.
23	(Regdanvimab or Regkirona or CT-P59).mp.
24	Peginterferon Lambda-1.mp.
25	(Baricitinib or Olumiant).mp.
26	(doxycycline and ivermectin) or (Doxteric or Stromectol).mp.
27	(Famotidine or Pepcid).mp.
28	(Fluvoxamine or Floxyfral or Luvox).mp.
29	(Paxlovid or (nirmatrelvir and ritonavir) or PF-07321332).mp.
30	(Ensitrelvir or Xocova or S-217622).mp.
31	MP-0420.mp.

Search line	Search syntax
32	Ensovibep.mp.
33	ADG20.mp.
34	MP-0423.mp.
35	(Kineret or anakinra).mp.
36	Lenzilumab.mp.
37	(Bebtelovimab or LY-CoV1404 or LY3853113)
38	(Umifenovir or Arbidol)
39	(Clevudine or Levovir or Revovir)
40	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
Included study designs	
41	Clinical Trial/
42	Randomized Controlled Trial/
43	controlled clinical trial/
44	multicenter study/
45	Phase 3 clinical trial/
46	Phase 4 clinical trial/
47	RANDOMIZATION/
48	Single Blind Procedure/
49	Double Blind Procedure/
50	Crossover Procedure/

Search line	Search syntax
51	PLACEBO/
52	randomi?ed controlled trial$.tw.
53	rct.tw.
54	(random$ adj2 allocat$).tw.
55	single blind$.tw.
56	double blind$.tw.
57	((treble or triple) adj blind$).tw.
58	Placebo$.tw.
59	Prospective Study/
60	41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
Excluded study designs	
61	Case Study/
62	case report.tw.
63	abstract report/ or letter/
64	editorial/
65	letter/
66	note/
67	61 or 62 or 63 or 64 or 65 or 66
68	60 not 67
69	3 and 40 and 68

Search line	Search syntax
Total hits	
70	limit 69 to yr="2021-Current"

*For further details of the search terms and fields used in EMBASE please see the OVID Database guide: https://ospguides.ovid.com/OSPguides/embase.htm
mp: multi-purpose (i.e. mp after a search term will search for references where this term appears across several fields including the title, abstract, subject heading and author keywords); tw: text word (i.e. tw after a search term will search for reference where the word appears in the title or abstract only).

別添 4: SLR4 に用いた検索式

SLR 4: December 2022 (updated search)

Embase and MEDLINE (MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions) search strategy*, optimized with MeSH terms applicable to EMBASE, used in December 2022 (updated search)

Search line	Search syntax
Population	
1	exp Coronavirinae/
2	(coronavirus or covid or covid19 or sars-cov-2 or sarscov2 or Sars-coronavirus-2 or Severe Acute Respiratory Syndrome Coronavirus 20 or 2019-nCoV).mp.
3	1 or 2
Intervention/comparators	
4	(Remdesivir or Veklury or GS-5734).mp.
5	(Prednisone or Deltasone or Prednicot or Rayos or Sterapred or Orasone or A07EA03).mp.
6	(Hydrocortisone or Cortef or Plenadren or NSC*10483).mp
7	(Methylprednisolone or Medrol).mp.
8	(Favipiravir or Favivir or Favir or Avigan or T-705).mp.
9	(Budesonide or Pulmicort).mp.
10	(AT-527 or RO7496998).mp.
11	(REGEN-COV or REGN-COV or Regeneron).mp.

Search line	Search syntax
12	(casirivimab and imdevimab) or (REGN10933 and REGN10987).mp.
13	(VIR-7831 or sotrovimab or GSK4182136 or Xevudy).mp.
14	Camostat mes*late.mp.
15	(Nitazoxanide or Alinia).mp.
16	(Colchicine or Colcrys or Mitigare).mp.
17	(Molnupiravir or MK-4482 or EIDD-2801).mp.
18	Bamlanivimab.mp.
19	(bamlanivimab and etesevimab).mp.
20	LY-CoV555.mp.
21	(LY-CoV555 and LYCoV016).mp.
22	((AZD7442 or AZD8895) and AZD1061).mp.
23	(Regdanvimab or Regkirona or CT-P59).mp.
24	Peginterferon Lambda-1.mp.
25	(Baricitinib or Olumiant).mp.
26	(doxycycline and ivermectin) or (Doxteric or Stromectol).mp.
27	(Famotidine or Pepcid).mp.
28	(Fluvoxamine or Floxyfral or Luvox).mp.
29	(Paxlovid or (nirmatrelvir and ritonavir) or PF-07321332).mp.
30	(Ensitrelvir or Xocova or S-217622).mp.
31	MP-0420.mp.
32	Ensovibep.mp.

Search line	Search syntax
33	ADG20.mp.
34	MP-0423.mp.
35	(Kineret or anakinra).mp.
36	Lenzilumab.mp.
37	(Bebtelovimab or LY-CoV1404 or LY3853113)
38	(Umifenovir or Arbidol)
39	(Clevudine or Levovir or Revovir)
40	or/4-39
Included study design	
41	Randomized Controlled Trials as Topic/
42	randomized controlled trial/
43	Random Allocation/
44	Double Blind Method/
45	Single Blind Method/
46	clinical trial/
47	clinical trial, phase i.pt
48	clinical trial, phase ii.pt
49	clinical trial, phase iii.pt
50	clinical trial, phase iv.pt
51	controlled clinical trial.pt
52	randomized controlled trial.pt

Search line	Search syntax
53	multicenter study.pt
54	clinical trial.pt
55	exp Clinical Trials as topic/
56	or/41-5
57	(clinical adj trial$).tw
58	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw
59	PLACEBOS/
60	placebo$.tw
61	randomly allocated.tw
62	(allocated adj2 random$).tw
63	or/57-62
64	56 or 63
Excluded study design	
65	case report.tw
66	letter/
67	historical article/
68	65 or 66 or 67
69	64 not 68
Total hits	
71	3 and 40 and 69

*For further details of the search terms and fields used in EMBASE please see the OVID Database guide: https://ospguides.ovid.com/OSPguides/embase.htm

mp: multi-purpose (i.e. mp after a search term will search for references where this term appears across several fields including the title, abstract, subject heading and author keywords); tw: text word (i.e. tw after a search term will search for reference where the word appears in the title or abstract only).

ICHUSHI search strategy used in December 2022

Search line	Search syntax
Population	
1	(コロナウイルス科/TH or コロナウイルス科/AL)
2	(コロナウイルス/TH or コロナウイルス/AL or Coronavirus/AL or コビッド/AL or Covid/AL or COVID-19/TH or COVID-19/AL or コビッド-19/AL or コビッド・ナインティーン/AL or SARS コロナウイルス-2/TH or SARS-COV-2/AL or SARSCOV2/AL or SARS-Coronavirus-2/AL or 重症急性呼吸器症候群コロナウイルス 2/AL or 2019-nCoV/AL or Novel/AL and (コロナウイルス/TH or Coronavirus/AL) or 新型コロナウイルス/AL)
3	#1 or #2
Intervention/comparators	
4	(Remdesivir/TH or レムデシビル/AL or Veklury/AL or ベクルリー/AL or GS-5734/AL)
5	(Prednisone/TH or Prednisone/AL or プレドニゾン/AL or Deltasone/AL or デルタゾン/AL or Prednicort/AL or プレドニコート/AL or Rayos/AL or レイオス/AL or Sterapred/AL or ステラプレド/AL or Orasone/AL or オラソン/AL or A07EA03/AL)
6	(Hydrocortisone/TH or Hydrocortisone/AL or ヒドロコルチゾン/AL or Cortef/AL or コルテフ/AL or Plenadren/AL or プレナドレン/AL or "NSC 10483"/AL)
7	(Methylprednisolone/TH or Methylprednisolone/AL or メチルプレドニゾロン/AL or Medrol/AL or メドロール/AL)
8	(Favipiravir/TH or Favipiravir/AL or ファビピラビル/AL or Favivir/AL or ファビビル/AL or Avifavir/AL or アビファビル/AL or Avigan/AL or アビガン/AL or T-705/AL)
9	(Budesonide/TH or Budesonide/AL or ブデソニド/AL or Pulmicort/AL or パルミコート/AL)

Search line	Search syntax
10	AT-527/AL or RO7496998/AL
11	(REGEN-COV/AL or REGN-COV/AL or Regeneron/AL or 抗体カクテル療法/AL)
12	(Casirivimab/TH or Casirivimab/AL or カシリビマブ/AL) and (Imdevimab/TH or imdevimab/AL or イムデビマブ/AL) or ((Casirivimab/TH or REGN10933/AL) and (Imdevimab/TH or REGN10987/AL)) or (Casirivimab-Imdevimab/TH or カシリビマブ・イムデビマブ/AL)
13	(Sotrovimab/TH or ソトロビマブ/AL or VIR-7831/AL or GSK4182136/AL)
14	(Camostat/TH or "Camostat mesylate"/AL and カモスタットメシル酸塩/AL)
15	(Nitazoxanide/TH or Nitazoxanide/AL or ニタゾキサニド/AL or Alinia/AL or アリニア/AL)
16	(Colchicine/TH or Colchicine/AL or コルヒチン/AL or Colcrys/AL or Mitigare/AL)
17	(Molnupiravir/TH or Molnupiravir/AL or モルヌピラビル/AL or MK-4482/AL or EIDD-2801/AL)
18	(Bamlanivimab/TH or Bamlanivimab/AL or バムラニビマブ/AL)
19	(Bamlanivimab/TH or Bamlanivimab/AL or バムラニビマブ/AL) and (エテセビマブ/AL or etesevimab/AL)
20	LY-CoV555/AL
21	LY-CoV555/AL and LYCoV016/AL
22	(AZD7442/AL or AZD8895/AL) and AZD1061/AL
23	(Regdanvimab/AL or レグダンビマブ/AL) or (Regkirona/AL or レッキロナ/AL) or CT-P59/AL
24	Peginterferon Lambda-1/AL or ペグインターフェロンラムダ-1/AL
25	(Baricitinib/TH or Baricitinib/AL or バリシチニブ/AL or Olumiant/AL or オルミエント/AL)
26	((Doxycycline/TH or Doxycycline/AL or ドキシサイクリン/AL) and (Ivermectin/TH or Ivermectin/AL or イベルメクチン/AL)) or ((Doxycycline/TH or Doxteric/AL or ドクステリック/AL) or (Ivermectin/TH or Stromectol/AL or ストロメクトール/AL))

Search line	Search syntax
27	(Famotidine/TH or Famotidine/AL or ファモチジン/AL or Pepcid/AL or ペプシッド/AL or ペプシド/AL)
28	(Fluvoxamine/TH or Fluvoxamine/AL or フルボキサミン/AL or Floxyfral/AL or フロキシフラル/AL or Luvox/AL or ルボックス/AL)
29	(Nirmatrelvir/TH or ニルマトレルビル/AL or PF-07321332/AL)
30	(Ensitrelvir/TH or ゾコーバ/AL) or (Ensitrelvir/TH or エンシトレルビル/AL) or (Ensitrelvir/TH or S-217622/AL)
31	MP0420/AL
32	Ensovibep/AL
33	ADG20/AL
34	MP-0423/AL
35	(Anakinra/TH or Kineret/AL) or (Anakinra/TH or anakinra/AL)
36	Lenzilumab/AL or レンジルマブ/AL
37	(Bebtelovimab/TH or Bebtelovimab/AL) or (Bebtelovimab/TH or ベブテロビマブ/AL) or (Bebtelovimab/TH or LY-CoV1404/AL) or (Bebtelovimab/TH or LY3853113/AL)
38	(Umifenovir/TH or Arbidol/AL) or (Umifenovir/TH or umifenovir/AL) or (Umifenovir/TH or ウミフェノビル/AL)
39	Levovir/AL or Revovir/AL or (Clevudine/TH or clevudine/AL) or (Clevudine/TH or クレブジン/AL)
40	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39
Included study designs	
41	(ランダム化比較試験/TH or RCT/AL) or ((((ランダム化比較試験/TH or ランダム化/AL) or (ランダム割付け/TH or ランダム化/AL)) or ((ランダム化比較試験/TH or 無作為化/AL) or (ランダム割付け/TH or 無作為化/AL))) and

Search line	Search syntax
	(比較試験/AL or 対照試験/AL))
42	ランダマイズ/AL and コントロール/AL and トライアル/AL
43	(ランダム/AL or 無作為/AL) and 割り付け/AL
44	(二重盲検法/TH or 二重盲検/AL)
45	盲検/AL
46	(臨床試験/TH or 臨床試験/AL)
47	(臨床試験/TH or 臨床試験/AL) and (第 I 相/AL or 第 1 相/AL or フェーズ 1/AL or フェーズ I/AL)
48	(臨床試験/TH or 臨床試験/AL) and (第 II 相/AL or 第 2 相/AL or フェーズ 2/AL or フェーズ II/AL)
49	(臨床試験/TH or 臨床試験/AL) and (第 III 相/AL or 第 3 相/AL or フェーズ 3/AL or フェーズ III/AL)
50	(臨床試験/TH or 臨床試験/AL) and (第 IV 相/AL or 第 4 相/AL or フェーズ 4/AL or フェーズ IV/AL or 市販後/AL)
51	比較臨床試験/AL
52	("ランダム化比較試験"/TH or "randomized controlled trial"/AL)
53	多施設/AL and 試験/AL
54	("臨床試験"/TH or "clinical trial"/AL)
55	クリニカルトライアル/AL
56	#41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55
57	クリニカル/AL and トライアル/AL
58	(single/AL or double/AL or trebe/AL or triple/AL) and ((視覚障害者/TH or blind/AL) or (マスク/TH or mask/AL))
59	(プラセボ/TH or プラセボ/AL)

Search line	Search syntax
60	(プラセボ/TH or placebo/AL)
61	randomly allocated/AL
62	ランダム/AL and アロケート/AL
63	#57 or #58 or #59 or #60 or #61 or #62
64	#56 or #63
Excluded study designs	
65	(ケース/AL or 症例/AL) and (レポート/AL or (研究/TH or 研究/AL))
66	(書簡/TH or letter/AL) or レター/AL or 速報/AL
67	ヒストリカル/AL and (記事/AL or (学術論文/TH or 論文/AL) or (研究/TH or 研究/AL))
68	#65 or #66 or #67
69	#64 not #68
70	#3 and #40 and #69
Total hits	
71	#70 and DT=2020/01/01:2022/12/06

別添 5：同定した臨床研究(論文)の詳細

Table 1. Study characteristics of RCTs for antiviral therapies

Author and year, trial identifier(s), enrollment, location	Intervention(s) and comparator	Patient characteristics	*Primary (efficacy) endpoint(s)*	Secondary endpoint(s)
Adhikari *et al*. 2021[16] Adhikari *et al*. 2021 favipiravir Nepal	> Favipiravir > Placebo (mild infection) > Remdesivir (moderate infection)	> Patients (aged 18-80 years) with COVID-19 confirmed with RT-PCR	> Clinical improvement or treatment failure *[Note: Not stated as primary endpoint]*	NR
Bernal *et al.* 2022[17] MOVe-OUT NCT04575597 Multinational	> Molnupiravir: Oral administration, 800 mg total delivered as four 200 mg capsules, BID for 5 days > Placebo: Oral administration, 800 mg delivered as four 200 mg capsules, BID for 5 days	> Non-hospitalized adults with mild or moderate COVID-19 with lab confirmed SARS-CoV-2 infection no more than 5 days prior to study randomization > At least one developed sign or symptom of COVID-19 and at ≥1 risk factor related to severe progression of COVID-19	> Incidence of hospitalization for any cause (defined as ≥24 hours of acute care in a hospital or any similar facility) or death at Day 29 *[Note: The incidence of adverse events was the primary safety end point]*	> WHO 11-point clinical progression scale and patient reported signs and symptoms through Day 29 > The time to sustained resolution or abatement of signs or symptoms

Author and year, trial identifier(s), enrollment, location	Intervention(s) and comparator	Patient characteristics	*Primary (efficacy) endpoint(s)*	Secondary endpoint(s)
Johnson *et al.* 2022b[21] MOVe-OUT NCT04575597 06/06/2021-02/10/2022 (Bernal *et al* 2022)[11] Africa, Asia-Pacific region, Europe, Latin America, North America	> Molnupiravir: Oral administration, 800 mg every 12 hours for 5 days > Placebo: Oral administration, every 12 hours for 5 days	> Non-hospitalized patients (aged ≥18 years) with laboratory confirmed mild-to-moderate COVID-19	> The use of respiratory interventions, (including conventional oxygen therapy, a high flow heated and humidified device, non-invasive mechanical ventilation, and invasive mechanical ventilation), acute care visits, and COVID-19-related acute care visits (mITT population)	NR
Bosaeed *et al.* 2022[22] Bosaeed *et al.* 2022 favipiravir Saudi Arabia	> Favipiravir: Oral administration, 1800 mg (nine tablets) BID as a loading dose on Day 1, followed by 800 mg (four tablets) BID as a maintenance dose for a total duration of 5-7 days of therapy > Placebo: Oral administration, 1800 mg (nine tablets) BID as a loading dose on Day 1 followed by 800 mg (four tablets) BID as a maintenance dose for a total duration of 5-7 days of therapy	> Patients from community settings who had been diagnosed with mild COVID-19	> Time from start of treatment to viral clearance, defined as conversion of SARS-CoV-2 RT-PCR results from positive to negative within 15 days	> Time to symptom resolution, hospitalization > Need to use antibiotics within 15 days after starting the medicine > ICU admission > Adverse events > 28-day mortality

Author and year, trial identifier(s), enrollment, location	**Intervention(s) and comparator**	**Patient characteristics**	***Primary (efficacy) endpoint(s)***	**Secondary endpoint(s)**
Hammond *et al.* 2022[23] EPIC-HR NCT04960202 Multinational	> Nirmatrelvir/ritonavir: 300 mg of nirmatrelvir plus 100 mg of ritonavir every 12 hours for 5 days (10 doses total) > Placebo: Administered every 12 hours for 5 days	> Confirmed SARS-CoV-2 infection and symptom onset no more than 5 days prior to randomization > At least one sign or symptom of COVID-19 on the day of randomization > At least one characteristic or coexisting condition associated with a high risk of progression to severe COVID-19	> Percentage of patients with COVID-19-related hospitalization or death from any cause through Day 28 in the two groups	> Primary comparison analyzed similarly among patients whose treatment began within 5 days after the onset of COVID-19 signs and symptom *[Note: Key endpoint]* > Detection and quantification of SARS-CoV-2 viral load in NP swabs by RT-PCR assay
EPIC-SR 202214	> Nirmatrelvir/ritonavir: Oral administration, every 12 hours for 5 days (10 doses total) > Placebo	> Patients (aged ≥18 years) with confirmed SARS-CoV-2 infection 5 days prior to randomization; initial onset of COVID-19 signs/symptoms within 5 days of randomization	> Self-reported sustained alleviation of all symptoms for 4 consecutive days	> Hospitalizations or deaths > Viral load > Adverse events

Author and year, trial identifier(s), enrollment, location	Intervention(s) and comparator	Patient characteristics	*Primary (efficacy) endpoint(s)*	Secondary endpoint(s)
Holubar *et al.* 2022[25] Holubar *et al.* 2022 favipiravir NCT04346628 US	> Favipiravir: 1800 mg BID on Day 1, then 800 mg BID on Days 2-10 > Placebo: 1800 mg BID on Day 1, then 800mg BID on Days 2-10	> Asymptomatic or symptomatic adults without respiratory distress who had a positive SARS-CoV-2 reverse transcription polymerase chain reaction assay (RT-PCR) collected within 72 hours of enrollment	> SARS-CoV-2 shedding cessation, defined as time from enrollment to the first of two consecutive negative nasal RT-PCRs	> Incidence of hospitalization or emergency department visits > Adverse events graded for severity
Gottlieb *et al.* 2022[26] PINETREE NCT04501952 Denmark, Spain, UK, and US	> Remdesivir: IV administration, 3-day course, 200 mg Day 1 and 100 mg Days 2-3 > Placebo: Same as intervention	> Patients testing positive for COVID-19 within 4 days of the start of study with symptoms for 7 days or less > Aged 12 years or older with at least one risk factor related to severe progression OR > Aged 60 years or older with or without a risk factor linked to severe progression	> COVID-19 related hospitalization or death from any cause by Day 28	> The composite of COVID-19-related medically attended visits or death from any cause by Days 14 and 28 > COVID-19-related hospitalization by Days 14 and 28 > The time-weighted average change in NP SARS-CoV-2 viral load from baseline to Day 7 > The time to alleviation of baseline COVID-19 symptoms as compared with those reported on the baseline FLUpro Plus questionnaire completed before the first infusion

Author and year, trial identifier(s), enrollment, location	Intervention(s) and comparator	Patient characteristics	*Primary (efficacy) endpoint(s)*	Secondary endpoint(s)
Kumarasamy *et al.* 2022[29] Kumarasamy *et al.* 2022 molnupiravir India	> Molnupiravir plus SOC: 800 mg BID of molnupiravir plus SOC for 5 days > SOC	> Adults with mild SARS-CoV-2 infection	> Rate of hospitalization up to Day 14	> Proportion with a 2-point improvement in WHO 11-Point Clinical Progression Scale > Rate of SARS-CoV-2 RT-PCR negativity in naso/oropharyngeal swab at Days 5, 10 and 14 > Incidence of adverse events
Painter *et al.* 2021[30] Painter *et al.* 2021 molnupiravir US	> Molnupiravir: 200 mg BID of molnupiravir for 5 days > Placebo: BID for 5 days	> Patients with signs and symptoms of COVID-19 within 7 days of enrollment, and a positive PCR test within 4 days of enrollment	> Viral load change (rate of positive viral culture at Days 3 and 5)	NR
Fischer *et al.* 2021[31] Fischer *et al.* 2021 molnupiravir [later portion of trial] **Fischer *et al.* 2022**[32] Fischer *et al.* 2022 molnupiravir NCT04405570 19/06/2020-25/01/2021 US	> Molnupiravir 200 mg: Oral administration, 200 mg BID for 5 days > Molnupiravir 400 mg: Oral administration, 400 mg BID for 5 days > Molnupiravir 800 mg: Oral administration, 800 mg BID for 5 days > Matching placebo	> Outpatients (unvaccinated adults) with signs and symptoms of COVID-19 within 7 days of enrollment, and a positive PCR test within 4 days of enrollment	> Time to viral RNA clearance, as measured by qRT-PCR, defined as viral RNA <1,018 copies/mL (limit of quantification)	> Time to infectious virus elimination by study end > Viral RNA change from baseline on Days 3, 5, 7, 14, and 28 > Severity and duration of self-reported COVID-19 symptoms > Adverse events that were grade 3 or higher and those that led to early treatment discontinuation

Author and year, trial identifier(s), enrollment, location	Intervention(s) and comparator	Patient characteristics	*Primary (efficacy) endpoint(s)*	Secondary endpoint(s)
Lowe *et al*. 2022a[33] FLARE NCT04499677 UK	> Favipiravir plus lopinavir-ritonavir: 1800 mg BID on day 1 followed by 400 mg four times daily on Days 2-7 plus lopinavir-ritonavir (400 mg/100 mg BID on Day 1, followed by 200 mg/50 mg four times daily on Days 2-7) > Favipiravir plus placebo > Lopinavir-ritonavir plus placebo > Placebo	> Outpatients with early COVID-19	> SARS-CoV-2 viral load at Day 5, accounting for baseline viral load	> The proportion of participants with undetectable viral loads at Day 5 > Rate of decrease in viral load during the 7-day treatment course > Duration of fever, proportion of participants with medication-related toxicity at Days 7 and 14 > The proportion of participants admitted to hospital or intensive care, or dead due to a COVID-19 related illness

Author and year, trial identifier(s), enrollment, location	Intervention(s) and comparator	Patient characteristics	*Primary (efficacy) endpoint(s)*	Secondary endpoint(s)
Lowe *et al.* 2022b[34] FLARE NCT04499677 06/10/20-04/11/21 UK	> Favipiravir plus lopinavir-ritonavir: Favipiravir administered at a dose of 1800 mg BID on Day 1, followed by 400 mg 4 times daily from Day 2-7; Lopinavir-ritonavir given at a dose of 400 mg/100 mg BID on Day 1, followed by 200 mg/50 mg 4 times daily from Day 2-7 > Favipiravir plus lopinavir-ritonavir placebo > Favipiravir placebo plus lopinavir-ritonavir > Placebos only	> Patients (aged 18-70 years) who had recently (within the last 5 days) developed symptoms of COVID-19, or who had tested positive for SARS-CoV-2 by PCR and were within 7 days of symptom onset, or who were asymptomatic but had tested positive by PCR within the previous 48 hours	> Viral load measured by qPCR performed on saliva samples at Day 5, accounting for the pretreatment Day 1 viral load	> Proportion of participants with undetectable viral loads at Day 5 > Rate of decrease in viral load during the 7-day treatment course > Duration of fever > Proportion of participants with medication-related toxicity at Days 7 and 14 > Proportion of participants admitted to hospital, intensive care of dead due to COVID-19-related illness
MOONSONG 2021[35] MOONSONG	> AT-527: 550 mg BID > AT-527: 1100 mg BID	> Adult mild or moderate COVID-19 patients > High-risk patients with underlying health conditions	> Reduction from baseline in the amount of SARS-CoV-2 virus	NR

Author and year, trial identifier(s), enrollment, location	Intervention(s) and comparator	Patient characteristics	*Primary (efficacy) endpoint(s)*	Secondary endpoint(s)
Ramachandran *et al.* 2022[36] Ramachandran *et al.* 2022 umifenovir CTRI/2020/09/027535 India	> Umifenovir: Oral administration, 800mg BID (2 x 400 mg) for 14 days > Placebo	> Asymptomatic, mild, or moderate patients (aged 18-75 years) at the time of signing an informed consent form with a positive NP swab test	> For mild-asymptomatic patients, the primary endpoint was time from randomization to nasopharyngeal swab negativity by two RT-PCR tests, for SARS-CoV-2 antigens, taken 24 hours apart > For moderate patients, the endpoint was time to improvement by one category from randomization on the WHO 8-category ordinal scale	> Time from randomization to clinical recovery or deterioration, assessed at Days 0, 7, 14, 21, and 28 on the WHO 8-category ordinal scale > The proportion of patients to clinical recovery or deterioration, at Days 0, 7, 14, 21, and 28 on the WHO defined 8-category ordinal scale

Author and year, trial identifier(s), enrollment, location	Intervention(s) and comparator	Patient characteristics	*Primary (efficacy) endpoint(s)*	Secondary endpoint(s)
Ruzhentsova *et al.* 2020[37]* ** Ruzhentsova *et al.* 2021 favipiravir NCT04501783 23/05/2020-30/06/2020 Russia	> Favipiravir: Oral administration at a loading dose of 1800 mg BID (with a 12-hour interval) on Day 1, followed by a maintenance dose 800 mg BID on Days 2-10 > SOC: ○ Umifenovir plus intranasal interferon alpha 2b: 200 mg umifenovir and 10000 IU/mL of interferon alpha 2b (3 drops in each nasal channel five times a day) OR ○ Umifenovir plus hydroxychloroquine: 200 mg umifenovir and 400 mg BID on Day 1 followed by 200 mg BID or 200 mg BID on Day 1 followed by 100 mg BID of hydroxychloroquine *[Note: Both SOC groups were treated for 10 days, and the SOC treatment depended on the severity of the condition of the patient]*	> Patients (aged 18-60 years) with confirmed mild-to-moderate COVID-19 with signs and symptoms of COVID-19 within 6 days of enrollment	> Time to clinical improvement > Time to viral clearance *[Note: Both from randomization to Day 28]*	> Rate of clinical improvement at Days 7 and 14 > Rate of viral clearance at Days 3, 5, 7, 10, 14, 21, and 28 > Time to body temperature normalization > Rate of resolution of lung changes on CT at Day 14 > WHO 8-Category Ordinal Scale at Days 7 and 14 > The time to resolution of the main disease symptoms > The rate of hospitalization for outpatients > The rate of artificial lung ventilation use > The rate of transfer to ICU > The death rate through Day 28 > Safety endpoints *[Note: Key secondary endpoints were the rate of clinical improvement at Day 7 and the rate of viral clearance at Day 5]*

Author and year, trial identifier(s), enrollment, location	**Intervention(s) and comparator**	**Patient characteristics**	***Primary (efficacy) endpoint(s)***	**Secondary endpoint(s)**
Yotsuyanagi *et al.* 2022[38] Yotsuyanagi *et al.* 2022 S-217662/ensitrelvir	> S-217622 (ensitrelvir): 375/125 mg > S-217622 (ensitrelvir): 750/250 mg > Placebo	NR	> Virological response by viral infectious titer	> Pharmacokinetics > Safety outcomes
Zhao *et al.* 2021[39] Zhao *et al.* 2021 favipiravir NCT04333589 China	> Favipirivir: Orally administered, 1600 mg (BID) on the first day, and 600 mg (BID) from Day 2-7. After that, the researchers decided whether to continue favipiravir according to the patient's condition, but no more than 14 days of treatment > Other drugs: Patients assigned to the control group received drugs other than favipiravir and treatment according to the needs of the disease	> Patients positive for COVID-19 via sputum, NP swabs, blood, feces, or other samples	> The primary outcome was time to achieve a consecutive twice (at intervals of more than 24 h) negative RT-PCR result for SARS-CoV-2 RNA in NP swab and sputum sample from the start of the study treatment	> Changes of blood routine and C-reactive protein > Count and proportion of T lymphocyte subsets in peripheral blood > Changes in cytokines

Author and year, trial identifier(s), enrollment, location	Intervention(s) and comparator	Patient characteristics	*Primary (efficacy) endpoint(s)*	Secondary endpoint(s)
Khoo *et al*. 2022[40] AGILE CST-2 NCT04746183 18/11/2020-16/03/2022 UK	> Molnupiravir: Oral administration, 800 mg BID (every 12 h, in the morning and evening with water) for 5 days on Days 1-5 (or Days 1-6 if the first dose was given in the evening), totaling ten 800 mg doses > Placebo: Oral administration, BID (every 12 h; in the morning and evening with water) for 5 days on Days 1-5 (or Days 1-6 if the first dose was given in the evening), totaling ten doses	> Adult outpatients (aged ≥18 years) with PCR-confirmed, mild-to-moderate SARS-CoV-2 infection, who were within 5 days of symptom onset	> The time from randomization to a negative SARS-CoV-2 PCR test	> 11-point WHO Clinical Progression Scale for COVID-19 at Days 15 and 29 > 32-item NEWS2 score (UK Royal College of Physicians, 2017), measuring acute illness, at Days 15 and 29 > FLU-PRO (version 1.2) questionnaire of the presence and severity of influenza-like symptoms across six domains at Days 15 and 29 > Overall survival and mortality > Time to hospital admission, hospitalization rates, duration of mechanical ventilation, duration of oxygen use, oxygen-free days, and the incidence of peripheral capillary oxygen saturation of <92% > Safety

Author and year, trial identifier(s), enrollment, location	Intervention(s) and comparator	Patient characteristics	*Primary (efficacy) endpoint(s)*	Secondary endpoint(s)
Golan *et al.* 2022[41] PRESECO NCT04600895 01/11/2020-01/10/2021 US, Mexico, Brazil	> Favipiravir: Oral administration, 1800 mg BID on Day 1, followed by 800 mg BID on Days 2-10 > Placebo: Oral administration, 9 pills BID on Day 1, followed by 2 pills BID on Days 2-10	> Adult patients (aged ≥18 years) with at least 2 moderate or severe COVID-19 symptoms > First positive RT-PCR or Rapid Antigen assay within 3 days of enrollment > First symptoms within 5 days of enrollment	> Time to sustained clinical recovery, calculated as the number of days from start of study medication to sustained symptom alleviation	> Proportion of patients with COVID-19 progression, defined as requiring emergency department visit or hospitalization > Time to undetectable SARS-CoV-2 load in saliva assays
Zhao *et al.* 2022[42] Zhao *et al.* 2022 arbidol hydrochloride NCT04260594 Patients enrolled by 19/02/2020 China	> SOC plus arbidol: Oral administration, 200 mg per time, 3 times a day for 14 days > SOC: Oral administration, 3 times a day for 14 days	> Patients (aged 18-65 years) with confirmed severe acute respiratory syndrome SARS-CoV-2 infection	> Negative conversion of SARS-CoV-2 within the first week, defined as the percentage of viral negative changes detected in pathogen nucleic acid on Day 7 after administration	> Viral clearance rate in the second week > Overall viral negative conversion rate > Clinical recovery rate > Alleviation of clinical symptoms

Author and year, trial identifier(s), enrollment, location	Intervention(s) and comparator	Patient characteristics	*Primary (efficacy) endpoint(s)*	Secondary endpoint(s)
McMahon *et al.* 2022[43] VIRCO NCT04445467 31/07/2020-19/09/2021 Australia	> Favipiravir: Oral administration, 1800 mg BID on Day 1 followed by 800 mg BID > Placebo: Oral administration, BID	> Adults (aged ≥18 years) with PCR confirmed COVID-19 on NP or combined nose and throat swab and onset of COVID-19 related symptoms (one or more of: fever, cough, sore throat, shortness of breath, fatigue, myalgia) in the prior 5 days	> Time to virological cure, defined as 2 successive swabs negative for SARS-CoV-2 by PCR	> Progression of disease severity > Symptom resolution > Safety
Sirijatuphat *et al.* 2022[44] Sirijatuphat *et al.* 2022 favipiravir TCTR20200514001 12/2020-06/2021 Thailand	> Favipiravir: Oral administration, 1800 mg BID for 1 day (9 tablets per dose) and 800 mg BID (4 tablets per dose) thereafter until clinical improvement or saliva RT–PCR became negative (min-max of 5-14 days) > Symptomatic therapy (placebo): IV fluid administration, oxygen therapy, and medication (e.g., antipyretics, antihistamines, antitussives, etc.) as required by each patient	> Patients (aged ≥18 years) with PCR-confirmed SARS-CoV-2 infection with mild-to-moderate symptoms, without pneumonia	> Time to clinical improvement, defined by a NEWS of ≤1	> Viral load and time to detectable load of SARS-CoV-2 > Safety

Author and year, trial identifier(s), enrollment, location	Intervention(s) and comparator	Patient characteristics	*Primary (efficacy) endpoint(s)*	Secondary endpoint(s)
Zou *et al.* 2022[45] Zou *et al.* 2022 molnupiravir ChiCTR2200056817 03/03/2021-21/03/2022 China	> Molnupiravir plus basic treatment: Oral administration, 800 mg BID for 5 days in the hospital plus basic treatment (vitamin C, lianhuaqingwen granule, and nasal irrigation) > Basic treatment	> Patients (aged ≥18 years and ≤80 years) who tested positive for SARS-CoV-2 Omicron variant and had initial onset of symptoms for ≤5 days prior to the day of treatment	> The time of viral RNA clearance measured using RT-PCR analysis of pharyngeal swab	> Percentage of patients negative for SARS-CoV-2 on Days 5, 7 and 10 > Safety

BID: twice daily; CT: computerized tomography; CTRI: Clinical Trial Registry of India; FLU-PRO: InFLUenza Patient-Reported Outcome; ICU: intensive care unit; IU: incidence units; IV: intravenous; mg: milligram; mITT: modified intention-to-treat; NEWS: National Early Warning Score; NP: nasopharyngeal; NR: not reported; PCR: polymerase chain reaction; RT-PCR: reverse transcription polymerase chain reaction; qPCR: quantitative polymerase chain reaction; RNA: ribonucleic acid; RT-PCR: reverse transcription polymerase chain reaction; RT-qPCR: reverse transcription-quantitative polymerase chain reaction; SCT: standard care treatment; SOC: standard of care; UK: United Kingdom: US: United States; WHO: World Health Organization.

Table 2. Patients baseline characteristics for RCTs for antiviral therapies

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Adhikari *et al*. 2021[16] Adhikari *et al*. 2021 favipiravir	Mild cases > Overall: 70 > Favipiravir: 38 > Placebo: 32 Moderate cases > Overall: 20 > Favipiravir: 11 > Placebo: 9	NR	NR	NR
Bernal *et al.* 2022[17] MOVe-OUT NCT04575597	> Overall: 1433 > Molnupiravir: 716 > Placebo: 717	Median (range) > Overall: 43.0 (18-90) > Molnupiravir: 42.0 (18-90) > Placebo: 44.0 (18-88)	Female, n (%) > Overall: 735 (51.3) > Molnupiravir arm: 384 (53.6) > Placebo arm: 351 (49.0)	≤3 days, n (%) > Overall: 684 (47.7) > Molnupiravir: 342 (47.8) > Placebo: 342 (47.7)
Johnson *et al.* 2022b[21] MOVe-OUT NCT04575597	> Molnupiravir: 716 > Placebo: 717	Median (range) > Molnupiravir: 43 (18-90) > Placebo: 44 (18-88)	Female, n (%) > Molnupiravir: 380 (53.5) > Placebo: 345 (49.2)	Median (range) > Molnupiravir: 4 (1-5) > Placebo: 4 (1-5)
Bosaeed, 2022[22] Bosaeed *et al.* 2022 favipiravir	> Favipiravir: 112 > Placebo: 119	Median (IQR) > Favipiravir: 37 (31.5-45) > Placebo: 36 (32-44)	Male, female, n (%) > Favipiravir: 72 (64.2), 40 (35.7%) > Placebo: 83 (69.7), 36 (30.2)	Median (IQR) > Overall: 3 (2-4)
Hammond *et al.* 2022[23] EPIC-HR NCT04960202	> Overall: 2246 > Nirmatrelvir-ritonavir: 1120 > Placebo: 1126	Median (range) > Overall: 46.00 (18.00-88.00) > Nirmatrelvir-ritonavir: 45.00 (18.00-86.00) > Placebo: 46.00 (18.00-88.00)	Male, n (%), female, n (%) > Overall: 1148 (51.1), 1098 (48.9) > Nirmatrelvir-ritonavir: 566 (50.5%), 554 (49.5) > Placebo: 582 (51.7), 544 (48.3)	> 3 days (mITT population only)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
EPIC-SR 2022[24]	Interim analysis > Nirmatrelvir-ritonavir: 333 > Placebo: 329 Follow-on analysis > Nirmatrelvir-ritonavir: 428 > Placebo: 426	NR	NR	> Within 5 days
Holubar *et al.* 2022[25] Holubar *et al.* 2022 favipiravir NCT04346628	mITT population > Favipiravir: 59 > Placebo: 57 smITT population > Favipiravir: 65 > Placebo: 70	Mean (SD), mITT population > Favipiravir: 43.4 (12.8) > Placebo: 43.4 (12.8) Mean (SD), smITT population > Favipiravir: 42.9 (12.3) > Placebo: 42.8 (12.6)	Female, mITT population, n (%) > Favipiravir: 28 (47.5%) > Placebo: 29 (50.9%) Female, smITT population, n (%) > Favipiravir: 32 (49.2%) > Placebo: 37 (52.9%)	Median (IQR), mITT population > Favipiravir: 5 (3-7) > Placebo: 5 (4-6) Median (IQR), smITT population, > Favipiravir: 5 (3-7) > Placebo: 5 (4-7)
Gottlieb *et al.* 2022[26] PINETREE NCT04501952	> Overall: 562 > Remdesivir: 279 > Placebo: 283	Mean (SD) > Overall: 50 (15) > Remdesivir: 50 (15) > Placebo: 51 (15)	Female, n (%) > Overall: 269 (47.9) > Remdesivir: 131 (47) > Placebo: 138 (48.8)	> Within 7 days
Kumarasamy *et al.* 2022[29] Kumarasamy *et al*. 2022 molnupiravir	> Overall: 1218 > Molnupiravir plus SOC: 608 > SOC: 610	NR *[Note: both arms were balanced for age]*	Male, % > Overall: 65 > Molnupiravir plus SOC: NR > SOC: NR	NR
Painter *et al.* 2021[30] Painter *et al.* 2021 molnupiravir	> Overall: 173	NR	NR	Median (range) > Overall: 4.62 (1.40-7.54)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Fischer *et al.* 2021[31] Fischer *et al.* 2021 molnupiravir [later portion of trial] **Fischer *et al.* 2022[32]** NCT04405570	> Molnupiravir 200 mg: 23 > Molnupiravir 400 mg: 62 > Molnupiravir 800 mg: 55 > Placebo: 62	Median (range) > Molnupiravir 200 mg: 32.0 (19-65) > Molnupiravir 400 mg: 42.5 (19-82) > Molnupiravir 800 mg: 42.0 (18-68) > Placebo: 39.0 (19-71)	Female, n (%) > Molnupiravir 200 mg: 11 (47.8) > Molnupiravir 400 mg: 32 (51.6) > Molnupiravir 800 mg: 27 (49.1) > Placebo: 34 (54.8)	Median (range) > Molnupiravir 200 mg: 4.00 (1.8 to 7.0) > Molnupiravir 400 mg: 4.85 (2.5 to 7.1) > Molnupiravir 800 mg: 4.60 (1.4 to 7.1) > Placebo: 4.55 (1.8 to 7.5)
Lowe *et al.* 2022a[33] FLARE NCT04499677	> Overall: 240 > Favipiravir plus lopinavir-ritonavir: 61 > Favipiravir plus placebo: 59 > Lopinavir-ritonavir plus placebo: 60 > Placebo: 60	Mean (SD) > Overall: 40.6 (12.2) > Favipiravir plus lopinavir-ritonavir: 40.3 (13.1) > Favipiravir plus placebo: 40.3 (12.1) > Lopinavir-ritonavir plus placebo: 38.6 (11.5) > Placebo: 40.6 (12.2)	Male, female, n (%) > Overall: 123 (51.2), 117 (48.8) > Favipiravir plus lopinavir-ritonavir: 31 (50.8), 30 (49.2) > Favipiravir plus placebo: 32 (54.2), 27 (45.8) > Lopinavir-ritonavir plus placebo: 29 (48.3), 31 (51.7) > Placebo: 31 (51.7), 29 (48.3)	≤5 days, >5 days, n (%) > Overall: 157 (65.7), 82 (34.3) > Favipiravir plus lopinavir-ritonavir: 43 (70.5), 19 (29.5) > Favipiravir plus placebo: 39 (66.1), 20 (33.9) > Lopinavir-ritonavir plus placebo: 38 (63.3), 22 (36.7) > Placebo: 37 (62.7), 22 (37.3)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Lowe *et al.* 2022b[34] FLARE NCT04499677	> Overall: 240 > Favipiravir plus lopinavir-ritonavir: 61 > Favipiravir plus placebo: 59 > Lopinavir-ritonavir plus placebo: 60 > Placebo: 60	Mean (SD) > Overall: 40 (12.2) > Favipiravir plus lopinavir-ritonavir: 40.3 (13.1) > Favipiravir plus placebo: 40.3 (12.1) > Lopinavir-ritonavir plus placebo: 38.6 (11.5) > Placebo: 40.6 (12.2)	Male, female, n (%) > Overall: 123 (51.2), 117 (48.8) > Favipiravir plus lopinavir-ritonavir: 31 (50.8), 30 (49.2) > Favipiravir plus placebo: 32 (54.2), 27 (45.8) > Lopinavir-ritonavir plus placebo: 29 (48.3), 31 (51.7) > Placebo: 31 (51.7), 29 (48.3)	≤5 days, >5 days, n (%) > Overall: 157 (65.7), 82 (34.3) > Favipiravir plus lopinavir-ritonavir: 43 (70.5), 18 (29.5) > Favipiravir plus placebo: 39 (66.1), 20 (33.9) > Lopinavir-ritonavir plus placebo: 38 (63.3), 22 (36.7) > Placebo: 37 (62.7), 22 (37.3)
MOONSONG 2021[35] MOONSONG	Prespecified subgroup analysis > AT-527 550 mg: 7 > Placebo: 11 Exploratory subgroup analysis > AT-527 1100 mg: 7 > Placebo: 11	Mean > Overall: 37	NR	NR

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Ramachandran *et al.* 2022[36] Ramachandran *et al.* 2022 umifenovir CTRI/2020/09/027535	> Umifenovir: 60 o Mild/asymptomatic: 40 o Moderate: 20 > Placebo: 63 o Mild/asymptomatic: 42 o Moderate: 21	Mean (SE) > Umifenovir: 46.08 (1.93) o Mild-asymptomatic: 42.35 (2.38) o Moderate: 53.55 (2.61) > Placebo: 47.35 (1.96) o Mild-asymptomatic: 45.50 (2.45) o Moderate: 51.05 (3.71)	Male, female, n (%) > Umifenovir: 48 (80), 12 (20) o Mild-asymptomatic: 31 (78), 9 (23) o Moderate: 17 (85), 3 (15) > Placebo: 44 (70), 19 (30) o Mild-asymptomatic: 28 (67), 14 (33) o Moderate: 16 (78), 5 (24)	No more than 7 days (for mild cases)
Ruzhentsova *et al.* 2020[37]* ** Ruzhentsova *et al.* 2021 favipiravir NCT04501783	> Favipiravir: 112 (83 outpatients) > SOC: 56 (44 outpatients)	Mean (SD) > Favipiravir: 41.7 (10.6) > SOC: 42.0 (10.4)	Male, n (%) > Favipiravir: 63 (56.2) > SOC: 26 (46.6)	Mean (SD), ≤3 days, 4 to 6 days, n (%) > Favipiravir: 3.5 (1.4), 53 (47.3), 59 (52.7) > SOC: 3.6 (1.4), 24 (42.9), 32 (57.1)
Yotsuyanagi *et al.* 2022[38] Yotsuyanagi *et al.* 2022 S-217622/ensitrelvir	> Overall: 46 > Ensitrelvir 375/125 mg: 23 > Ensitrelvir 750/250 mg: 23 *[Note: Numbers reported assume no participants discontinued the study]*	NR	NR	NR
Zhao *et al.* 2021[39] Zhao *et al.* 2021 favipiravir NCT04333589	> Overall: 55 > Favipiravir: 36 > Control: 19	Mean (SD) > Overall: 55.7 (13.6) > Favipiravir: 55.8 (14.2) > Control: 55.5 (12.6)	Female, male, n (%) > Overall: 30 (54.5), 25 (45.5) > Favipiravir: 20 (55.6), 16 (44.4) > Control: 10 (52.6), 9 (47.4)	NR

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Khoo *et al*. 2022[40] AGILE CST-2 NCT04746183	> Overall: 180 > Molnupiravir: 90 > Placebo: 90	Median (IQR) > Overall: 43 (28-55) > Molnupiravir: 45 (31-55) > Placebo: 43 (28-54)	Male, female, n (%) > Overall: 77 (43), 103 (57) > Molnupiravir: 38 (42), 52 (58) > Placebo: 39 (43), 51 (57)	Median (IQR) > Overall: 3.0 (3.0-4.0) > Molnupiravir: 3.5 (3.0-4.0) > Placebo: 3.0 (3.0-4.0)
Golan *et al.* 2022[41] PRESECO NCT04600895	> Favipiravir: 599 > Placebo: 588	Aged <60 years, n (%) > Favipiravir: 506 (84.5) > Placebo: 506 (86.1) Aged ≥60 years, n (%) > Favipiravir: 93 (15.5) > Placebo: 82 (13.9)	Male, n (%), female, n (%) > Favipiravir: 282 (47.1), 317 (52.9) > Placebo: 261 (44.4), 327 (55.6)	Median (min-max) > Favipiravir: 3 (0-6) > Placebo: 3 (0-7)
Zhao *et al.* 2022[42] Zhao *et al.* 2022 arbidol hydrochloride NCT04260594	> Overall: 97 > SOC plus arbidol: 64 > SOC: 33	Mean (SD) > Overall: 46.51 (11.23) > SOC plus arbidol: 46.16 (11.21) > SOC: 47.18 (11.42)	Male, n (%) > Overall: 44 (45.4) > SOC plus arbidol: 27 (42.2) > SOC: 17 (51.5)	NR
McMahon *et al.* 2022[43] VIRCO NCT04445467	> Favipiravir: 99 > Placebo: 100	Median (IQR) > Favipiravir: 36.0 (28.0-49.0) > Placebo: 35.0 (27.5-52.5)	Male, n (%) > Favipiravir: 55 (55.6) > Placebo: 54 (54.0)	NR
Sirijatuphat *et al.* 2022[44] Sirijatuphat *et al.* 2022 favipiravir TCTR20200514001	> Favipiravir: 64 > Placebo: 32	Median (IQR) > Favipiravir: 32 (27-39) > Placebo: 28 (25-35)	Male, n (%) > Favipiravir: 21 (33.9) > Placebo: 12 (38.7)	Median (IQR) > Favipiravir: 0 (0-7) > Placebo: 0 (0-6)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Zou *et al.* 2022[45] Zou *et al.* 2022 molnupiravir ChiCTR2200056817	> Molnupiravir plus basic treatment: 80 > Basic treatment: 36	Median (range) > Molnupiravir plus basic treatment: 39 (20-63) > Basic treatment: 42 (22-61)	Male, n (%) > Molnupiravir plus basic treatment: 43 (55.8) > Basic treatment: 17 (54.8)	≤5 days prior to the day of treatment

CTRI: Clinical Trial Registry of India; IQR: interquartile range; mg: milligram; ITT: intention-to-Treat; mITT: modified intention-to-treat population; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; smITT: symptomatic modified intention-to-treat population; SOC: standard of care; US: United States.

Table 3. Results from RCTs assessing antiviral therapies; primary outcome(s)

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Adhikari *et al*. 2021[16] Adhikari *et al*. 2021 favipiravir	Mild cases > Clinical improvement, n (%): o Favipiravir: 30 (78.9) o Placebo: 27 (84.4) > Treatment failure, n (%): o Favipiravir: 8 (21.1) o Placebo: 5 (15.6) Moderate cases > Clinical improvement, n (%): o Favipiravir: 9 (81) o Placebo: 8 (88.9) > Treatment failure, n (%): o Favipiravir: 2 (18.2) o Placebo: 1 (11.1)	Patients who experienced an AE, n (%) > Favipiravir: 3 (6.12) > Remdesivir: 0 (0.0) > Placebo: 0 (0.0)
Bernal *et al*. 2022[17] MOVe-OUT NCT04575597	Number of hospitalizations or deaths through Day 29 in all-randomized sample, n (%) > Molnupiravir: 48/709 (6.8) > Placebo: 68/699 (9.7) > Difference: -3.0% (95% CI: -5.9 to -0.1)	Participants who experienced ≥1 AE, n (%) > Molnupiravir: 216/710 (30.4) > Placebo: 231/701 (33) > Estimated Difference: -2.5 Participants who experienced ≥1 SAE, n (%) > Molnupiravir: 49/710 (6.9) > Placebo: 67/701 (9.6) > Estimated Difference: -2.7
Johnson *et al*. 2022b[20] MOVe-OUT NCT04575597	Proportion of patients requiring all respiratory interventions (mITT population), n (%) > Molnupiravir: 42 (5.9) > Placebo: 63 (9.0) > RRR (95% CI): 34.3% (4.3-54.9) Proportion of patients requiring all respiratory interventions (hospitalized mITT population), n (%) > Molnupiravir: 31 (64.6) > Placebo: 55 (82.1) > RRR (95% CI): 21.3% (0.2-38.0)	NR

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Bosaeed *et al.* 2022[22] Bosaeed *et al.* 2022 favipiravir	Time (days) to viral clearance within 15 days, median (IQR) > Favipiravir: 10 (6-12) > Placebo: 8 (6-12) > HR: 0.87 for the favipiravir group (95% CI: 0.571-1.326; p=0.51) *[Note: Endpoints for hospitalization or death are also available in the DEF]*	NR
Hammond *et al.* 2022[23] EPIC-HR NCT04960202	COVID-19-related hospitalization or all-cause mortality by Day 28 (interim analysis), n (%) > Nirmatrelvir plus ritonavir: 3/389 (0.77) > Placebo: 27/385 (7.01) > Difference: -6.32% (95% CI: -9.04 to -3.59; P<0.001) > RRR: 89.1% COVID-19-related hospitalization or all-cause mortality by Day 28 (final analysis), n (%) > Nirmatrelvir plus ritonavir: 5/697 (0.72) > Placebo: 44/682 (6.53) > Difference ([95% CI], p-value): -5.81 percentage points ([-7.78 to -3.84], P<0.001) > RRR: 88.9% *[Note: Further endpoints for hospitalization or death are available in the DEF]*	Patients who experienced an AE, n (%) > Nirmatrelvir plus ritonavir: 251/1109 (22.6) > Placebo: 266/1115 (23.9) Patients who experienced a SAE, n (%) > Nirmatrelvir plus ritonavir: 18/1109 (1.6) > Placebo: 74/1115 (6.6)
EPIC-SR 2022[24]	Incidence of hospitalization or death (interim analysis), n > Nirmatrelvir plus ritonavir: 2/333 > Placebo: 8/329 Incidence of hospitalization or death (follow on analysis), n > Nirmatrelvir plus ritonavir: 3/428 > Placebo: 10/426 > Reduction: 70%, p=0.051	Patients who experienced a TEAE, % > Nirmatrelvir plus ritonavir: 22 > Placebo: 21 Patients who experienced a SAE, %: > Nirmatrelvir plus ritonavir: 1.4 > Placebo: 1.9

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Holubar *et al.* 2022[25] Holubar *et al.* 2022 favipiravir NCT04346628	Time (days) until shedding cessation, median (IQR) > Favipiravir: 14 (9-21) > Placebo: 13 (9-14) > Adjusted HR: 0.76 (CI: 0.481.20; p=0.24) *[Note: Endpoints for hospitalization are also available in the DEF]*	Occurrence of AEs through Day 28, n > Favipiravir: 27 > Placebo: 15
Gottlieb *et al.* 2022[26] PINETREE NCT04501952	COVID-19-related hospitalization or all-cause mortality by Day 28, n (%) > Remdesivir: 2/279 (0.7) > Placebo: 15/283 (5.3) > Risk reduction: 87% > HR ([95% CI], p-value): 0.13 ([0.03-0.59], p=0.008)	Occurrence of AEs, n (%) > Remdesivir: 118/279 (42.3) > Placebo: 131/283 (46.3) Occurrence of SAEs, n (%) > Remdesivir: 5/279 (1.8) > Placebo: 19/283 (6.7)
Kumarasamy *et al*. 2022[29] Kumarasamy *et al*. 2022 molnupiravir	Proportion of patients requiring hospitalization by Day 14, n (%) > Molnupiravir plus SOC: 9 (1.5) > SOC: 26 (4.3)	Patients who experienced a mild and self-limiting AE, % > Molnupiravir plus SOC: 4.8 > SOC: 2.6 Patients who experienced a SAE, % > Molnupiravir plus SOC: 0 > SOC: 0
Painter *et al.* 2021[30] Painter *et al.* 2021 molnupiravir	Patients receiving molnupiravir were more likely to have a negative viral culture versus placebo at Day 3 (p=0.56) and Day 5 (p=0.001) *[Note: Total patients analyzed n=78]*	NR

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Fischer *et al.* 2021[31] Fischer *et al.* 2021 molnupiravir [later portion of trial] **Fischer *et al*. 2022[32]** NCT04405570	Time (days) to viral clearance, median (95% CI) > Molnupiravir 200 mg: 22 (15.0-28.0) > Molnupiravir 400 mg: 27 (15.0-28.0) > Molnupiravir 800 mg: 14 (13.0-14.0) > Placebo: 15 (15.0-27.0) Molnupiravir 800 mg was significantly superior to placebo (p=0.013), and the placebo was non-significantly superior to molnupirvir 200 mg and 400 mg (p>0.5)	Patients who experienced an AE, n (%) > Molnupiravir 200 mg: 11 (48) > Molnupiravir 400 mg: 20 (32) > Molnupiravir 800 mg: 11 (20) > Placebo: 18 (29) Patients who experienced any AE leading to death, n > Molnupiravir 200 mg: 0 > Molnupiravir 400 mg: 0 > Molnupiravir 800 mg: 0 > Placebo: 1 Patients who experienced a SAE, n (%) > Molnupiravir 200 mg: 0 (0) > Molnupiravir 400 mg: 2 (3) > Molnupiravir 800 mg: 1 (2) > Placebo: 1 (2)
Lowe *et al.* 2022a[33] FLARE NCT04499677	Undetectable viral load (log_{10}) at Day 5 (ITT population) accounting for baseline viral load, coefficient ([95% CI], p-value) > Favipiravir plus lopinavir-ritonavir: 0.59 ([-0.32 to 1.50], p=0.20) > Favipiravir plus placebo: -0.57 ([-1.21 to 0.07], p=0.08) > Lopinavir-ritonavir plus placebo: -0.18 ([-0.82 to 0.46], p=0.58) Undetectable viral load (log_{10}) at Day 5 (ITT population) accounting for baseline viral load, coefficient ([95% CI], p-value) > Favipiravir plus lopinavir-ritonavir: 0.65 ([-0.33 to 1.63], p=0.19) > Favipiravir plus placebo: -0.59 ([-1.29 to 0.11], p=0.10) > Lopinavir-ritonavir plus placebo: -0.18 ([-0.87 to 0.51], p=0.61)	Patients who experienced ≥1 related AE, n (%) > Favipiravir plus lopinavir-ritonavir: 53 (87.9) > Favipiravir plus placebo: 27 (45.8) > Lopinavir-ritonavir plus placebo: 56 (93.3) > Placebo: 21 (35.0) Number of related AEs, n (%) > Favipiravir plus lopinavir-ritonavir: 108 (67.9) > Favipiravir plus placebo: 44 (47.3) > Lopinavir-ritonavir plus placebo:116 (65.9) > Placebo: 27 (29.3)

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Lowe *et al.* 2022b[34] FLARE NCT04499677	Change in viral load at Day 5 (ITT population) accounting for baseline viral load, coefficient ([95% CI], p-value) > Favipiravir plus lopinavir-ritonavir: 0.59 ([-0.32 to 1.50], p=0.20) > Favipiravir plus placebo: -0.57 ([-1.21 to 0.07], p=0.08) > Lopinavir-ritonavir plus placebo: -0.18 ([-0.82 to 0.46], p=0.58) Change in viral load at Day 5 (mITT population) accounting for baseline viral load, coefficient ([95% CI], p-value) > Favipiravir plus lopinavir-ritonavir: 0.65 ([-0.33 to 1.63], p=0.19) > Favipiravir plus placebo: -0.59 ([-1.29 to 0.11], p=0.10) > Lopinavir-ritonavir plus placebo: -0.18 ([-0.87 to 0.51], p=0.61)	Patients who experienced ≥1 AE, n (%) > Favipiravir plus lopinavir-ritonavir: 55 (90.1) > Favipiravir plus placebo: 38 (64.4) > Lopinavir-ritonavir plus placebo: 59 (98.3) > Placebo: 39 (65.0) Patients who experienced ≥1 related AE, n (%) > Favipiravir plus lopinavir-ritonavir: 53 (87.9) > Favipiravir plus placebo: 27 (45.8) > Lopinavir-ritonavir plus placebo: 56 (93.3) > Placebo: 21 (35.0) Occurrence of SAE, n > Favipiravir plus lopinavir-ritonavir: 1 > Favipiravir plus placebo: 1 > Lopinavir-ritonavir plus placebo: 1 > Placebo: 0
MOONSONG 2021[35] MOONSONG	Reduction in SARS-CoV-2 viral load from baseline to Day 7 (log_{10}) > AT-527 550 mg: 0.5 > AT-527 1100 mg: 0.5	Patients who experienced an AE, % > AT-527 550 mg: 20 > AT-527 1100 mg: 27 > Placebo: 20 3 non-drug related SAEs in each of the treatment groups
Ramachandran *et al.* 2022[36] Ramachandran *et al.* 2022 umifenovir CTRI/2020/09/027535	Proportion of patients with NP swab negativity on Day 5, n (%) > Umifenovir: 29/40 (73) > Placebo: 17/42 (40) > Difference: 32%, p=0.002 *[Note: the primary efficacy endpoint was "time from randomization to nasopharyngeal swab negativity by two RT-PCR tests, for SARS-CoV-2 antigens, taken 24 hours apart." However, this was presented in a figure in the publication and not reported clearly]*	Patients who experienced an AE, n > Umifenovir: 7 > Placebo: 7

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Ruzhentsova *et al.* 2020[37]* ** Ruzhentsova *et al.* 2021 favipiravir NCT04501783	Time (days) to clinical improvement for outpatient participants, median (IQR) > Favipiravir: 6 (4-12) > SOC: 14 (5-28) > HR: 1.65 (95% CI: 1.08-2.52; p=0.019; significant improvement) Time (days) to viral clearance for outpatient participants, median (IQR) > Favipiravir: 3 (3-3.5) > SOC: 3 (3-7) > HR: 1.11 (95% CI: 0.76-1.61; p=0.46; non-significant) *[Note: Endpoints for hospitalization are also available in the DEF]*	Patients who experienced an AE, n (%)[1] > Favipiravir: 6/83 (7) > SOC: 14/44 (38) Patients who experienced a SAE, n (%)[2] > Favipiravir: 2/83 (2) > SOC: 0/44 (0)
Yotsuyanagi *et al.* 2021[38] Yotsuyanagi *et al*. 2021 ensitrelvir	Viral titer reduction compared with placebo on Day 4: > Ensitrelvir 375/125mg: -3 log_{10} ($TCID_{50}$/mL) (-2.42 log_{10} ($TCID_{50}$/mL) compared to baseline) > Ensitrelvir 750/250mg: -1.54 log_{10} ($TCID_{50}$/mL)	NR
Zhao *et al.* 2021[39] Zhao *et al.* 2021 favipiravir NCT04333589	Time (days) to achieve negative NP and sputum swab, median > Favipiravir: 17 > Control: 26 > HR: 2.1 (95% CI: 1.1–4.0; p=0.038; significant)	Occurrence of AEs, n > Favipiravir: 12 > Control: 7

* During the third update a discrepancy between report and reference was found. Results reported in reference1. Ruzhentsova, T., et al., *Phase 3 trial of coronavir (favipiravir) in patients with mild to moderate COVID-19.* Social Science Research Network Preprint Repository, 2020, 2. Ruzhentsova, T.A., et al., *Phase 3 trial of coronavir (favipiravir) in patients with mild to moderate COVID-19.* Am J Transl Res, 2021. 13(11): p. 12575-12587. for patients who experienced an AE: 80/108 and 33/55 for favipravir and SOC, respectively. Results reported for total population.

** During the third update a discrepancy between report and reference was found. Results reported in reference1. Ruzhentsova, T., et al., *Phase 3 trial of coronavir (favipiravir) in patients with mild to moderate COVID-19.* Social Science Research Network Preprint Repository, 2020, 2. Ruzhentsova, T.A., et al., *Phase 3 trial of coronavir (favipiravir) in patients with mild to moderate COVID-19.* Am J Transl Res, 2021. 13(11): p. 12575-12587. for patients who experienced a SAE: 2/108 and 1/55 favipravir and SOC, respectively. Results reported for total population.

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Khoo *et al*. 2022[40] AGILE CST-2 NCT04746183	Time (days) from randomization to a negative SARS-CoV-2 PCR test, median (95 CI%) > Molnupiravir: 8 (8-9) > Placebo: **11** (10-11) > Molnupiravir group versus placebo group log-rank p-value: 0.074 > Molnupiravir group versus placebo group Breslow-Gehan-Wilcoxon p-value: 0.032	Patients who experienced an AE, n (%) > Molnupiravir: 73 (81) > Placebo: **68 (76)** Patients who experienced a SAE, n (%) > Molnupiravir: 0 (0) > Placebo: **4** (4) Occurrence of treatment discontinuation, n > Molnupiravir: 1 > Placebo: **0**
Golan *et al.* 2022[41] PRESECO NCT04600895	Time (days) to sustained clinical recovery (mITT population), median (95% CI) > Favipiravir: 7 (7-8) > Placebo: 7 (6-8) > Favipiravir group versus placebo group p-value: 0.8	Patients who experienced an AE, n (%) > Favipiravir: 84 (13.8) > Placebo: 89 (14.8) Patients who experienced a SAE, n (%) > Favipiravir: 12 (2.0) > Placebo: 14 (2.3) Patients who experienced a CTCAE Grade 3 or 4 TEAE, n (%) > Favipiravir: 2 (0.3) > Placebo: 1 (0.2) Occurrence of treatment discontinuation due to AE, n (%) > Favipiravir: 7 (1.2) > Placebo: 9 (1.5)
Zhao *et al.* 2022[42] Zhao *et al.* 2022 arbidol hydrochloride NCT04260594	Negative conversion rate of SARS-CoV-2 within the first week, n (%) > SOC plus arbidol: 45 (70.3) > SOC: 14 (42.4) > Difference ([95% CI], p-value): 27.9% ([7.7-48.1], p=0.008)	Patients who experienced an AE, n > SOC plus arbidol: 18 > SOC: 5 Patients who experienced a SAE, n > SOC plus arbidol: 0 > SOC: 0 Occurrence of treatment discontinuation due to AE, n > SOC plus arbidol: 0 > SOC: 0

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
McMahon *et al.* 2022[43] VIRCO NCT04445467	Difference in time to virological cure for favipiravir group versus placebo group > Log-rank p-value: 0.6	Patients who experienced ≥1 AE, n > Favipiravir: 63 > Placebo: 65 Patients who experienced a related AE, n > Favipiravir: 24 > Placebo: 27 Occurrence of a SAE, n > Favipiravir: 14 > Placebo: 9
Sirijatuphat *et al.* 2022[44] Sirijatuphat *et al.* 2022 favipiravir TCTR20200514001	Time (days) to sustained clinical improvement by NEWS, median (range) > Favipiravir: 2 (1-28) > Placebo: 14 (1-28) > Favipiravir group versus placebo group p-value <0.001 Proportion of patients with clinical improvement by NEWS by Day 14, n (%) > Favipiravir: 49 (79.0) > Placebo: 10 (32.3) > Favipiravir group versus placebo group p-value <0.001	Occurrence of AEs, n > Favipiravir: 36 > Placebo: 10 Occurrence of discontinuation due to AE, n > Overall: 1
Zou *et al.* 2022[45] Zou *et al.* 2022 molnupiravir ChiCTR2200056817	Time (days) for viral clearance, median (95% CI): > Molnupiravir plus basic treatment: 9 (7-9) > Basic treatment: 10 (9-11) > Molnupiravir group versus basic treatment group p-value=0.0092	Patients who experienced a grade ≥3 AE, n (%) > Molnupiravir plus basic treatment: 0 (0.0) > Basic treatment: 0 (0.0) Occurrence of treatment discontinuation due to AE, n (%) > Molnupiravir plus basic treatment: 0 (0.0) > Basic treatment: 0 (0.0)

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; COVID-19: Coronavirus disease 2019; CI: confidence interval; CTCAE: common terminology criteria for adverse events; CTRI: Clinical Trial Registry of India; DEF: data extraction form; HR: hazard ratio; mITT: modified intention-to-treat; mg: milligram; mL: milliliter; NEWS: National Early Warning Score; NP: nasopharyngeal; NR: not reported; IQR: interquartile range; ITT: intention-to-treat; RRR: relative risk reduction; SAE: Serious Adverse Event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SOC: standard of care; TEAE: treatment emergent adverse event; UK: United Kingdom; US: United States; WHO: World Health Organization.

Table 4. RCTs assessing neutralizing antibodies

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Weinreich *et al.* 2020[46]	*The BMJ*-MAGIC-WHO	REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with COVID-19	Journal article	REGEN-COV NCT04425629	2
Weinreich *et al.* 2021a[47]	Identified by researchers, outside of the searches specified in section 2	REGEN-COV Antibody Cocktail Clinical Outcomes Study in COVID-19 Outpatients	Journal article (pre-print)		3
Weinreich *et al.* 2021b[48]	OVID	REGEN-COV Antibody Cocktail Combination and Outcomes in Outpatients with COVID-19	Journal article (published)		
Gupta *et al.* 2021[49]	NIH guidelines	Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab	Journal article (pre-print)	COMET-ICE NCT04545060	3
Gupta *et al.* 2022a[50]	OVID	Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients with Mild to Moderate COVID-19	Journal article (published)		
Shapiro *et al.* 2022[52]	CROI 2022	Intramuscular sotrovimab is noninferior to intravenous sotrovimab for COVID-19	Conference abstract	COMET-TAIL NCT04913675	3
Gupta *et al.* 2022c[53]	December ID Week 2022	Safety, Tolerability, and Viral Pharmacodynamics of the IgG Monoclonal Antibody Sotrovimab Administered via Intramuscular Injection for the Treatment of Early Mild-to-Moderate COVID-19	Conference abstract	COMET-PEAK (Parts B and C) NCT04779879	2
Chen *et al.* 2020[54]	OVID	SARS-CoV-2 Neutralizing Antibody LY-CoV555 in outpatients with COVID-19	Journal article	BLAZE-1 NCT04427501	2
Gottlieb *et al.* 2021[55]	OVID	Effect of Bamlanivimab as Monotherapy or in Combination with Etesevimab on Viral Load in Patients with Mild to Moderate COVID-19: a Randomized Clinical Trial	Journal article		
Dougan *et al.* 2021a[56]	OVID	Bamlanivimab + etesevimab for treatment of COVID-19 in high-risk ambulatory patients	Conference abstract		3
Dougan *et al.* 2021b[57]	OVID	Bamlanivimab plus Etesevimab in Mild or Moderate COVID-19	Journal article		
Dougan *et al.* 2022[59]	OVID	A Randomized, Placebo-Controlled Clinical Trial of Bamlanivimab and Etesevimab Together in High-Risk Ambulatory Patients With COVID-19 and Validation of the Prognostic Value of Persistently High Viral Load	Journal article		

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Chen *et al.* 2022[60]	Clinicaltrials.gov	Bamlanivimab and Etesevimab Improve Symptoms and Associated Outcomes in Ambulatory Patients at Increased Risk for Severe Coronavirus Disease 2019: Results from the Placebo-Controlled Double-Blind Phase 3 BLAZE-1 Trial	Journal article		2/3 (Results from phase 3)
Williams *et al.* 2022[61]	ATS 2021-2022	Bebtelovimab, Alone and Together with Bamlanivimab and Etesevimab, as a Broadly Neutralizing Monoclonal Antibody Treatment and a Slow Intravenous Push Option for Ambulatory COVID-19	Conference abstract	BLAZE-4 NCT4634409	2
Davis *et al.* 2022[62]	OVID	Pharmacokinetics and pharmacodynamics of casirivimab and imdevimab in a dose-ranging study in outpatients with COVID-19	Conference abstract	Davis *et al*. 2022 casirivimab/imdevimab NCT04666441	2
Huang *et al.* 2021[63]	OVID	Effectiveness of casirivimab and imdevimab, and sotrovimab during Delta variant surge: a prospective cohort study and comparative effectiveness randomized trial	Journal article (pre-print)	UPMC Quality Improvement Review Committee Project ID 3282. University of Pittsburgh Institutional Review Board STUDY210220179 NCT04790786	4 *(Please note that this is described as a phase 4 (post-marketing) trial; however, patients were randomized to treatment, rather than assigned according to physician's discretion.)*
Chew *et al.* 2021[64]	OVID	Bamlanivimab reduces nasopharyngeal SARS-CoV-2 RNA levels but not symptom duration in non-hospitalized adults with COVID-19	Journal article (pre-print)	ACTIV-2/A5401 NCT04518410	2
Chew *et al.* 2022[65]	OVID	Antiviral and clinical activity of bamlanivimab in a randomized trial of non-hospitalized adults with COVID-19	Journal article		
Boucau *et al.* 2022[66]	OVID	Monoclonal antibody treatment drives rapid culture conversion in SARS-CoV-2 infection	Journal article		2/3
Kumarasamy *et al.* 2022[67]	CROI 2022	Interim results from the randomized, controlled EMPATHY phase II/III study evaluating ensovibep, a DARPin therapeutic, in patients with mild to moderate COVID-19	Conference abstract	EMPATHY NCT04828161	2/3
Streinu-Cercel *et al.* 2022[68]	OVID	Efficacy and Safety of Regdanvimab (CT-P59): A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Trial in Outpatients with Mild to Moderate Coronavirus Disease 2019	Journal article	CT-P59 NCT04602000	2/3 (Results from phase 2)

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Montgomery *et al.* 2022a[69]	ECCMID 2022	Efficacy and safety of intramuscular administration of AZD7442 (tixagevimab/cilgavimab) for early outpatient treatment of COVID-19: the TACKLE phase III trial	Conference abstract	TACKLE NCT04723394	3
Montgomery *et al.* 2022b[70]	Clinicaltrials.gov	Efficacy and safety of intramuscular administration of tixagevimab-cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomized, double-blind, placebo-controlled trial	Journal article		
Hobbs *et al.* 2022[71]	December ID Week 2022	Outpatient Treatment With the SARS-CoV-2-Neutralizing Antibody Combination AZD7442 (Tixagevimab/Cilgavimab) for Preventing COVID-19 Hospitalizations in the Phase 3 TACKLE Trial	Conference abstract		
STAMP 2022[72]	Adagio Therapeutics 2022	Adagio Therapeutics Announces ADG20 (adintrevimab) is the First Monoclonal Antibody to Meet Primary Endpoints with Statistical Significance Across Pre- and Post-exposure Prophylaxis and Treatment for COVID-19 and Plans to Seek US Emergency Use Authorization	Press release	STAMP	2/3
O'Brien *et al.* 2022[73]	OVID	Effect of Subcutaneous Casirivimab and Imdevimab Antibody Combination vs Placebo on Development of Symptomatic COVID-19 in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Clinical Trial	Journal article	O'Brien *et al.* 2022 casirivimab/imdevimab NCT04452318	3
Mazzaferri *et al.* 2022[74]	OVID	Exploratory data on the clinical efficacy of monoclonal antibodies against SARS-CoV-2 Omicron variant of concern	Journal article	MANTICO NCT05205759	3
Portal-Celhay *et al.* 2022[75]	OVID	Virologic Efficacy of Casirivimab and Imdevimab COVID-19 Antibody Combination in Outpatients With SARS-CoV-2 Infection A Phase 2 Dose-Ranging Randomized Clinical Trial	Journal article	Portal-Celhay *et al.* 2022 casirivimab/imdevimab NCT04666441	2
Kim *et al.* 2022[76]	OVID	A Randomized Clinical Trial of Regdanvimab in High-Risk Patients with Mild-to-Moderate Coronavirus Disease 2019	Journal article	Kim *et al.* 2022 regdanvimab NCT04602000	3
Schilling *et al.* 2022[77]	OVID	Pharmacometric assessment of the in vivo antiviral activity of ivermectin in early symptomatic COVID-19	Journal article (pre-print)	PLATCOV NCT05041907	2

BMJ: British Medical Journal; COVID-19: COVID-19: Coronavirus disease 2019; MAGIC: Making GRADE the Irresistible Choice; NIH: National Institutes of Health; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; US: United States; WHO: World Health Organization.

Table 5. Study characteristics of RCTs for neutralizing antibodies

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Weinreich *et al.* 2020[46] REGEN-COV (phase 2 portion) NCT04425629 16/06/2020-13/08/2020 US	> 2.4 g casirivimab/imdevimab: IV administration, 250 mL of 2.4 g ReGN-COV2 (casirivimab/imdevimab in equal doses) over one hour on Day 1 (single dose) > 8 g casirivimab/imdevimab: IV adminstration, 250 mL of 8 g ReGN-COV2 (casirivimab/imdevimab in equal doses) over one hour on Day 1 (single dose) > Placebo: IV administration, 250 mL of saline placebo over one hour on Day 1 (single dose)	> Patients (aged ≥18 years) with confirmed SARS-CoV-2 infection (positive test ≤72 hours before randomization and symptom onset ≤7 days before randomization), non-hospitalized, and oxygen saturation ≥93% of room air	> Viral load change through Day 7 > Physician visit rate through Day 29	NR

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Weinreich *et al.* 2021[47],[48] REGEN-COV (phase 3 portion) NCT04425629 24/09/2020-17/01/2021 US, Chile, Mexico, Romania	> 1.2 g casirivimab/imdevimab (low dose): IV administration, 250 mL of 1.2 g ReGN-COV2 (casirivimab/imdevimab in equal doses) over one hour on Day 1 (single dose) > 2.4 g casirivimab/imdevimab (high dose): IV administration, 250 mL of 2.4 g ReGN-COV2 (casirivimab/imdevimab in equal doses) over one hour on Day 1 (single dose) > Placebo: IV administration, 250 mL of saline placebo over one hour on Day 1 (single dose)	> Patients (aged ≥18 years) with confirmed SARS-CoV-2 infection (positive test ≤72 hours before randomization and symptom onset ≤7 days before randomization), non-hospitalized, and oxygen saturation ≥93% of room air	> Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through Day 29	> Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from Day 4 through Day 29 > Time to COVID-19 symptoms resolution (19 of the 23 recorded symptoms) > Safety

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Gupta *et al.* 2021[49] COMET-ICE NCT04545060 27/08/2020-04/03/2021 US, Canada, Brazil, and Spain **Gupta *et al.* 2022a**[50] COMET-ICE NCT04545060 27/08/2020-08/04/2021 Brazil, Canada, Peru, Spain, and US	> Sotrovimab: IV administration, single 500 mg, over 1 hour at day 1 > Placebo: IV administration, single dose over 1 hour at day 1	> Patients (aged ≥18 years) with confirmed SARS-CoV-2 infection, symptom onset ≤5 days before randomization, and high risk for COVID-19 progression > Exclusion criteria included being currently hospitalized, likely to require hospitalization, and symptoms consistent with severe COVID-19	> Proportion of patients with hospitalization for more than 24 hours or death, due to any cause, through Day 29	> Proportion of patients with progression to severe or critical respiratory COVID-19 requiring supplemental oxygen (severe disease) or mechanical ventilation (critical disease) through Day 29 > All-cause mortality at Day 29 > Mean change in FLUpro score > Changes in viral load from baseline to Day 8 using a quantitative RT-PCR test
Shapiro *et al.* 2022[52] COMET-TAIL NCT04913675 06/2021-08/2021 US	> Sotrovimab IV: IV administration, single 500mg dose > 500 mg sotrovimab IM: IM administration, single 500mg dose > 250 mg sotrovimab IM: IM administration, single 250mg dose *[discontinued early due to a greater number of hospitalizations seen]*	> Patients (aged ≥12 years) with a high risk of disease progression	> The efficacy of 500 mg IM versus 500 mg IV sotrovimab in preventing hospitalization for >24 hours for acute management of illness due to any cause or death	NR

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Gupta *et al.* 2022c[53] COMET-PEAK (Parts B and C) NCT04779879 02/2021-07/2021 Multinational	> Sotrovimab IV: IV administration, single dose of 500 mg sotrovimab > Sotrovimab IM: IV administration, single dose of 500 or 250 mg sotrovimab	> Adult patients (aged ≥ 18 years) with early mild-to-moderate COVID-19	> Compare the virologic response to sotrovimab IM to IV, with an endpoint of mean AUC of SARS-CoV-2 viral load, as measured by RT-qPCR from day 1 to day 8 ($AUC_{(D1-8)}$) in NP swabs and predefined 90% CI limits of 0.5-2.0 indicating equivalence	> Safety
Chen *et al.* 2020[54] BLAZE-1 NCT04427501 17/06/2020-21/09/2020 US	> Bamlanivimab: IV administration, single dose of either 700, 2800 or 7000 mg of LY-CoV555 (bamlanivimab) over approximately 1 hour > Placebo: IV administration of placebo over 1 hour	> Patients with confirmed SARS-CoV-2 infection and ≥1 mild-or-moderate symptoms > Exclusion criteria included oxygen saturation ≤93%, respiratory rate ≥30 per minute, heart rate ≥125/ minute, or requires (or anticipated impending need for) mechanical ventilation	> Change in viral load	> Safety assessments > Patient reported symptom burden > COVID-19-related inpatient hospitalization, a visit to the emergency department, or death

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Gottlieb *et al.* 2021[55] BLAZE-1 NCT04427501 17/06/2020-03/09/2020 US	> Bamlanivimab: IV administration, single dose of either 700, 2800 or 7000 mg of bamlanivimab > Bamlanivimab/etesevimab: IV administration, single dose of 2800 mg bamlanivimab and 2800 mg etesevimab > Placebo: IV administration of placebo over 1 hour	> Patients (aged ≥18 years) with confirmed SARS-CoV-2 infection, ≥1 mild-to-moderate symptoms, and a positive test <3 days before treatment > Exclusion criteria included oxygen saturation ≤93%, respiratory rate ≥30 per minute, heart rate ≥125/ minute, or requires (or anticipated impending need for) mechanical ventilation	> Effect on viral load from baseline to Day 11 (± 4 days)	> Time to viral clearance > Proportion of patients with viral clearance at Days 7, 11, 15, and 22 > Viral lead area under the curve at Day 29 > Change in symptom score at Days 7, 11, 15, and 22 > Time to symptom improvement > Time to symptom resolution > Proportion of patients with a COVID-19-related hospitalization, emergency department visit, or death at Day 29

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Dougan *et al.* 2021a[56] BLAZE-1 NCT04427501 04/09/2020-08/12/2020 US	> Bamlanivimab/etesevimab: IV administration, single dose of 2800 mg bamlanivimab and 2800 mg etesevimab > Placebo: IV administration of placebo over 1 hour	> Outpatients with confirmed SARS-CoV-2 infection, ≥1 mild-to-moderate symptoms, and a positive test <3 days before treatment > Exclusion criteria included oxygen saturation ≤93%, respiratory rate ≥30 per minute, heart rate ≥125/ minute, or requires (or anticipated impending need for) mechanical ventilation	> Proportion of patients with COVID-19 related hospitalization or any cause death by Day 28	NR

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Dougan *et al*. 2021b[57] BLAZE-1 NCT04427501 04/09/2020-08/12/2020 US	> Bamlanivimab/etesevimab: IV administration, single dose of 2800 mg bamlanivimab and 2800 mg etesevimab > Placebo: IV administration of placebo over 1 hour	> Outpatients with confirmed SARS-CoV-2 infection, ≥1 mild-to-moderate symptoms, at least one for severe COVID-19 risk factor, and a positive test <3 days before treatment > Exclusion criteria included oxygen saturation ≤93%, respiratory rate ≥30 per minute, heart rate ≥125/ minute, or requires (or anticipated impending need for) mechanical ventilation	> Overall clinical status of the patients, defined as COVID-19-related hospitalization (acute care for ≥24 hours) or death from any cause by Day 29	> Composite of COVID-19 related hospitalization, a visit to an emergency department, or death from any cause at Day 29 > Time to sustained patient reported resolution of symptoms > A reduction in the SARS-CoV-2 viral load from baseline to Days 3 and 5 > Time to viral clearance > The area under the response-time curve for the viral load through Day 7 > The time to a reduction and resolution of symptoms > Safety

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Dougan *et al.* 2022[59] BLAZE-1 NCT04427501 09/12/20-07/01/21 US	> Bamlanivimab and etesevimab: IV administration, single dose of 700 mg bamlanivimab and 1400 mg etesevimab > Placebo: IV administration, single dose	> Non-hospitalized patients (aged ≥12 years) with mild-to-moderate COVID-19 symptoms and ≥1 risk factor for progressing to severe COVID-19 and/or hospitalization	> Proportion of patients experiencing COVID-19-related hospitalization (≥24 hours of acute care) or any-cause death by Day 29	> Change in SARS-CoV-2 viral load from baseline to Days 3, 5, and 7 (±2 days) > Time to viral clearance > Percentage of patients with PHVL at Day 7 (±2 days) > Time to sustained symptom improvement and resolution > Safety
Chen *et al.* 2022[60] BLAZE-1 NCT04427501 09/12/2020-07/01/2021 US	> Bamlanivimab and etesevimab: IV administration, single dose of 700 mg bamlanivimab and 1400 mg etesevimab > Placebo: IV administration, single dose	> Adolescent (aged 12-17 years) and adult (aged ≥18 years) patients with ≥1 risk factor for progression to severe COVID-19	> Time to sustained symptom resolution, symptom resolution, sustained complete symptom resolution, and symptom improvement	> Time to first sustained resolution for each symptom presented (excluding loss of appetite, loss of taste, and loss of smell) > COVID-19-related hospitalizations through Day 29

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Williams *et al*. 202246[61] BLAZE-4 NCT4634409 05/2021-07/2021	Open-label population: > BEB 175 mg > BEB 175 mg + BAM 700mg + ETE 1400 mg > IV administration over 30 seconds	> Patients with a laboratory diagnosis within 3 days of randomization	NR *[note: the reported primary outcome was safety]*	> The proportion of patients with persistently high viral load (log viral load >5.27) on Day 7 > Time to sustained symptom resolution > COVID-19 hospitalization and all-cause mortality through Day 29
Davis *et al*. 2022[62] Davis *et al*. 2022 casirivimab/imdevimab NCT04666441	> Casirivimab/imdevimab IV: IV administration, single dose of 300 mg, 500 mg, 1200 mg, or 2400 mg of casirivimab/imdevimab > Casirivimab/imdevimab SC: SC administration, single dose of 600 mg or 1200 mg casirivimab/ imdevimab	> Outpatients (aged ≥18 years and ≤50 years) with mild to moderate COVID-19, SARS-CoV-2 PCR-positive and seronegative	> Efficacy, safety, and tolerability	NR

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Huang *et al*. 2021[63] UPMC Quality Improvement Review Committee Project ID 3282. University of Pittsburgh Institutional Review Board STUDY210220179 NCT04790786 14/07/2021-29/09/2021 US	> Casirivimab/imdevimab (dosage NR) > Sotrovimab (dosage NR)	> Patients (aged 12-120 years) who received mAb treatment at UPMC infusion centers and emergency departments	> Hospital-free days ≤ 28 days	> Mortality at Day 28

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Chew *et al.* 2021[64] ACTIV-2/A5401 NCT04518410 19/08/2020-15/11/2020 US	> Bamlanivimab: IV administration, single dose of 7000 or 700 mg bamlanivimab > Placebo: IV administration, single dose	> Patients with documented SARS-CoV-2 infection by an FDA-authorized antigen or nucleic acid test from a sample collected within 7 days prior to anticipated study entry > No more than 10 days of COVID-19 symptoms at time of anticipated study entry > Ongoing symptoms (not including loss of taste or smell) within 48 hours prior to study entry > Resting peripheral oxygen saturation levels 92%, and without the need for hospitalization	> Detection of NP SARS-CoV-2 RNA at Days 3, 7, 14, 21, and 28 > Time to improvement of all of 13 targeted COVID-19 symptoms by daily self-assessment through Day 28 > Grade 3 or higher TEAEs through Day 28 *[Note: Additional primary outcomes reported on clinicaltrials.gov]*	> Quantitative NP SARS-COV-2 RNA > Composite all-cause hospitalizations and death > Area under the curve of symptom scores from Day 0 through Day 28 > Plasma bamlanivimab concentrations > Plasma and serum inflammatory biomarkers > Safety through week 24 *[Note: Additional secondary outcomes reported on clinicaltrials.gov]*

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Chew *et al.* 2022[65] ACTIV-2/A5401 NCT04518410 12/10/20-17/11/20 US	> Bamlanivimab: IV administration, single dose over a 1-hour period, 7000 or 700 mg of bamlanivimab > Placebo: IV administration, single dose over a 1-hour period	> Non-hospitalized patients (aged ≥18 years) with documented SARS-CoV-2 infection by an FDA-authorized antigen or nucleic acid test from a sample collected within 7 days prior to anticipated study entry	> Detection of SARS-CoV-2 RNA from NP swabs at Days 3, 7, 14, 21, and 28 > Duration of targeted COVID-19-associated symptoms from Day 0	> All-cause hospitalization and death > Quantitative NP SARS-CoV-2 RNA levels > AUC of symptom scores from Days 0-28 > Progression of 1 or more COVID-19-associated symptoms to worse status than recorded at study entry > Safety
Boucau *et al.* 2022[66] ACTIV-2/A5401 NCT04518410 19/08/20-17/11/20 US	> Bamlanivimab: IV administration, single dose of 7000 mg (n=20) or 700 mg (n=10) of bamlanivimab > Placebo: IV administration, single dose	> Non-hospitalized participants with positive SARS-CoV-2 antigen or nucleic acid test within 7 days and less than 10 days of COVID-19 symptoms	> Viral culture dynamics (viral load by qPCR and viral culture)	NR

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Kumarasamy *et al.* 2022[67] EMPATHY NCT04828161 US, Hungary, India, Netherlands, Poland, South Africa	> Ensovibep: IV administration, single dose of 75, 225, or 600 mg, given over 60 minutes > Placebo: IV administration, single dose given over 60 minutes	> Patients (aged ≥ 18 years) positive for COVID-19 and the presence of ≥2 COVID-19 symptoms and onset within 7 days prior to dosing	> Time-weighted change from baseline in log_{10} SARS-CoV-2 viral load in NP swabs to Day 8	> Proportion of patients with hospitalizations and/or ER visits related to COVID-19, or death from any cause to Day 29 > Time to sustained clinical recovery based on resolution or improvement in clinical symptoms (patient reported outcome) with no worsening up to Day 29 > Safety

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Streinu-Cercel *et al.* 2022[68] CT-P59 NCT04602000 07/10/2020-18/12/2020 South Korea, Romania, Spain, and US	> Regdanvimab: IV administration, single dose of 40 or 80 mg/kg regdanvimab re-constituted in 250mL of 0.9% sodium chloride, given over 90±15 minutes (Day 1) > Placebo: IV administration, single dose of re-constituted in 250mL of 0.9% sodium chloride, given over 90±15 minutes (Day 1)	> Patients with mild-to-moderate disease as defined by the WHO criteria with oxygen saturation >94% on room air, not requiring oxygen support, onset of symptoms within 7 days before study drug administration, and presenting with symptoms 2 days prior to randomization	> Time to conversion to negative NP swab specimen based on RT-qPCR (negative titer threshold of 2.33 $\log_{10}$ copies/mL) up to Day 28 > Time to clinical recovery up to Day 14	> The proportion of patients with clinical symptoms requiring oxygen therapy or hospitalization due to COVID-19 up to Day 28 > The proportion of patients achieving conversion to negative RT-qPCR result > The proportion of patients with hospital admission > The proportion of patients requiring supplementary oxygen > The proportion of patients with mechanical ventilation use > The proportion of patients requiring rescue therapy > The proportion of patients with ICU admission > The proportion of patients with all-cause mortality

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Montgomery *et al.* 2022a[69] TACKLE NCT04723394	> Tixagevimab/cilgavimab : IM administration, single dose 600 mg of two injections of AZD7442 (tixagevimab/cilgavimab; 300 mg of each)) > Placebo: IM administration, single dose	> Non-hospitalized adult patients (aged ≥18 years) with mild-to-moderate COVID-19 and dosed ≤ 7 days from symptom onset	> Severe COVID-19 or death from any cause through Day 29	> Safety
Montgomery *et al.* 2022b[70] TACKLE NCT04723394 28/01/21-22/07/21 US, Latin America, Europe, and Japan	> Tixagevimab-cilgavimab: IM administration, single dose of two consecutive 3 mL injections of 300 mg tixagevimab and 300 mg cilgavimab > Placebo: IM administration, single dose given as two consecutive 3 mL injections	> Non-hospitalized patients (aged ≥18 years) with laboratory-confirmed SARS-CoV-2 infection, determined by RT-PCR or an antigen test, from a sample collected 3 or less days before enrollment > WHO Clinical Progression Scale score of >1 to <4 > Mild-to-moderate COVID-19, receiving the study drug ≤7 days from self-reported symptom onset	> Proportion of patients with severe COVID-19 or death from any cause to day 29, with severe COVID-19 being defined as a minimum of either pneumonia (fever, cough, tachypnoea or dyspnea, and lung infiltrates) or hypoxaemia (oxygen saturation <90% in room air, severe respiratory distress, or both), plus a WHO Clinical Progression Scale score of 5 or more	> Incidence of respiratory failure, levels of SARS-CoV-2 RNA in nasal swab, and progression of participant-reported COVID-19-associated symptoms through Day 29 > Death from any cause or hospitalization for COVID-19 complications or sequalae to Day 169 > Safety

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Hobbs *et al.* 2022[71] TACKLE NCT04723394 28/01/2021-21/08/2021 Multinational	> Tixagevimab/cilgavimab (AZD7442): IM adminstration, single dose of 600 mg (two consecutive injections, 300 mg of each tixagevimab and cilgavimab) > Placebo: IM administration, single dose of two consecutive injections	> Non-hospitalized adults with mild to moderate COVID-19, dosed ≤7 days from symptom onset	> Severe COVID-19 or death from any cause through Day 169, defined as a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, and lung infiltrates) or hypoxemia (SpO_2 <90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher *[Note: Severe COVID-19 definition from clinicaltrials.gov]*	> Safety
STAMP 2022[72] STAMP	> Adintrevimab: IM administration, single dose of 300mg of adintrevimab > Placebo: IM administration, single dose	> Patients with mild-to-moderate COVID-19	> COVID-related hospitalization or all-cause mortality at Day 29 *[note: primary endpoint not specified]*	NR

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
O'Brien *et al.* 2022[73] O'Brien *et al.* 2022 casirivimab/imdevimab NCT04452318 13/07/2020-28/01/2021 US, Romania, Moldova	> Casirivimab/imdevimab: SC administration, single dose of 1200 mg (1200 mg/mL) of casirivimab and imdevimab (four injections of 2.5mL solution) (Day 1) > Placebo: SC administration, single dose (four injections of 2.5mL solution) (Day 1)	> Adult participants (aged ≥18 years) (irrespective of weight) at the signing of informed consent OR > Adolescent participants (aged ≥12 to <18 years) OR > Pediatric participants (aged <12 years at the signing of the assent (parent/guardian signs the informed consent)) OR > Asymptomatic household contact of someone who has tested positive for COVID-19 and has been judged by the investigator to be in good health	> Proportion of participants who had a positive RT-qPCR result at baseline or during the 28-day efficacy assessment period and who developed signs and symptoms of COVID-19 within 14 days of the positive RT-qPCR result	> The number of weeks of symptomatic SARS-CoV-2 infection > The number of weeks of high viral load (>4 log_{10} copies/mL) *[Note: The full list of secondary endpoints is available in the supplementary materials]*

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Mazzaferri *et al.* 2022[74] MANTICO NCT05205759 Patients enrolled from 09/12/2021 Italy	> Bamlanivimab and etesevimab: IV administration, single dose over a 1-hour period, 700 mg of bamlanivimab and 1400 mg of etesevimab > Sotrovimab: IV administration, single dose over a 1-hour period, 500 mg dose > Casirivimab and imdevimab: IV administration, single dose over a 1-hour period, 600 mg of casirivimab and 600 mg of imdevimab	> Outpatients (aged ≥50 years) with a positive test (direct antigen or nucleic acid SARS-CoV-2) and mild-to-moderate COVID-19 symptoms within 4 days of the onset	> COVID-19 progression, defined as hospitalization, need of supplemental oxygen therapy, or death from any cause through Day 14	> Emergency department visits through Day 28, all-cause mortality through Day 28, duration of supplemental oxygen therapy, and rate and duration of non-invasive ventilation and mechanical ventilation > Time to sustained patient-reported symptom resolution
Portal-Celhay *et al.* 2022[75] Portal-Celhay *et al.* 2022 casirivimab/imdevimab NCT04666441 15/12/2020-04/03/2021 US	> Casirivimab/imdevimab IV: IV administration, single dose of 300, 600, 1200 or 2400 mg > Casirivimab/imdevimab SC: SC administration, single dose of 600 or 1200 mg > Placebo: IV or SC administration, single dose	> Patients (aged ≥18 years) with a positive SARS-CoV-2 diagnostic test from a sample collected within 72 hours prior to randomization	> Time-weighted average daily change from Day 1/baseline to Day 7 in viral load in NP swab samples (measured by RT-qPCR)	> Evaluation of additional virologic efficacy and tolerability > Safety

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Kim *et al.* 2022[76] Kim *et al.* 2022 regdanvimab NCT04602000 18/01/2021-24/04/2021 US, European Union, and Asia	> Regdanvimab: IV administration, single dose over 60 ± 15 minutes, 40 mg/kg reconstituted in 250 mL of 0.9% sodium chloride > Placebo: IV administration, single dose over 60 ± 15 minutes, reconstituted in 250 mL of 0.9% sodium chloride	> Patients (aged ≥18 years) with COVID-19 confirmed by rapid antigen kit or RT-PCR, with ≥1 COVID-19-associated symptom with onset ≤7 days and ≥1 pre-specified symptom ≤48 hours before drug administration > Oxygen saturation of >94% on room air and did not require supplemental oxygen	> Proportion of patients with disease progression up to day 28 in high-risk patients, defined as meeting at least 1 of the following COVID-19 events: hospitalization, oxygen therapy, or mortality due to SARS-CoV-2 infection	> Disease progression up to Day 28 > Time to clinical recovery up to Day 14 > Safety
Schilling *et al.* 2022[77] PLATCOV NCT05041907 Patients enrolled from 30/09/2021 Thailand	> Casirivimab/imdevimab: IV administration, single dose of 600 mg of casirivimab and 600 mg of imdevimab > No study drug *[Note: Ivermectin group was not assessed in this report]*	> Patients (aged 18-50 years) presenting to the Acute Respiratory Infections outpatient clinic for COVID-19, with early symptomatic COVID-19 (symptoms for no more than 4 days), oxygen saturation ≥96%, and unimpeded in activities of daily living	> The rate of viral clearance (expressed as a slope coefficient and presented as a half-life)	> All-cause hospitalization for clinical deterioration until Day 28 > Safety

AE: adverse event; AESI: adverse event of special interest; AUC: area under the curve; BAM: Bamlanivimab; BEB: Bebtelovimab; Ct: cycle threshold; ED: emergency department; ETE: Etesevimab; FDA: Food and Drug Administration; ICU: intensive care unit; IM: intramuscular; IV: intravenous; mAB: monoclonal antibody; mg: milligram; mL: milliliter; NP: nasopharyngeal; PCR: polymerase chain reaction; PHVL: persistently high viral load; qPCR: quantitative polymerase chain reaction; RT-PCR: reverse transcription-polymerase chain reaction; RNA: ribonucleic acid; RT-qPCR reverse transcription-quantitative polymerase chain reaction; SAE: serious adverse event; SC: subcutaneous; TEAE: Treatment Emergent Adverse Events; US: United States; WHO: World Health Organization.

Table 6. Patients baseline characteristics for RCTs for neutralizing antibodies

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Weinreich *et al.* 2020[46] REGEN-COV (phase 2 portion) NCT04425629	> Overall: 269 > 2.4 g casirivimab/ imdevimab: 92 > 8 g casirivimab/ imdevimab: 90 > Placebo: 93	Median (IQR) > Overall: NR > 2.4 g casirivimab/ imdevimab: 43.0 (33.5-51.0) > 8 g casirivimab/ imdevimab: 44 (36.0-53.0) > Placebo: 45.0 (34.0-54.0)	Male, n (%) > Overall: 134 (49) > 2.4 g casirivimab/ imdevimab: 46 (50) > 8 g casirivimab/ imdevimab: 38 (42) > Placebo: 50 (54)	Median (range) > Overall: NR > 2.4 g casirivimab/ imdevimab: 3.5 (0-7) > 8 g casirivimab/ imdevimab: 3.0 (0-8) > Placebo: 3.0 (0-8)
Weinreich *et al.* 2021[47],[48] REGEN-COV (phase 3 portion) NCT04425629	> Overall: 3088 > 2.4 g casirivimab/ imdevimab: 1355 > Placebo (2.4 g portion): 1341 > 1.2 g casirivimab/ imdevimab: 736 > Placebo (1.2 g portion): 748	Median (IQR) > 2.4 g casirivimab/ imdevimab: 50.0 (39.0-60.0) > Placebo (2.4 g portion): 50.0 (37.0-58.0) > 1.2 g casirivimab/ imdevimab: 48.5 (37.0-57.5) > Placebo (1.2 g portion): 48.0 (35.0-57.0)	Male, n (%) > Overall: 1977 (48.7) > 2.4 g casirivimab/ imdevimab: 656 (48.4) > Placebo (2.4 g portion): 633 (47.2) > 1.2 g casirivimab/ imdevimab: 364 (49.5) > Placebo (1.2 g portion): 352 (47.1)	Median (range) > 2.4 g casirivimab/ imdevimab: 3.0 (2-5) > Placebo (2.4 g portion): 3.0 (2-5) > 1.2 g casirivimab/ imdevimab: 3.0 (2-5) > Placebo (1.2 g portion): 3.0 (2-4)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Gupta *et al.* 2021[49] COMET-ICE NCT04545060 **Gupta *et al.* 2022a[50]** COMET-ICE NCT04545060	Interim analysis > Overall: ITT, 583; Safety, 868 > Sotrovimab: ITT, 291; safety, 430 > Placebo: ITT, 292; safety, 438 Final analysis > Overall: 1057 > Sotrovimab: 528 > Placebo: 529	Interim analysis Median (range) (ITT population) > Overall: 53.0 (18-96) > Sotrovimab: 53.0 (18-96) > Placebo: 52.5 (18-88) Final analysis Median (IQR), ≥65 years, >70 years, n (%) > Sotrovimab: 53 (41.5-62), 105 (20), 56 (11) > Placebo: 53 (43-63), 108 (20), 56 (11)	Interim analysis Male, n (%) (ITT population) > Overall: 266 (46) > Sotrovimab: 135 (46) > Placebo: 131 (45) Final analysis Female, male, n (%) > Overall: 572 (54), 485 (46) > Sotrovimab: 299 (57), 229 (43) > Placebo: 273 (52), 256 (48)	Interim analysis NR Final analysis Within the prior 5 days

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Shapiro *et al.* 2022[52] COMET-TAIL NCT04913675	> Overall: 754 > 500mg IV sotrovimab: 378 > 500mg IM sotrovimab: 376	≥65, % > Overall: ~25% > 500mg IV sotrovimab: NR > 500mg IM sotrovimab: NR	NR	≤7 days (according to clinicaltrials.gov)
Gupta *et al.* 2022c[53] COMET-PEAK (Parts B and C) NCT04779879	Part B: > Overall: 166 > Sotrovimab 500 mg IV: 84 > Sotrovimab 500 mg IM: 82 Part C: > Overall: 157 > Sotrovimab 500 mg IV: 79 > Sotrovimab 250 mg IM: 78	Part B, median: > Overall: 47 > Sotrovimab 500 mg IV: NR > Sotrovimab 500 mg IM: NR Part C, median: > Overall: 52 > Sotrovimab 500 mg IV: NR > Sotrovimab 250 mg IM: NR	NR	NR
Chen *et al.* 2020[54] BLAZE-1 NCT04427501	> Overall: 452 > 700, 2800 or 7000 mg bamlanivimab: 317 > Placebo: 150	Median (range) > Overall: NR > 700, 2800 or 7000 mg bamlanivimab: 45 (18-86) > Placebo: 46 (18-77)	Female, n (%) > Overall: NR > 700, 2800 or 7000 mg bamlanivimab: 171 (55.3) > Placebo: 78 (54.5)	Median > Overall: NR > 700, 2800 or 7000 mg bamlanivimab: 4 > Placebo: 4

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Gottlieb *et al.* 2021[55] BLAZE-1 NCT04427501	> Overall: 592 > 700 mg bamlanivimab: 104 > 2800 mg bamlanivimab: 109 > 7000 mg bamlanivimab: 104 > 2800 mg bamlanivimab and 2800 mg etesevimab: 114 > Placebo: 161	Median (IQR) > Overall Mean (SD): 44.7 (15.7) > 700 mg bamlanivimab: 39 (31-58) > 2800 mg bamlanivimab: 45 (31-56) > 7000 mg bamlanivimab: 46 (34-55) > 2800 mg bamlanivimab and 2800 mg etesevimab: 44 (30-60) > Placebo: 46 (35-57)	Female, n (%) > Overall: 315 (54.6) > 700 mg bamlanivimab: 63 (62.4) > 2800 mg bamlanivimab: 51 (47.7) > 7000 mg bamlanivimab: 58 (57.4) > 2800 mg bamlanivimab and 2800 mg etesevimab: 58 (51.8) > Placebo: 85 (54.5)	Within 4 days (median)
Dougan *et al.* 2021a[56] BLAZE-1 NCT04427501	> Overall: 1035 > 2800 mg bamlanivimab and 2800 mg etesevimab: 518 > Placebo: 517	Mean (SD) > Overall: 53.8 (16.8) > 2800 mg bamlanivimab and 2800 mg etesevimab: NR > Placebo: NR	Female, n (%) > Overall: 538 (52) > 2800 mg bamlanivimab and 2800 mg etesevimab: NR > Placebo: NR	Within 3 days of laboratory diagnosis
Dougan *et al.* 2021b[57] BLAZE-1 NCT04427501	> Overall: 1035 > 2800 mg bamlanivimab and 2800 mg etesevimab: 518 > Placebo: 517	Mean (SD) > Overall: 53.8 (16.8) > 2,800 mg bamlanivimab and 2,800 mg etesevimab: 54.3 (17.1) > Placebo: 53.3 (16.4)	NR *[Note: Conference abstract states- female: 538 (52%)]*	Median (range) > Overall: 4 (0-29) > 2800 mg bamlanivimab and 2800 mg etesevimab: 4 (0-29) > Placebo: 4 (0-13)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Dougan *et al.* 2022[59] BLAZE-1 NCT04427501	> Balmanivimab/etesevimab: 511 > Placebo: 258	Median (range) > Balmanivimab/ etesevimab: 57 (12-93) > Placebo: 55 (13-89)	Male, n (%) > Balmanivimab/ etesevimab: 247 (48.3) > Placebo: 114 (44.2)	Median (range) > Balmanivimab/ etesevimab: 4 (0-19) > Placebo: 3 (1-15)
Chen *et al.* 2022[60] BLAZE-1 NCT04427501	> Overall: 769 > Balmanivimab/etesevimab: 511 > Placebo: 258	Median (min-max) > Overall: 56 (12-93) > Balmanivimab/ etesevimab: 57 (12-93) > Placebo: 55 (13-89)	Male, n (%) > Overall: 361 (46.9) > Balmanivimab/ etesevimab: 247 (48.3) > Placebo: 114 (44.2)	Median (min-max) > Overall: NR > Balmanivimab/etesevimab: 3 (1-15) > Placebo: 4 (0-19)
Williams *et al*. 2022[61] BLAZE-4 NCT4634409	Open-label population > Bebtelovimab: 100 > Bebtelovimab (BEB)+ Bamlanivimab (BAM) and etesevimab (ETE): 176 *[Note: the BEB + BAB + ETE population presented here were using the expanded CDC criteria for high-risk]*	NR	NR	Randomization ≤3 days from symptom onset
Davis *et al.* 2022[62] Davis *et al*. 2022 casirivimab/imdevimab NCT04666441	NR	NR	NR	≤7 days (according to clinicaltrials.gov)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Huang *et al*. 2021[63] UPMC Quality Improvement Review Committee Project ID 3282. University of Pittsburgh Institutional Review Board STUDY210220179 NCT04790786	> Casirivimab/imdevimab: 2454 > Sotrovimab: 1104	Mean (SD) > Casirivimab/imdevimab: 54 (18) > Sotrovimab: 53 (18)	Female, n (%) > Casirivimab/imdevimab: 1320 (54) > Sotrovimab: 599 (54)	Mean > Casirivimab/imdevimab: 4.5 > Sotrovimab: 4.6

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Chew *et al.* 2021[64] ACTIV-2/A5401 NCT04518410	> Overall (7000 mg): 94 > Overall (700 mg): 223 > Bamlanivimab (7000 mg): 48 > Bamlanivimab (700 mg): 111 > Placebo (7000 mg): 46 > Placebo (700 mg): 112	Median (IQR) > Overall (7000 mg): 44.5 (30.0-56.0) > Overall (700 mg): 47.0 (35.0-55.0) > Bamlanivimab (7000 mg): 45.5 (33.5-57.5) > Bamlanivimab (700 mg): 46.0 (35.0-54.0) > Placebo (7000 mg): 42.0 (28.0-54.0) > Placebo (700 mg): 48.5 (36.0-55.0)	Female, male, n (%) > Overall (7000 mg): 49 (52.1), 45 (47.9) > Overall (700 mg): 113 (50.7), 110 (49.3) > Bamlanivimab (7000 mg): 26 (54.2), 22 (45.8) > Bamlanivimab (700 mg): 57 (51.4), 54 (48.6) > Placebo (7000 mg): 23 (50.0), 23 (50.0) > Placebo (700 mg): 56 (50.0), 56 (50.0)	Median (IQR) > Overall (7000 mg): 6 (4.0-7.0) > Overall (700 mg): 6 (4.0-8.0) > Bamlanivimab (7000 mg): 6 (4.0-8.0) > Bamlanivimab (700 mg): 6 (4.0-8.0) > Placebo (7000 mg): 5.5 (4.0-7.0) > Placebo (700 mg): 6 (4.0-7.0)
Chew *et al.* 2022[65] ACTIV-2/A5401 NCT04518410	> Bamlanivimab (7000 mg): 48 > Placebo (7000 mg): 46 > Bamlanivimab (700 mg): 111 > Placebo (700 mg): 112	Median (IQR) > Bamlanivimab (7000 mg): 45.5 (33.5-57.5) > Placebo (7000 mg): 42.0 (28.0-54.0) > Bamlanivimab (700 mg): 46.0 (35.0-54.0) > Placebo (700 mg): 48.5 (36.0-55.0)	Male, female, n (%) > Bamlanivimab (7000 mg): 22 (45.8), 26 (54.2) > Placebo (7000 mg): 23 (50.0), 23 (50.0) > Bamlanivimab (700 mg): 54 (48.6), 57 (51.4) > Placebo (700 mg): 56 (50.0), 56 (50.0)	≤5 days, >5 days, n (%) > Bamlanivimab (7000 mg): 17 (35.4), 31 (64.6) > Placebo (7000 mg): 17 (37.0), 29 (63.0) > Bamlanivimab (700 mg): 41 (36.0), 70 (63.1) > Placebo (700 mg): 41 (36.6), 71 (63.4)
Boucau *et al.* 2022[66] ACTIV-2/A5401 NCT04518410	> Bamlanivimab: 30 > Placebo: 39	Median (range) > Bamlanivimab: 50.5 (25-73) > Placebo: 50 (20-71)	Female, n (%) > Bamlanivimab: 15 (50) > Placebo: 24 (62)	Median (range) > Bamlanivimab: 5 (3-8) > Placebo: 4 (1-10)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Kumarasamy *et al.* 2022[67] EMPATHY NCT04828161	> Ensovibep (75 mg): 101 > Ensovibep (225 mg): 100 > Ensovibep (600 mg): 100 > Placebo: 99	NR	NR	≤7 from symptom onset to dosing
Streinu-Cercel *et al.* 2022[68] CT-P59 NCT04602000	> Regdanvimab 40 mg/kg: 105 > Regdanvimab 80 mg/kg: 111 > Either dosage of intervention: 216 > Placebo: 111	Median (IQR), ≥60 years, <60 years > Regdanvimab 40 mg/kg: 51.0 (42-60), 27 (25.7), 78 (74.3) > Regdanvimab 80 mg/kg: 51.0 (40-60), 28 (25.2), 83 (74.8) > Either dosage of intervention: 51.0 (40-60), 55 (25.5), 161 (74.5) > Placebo: 52.0 (41-61), 30 (27.0), 81 (73.0)	Male, n (%) > Regdanvimab 40 mg/kg: 59 (56.2) > Regdanvimab 80 mg/kg: 59 (53.2) > Either dosage of intervention: 118 (54.6) > Placebo: 48 (43.2)	Median (IQR) > Overall: 3.0 (2-4)
Montgomery *et al.* 2022a[69] TACKLE NC04723394	> Overall: 903 > AZD7442: 452 > Placebo: 451	Mean > Overall: 46 > AZD7442: NR > Placebo: NR	Female, % > Overall: 50 > AZD7442: NR > Placebo: NR	NR

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Montgomery *et al.* 2022b[70] TACKLE NCT04723394	> Overall: 903 > Tixagevimab/cilgavimab: 452 > Placebo: 451	Mean (SD) > Overall: 46.1 (15.2) > Tixagevimab/ cilgavimab: 46.3 (15.4) > Placebo: 45.9 (15.0)	Male, female, n (%) > Overall: 448 (50), 448 (50) > Tixagevimab/ cilgavimab: 213 (47), 239 (53) > Placebo: 216 (48), 235 (52)	Mean (SD) > Overall: 5.0 (1.6) > Tixagevimab/cilgavimab: 4.9 (1.6) > Placebo: 5.0 (1.6)
Hobbs *et al.* 2022[71] TACKLE NCT04723394	> Overall: 903 > Tixagevimab/cilgavimab: 452 > Placebo: 451	NR	NR	≤7 days from onset of symptoms
STAMP 2022[72] STAMP	> Overall: 336 > Adintrevimab: 169 > Placebo: 167	NR	NR	NR *[Note: Subgroup treated within 3 days of symptom onset]*
O'Brien *et al.* 2022[73] O'Brien *et al.* 2022 casirivimab/imdevimab NCT04452318	> Overall: 207 > Casirivimab/imdevimab: 101 > Placebo: 106	Mean (SD) > Casirivimab/ imdevimab: 39.2 (17.7) > Placebo: 42.5 (18.3), 11 (10.4), 39 (36.8) ≥12 to <18, ≥50, n (%) > Casirivimab/ imdevimab: 15 (14.9), 31 (30.7) > Placebo: 11 (10.4), 39 (36.8)	Female, male, n (%) > Casirivimab/ imdevimab: 50 (49.5), 51 (50.5%) > Placebo: 63 (59.4), 43 (40.6)	Within 4 days

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Mazzaferri *et al.* 2022[74] MANTICO NCT05205759	Total, Delta variant, Omicron variant > Overall: 319, 141, 170 > Sotrovimab: 107, 43, 61 > Bamlanivimab/etesevimab: 106, 48, 57 > Casirivimab/imdevimab: 106, 50, 52	Median (IQR) [range] (Delta variant) > Sotrovimab: 65.8 (16.4) [50-90] > Bamlanivimab/ etesevimab: 68.6 (11.8) [50-92] > Casirivimab/imdevimab: 63.2 (12.0) [50-89] Median (IQR) [range] (Omicron variant) > Sotrovimab: 64.2 (15) [50-90] > Bamlanivimab/ etesevimab: 64.8 (14.6) [50-86] > Casirivimab/imdevimab: 65.3 (14.8) [50-86]	Male, n (%) (Delta variant) > Sotrovimab: 22 (51.16) > Bamlanivimab/ etesevimab: 21 (43.75) > Casirivimab/ imdevimab: 26 (52.00) Male, n (%) (Omicron variant) > Sotrovimab: 36 (59.02) > Bamlanivimab/ etesevimab: 30 (52.63) > Casirivimab/ imdevimab: 35 (67.31)	Within 4 days

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Portal-Celhay *et al.* 2022[75] Portal-Celhay *et al.* 2022 casirivimab/imdevimab NCT04666441	> Casirivimab/imdevimab 300 mg IV: 80 > Casirivimab/imdevimab 600 mg IV: 68 > Casirivimab/imdevimab 1200 mg IV: 72 > Casirivimab/imdevimab 2400 mg IV: 62 > Casirivimab/imdevimab 600 mg SC: 75 > Casirivimab/imdevimab 1200 mg SC: 73 > Pooled placebo: 77	Mean (SD) > Casirivimab/imdevimab 300 mg IV: 33.8 (8.90) > Casirivimab/imdevimab 600 mg IV: 33.9 (9.16) > Casirivimab/imdevimab 1200 mg IV: 34.1 (10.51) > Casirivimab/imdevimab 2400 mg IV: 36.3 (9.16) > Casirivimab/imdevimab 600 mg SC: 33.5 (9.18) > Casirivimab/imdevimab 1200 mg SC: 33.5 (10.88) > Pooled placebo: 35.1 (9.97)	Male, female, n (%) > Casirivimab/imdevimab 300 mg IV: 33 (41.3), 47 (58.8) > Casirivimab/imdevimab 600 mg IV: 39 (57.4), 29 (42.6) > Casirivimab/imdevimab 1200 mg IV: 29 (40.3), 43 (59.7) > Casirivimab/imdevimab 2400 mg IV: 28 (45.2), 34 (54.8) > Casirivimab/imdevimab 600 mg SC: 36 (48.0), 39 (52.0) > Casirivimab/imdevimab 1200 mg SC: 35 (47.9), 38 (52.1) > Pooled placebo: 31 (40.3), 46 (59.7)	NR
Kim *et al.* 2022[76] Kim *et al.* 2022 regdanvimab NCT04602000	> Overall: 1315 > Regdanvimab: 656 > Placebo: 659	Median (IQR) > Overall: 48.0 (38-59) > Regdanvimab: 49.0 (38-59) > Placebo: 47.0 (37-58)	Male, female, n (%) > Overall: 674 (51.3), 641 (48.7) > Regdanvimab: 347 (52.9), 309 (47.1) > Placebo: 327 (49.6), 332 (50.4)	Median (IQR) > Overall: 4.0 (3-5) > Regdanvimab: 4.0 (3-5) > Placebo: 4.0 (3-5)
Schilling *et al.* 2022[77] PLATCOV NCT05041907	> Casirivimab/imdevimab: 40 > No study drug: 45 *[Note: mITT population for casirivimab/imdevimab and no study drug were 10 and 41, respectively]*	Median (range) > Casirivimab/ imdevimab: 26.5 (3.7-7.8) > No study drug: 27 (20-43)	Male, % > Casirivimab/imdevimab: 20 > No study drug: 44	Reported symptoms for no more than 4 days

CDC: Centers for Disease Control and Prevention; g: gram; IM: intramuscular; IQR: interquartile range; ITT: intention-to-treat; IV: intravenous; kg: kilogram; mg: milligram; mITT: modified intention-to-treat; NA: Not applicable NR: Not reported; SC: subcutaneous; SD: standard deviation; UPMC: University of Pittsburgh Medical Center.

Table 7. Results from RCTs assessing neutralizing antibodies; primary outcome(s)

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Weinreich *et al.* 2020[46] REGEN-COV (phase 2 portion) NCT04425629	Time-weighted average change from baseline in viral load at Day 7 versus placebo group, LSM (95% CI) > 2.4 g casirivimab/imdevimab: -0.25 log_{10} copies/mL (-0.60 to 0.10) > 8.0 g casirivimab/imdevimab: -0.56 log_{10} copies/mL (-0.91 to -0.21) Patients with at ≥1 COVID-19-related medically attended visit within 29 days versus placebo group, difference (95% CI) > 2.4 g casirivimab/imdevimab: -3 percentage points (-18 to 11) > 8.0 g casirivimab/imdevimab: -3 percentage points (-18 to 11)	Patients who experienced a SAE, n (%) > 2.4 g casirivimab/imdevimab: 1 (1) > 8.0 g casirivimab/imdevimab: 0 (0) > Placebo: 2 (2) Patients who experienced an AE of special interest*, n (%) > 2.4 g casirivimab/imdevimab: 0 (0) > 8.0 g casirivimab/imdevimab: 2 (2) > Placebo: 2 (2) *No SAE of special interest was reported across the treatment groups
Weinreich *et al.* 2021[47],[48] REGEN-COV (phase 3 portion) NCT04425629	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through Day 29 > 2.4 g REGN-COV2: 18 > Placebo (2.4 g REGEN-COV2 group): 62 > Difference, % ([95% CI], p-value): 71.3 ([51.7-82.9], p<0.0001), significant difference Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through Day 29 > 1.2 g REGN-COV2: 7 > Placebo (1.2g REGEN-COV2 group): 24 > Difference, % ([95% CI], p-value): 70.4 ([31.6-87.1], p=0.0024), significant difference *[Note: 8.0g REGEN-COV2 arm was discontinued at protocol amendment and not analyzed for efficacy; demographic data are provided in the Supplementary material]*	Patients who experienced an AE, n (%) > 1.2 g casirivimab/imdevimab: 59/827 (7.1) > 2.4 g casirivimab/imdevimab: 142/1849 (7.7) > 8.0 g casirivimab/imdevimab: 85/1012 (8.4) > Placebo: 189/1843 (10.3) Patients who experienced a SAE, n (%) > 1.2 g casirivimab/imdevimab: 9/827 (1) > 2.4 g casirivimab/imdevimab: 24/1849 (1) > 8.0 g casirivimab/imdevimab: 17/1012 (2) > Placebo: 74/1843 (4) Patients who experienced a grade 3 or 4 AE, n (%) > 1.2 g casirivimab/imdevimab: 11/827 (1) > 2.4 g casirivimab/imdevimab: 18/1849 (1) > 8.0 g casirivimab/imdevimab: 15/1012 (1) > Placebo: 62/1843 (3)

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Gupta *et al.* 2021[49] COMET-ICE NCT04545060 **Gupta *et al.* 2022a**[50] COMET-ICE NCT04545060	Interim analysis: Proportion of patients hospitalized >24 hours or death for any cause, n (%) > Sotrovimab: 3/291 (1) > Placebo: 21/292 (7) > RR ([95% CI], p-value): 0.15 ([0.04-0.56], p=0.002), significant difference Final analysis: All-cause hospitalization >24 hours for acute illness management or death due to any cause through Day 29, n > Sotrovimab: 6/528 > Placebo: 30/529 > RR ([95% CI], p-value): -4.53 ([-6.70 to -2.37], p<0.001), threshold defined as P <0.2758)	Patients who experienced an AE, n (%) > Sotrovimab: 73/430 (17) > Placebo: 85/438 (19) Patients who experienced a SAE, n (%) > Sotrovimab: 7/430 (2) > Placebo: 26/438 (6)
Shapiro *et al.* 2022[52] COMET-TAIL NCT04913675	Proportion of patients hospitalized for >24 hours for acute management of illness due to any cause or death, n (%) > 500 mg sotrovimab IV: 5/378 (1.3) > 500 mg sotrovimab IM: 10/376 (2.7) > The 3.5% non-inferiority margin was met. Adjusted risk difference, % (95% CI): 1.07 (-1.25 to 3.39)	Disease-related AEs were balanced between treatment groups Total SAE was ~1% and was considered unrelated to treatment

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Gupta *et al.* 2022c[53] COMET-PEAK (Parts B and C) NCT04779879	Ratio of least square geometric mean viral load $AUC_{(D1-8)}$ for sotrovimab IM group vs IV group, LS geometric mean (90% CI) > Part B: 1.04 (0.98-1.09) > Part C: 1.02 (0.94-1.11)	Occurrence of injection site reactions, n (%) > Part B 500 mg IV: 0 (0) > Part B 500 mg IM: 10 (12) > Part C 500 mg IV: 0 (0) > Part C 250 mg IM: 4 (5) Occurrence of grade 3 SAEs, n > Part B 500 mg IV: 1 > Part B 500 mg IM: 2 > Part C 500 mg IV: 0 > Part C 250 mg IM: 1 Occurrence of grade 4 SAEs, n > Part B 500 mg IV: 0 > Part B 500 mg IM: 2 > Part C 500 mg IV: 0 > Part C 250 mg IM: 1 Occurrence of grade 5 SAEs, n > Part B 500 mg IV: 0 > Part B 500 mg IM: 0 > Part C 500 mg IV: 0 > Part C 250 mg IM: 1
Chen *et al.* 2020[54] BLAZE-1 NCT04427501	Mean change in viral load from baseline at Day 11 for bamlanivimab group versus placebo group, difference ([95% CI], p-value) > 700 mg bamlanivimab: -0.2 ([-0.66 to 0.25], p=0.38), no significant difference > 2800 mg bamlanivimab: -0.53 ([-0.98 to -0.08], p=0.02), [assumed] significant reduction > 7000 mg bamlanivimab: 0.09 ([-0.37 to 0.55], p=0.7), no significant difference *[Note: Endpoints for hospitalization are also available in the DEF]*	Patients who experienced an AE, n (%) > 700 mg bamlanivimab: 24 (23.8) > 2800 mg bamlanivimab: 23 (21.5) > 7000 mg bamlanivimab: 22 (21.8) > Placebo: 35 (24.5)

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Gottlieb *et al.* 2021[55] BLAZE-1 NCT04427501	Mean change in viral load from baseline at Day 11 for bamlanivimab groups versus placebo group, difference ([95% CI], p-value) > 700 mg bamlanivimab: 0.09 ([-0.35 to 0.52], p=0.69), no significant difference > 2800 mg bamlanivimab: -0.27 ([-0.71 to 0.26], p=0.21), no significant difference > 7000 mg bamlanivimab: 0.31 ([-0.13 to 0.76], p=0.16), no significant difference > 2800 mg bamlanivimab and 2800 mg etesevimab: -0.57 ([-1.00 to -0.14], p=0.01), significant difference Change in hospitalizations from baseline to Day 29 for bamlanivimab groups versus placebo, % ([95% CI], p-value) *[No deaths reported]* > 700 mg bamlanivimab: -4.8 ([-8.9 to -0.6], p=0.09), no significant difference > 2800 mg bamlanivimab: -3.9 ([-8.4 to 0.6], p=0.21), no significant difference > 7000 mg bamlanivimab: -3.8 ([-8.3 to 0.8], p=0.21), no significant difference > 2800 mg bamlanivimab and 2800 etesevimab: -4.9 ([-8.9 to -0.8], p=0.49), no significant difference *[Note: Change in hospitalizations was not the primary endpoint but was included here for reference]*	Patients who experienced ≥1 TEAE, n (%) > 700 mg bamlanivimab: 27 (26.7) > 2800 mg bamlanivimab: 26 (24.3) > 7000 mg bamlanivimab: 22 (21.8) > 2800 mg bamlanivimab and 2800 etesevimab: 19 (17) > Placebo arm: 42 (26.9)
Dougan *et al.* 2021a[56] BLAZE-1 NCT04427501	Hospitalization rate due to COVID-19 or any cause death with bamlanivimab/etesevimab group versus placebo group by Day 28 > 70%, p=0.0004; significant reduction with bamlanivimab/etesevimab group	Patients who experienced an AE, n (%) > Bamlanivimab/etesevimab: 69 (13.3) > Placebo: 60 (11.6)
Dougan *et al.* 2021b[57] BLAZE-1 NCT04427501	Number of COVID-19-related hospitalizations or deaths through study Day 29, n > Bamlanivimab/etesevimab: 11/518 > Placebo: 36/517 > Reduction rate: 70%, p=0.001	Patients who experienced an AE, n (%) > Bamlanivimab/etesevimab: 69/518 (13.3) > Placebo: 60/517 (11.6) Patients who experienced a SAE, n (%) > Bamlanivimab/etesevimab: 7/518 (1.4) > Placebo: 5/517 (1)

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Dougan *et al.* 2022[59] BLAZE-1 NCT04427501	Overall reduction in COVID-19-related hospitalization or all-cause death by Day 29, % > Balmanivimab/etesevimab group versus placebo group: 87 Proportion of patients who experienced COVID-19-related hospitalization or all-cause death by Day 29, n (%) > Balmanivimab/etesevimab: 4 (0.8) > Placebo: 15 (5.8) > Difference, % ([95% CI], p-value): -5.0 ([-8.0 to -2.1], p<0.001)	Patients who experienced a SAE, n (%) > Balmanivimab/etesevimab: 6 (1.2) > Placebo: 2 (0.8) Patients who experienced a TEAE, n (%) > Balmanivimab/etesevimab: 46 (9.0) > Placebo: 25 (9.7)
Chen *et al.* 2022[60] BLAZE-1 NCT04427501	Time to key symptom endpoints for balmanivimab/etesevimab group versus placebo group, p-value > Sustained symptom resolution: p=0.009 > Symptom resolution: p=0.016 > Sustained complete symptom resolution: p=0.01 Time (days) to symptom improvement, median > Balmanivimab/etesevimab: 7 > Placebo: 9 > p-value: 0.009 Proportion of patients demonstrating key symptom endpoints by Day 11 for balmanivimab/etesevimab group versus placebo group: > Sustained symptom resolution: 57.8% vs 47.7%, p=0.008 > Symptom resolution: 61.8% vs 50.8%, p=0.004 > Symptom improvement: 52.7% vs 40.7%, p=0.002	NR
Williams *et al.* 2022†[61] BLAZE-4 NCT4634409	The primary endpoint was safety *[Note: Endpoints for hospitalization and death by day 29 are also available in the DEF]*	Patients who experienced a TEAE, n (%) > Bebtelovimab: 20/100 (20) > Bebtelovimab/bamlanivimab/etesevimab: 8/50 (16) Patients who experienced a SAE, n (%) > Bebtelovimab: 18/176 (10.2) > Bebtelovimab/bamlanivimab/etesevimab: 2/176 (1.1)

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Davis *et al.* 2022[62] Davis *et al*. 2022 casirivimab/imdevimab NCT04666441	All 6 casirivimab and imdevimab dose groups showed comparable virologic reduction through Day 7 versus placebo	Comparable safety for all dose groups
Huang *et al.* 2021[63] UPMC Quality Improvement Review Committee Project ID 3282. University of Pittsburgh Institutional Review Board STUDY210220179 NCT04790786	Number of patients with 28 hospital-free days, n (%) *[No deaths]* > Casirivimab/imdevimab: 2163/2454 (88.1) > Sotrovimab: 964/1104 (87.3)	Patients who experienced an AE, n (%) > Casirivimab/imdevimab: 17/2163 (0.5) > Sotrovimab: 6/1104 (0.5) Patients who experienced a SAE, n (%) > Casirivimab/imdevimab: 7/2163 (0.2) > Sotrovimab: 4/1104 (0.4)
Chew *et al.* 2021[64] ACTIV-2/A5401 NCT04518410	Detection of NP SARS-CoV-2 RNA at Day 3 (log_{10} copies/mL) > Bamlanivimab 7000 mg: 2.2 > Placebo 7000 mg: 3.4 o P=0.07; significant difference > Bamlanivimab 700 mg: 2.9 > Placebo 700 mg: 3.9 o P=0.002; significant difference *[Note: Detection of NP SARS-CoV-2 RNA at Days 7, 14, and 21 were also primary endpoints]* Time (days) to improvement of all of 13 targeted COVID-19 symptoms (by self-assessment through Day 28) > Bamlanivimab: 24 > Placebo: 20.5 o Difference: 3.5, p=0.08; no significant difference *[Note: Endpoints for hospitalization or death are also available in the DEF]*	Patients who experienced a grade 3 AE, n (%) > Bamlanivimab 7000 mg: 6/48 (12.5) > Placebo 7000 mg: 6/48 (13.0) > Balanivimab 700 mg: 10/111 (9.0) > Placebo 700 mg: 6/112 (5.4) Patients who experienced a grade 2+ AE, n (%) > Bamlanivimab 7000 mg: 18/48 (37.5) > Placebo 7000 mg: 14/48 (30.4) > Balanivimab 700 mg: 41/111 (36.9) > Placebo 700 mg: 25/111 (22.3) Patients who experienced a SAE, n (%) > Bamlanivimab 7000 mg: 2/48 (4.2) > Placebo 7000 mg: 4/48 (8.7) > Balanivimab 700 mg: 4/111 (3.6) > Placebo 700 mg: 3/111 (2.7)

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Chew *et al.* 2022[65] ACTIV-2/A5401 NCT04518410	Detection of SARS-CoV-2 RNA from NP swabs at Days 3, 7, 14, 21, and 28, n (%) > Bamlanivimab (7000 mg): 8 (17.4), 11 (23.9), 24 (52.2), 32 (69.6), 34 (72.3) > Placebo (7000 mg): 8 (18.2), 10 (23.3), 28 (66.7), 32 (80.0), 33 (78.6) > Bamlanivimab (700 mg): 8 (7.6), 13 (12.5), 35 (35.0), 66 (64.1), 70 (72.2) > Placebo (700 mg): 7 (6.5), 17 (16), 33 (32.4), 56 (53.8), 66 (64.1)	Patients who experienced a grade 3 or higher TEAE, n (%) > Bamlanivimab (7000 mg): 6 (12.5) > Placebo (7000 mg): 6 (13) > Bamlanivimab (700 mg): 12 (10.8) > Placebo (700 mg): 7 (6.3) Patients who experienced a SAE, n (%) > Bamlanivimab (7000 mg): 2 (4.2) > Placebo (7000 mg): 4 (8.7) > Bamlanivimab (700 mg): 4 (3.6) > Placebo (700 mg): 3 (2.7)
Boucau *et al.* 2022[66] ACTIV-2/A5401 NCT04518410	Proportion of patients that were culture-positive at Days 1, 2, 3 and 7, n (%) > Bamlanivimab: 0 (0.0), 0 (0.0), 0 (0.0), 0 (0.0) > Placebo: 16 (41.0), 7 (17.9), 8 (21.6), 1 (2.7) o p-value of bamlanivimab group versus placebo group at Day 1 was <0.0001, significant difference	NR
Kumarasamy *et al*. 2022[67] EMPATHY NCT04828161	Participants achieving sustained clinical recovery by Day 8, % > Ensovibep 75 mg: 30 > Ensovibep 225 mg: 20 > Ensovibep 600 mg: 10 > Placebo: 10 *[Note: the primary efficacy endpoint was "time-weighted change from baseline in log_{10} SARS-CoV-2 viral load in nasopharyngeal swabs to Day 8, versus placebo", however, this was shown within a figure in the publication and not reported clearly]* *[Note: Endpoints for hospitalization are also available in the DEF]*	Patients who experienced a TEAE, % > Pooled ensovibep: 41.7 > Placebo: 51 No SAEs were observed

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Streinu-Cercel *et al.* 2022[68] CT-P59 NCT04602000	Time (days) to negative RT-qPCR for regdanvimab groups versus placebo group, median ([95% CI], p-value), significant threshold of p=0.05 > Regdanvimab 40 mg/kg: 12.8 ([9.0-12.9], p=0.06) > Regdanvimab 80 mg/kg: 11.9 ([8.9-12.9], p=0.21) > Either dosage of intervention: 12.7 ([9.0-12.8], p=0.08) > Placebo: 12.9 (12.7-13.9) Time (days) to Clinical Recovery up to Day 14 for regdanvimab groups versus placebo group, median ([95% CI], p value), significant threshold of p=0.05 > Regdanvimab 40 mg/kg: 5.3 ([4.0-6.8], p=0.01) > Regdanvimab 80 mg/kg: 6.2 ([5.5-7.9], p=0.04) > Either dosage of intervention: 5.7 ([5.2-6.8], p=0.01) > Placebo: 8.8 (6.8-11.6) *[Note: Endpoints for hospitalization or death are also available in the DEF]*	Patients who experienced a TEAE, n (%) > Regdanvimab 40 mg/kg: 31/105 (29.5) > Regdanvimab 80 mg/kg: 27 (24.5) > Placebo: 34/110 (30.9) Patients who experienced ≥1 grade 3 TEAE (related to study drug), n (%) > Regdanvimab 40 mg/kg: 1/105 (1.0) > Regdanvimab 80 mg/kg: 0/110 (0.0) > Placebo: 0/110 (0.0)
Montgomery *et al.* 2022a[69] TACKLE NCT04723394	Relative reduced risk of developing severe COVID-19 or death through Day 29, % > AZD7442: 4 > Placebo: 9 > Risk reduction, % ([95% CI], p-value): 50 ([15-71], p = 0.010)	Patients who experienced an AE, % > AZD7442: 29 > Placebo: 36 Patients who experienced a SAE, % > AZD7442: 7 > Placebo: 12 AEs of special interest were balanced between treatment groups *[Note: These safety outcomes were also primary endpoints]*

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Montgomery *et al.* 2022b[70] TACKLE NCT04723394	Proportion of patients with severe COVID-19 or death from any cause through Day 29 (mITT population), n (%) > Tixagevimab/cilgavimab: 18 (4) > Placebo: 37 (9) > RRR, % ([95% CI], p-value): 50.5 ([14.6-71.3], p=0.0096)	Patients who experienced an AE, n (%) > Tixagevimab/cilgavimab: 132 (29) > Placebo: 163 (36) Patients who experienced a SAE (including death), n (%) > Tixagevimab/cilgavimab: 33 (7) > Placebo: 54 (12) Patients who experienced an AE of special interest, n (%) > Tixagevimab/cilgavimab: 15 (3) > Placebo: 15 (3)
Hobbs *et al.* 2022[71] TACKLE NCT04723394	Incidence of death or hospitalization for COVID-19 complications or sequalae through Day 169, n (%) > Tixagevimab/cilgavimab: 20 (5.0) > Placebo: 40 (9.8) > RRR, % ([95% CI], p-value): 49.1 ([14.5-69.7], p=0.0009 (for Tixagevimab/cilgavimab group versus placebo group)	Patients who experienced an AE, % > Tixagevimab/cilgavimab: 38.5 > Placebo: 43.5
STAMP 2022[72] STAMP	Incidence of hospitalization or death through Day 29, n (%) > Adintrevimab: 8/169 (4.7) > Placebo: 23/167 (13.8) > Standard risk difference, % ([95% CI], p-value): -8.6% ([-14.65 to -2.57], p=0.0052) > RRR: 66%	Occurence of AEs, including SAEs, was lower in the adintrevimab group versus the placebo group

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
O'Brien *et al.* 2022[73] O'Brien *et al.* 2022 casirivimab/imedevimab NCT04452318	Proportion of participants (seronegative) who developed signs and symptoms of COVID-19 within 14 days of a positive RT-qPCR result at baseline or during the efficacy assessment period, n (%) > Casirivimab/imdevimab: 29/100 (29.0) > Placebo: 44/104 (42.3) > Adjusted OR ([95% CI], p-value): 0.54 ([0.30-0.97], p = 0.04), > Absolute risk difference, % (95% CI): -13.3 (-26.3 to -0.3) *[Note: Endpoints for hospitalization or death are also available in the DEF]*	Patients who experienced ≥1 TEAE, n (%) > Casirivimab/imdevimab: 52/155 (33.5) > Placebo: 75/156 (48.1) 25.8% of the casirivimab/imdevimab group experienced COVID-related TEAEs
Mazzaferri *et al.* 2022[74] MANTICO NCT05205759	Proportion of patients that experienced COVID-19 progression through Day 14 (Delta variant), n (%) > Sotrovimab: 0 (0.0) > Bamlanivimab/etesevimab: 0 (0.0) > Casirivimab/imdevimab: 0 (0.0) Proportion of patients that experienced COVID-19 progression through Day 14 (Omicron variant), n (%) > Sotrovimab: 0 (0.0) > Bamlanivimab/etesevimab: 2 (3.51) > Casirivimab/imdevimab: 0 (0.0) *[Note: Data regarding emergency department visits, all-cause mortality, duration of supplemental oxygen therapy, and rate and duration of non-invasive ventilation and mechanical ventilation are also available in the DEF]*	NR

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Portal-Celhay *et al.* 2022[75] Portal-Celhay *et al.* 2022 casirivimab/imdevimab NCT04666441	Time-weighted average daily change from baseline in viral load (log_{10} copies/mL) to Day 7 for casirivimab groups versus matched placebo group, LS mean difference ([95% CI], p-value) > Casirivimab/imdevimab 300 mg IV: -0.57 ([-0.88 to -0.25], p<0.001) > Casirivimab/imdevimab 600 mg IV: -0.66 ([-0.99 to -0.34], p<0.001) > Casirivimab/imdevimab 1200 mg IV: -0.56 ([-0.89 to -0.24], p<0.001) > Casirivimab/imdevimab 2400 mg IV: -0.71 ([-1.05 to -0.38], p<0.001) > Casirivimab/imdevimab 600 mg SC: -0.56 ([-0.88 to -0.24], p<0.001) > Casirivimab/imdevimab 1200 mg SC: -0.56 ([-0.87 to -0.24], p<0.001)	Occurrence of AEs, n > Casirivimab/imdevimab 300 mg IV: 115 > Casirivimab/imdevimab 600 mg IV: 114 > Casirivimab/imdevimab 1200 mg IV: 116 > Casirivimab/imdevimab 2400 mg IV: 115 > Casirivimab/imdevimab 600 mg SC: 114 > Casirivimab/imdevimab 1200 mg SC: 114 > Placebo (IV): 57 > Placebo (SC): 58 Patients who experienced a TEAE, SAE, n (%): > Casirivimab/imdevimab 300 mg IV: 10 (8.7), 0 (0.0) > Casirivimab/imdevimab 600 mg IV: 16 (14.0), 0 (0.0) > Casirivimab/imdevimab 1200 mg IV: 22 (19.0), 1 (0.9) > Casirivimab/imdevimab 2400 mg IV: 9 (7.8), 1 (0.9) > Casirivimab/imdevimab 600 mg SC: 5 (4.4), 0 (0.0) > Casirivimab/imdevimab 1200 mg SC: 12 (10.5), 0 (0.0) > Placebo (IV): 10 (7.5), 0 (0.0) > Placebo (SC): 6 (10.3), 0 (0.0)
Kim *et al.* 2022[76] Kim *et al.* 2022 regdanvimab NCT04602000	Proportion of patients with disease progression up to Day 28 (ITT High-risk patients), n (%) [95% CI] > Regdanvimab: 14 (3.1) [1.9-5.2] > Placebo: 48 (11.1) [8.4-14.4] Proportion of patients with disease progression up to Day 28 (ITT), n (%) [95% CI] > Regdanvimab: 16 (2.4) [1.5-3.9] > Placebo: 53 (8.0) [6.2-10.4]	Patients who experienced a TEAE, n (%) > Regdanvimab: 198 (30.4) > Placebo: 202 (31.1) Patients who experienced a grade ≥3 TEAE, n (%) > Regdanvimab: 61 (9.4) > Placebo: 69 (10.6) Patients who experienced a TESAE, n (%) > Regdanvimab: 4 (0.6) > Placebo: 1 (0.2)

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Schilling *et al.* 2022[77] PLATCOV NCT05041907	Time to viral clearance for casirivimab/imdevimab group versus no study drug group > 52.3% faster (95% CI: -7.0% to 115.1%)	Patients who experienced any grade ≥3 AE, n > Casirivimab/imdevimab: 0 > No study drug: 2 Patients who experienced a SAE, n > Casirivimab/imdevimab: 0 > No study drug: 2

*Events were grade 2 or higher hypersensitivity reactions or infusion-related reactions. †Results for the double-blinded low-risk population for Williams *et al*. 2022 are not presented here but can be found in the DEF.
AE: adverse event; CI: confidence interval; DEF: data extraction form; COVID: Coronavirus disease; COVID-19: Coronavirus disease 2019; g: grams; ITT: intention-to-treat; IV: intravenous; kg: kilogram; LS: least squares; LSM: least squares mean; mg: milligram; mL: milliliter; NP: nasopharyngeal; OR: odds ratio; RNA: ribonucleic acid; RR: relative risk; RRR: relative risk ratio; RT-qPCR: reverse transcription-quantitative polymerase chain reaction; SAE: severe adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SC: subcutaneous; TEAE: treatment emergent adverse event; TESAE: treatment emergent serious adverse event; TRAE: treatment-related adverse event.

Table 8. RCTs assessing interferons (interferon lambda)

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Feld *et al.* 2021[78]	*The BMJ*-MAGIC-WHO	Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomized trial	Journal article	Feld *et al.* 2021 peginterferon lambda NCT04354259	2
Jagannathan *et al.* 2021[79]	*The BMJ*-MAGIC-WHO	Peginterferon Lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial	Journal article	Jagannathan *et al.* 2021 peginterferon Lambda-1a NCT04331899	2

BMJ: British Medical Journal; COVID-19: Coronavirus disease 2019; MAGIC: Making GRADE the Irresistible Choice; WHO: World Health Organization.

Table 9. Study characteristics of RCTs for interferons (interferon lambda)

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Feld *et al.* 2021[78] Feld *et al.* 2021 peginterferon lambda NCT04354259 18/05/2020-04/09/2020 Canada	> Peginterferon lambda: SC injection, 180 µg single dose > Placebo: SC injection of saline placebo, single dose	> Individuals with SARS-CoV-2 infection confirmed by NP swab, within 7 days of symptom onset (or first positive test if asymptomatic) > Patients were excluded if hospitalization was required	> Proportion of individuals with a negative mid-turbinate swab for SARS-CoV-2 at Day 7	> Time to undetectable SARS-CoV-2 RNA > Quantitative change in SARS-CoV-2 RNA over time > Anti-SARS-CoV-2 IgG antibody positivity > Incidence and severity of adverse events > The proportion of patients admitted to hospital by Day 14 *[Complete list of secondary endpoints outlined in the appendix]*

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Jagannathan *et al.* 20216[79] Jagannathan *et al.* 2021 peginterferon Lambda-1a NCT04331899 24/04/2020-17/07/2020 US	> Peginterferon lambda: SC injection, 180 µg (0.45 mL), single dose > Placebo: SC injection of saline placebo (0.45 mL), single dose	> Adults (aged 18-65 years) RT-PCR positive for SARS-CoV-2 within 72 hours from swab to the time of enrollment > Symptomatic individuals were eligible given the presence of mild to moderate symptoms without signs of respiratory distress > Asymptomatic individuals were eligible if infection was initial diagnosis of SARS-CoV-2 infection > Excluded criteria included current or imminent hospitalization, respiratory rate >20 breaths per minute, and room air oxygen saturation <94%	> Time to first of two consecutive negative oropharyngeal tests for SARS-CoV-2 by RT-PCR	> Time to alleviation of all symptoms, defined as the first day where no symptoms were reported > SARS-CoV-2 oropharyngeal viral RNA levels over time > SARS-CoV-2 oropharyngeal viral RNA area under the curve > Incidence of emergency department visits or hospitalizations within 28 days of initiation of treatment

IgG: Immunoglobulin G; mL: milliliter; NP: nasopharyngeal; RNA: ribonucleic acid; RT-PCR: reverse transcription-polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SC: subcutaneous; US: United States; µg: microgram.

Table 10. Patients baseline characteristics for RCTs for an interferon (interferon lambda)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Feld *et al.* 2021[78] Feld *et al.* 2021 peginterferon lambda NCT04354259	> Peginterferon lambda: 30 > Placebo: 30	Median (IQR) > Peginterferon lambda: 48 (30-53) > Placebo: 39 (33-55)	Female, n (%) > Peginterferon lambda: 18 (60) > Placebo: 17 (57)	Mean (SD) > Peginterferon lambda: 4.3 (1.7) > Placebo: 4.7 (1.7)
Jagannathan *et al.* 2021[79] Jagannathan *et al.* 2021 peginterferon Lambda-1a NCT04331899	> Overall: 120 > Peginterferon lambda: 60 > Placebo: 60	Median (range) > Overall: 36 (18-71) > Peginterferon lambda arm: 37 (18-66) > Placebo arm: 34 (20-71)	Female, n (%) > Overall: 50 (41.7) > Peginterferon lambda: 24 (40.0) > Placebo: 26 (43.3)	Median (IQR) > Overall: 5 (3-6) > Peginterferon lambda: 4 (3-6) > Placebo: 5 (3-5)

IQR: interquartile range; NR: not reported; SD: Standard Deviation.

Table 11. Results from RCTs assessing interferons (interferon lambda); primary outcome(s)

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Feld *et al.* 2021[78] Feld *et al.* 2021 peginterferon lambda NCT04354259	Undetectable SARS-CoV-2 RNA for peginterferon lambda group versus placebo group at Day 7, OR ([95% CI], p-value) > 2.32 ([0.74-7.81], p=0.15), no significant difference Undetectable SARS-CoV-2 RNA for peginterferon lambda group versus placebo group at Day 7 after adjusting for baseline viral load, OR ([95% CI], p-value) > 4.12 ([1.15 to 16.73], p=0.029), significant increase Undetectable SARS-CoV-2 RNA for peginterferon lambda group versus placebo group at Day 7 for patients with baseline viral load ≥108 copies per mL, OR ([95% CI], p-value) > 6.25 ([1.49 to 31.06], p=0.012), significant increase *[Note: Endpoints for hospitalization or death are also available in the DEF]*	Patients who experienced an AE, n (%) > Peginterferon lambda: 2 (7) > Placebo: 1 (3) Patients who experienced a SAE, n (%) > Peginterferon lambda: 1 (3) > Placebo: 1 (3)
Jagannathan *et al.* 2021[79] Jagannathan *et al.* 2021 peginterferon Lambda-1a NCT04331899	Viral shedding cessation for peginterferon lambda group versus placebo group, aHR ([95% CI], p-value) > 0.81 ([0.56-1.19], p=0.29), no significant difference *[Note: Endpoints for hospitalization are also available in the DEF]*	Patients who experienced an AE, n (%) > Peginterferon lambda: 25 (42) > Placebo: 21 (35) Patients who experienced a SAE, n (%) > Peginterferon lambda: 2 (3) > Placebo: 2 (3)

AE: adverse event; aHR: adjusted hazard ratio; BMJ: British Medical Journal; CI: confidence interval; DEF: data extraction form; OR: odds ratio; RNA: ribonucleic acid; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Table 12. RCT assessing the H2 antagonist, famotidine

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Brennan *et al.* 2022[80]	OVID	Oral famotidine versus placebo in non-hospitalized patients with COVID-19: a randomized, double-blind, data-intense, phase 2 clinical trial	Journal article	Brennan *et al.* 2022 famotidine NCT04724720	2

COVID-19: Coronavirus disease 2019.

Table 13. Study characteristics of the RCT assessing famotidine for the treatment of COVID-19

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Brennan *et al.* 2022[80] Brennan *et al.* 2022 famotidine NCT04724720 01/2021-04/2021 US	Famotidine and placebo (microcrystalline cellulose)	Patients with a laboratory confirmed SARS-CoV-2 test less than 72 hours prior to randomization and at least three symptoms of moderate severity	Time to symptom resolution (by Day 28)	The impact of earlier symptom resolution of famotidine on an individual symptom level

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; US: United States.

Table 14. Patient baseline characteristics in RCTs of famotidine for the treatment of COVID-19

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Brennan *et al.* 2022[80] Brennan *et al.* 2022 famotidine NCT04724720	> Overall: 55 > Famotidine: 27 > Placebo: 28	Mean (SD) > Overall: 35 (20) > Famotidine: 35 (18) > Placebo: 31.5 (13)	Male, female, n (%) > Overall: 29 (36.4), 35 (63.3) > Famotidine: 10 (37), 17 (63) > Placebo: 13 (35.7), 18 (64.3)	Median (IQR) > Overall: 4 (2) > Famotidine arm: 4 (3) > Placebo arm: 4 (2)

IQR: interquartile range; SD: standard deviation.

Table 15. Results from RCT assessing famotidine for the treatment of COVID-19

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Brennan *et al.* 2022[80] Brennan *et al.* 2022 famotidine NCT04724720	Time (days) to 50% symptom resolution by study Day 28, estimated time (95% CI) > Famotidine: 8.2 (7-9.8) > Placebo: 11.4 (10.3-12.6) Time to symptom resolution by Day 28 famotidine group versus placebo group > ITT population: p=0.4 (0.05 threshold) > PP population: p=0.3 (0.05 threshold) *[Note: Endpoints for hospitalization or death are also available in the DEF]*	Patients who experienced an AE, n > Famotidine: 3 > Placebo: 2 Patients who experienced a SAE, n > Famotidine: 3 > Placebo: 2

AE: adverse event; CI: confidence interval; DEF: data extraction form; ITT: intention-to-treat; PP: per-protocol; SAE: serious adverse event.

Table 16. RCTs assessing steroids (budesonide)

Author and year	Source	Title	Report type	Trial identifier(s)	Phase
Ramakrishnan *et al.* 2021[81]	OVID	Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomized controlled trial	Journal article	STOIC NCT04416399	2
Yu *et al.* 2021a[82]	NIH guidelines	Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial	Journal article (pre-print)	PRINCIPLE trial ISRCTN86534580	NR *[Appears to be phase 3]*
Yu *et al.* 2021b[83]	OVID	Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomized, controlled, open-label, adaptive platform trial	Journal article (published)		

COVID-19: Coronavirus disease 2019; NIH: National Institutes of Health; NR: not reported; UK: United Kingdom.

Table 17. Study characteristics of RCTs for steroids (budesonide)

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Ramakrishnan *et al.* 2021[81] STOIC NCT04416399 16/07/2020-09/12/2020 UK	> Budesonide: dry powder inhaler at a dose of 400 µg per actuation; two puffs BID; total dose 1600 µg daily > Usual care (symptomatic treatment according to NHS advice)	> Adults (aged ≥18 years) with symptoms of COVID-19 (new onset cough and fever or anosmia, or both) within 7 days > Patient requiring hospitalization at time of study consent were excluded	> COVID-19-related urgent care visits including emergency department or hospitalization	> Self-reported time to symptom resolution > Viral symptoms measured by the CCQ and the FLUPro > Blood oxygen saturation and body temperature > SARS-CoV2 viral load

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Yu *et al.* 2021a[82] PRINCIPLE trial ISRCTN86534580 [trial does not appear on clinicaltrials.gov] 27/11/2020-25/03/2021 [cut-off date for presented data] UK **Yu *et al.* 2021b[83]** PRINCIPLE trial ISRCTN86534580 27/11/2020-31/03/2021 UK	> Budesonide plus usual care: Budesonide inhaled 800 µg BID for 14 days > Usual care (undefined but likely focused on management of symptoms, as per UK National Health Service (NHS) practice)	> People (aged ≥65 years, or ≥50 years with comorbidities) in the community with ongoing symptoms from PCR-confirmed or suspected COVID-19 which started within the past 14 days > Exclusion criteria included being currently hospitalized or admitted to hospital and already taking inhaled or systemic corticosteroids	Within 28 days of randomization: > Time to first reported recovery > Hospitalization or death related to COVID-19	> Binary outcome of early sustained recovery > Daily rating of how well participants feel > Time to initial alleviation of symptoms > Time to sustained alleviation of symptoms > Time to initial reduction of severity of symptoms > Contacts with health service > Hospital assessment without admission > Oxygen administration > ICU admission > Mechanical ventilation > Adherence to study treatment > WHO-5 Wellbeing Index > Reports of new household infections *[Full list of secondary outcomes listed within supplementary appendix]*

BID: twice daily; CCQ: Common Cold Questionnaire; COVID-19: Coronavirus disease 2019; FLUPro: InFLUenza Patient Reported Outcome; ICU: intensive care unit; NHS: National Health Service; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization; UK: United Kingdom; µg: microgram.

Table 18. Patients baseline characteristics for RCTs for steroids (budesonide)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Ramakrishnan *et al.* 2021[81] STOIC NCT04416399	> Budesonide: 70 > Usual care: 69	Mean (range) > Budesonide: 44 (19-71) > Usual care: 46 (19-79)	Female, n (%) > Budesonide: 39 (56) > Usual care: 41 (59)	Median (IQR) > Budesonide: 3 (2-5) > Usual care: 3 (2-4)
Yu *et al.* 2021a[82] PRINCIPLE trial ISRCTN86534580 [trial does not appear on clinicaltrials.gov] **Yu *et al.* 2021b**[83] PRINCIPLE trial ISRCTN86534580	> Budesonide: 1032 > Usual care: 1943 > Budesonide: 1073 > Usual care: 1988	<65 years, ≥65 years, n (%) > Budesonide: 277 (34.4), 528 (65.6) > Usual care: 456 (41.5), 644 (58.5) [in COVID-positive analysis population] Mean (SD), <65 years n (%), ≥65 years n (%) > Budesonide: 64.7 (7.3), 297 (36), 536 (64) > Usual care: 63.8 (7.8), 475 (42), 651 (58)	Male, n (%) > Budesonide: 390 (48.4) > Usual care: 528 (48.0) [in COVID-positive analysis population] Female, male, n (%) > Budesonide: 429 (52), 404 (48) > Usual care: 586 (52), 540 (48)	Median (IQR) > Budesonide: 6.0 (4.0-9.0) > Usual care: 6.0 (4.0-9.0) [in COVID-positive analysis population]

COVID: Coronavirus disease; IQR: interquartile range; NR; not reported; SD: standard deviation.

Table 19. Results from RCTs assessing steroids (budesonide); primary outcome(s)

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Ramakrishnan *et al.* 2021[81] STOIC NCT04416399	Rate of hospitalization for budesonide group versus usual care group, difference (95% CI) > 0.131 (0.043-0.218) > p=0.004; significant reduction difference Proportion of patients with symptom resolution at Day 14 for budesonide group versus usual care group, difference (95% CI) > 0.10 (-0.04 to 0.24) > p=0.166; no significant difference	Patients who experienced an AE, n (%) > Budesonide: 5 (7) > Usual care: NR
Yu *et al.* 2021a[82] PRINCIPLE trial ISRCTN86534580 [trial does not appear on clinicaltrials.gov] **Yu *et al.* 2021b[83]** PRINCIPLE trial ISRCTN86534580	Benefit in time (days) to first reported recovery for budesonide group vs usual care group, median (95% BCI) > 3.011 (1.124-5.410) > probability of superiority = 0.999*; significant improvement Estimated benefit in patients hospitalized or dead at Day 28 for budesonide group vs usual care group, % (95% BCI) > 2.1 (-0.7 to 4.8) > probability of superiority = 0.928*; not significant Time (days) to first reported recovery (outpatient cohort), median (95% BCrI) > Budesonide: 11.8 (10.0-14.1); probability of superiority >0.999* > Usual care: 14.7 (12.3-18.0); probability of superiority >0.999* > HR/OR: 1.21 (1.08-1.36); probability of superiority >0.999* Patients hospitalized or dead at Day 28 (outpatient cohort), (%) > Budesonide: 6.8 > Usual care: 8.8 > Estimated benefit, % (95% BCI): 2 (-0.2 to 4.5) > HR/OR: 0.75 (0.55-1.03); p=0.963 *Predefined superiority threshold of 0.975	Patients who experienced a SAE, n (%) > Budesonide: 2/70 (7) > Usual care: NR

AE: adverse event; BCI: Bayesian credible interval; BCrI: Bayesian credible interval; CI: confidence interval; HR: hazard ratio; NR: not reported; OR: odds ratio; SAE: serious adverse event.

Table 20. RCTs assessing a selective serotonin reuptake inhibitor (fluvoxamine)

Author and year	Source	Report title	Report type	Trial identifier(s)	Phase
Lenze *et al.* 2020[84]	OVID	Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients with Symptomatic COVID-19	Journal article	STOP COVID trial NCT04342663	2
Seo *et al.* 2022[85]	OVID	Fluvoxamine Treatment of Patients with Symptomatic COVID-19 in a Community Treatment Center: A Preliminary Result of Randomized Controlled Trial	Journal article	Seo *et al.* 2022 fluvoxamine NCT04711863	2
Reis *et al.* 2022[86],[87]	OVID	Effect of early treatment with fluvoxamine on risk of emergency care and hospitalization among patients with COVID-19: the TOGETHER randomized, platform clinical trial	Journals article	TOGETHER NCT04727424	3
Bramante *et al.* 2022[88]	OVID	Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19	Journal article	COVID-OUT NCT04510194	3
McCarthy *et al.* 2022[89]	OVID	Fluvoxamine for Outpatient Treatment of COVID-19: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial	Journal article (pre-print)	ACTIV-6 NCT04885530	3

COVID-19: Coronavirus disease 2019.

Table 21. Study characteristics of RCTs for a selective serotonin reuptake inhibitor (fluvoxamine)

Trial report, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Lenze *et al.* 2020[84] STOP COVID trial NCT04342663 10/04/2020-05/08/2020 US	> Fluvoxamine: 50 mg first dose; two days at 100 mg BID as tolerated; 100 mg three times daily as tolerated through Day 15 > Matched placebo: Same as intervention	> Adult outpatients living in the community (aged ≥18 years) with SARS-CoV-2, confirmed by PCR testing > Symptomatic within 7 days of the first dose of study medication > Excluded characteristics included hospitalization, oxygen saturation >92%, and requiring home oxygen	Clinical deterioration within 15 days of randomization; defined as both: > Shortness of breath or hospitalization for shortness of breath or pneumonia > Oxygen saturation less than 92% on room air or need for supplemental oxygen to achieve oxygen saturation of 92% or greater)	> Clinical deterioration on a Likert-type scale 1. Oxygen saturation <92% but no supplemental oxygen requirement 2. Oxygen saturation <92% plus supplemental oxygen requirement 3. 2 plus hospitalization related to dyspnea or hypoxia 4. 3 plus ventilator support needed for <3 days 5. 3 plus ventilator support needed for ≥3 days 6. Death > The number of days requiring supplemental oxygen, hospitalization, or ventilator support > Symptomatic severity during the 15 days of the trial using a continuous scale of each patient's most severe baseline symptom on an 11-point scale

Trial report, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Seo *et al.* 2022[85] Seo *et al.* 2022 fluvoxamine NCT04711863 15/01/2021-08/02/2021 South Korea	> Fluvoxamine: Oral administration, 50 mg on Day 1 followed by 100 mg BID for approximately 10 days > Matched placebo (ursodeoxycholate): Same as intervention	> Patients with mild symptoms associated with COVID-19 admitted to a community treatment center > Onset of symptoms consistent with COVID-19 within 7 days of randomization > Had a laboratory confirmed SARS-CoV-2 test within 72 hours of randomization	Definition of clinical deterioration: > Decrease in oxygen saturation (SpO_2 <94%) on room air > Supplemental oxygen required to maintain an oxygen saturation ≥94% > Aggravation of pneumonia with dyspnea: clinically devastating condition judged by clinician plus increased infiltration of chest X-ray or minute respiratory rate over 25 > WHO Clinical Progression ≥4 including intubation and death)	> All the categories of clinical deterioration described as primary endpoints and days to clinical deterioration

Trial report, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Reis *et al*. 2022[86], [87] TOGETHER NCT04727424 02/06/2020-09/09/2021 (enrollment for the fluvoxamine group began on 20/01/2021) Brazil	> Fluvoxamine: Oral administration, 100 mg BID for 10 days > Matched placebo: Same as intervention	> Outpatients with an acute condition consistent with COVID-19 (beginning within 7 days of screening) OR > Positive rapid test for SARS-CoV-2 done at the time of screening with a positive test within 7 days of symptom onset	> Medical admission to a hospital setting due to COVID-19-related illness defined as COVID-19 emergency setting visits with participants remaining under observation for more than 6 hours OR > Referral to further hospitalization due to the progression of COVID-19 within 28 days of randomization	NR

Trial report, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Bramante *et al.* 2022[88] COVID-OUT NCT04510194 30/12/2020-28/01/2022 US	> Metformin active: Metformin and placebo, metformin and ivermectin, or metformin and fluvoxamine o Metformin: Oral administration, increase dose over 6 days to 1500 mg/day for 14 days > Metformin control: Placebo alone, ivermectin alone, or fluvoxamine alone o Matched placebo > Ivermectin active: Metformin and ivermectin or ivermectin alone o Ivermectin: Oral administration, 390-470 µg/kg/day for 3 days > Ivermectin control: Placebo alone or metformin alone o Matched placebo > Fluvoxamine active: Metformin and fluvoxamine or fluvoxamine alone o Fluvoxamine: Oral administration, 50 mg twice daily for 14 days > Fluvoxamine control: Placebo alone or metformin alone o Matched placebo	> Patients (aged 30-85 years) with a BMI associated with overweight or obesity > Proof of SARS-CoV-2 infection within the past 3 days and an onset of symptoms within 7 days before randomization	> Severe COVID-19 through 14 days, defined as composite of hypoxemia, emergency department visit, hospitalization, or death	> Daily symptom severity > Drug discontinuations

Trial report, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
McCarthy *et al.* 2022[89] ACTIV-6 NCT04885530 06/08/2021-27/05/2022 US	> Fluvoxamine: Oral administration, 50 mg daily for 10 days > Placebo: Oral administration for 10 days	> Patients (aged ≥30 years) with confirmed SARS-CoV-2 infection ≤10 days, and experiencing ≥2 COVID-19 symptoms for ≤7 days from time of consent	> Time to recovery, defined as the third of 3 consecutive days without symptoms	> Hospitalization or death by Day 28 > Time unwell > COVID-19 Clinical Progression Scale score on Days 7, 14, and 28 > Mortality, urgent or emergency care visit, or hospitalization through Day 28

BID: twice daily; BMI: body-mass index; COVID: Coronavirus disease; COVID-19: Coronavirus 2019; kg: kilogram; mg: milligram; NR: not reported; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SpO_2: peripheral capillary oxygen saturation; US: United States; WHO: World Health Organization; µg: microgram.

Table 22. Patients baseline characteristics for RCTs for a selective serotonin reuptake inhibitor (fluvoxamine)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Lenze *et al.* 2020[84] STOP COVID trial NCT04342663	> Fluvoxamine: 80 > Placebo: 72	Mean (IQR) > Fluvoxamine: 46 (35-58) > Placebo: 45 (36-54)	Female, n (%) > Fluvoxamine: 56 (70) > Placebo: 53 (74)	Median (IQR) > Fluvoxamine: 4 (3-5) > Placebo: 4 (3-5)
Seo *et al.* 2022[85] Seo *et al.* 2022 fluvoxamine NCT04711863	> Fluvoxamine: 26 > Placebo: 26	Median (IQR) > Fluvoxamine: 54 (44.0-60.3) > Placebo: 51.5 (42.0-59.3)	Male, n (%) > Fluvoxamine: 18 (69.2) > Placebo: 13 (50)	Median (IQR) > Overall: 1 (0-1)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Reis *et al.* 2022[86],[87] TOGETHER NCT04727424	> Fluvoxamine: 741 > Placebo: 756	<50, ≥50, not specified, n (%) > Fluvoxamine: 379 (51), 327 (44), 46 (6) > Placebo: 368 (49), 328 (43), 49 (6)	n (%) > Fluvoxamine: Female: 409 (55%) Male:332 (45%) > Placebo: Female: 453 (60%) Male: 303 (40%)	0-3 days, 4-7 days, unspecified, n (%) > Fluvoxamine: 328 (44), 239 (32), 174 (23) > Placebo: 310 (41), 267 (35), 179 (24)
Bramante *et al.* 2022[88] COVID-OUT NCT04510194	> Metformin active: 663 > Metformin control: 660 > Ivermectin active: 410 > Ivermectin control: 398 > Fluvoxamine active: 334 > Fluvoxamine control: 327	Median (IQR) > Metformin active: 46 (38-55) > Metformin control: 45 (37-55) > Ivermectin active: 46 (39-55) > Ivermectin control: 45 (37-56) > Fluvoxamine active: 46 (38-53) > Fluvoxamine control: 43 (37-55)	Female, n (%) > Metformin active: 359 (54.1) > Metformin control: 382 (57.9) > Ivermectin active: 216 (52.7) > Ivermectin control: 226 (56.8) > Fluvoxamine active: 170 (50.9) > Fluvoxamine control: 188 (57.5)	Mean (SD), ≤4 days, n (%) > Metformin active: 4.8 (1.9), 298 (45.6) > Metformin control: 4.8 (1.9), 305 (47.5) > Ivermectin active: 4.6 (1.9), 199 (49.0) > Ivermectin control: 4.8 (1.8), 174 (44.5) > Fluvoxamine active: 5.0 (2.2), 147 (44.5) > Fluvoxamine control: 4.7 (1.8), 146 (45.3)
McCarthy *et al.* 2022[89] ACTIV-6 NCT04885530	> Overall: 1288 > Fluvoxamine: 674 > Placebo: 614	Median (IQR) > Overall: 47.0 > Fluvoxamine: 47.0 (37.0-56.8) > Placebo: 48.0 (39.0-58.0)	Female, male, prefer not to answer, n (%) > Overall: 734 (56.99), 551 (42.78), 3 (0.23) > Fluvoxamine: 387 (57.42), 286 (42.43), 1 (0.15) > Placebo: 347 (56.51), 265 (43.16), 2 (0.33)	Mean (range) > Overall: 4 (2-5) > Fluvoxamine: 4 (2-5) > Placebo: 4 (2-5)

IQR: interquartile range; NR: not reported.

Table 23. Results from RCTs assessing a selective serotonin reuptake inhibitor (fluvoxamine); primary outcome(s)

Trial report, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Lenze *et al.* 2020[84] STOP COVID trial NCT04342663	Absolute difference in proportions with clinical deterioration for fluvoxamine group versus placebo group (95% CI, survival analysis for clinical deterioration using a log-rank test) > 8.7 (1.8-16.4) > p=0.009; significantly lower with fluvoxamine group versus placebo group *[Note: Clinical deterioration was ranked using the WHO ordinal scale for COVID-19 trials, which includes hospitalization]*	Patients who experienced a SAE, n > Fluvoxamine: 1 > Placebo: 6 Patients who experienced a "other" AE, n > Fluvoxamine: 11 > Placebo: 12
Seo *et al.* 2022[85] Seo *et al.* 2022 fluvoxamine NCT04711863	Clinical deterioration (absolute difference is a difference in proportions), n (%) > Fluvoxamine: 2/26 (7.7%), p>0.99 > Placebo: 2/26 (7.7%), p>0.99 > Difference ([95% CI], p-value): 0 ([-17.37 to 17.37], p>0.99)	Occurrence of drug related AEs linked to termination of treatment, n > Fluvoxamine: 10 > Placebo: 1
Reis *et al.* 2022[86],[87] TOGETHER NCT04727424	Proportion of primary outcome events and RR of hospitalization defined as either retention in a COVID-19 emergency setting or transfer to tertiary hospital due to COVID-19 for patients allocated fluvoxamine versus placebo, n (%) > ITT analysis: o Fluvoxamine: 79/741 (11) o Placebo: 119/756 (16) o RR (95% BCI): 0.68 (0.52-0.88); probability of superiority: 99.8%* > mITT analysis: o Fluvoxamine: 78/740 (11) o Placebo: 115/752 (15) o RR (95% BCI): 0.69 (0.53-0.90); probability of superiority: 99.7% *Surpassed prespecified superiority threshold of 97·6% (risk difference 5.0%)	Patients who experienced a TEAE (Grade 1, 2, 3, 4, 5), n (%) > Fluvoxamine: 20 (3), 72 (10), 38 (5), 21 (3), 18 (2) > Placebo: 11 (1), 81 (11), 50 (7), 20 (3), 26 (3)

Trial report, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Bramante *et al.* 2022[88] COVID-OUT NCT04510194	Rate of severe COVID-19 through Day 14 (mITT population), n (%) > Metformin active: 154 (23.6) > Metformin control: 179 (27.4) o Adjusted OR for active group versus control group ([95% CI], p-value): 0.84 ([0.66-1.09], p=0.19) > Ivermectin active: 105 (25.8) > Ivermectin control: 96 (24.6) o Adjusted OR for active group versus control group ([95% CI], p-value): 1.05 ([0.76-1.45], p=0.78) > Fluvoxamine active: 79 (24.0) > Fluvoxamine control: 80 (24.9) o Adjusted OR for active group versus control group ([95% CI], p-value): 0.94 ([0.66-1.36], p=0.75)	Patients who experienced total interruption/discontinuation of treatment, n (%) > Metformin active: 201 (30.3) > Metformin control: 164 (24.8) > Ivermectin active: 92 (22.4) > Ivermectin control: 156 (26.9) > Fluvoxamine active: 117 (35.0) > Fluvoxamine control: 156 (26.9)
McCarthy *et al.* 2022[89] ACTIV-6 NCT04885530	Time to recovery (mITT population), median (IQR) > Fluvoxamine: 12 (12-13) > Placebo: 13 (12-13)	Patients who experienced an AE, n (%) > Fluvoxamine: 32 (5.2) > Placebo: 35 (6.2) Patients who experienced a SAE, n (%) > Fluvoxamine: 3 (0.49) > Placebo: 5 (0.88)

AE: adverse event; BCI: Bayesian credible interval; CI: confidence interval; COVID-19: Coronavirus 2019; ITT: intention-to-treat; IQR: interquartile range; mITT: modified intention-to-treat; OR: odds ratio; RR: relative risk; SAE: serious adverse event; TEAE: Treatment emergent adverse event.

Table 24. RCTs assessing the serine protease inhibitor, camostat mesylate

Author and year	Source	Report title	Report type	Trial identifier(s)	Phase
Chupp *et al.* 2022[90]	OVID	A Phase 2 Randomized, Double-Blind, Placebo-controlled Trial of Oral Camostat Mesylate for Early Treatment of COVID-19 Outpatients Showed Shorter Illness Course and Attenuation of Loss of Smell and Taste	Journal article	Chupp *et al.* 2022 camostat mesylate NCT04724720	2
Jilg *et al.* 2022a[91]	CROI 2022	A randomized controlled trial of camostat in outpatients with COVID-19	Conference abstract	CAMELOT NCT04583592	2
Jilg *et al.* 2022b[92]	CROI 2022	Camostat is not effective for mild-moderate COVID-19 in a phase 2 Trial of ACTIV-2	Conference abstract	ACTIV-2/A5401 NCT04518410	2
Tobback *et al.* 2022[93]	OVID	Efficacy and safety of camostat mesylate in early COVID-19 disease in an ambulatory setting: a randomized placebo-controlled phase II trial	Journal article	Tobback *et al.* 2022 camostat mesylate NCT04625114	2

COVID: Coronavirus disease; COVID-19: Coronavirus 2019; CROI: Conference on Retroviruses and Opportunistic Infections; RCT: Randomized controlled trial.

Table 25. Study characteristics of RCTs assessing camostat mesylate for the treatment of COVID-19

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Chupp *et al.* 2022[90] Chupp *et al.* 2022 camostat mesylate NCT04353284 06/2020-04/2021 US	> Camostat mesylate: Oral administration, camostat mesylate 200 mg 4 times a day for 7 days > Matching placebo	> Patients with a first positive RT-PCR for COVID-19 within 3 days before enrollment with at least one compatible COVID-19 symptom	> Reduction of 4-day log_{10} NP swab viral load by 0.5 log_{10} compared to placebo	> Change in log_{10} NP viral load from baseline (Day 0), Day 2 and Day 6 post-randomization > COVID-19 PRO daily self-scoring tool (FLUpro) (symptom severity scoring system)
Jilg *et al.* 2022a[91] CAMELOT NCT04583592 08/11/2020-31/03/2021 US	> Camostat mesylate: Oral administration, two 100 mg tablets (200 mg total) taken four times daily for 14 days, plus SOC > Placebo plus SOC	> Patients (aged ≥18 years) with laboratory confirmed mild or moderate COVID-19 infection (SpO_2 >94% at screening) with ≥1 risk factors for severe illness	> Hospitalization or death within 28 days	> Positivity for SARS-CoV-2 by PCR on mid-nasal turbinate swabs on Days 7 and 15 compared to baseline *[Note: An extensive list can be found on clinicaltrials.gov]*

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparators	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Jilg *et al.* 2022b[92] ACTIV-2/A5401 NCT04518410 US	> Camostat mesylate: Oral administration, 200 mg every 6 hours for 7 days > Placebo	> Laboratory confirmed COVID-19 infection > Treatment ≤7 days of symptom onset > One or more symptom within 24 hours of participating > Oxygen levels of ≥92% obtained at rest	> COVID-19 symptom duration (Phase 2) [Time Frame: Up to Day 28] > Quantification of SARS-CoV-2 RNA (Phase 2) [Day 3, 7, and 14] > Proportion of participants with new AE ≥ Grade 3 (Phases 2 & 3) [Through Day 28] > Cumulative incidence of death due to any cause or hospitalization due to any cause (Phase 3) [Through Day 28] *[Note: reported on clinicaltrials.gov but not within abstract]*	NR *[Note: An extensive list can be found on clinicaltrials.gov]*
Tobback *et al.* 2022[93] Tobback *et al.* 2022 camostat mesylate NCT04625114 04/11/2020-06/2021 Belgium	> Camostat mesylate: Oral administration, three 100 mg tablets, 3 times daily for 5 days > Placebo: Oral administration, 3 tablets, 3 times daily for 5 days	> Patients (aged ≥18 years) with confirmed COVID-19 infection by RT-PCR showing Ct value below 30	> Change in the shedding of the SARS-CoV-2 virus as measured by Ct obtained from NP swabs on Days 1 and 5	> Time to clinical improvement > Safety

AE: adverse event; COVID-19: Coronavirus 2019; CROI: Conference on Retroviruses and Opportunistic Infections; Ct: cycle threshold; FLUPro: InFLUenza Patient Reported Outcome; mg: milligram; NP: nasopharyngeal; NR: not reported; PRO: patient reported outcome; RNA: ribonucleic acid; RT-PCR: reverse transcription-polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SOC: standard of care; SpO_2: peripheral capillary oxygen saturation; US: United States.

Table 26. Patient baseline characteristics of RCTs assessing camostat mesylate for the treatment of COVID-19

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset
Chupp *et al.* 2022[90] Chupp *et al.* 2022 camostat mesylate NCT04353284	> Overall: 70 > Camostat: 35 > Placebo: 35	Mean (range) > Overall: 44.1 (20.6-78.2) > Camostat: 44.1 (23.2-78.2) > Placebo: 44.1 (20.6-69.4)	Female, n (%) > Total: 28 (40) > Camostat: 13 (37.1) > Placebo: 15 (42.9)	The mean time from symptom onset until enrollment was not prospectively determined but was generally in the 2-to-3-day range
Jilg *et al.* 2022a[91] CAMELOT NCT04583592	> Camostat: 194 > Placebo: 101	Mean (SD) > Camostat: 52 (17) > Placebo: 51 (18)	Female, n (%) > Camostat: 108 (55.7) > Placebo: 61 (60.4)	76% were randomized ≤5 days from symptom onset
Jilg *et al.* 2022b[92] ACTIV-2/A5401 NCT04518410	> Overall: 215 > Camostat: 108 > Placebo: 107	Median > Overall: 37 > Camostat: NR > Placebo: NR	Female, % > Overall: 54 > Camostat: NR > Placebo: NR	47% were randomized ≤5 days from symptom onset
Tobback *et al.* 2022[93] Tobback *et al.* 2022 camostat mesylate NCT04625114	> Overall: 96 > Camostat: 66 > Placebo: 30	Median (IQR) > Overall: 40 (25-53) > Camostat: 38 (25-53) > Placebo: 37 (22-51)	Female, n (%) > Overall: 49 (54.4) > Camostat: 33 (54.1) > Placebo: 16 (55.2)	Median (IQR), days > Overall: 3 (1-4) > Camostat: NR > Placebo: NR

IQR: interquartile range; SD: Standard Deviation.

Table 27. Results from RCTs assessing camostat mesylate for the treatment of COVID-19

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Chupp *et al.* 2022[90] Chupp *et al.* 2022 camostat mesylate NCT04353284	Reduction in viral load at Day 4 (log_{10}) > Camostat: -2.0 > Placebo: -2.8 > Difference in means ([95% CI], p-value): 0.74 ([-0.03 to 1.51], p = 0.06)	Patients who experienced an AE, n (%) > Camostat: 11/35 (31.4) > Placebo: 6/35 (17.1) Patients who experienced a SAE, n (%) > Camostat: 1/35 (0.03) > Placebo: 1/35 (0.03)
Jilg *et al.* 2022a[91] CAMELOT NCT04583592	Hospitalization/death at Day 28, % > Camostat: 5.3 > Placebo: 6.1 > No significant difference	Patients who experienced an AE, % > Camostat: 8.7 > Placebo: 13.1
Jilg *et al.* 2022b[92] ACTIV-2/A5401 NCT04518410	Days to symptom improvement, median (IQR) > Camostat: 9 (5-20) > Placebo: 9 (6-19) > No significant differences in the proportion of participants with NP SARS-CoV-2 RNA *[Note: Endpoints for hospitalization or death are also available in the DEF]*	Patients who experienced a ≥ Grade 3 AE, % > Camostat: 7.4 > Placebo: 6.5 > No significant difference
Tobback *et al.* 2022[93] Tobback *et al.* 2022 camostat mesylate NCT04625114	Difference in the mean change in Ct between Day 1 and 5 for camostat group versus placebo group > 1.183 (p=0.511)	Patients who experienced an AE, n (%) > Camostat: 59 (96.7) > Placebo: 23 (79.3) Discontinuation of treatment, n (%) > Camostat: 5 (7.6) > Placebo: 1 (3.3)

AE: adverse event; CI: confidence interval; Ct: cycle threshold; DEF: data extraction form; IQR: interquartile range; NP: nasopharyngeal; RNA: ribonucleic acid; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Table 28. RCTs assessing anti-inflammatory therapies

Author and year	Source	Report title	Report type	Trial identifier(s)	Phase
Dorward *et al.* 2022[94]	OVID	Colchicine for COVID-19 in the community (PRINCIPLE): a randomized, controlled, adaptive platform trial	Journal article	PRINCIPLE ISRCTN86534580 [trial does not appear on clinicaltrials.gov]	NR
Tardif *et al.* 2021[95]	OVID	Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomized, double-blinded, adaptive, placebo-controlled, multicenter trial	Journal article	COLCORONA NCT04322682	3
Audemard-Verger *et al.* 2022[96]	OVID	Efficacy and safety of anakinra in adults presenting deteriorating respiratory symptoms from COVID-19: A randomized controlled trial	Journal article	ANACONDA NCT04364009	3

COVID-19: Coronavirus 2019; NR: Not Reported.

Table 29. Study characteristics of RCTs for anti-inflammatory therapies

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Dorward *et al.* 2022[94] PRINCIPLE ISRCTN86534580 [trial does not appear on clinicaltrials.gov] 02/04/2020-26/05/2021 UK	> Colchicine: Inhaled colchicine 500 µg daily plus usual care for 14 days > Usual care: Usual care or usual care plus other interventions for 14 days	> Patients (aged ≥65 years, or 50 to 65 years with comorbidities) with ongoing symptoms from PCR-confirmed COVID-19 or suspected COVID-19, which started within 14 days of the study	> Time to first self-reported recovery (defined as the first instance that participant reports feeling recovered) > Admission to hospital/death related to COVID-19, within 28 days	> Binary outcome of early sustained recovery > Daily rating of how well participants feel > Time to initial alleviation of symptoms > Time to sustained alleviation of symptoms > Time to initial reduction of severity of symptoms > Worsening of symptoms > Contacts with healthcare service > Hospital assessment without admission > Oxygen administration > ICU admission > Mechanical ventilation > Adherence to study treatment > WHO-5 Wellbeing Index > Serious adverse events > All-cause death or urgent, non-elective hospital admission > Reports of new household infections *[Full list of secondary outcomes listed within supplementary appendix]*

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Tardif *et al.* 2021[95] COLCORONA NCT04322682 23/03/2020-22/12/2020 US, Brazil, Canada, Greece, South Africa, Spain	> Colchicine: Oral administration, 0.5 mg colchicine BID for the first 3 days and then once daily for 27 days thereafter > Placebo: Orally administration, BID for the first 3 days and then once per day for 27 days thereafter *[Note: Study medication was delivered at the patient's house within 4 hours of enrollment]*	> Patients (aged ≥40 years) who received a diagnosis of COVID-19 within 24 h of enrollment > Not currently being treated in hospital and not under immediate consideration for hospital treatment or admission > Presented ≥1 high-risk criteria > The diagnosis of COVID-19 was made by local laboratories using PCR testing on a NP swab specimen: o Diagnosis was also accepted as an epidemiological link with a household member who received a positive NP test result for patients with symptoms compatible with COVID-19, or by a clinical algorithm in a symptomatic patient without an obvious alternative cause, as per official guidelines	> Death or hospital admission because of COVID-19 infection in the 30 days after randomization	> Death > Hospitalization for COVID-19 > The need for mechanical ventilation in the 30 days after randomization > Pneumonias and other serious adverse events > Non-serious adverse events

Author and year, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Audemard-Verger *et al.* 2022[96] ANACONDA NCT04364009 27/04/2020-6/10/2020 France	> Anakinra plus oSOC: IV administration, 400 mg/day (100 mg every 6 hours) for 3 days, then 200 mg/day (100 mg every 12 hours) for 7 days - total duration of 10 days of treatment > oSOC: including antiviral drugs, hydroxychloroquine, corticosteroids, anticoagulants, hydration, nutrition, extra-renal purification, oxygen therapy and vasopressive drugs	> Patients (aged ≥18 years) with confirmed SARS-CoV-2 infection, confirmed with RT-PCR and/or typical chest or computed tomographic scan of COVID-19 pneumonia and required oxygen therapy	> Treatment success at Day 14, defined as a patient being alive and not requiring either of the following: invasive mechanical ventilation or extracorporeal membrane oxygenation	> Treatment success assessed with the WHO Clinical Progression Scale, NEWS, and biological parameters, at Days 3, 10, 14 and 28 > Overall survival > Time to hospital discharge, ICU admission, ventilatory support, and oxygen supply withdrawal over the 28-day follow-up > Safety

BID: twice daily; COVID-19: Coronavirus 2019; ICU: intensive care unit; IgG: Immunoglobulin G; mg: milligram; NEWS: National Early Warning Score; NP: nasopharyngeal; oSOC: optimized standard of care; PCR: polymerase chain reaction; RNA: ribonucleic acid; RT-PCR: reverse transcription-polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; UK: United Kingdom; US: United States; WHO: World Health Organisation; µg: microgram.

Table 30. Patients baseline characteristics for RCTs for anti-inflammatory therapies

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset (days)
Dorward *et al.* 2022[94] PRINCIPLE ISRCTN86534580 [trial does not appear on clinicaltrials.gov]	> Overall: 2293 > Colchicine: 212 > Usual care: 2081	Mean (SD) > Overall: 60.5 (10.2) > Colchicine: 48.5 (13.2) > Usual care: 61.7 (9.0)	Female, male, other, n (%) > Overall: 1,216 (53.9), 1039 (46.1), 1 (0.0) > Colchicine: 98 (47.6), 107 (51.9), 1 (0.5) > Usual care: 1,118 (54.5), 932 (45.5), 0 (0.0)	Median (IQR) > Overall: 6.0 (4.0-9.0)
Tardif *et al.* 2021[95] COLCORONA NCT04322682	> Overall: 4488 > Colchicine: 2235 > Placebo: 2253	Mean (IQR) > Overall: NR > Colchicine: 53.0 (47.0-61.0) > Placebo: 54.0 (47.0-61.0)	Female, n (%) > Overall: NR > Colchicine: 1238 (55.4) > Placebo: 1183 (52.5)	NR
Audemard-Verger *et al.* 2022[96] ANACONDA NCT04364009	> Overall: 71 > Anakinra plus oSOC: 37 > oSOC: 34	Mean (SD) > Overall: NR > Anakinra plus oSOC: 71 (15) > oSOC: 70 (14)	Female, n (%) > Overall: NR > Anakinra plus oSOC: 9 (24) > oSOC: 10 (29)	Median (IQR) > Overall: NR > Anakinra plus oSOC: 9 (7-11) > oSOC: 9 (7-11)

IQR: Interquartile range; NR: Not reported; oSOC: optimized standard of care; SD: standard deviation.

Table 31. Results from RCTs assessing anti-inflammatory therapies

Author and year, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Dorward *et al.* 2022[94] PRINCIPLE ISRCTN86534580 [trial does not appear on clinicaltrials.gov]	Days to first reported recovery, median > Colchicine: 15 > Usual care: 14 > Benefit ([95% BCI], p-value): 1.14 ([-1.86 to 5.21], p=0.241) Patients hospitalized or dead at Day 28, n (%) > Colchicine: 6/156 (3.8) > Usual care: 4/133 (3.0) > OR, % ([95% BCI], p-value): -0.4 ([-2.7 to 2.4], p=0.714) ○ Prespecified superiority threshold 0.99; therefore, insignificant	Patients who experienced a SAEs, n > Colchicine: 1 > Usual care: 1
Tardif *et al.* 2021[95] COLCORONA NCT04322682	Odds of composite endpoint (mortality or hospitalization) by Day 30 with colchicine group versus placebo group, odds ([95% CI], p-value) > 0.79 (]0.61-1.03], p=0.081) ○ not significant [however, significant in subgroup with confirmed diagnosis of COVID-19] Odds of mechanical ventilation with colchicine group versus placebo group, odds (95% CI) > 0.53 (0.25-1.09)	Patients who experienced a TRAE, n (%) Colchicine: 532 (24.2) Placebo: 344 (15.5) Patients who experienced a SAEs, n (%) Colchicine: 108 (4.9) Placebo: 139 (6.3)
Audemard-Verger *et al.* 2022[96] ANACONDA NCT04364009	Patients with treatment success at Day 14, n (%) > Anakinra plus oSOC: 26 (70) > oSOC: 31 (91) > Risk difference, % ([95% CI], p-value): -21 ([-39 to -2], p=0.027)	Patients who experienced ≥1 AE, n (%) > Anakinra plus oSOC: 32 (87) > oSOC: 22 (65) > p=0.016 Patients who experienced ≥1 SAE, n (%) > Anakinra plus oSOC: 19 (51) > oSOC: 18 (53) > p=0.89

AE: adverse event; BCI: Bayesian confidence interval; CI: confidence interval; COVID-19: Coronavirus 2019; oSOC: optimized standard of care; OR: odds ratio; SAE: serious adverse event; TRAE: treatment-related adverse event.

Table 32. RCTs assessing antiparasitic (nitazoxanide)

Author and year	Source	Report title	Report type	Trial identifier(s)	Phase
Rocco *et al.* 2021[97]	OVID	Early use of nitazoxanide in mild COVID-19 disease: randomized, placebo-controlled trial	Journal article	Rocco *et al.* 2021 nitazoxanide NCT04552483	2
Rossignol *et al.* 2021[98]	clinicaltrials.gov	Early treatment with nitazoxanide prevents worsening of mild and moderate COVID-19 and subsequent hospitalization	Journal article (pre-print)	Rossignol *et al.* 2021 nitazoxanide NCT04486313	3
Rossignol *et al.* 2022[99]	OVID	A randomized double-blind placebo-controlled clinical trial of nitazoxanide for treatment of mild or moderate COVID-19	Journal article (published)	Rossignol *et al.* 2022 nitazoxanide NCT04486313	3
Mehdat *et al.* 2022[100]	OVID	Sofosbuvir/ledipasvir in combination or nitazoxanide alone are safe and efficient treatments for COVID-19 infection: A randomized controlled trial for repurposing antivirals	Journal article	Mehdat *et al.* 2022 nitazoxanide and sofobuvir/ledipasvir NCT04498936	4

COVID-19: Coronavirus 2019.

Table 33. Study characteristics of RCTs for antiparasitic (nitazoxanide)

Trial report, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Rocco *et al*. 2021[97] Rocco *et al.* 2021 nitazoxanide NCT04552483 08/06/2020-20/08/2021 Brazil	> Nitazoxanide: Oral administration, 500 mg (20 mg/mL, 25 mL) taken three times a day for 5 days > Placebo: Oral administration, color-matched, 25 mL three times daily	> Consecutive adult patients (aged ≥18 years) who presented with clinical symptoms of COVID-19 (defined for the purposes of this trial as dry cough, fever and/or fatigue) of no longer than 3 days' duration	> Complete symptom resolution after 5 days	> Reduction in viral load on NP swab specimens > Improvement in laboratory parameters > Incidence of hospital admission > Adverse events
Rossignol *et al*. 2021[98] Rossignol *et al.* 2021 nitazoxanide NCT04486313 18/08/2020-08/01/2021 US and Puerto Rico **Rossignol *et al*. 2022**[99] Rossignol *et al.* 2022 nitazoxanide NCT04486313	> Nitazoxanide: Oral administration, two 300 mg tablets (600 mg per dose) with food BID, for 5 days > Placebo	> Outpatients (aged ≥12 years) presenting within 72 hours of onset of symptoms of mild or moderate COVID-19 > Minimum symptom requirements were: o At least two respiratory symptom domains (head, throat, nose, chest, cough) with a score of ≥2 as determined by scoring the FLUpro questionnaire administered at screening (only one domain score required to be ≥2 if pulse rate ≥90 beats per minute) OR o Respiratory rate ≥16 breaths per minute), with no improvement in overall symptom severity from the prior day	> Time from the first dose to sustained response (TSR), a measure of meaningful within-subject change in symptoms	> The rate of progression to severe COVID-19 illness
Mehdat *et al*. 2022[100]	> Sofosbuvir/ledipasvir plus SCT: Oral administration, 400 mg (sofosbuvir) and 90 mg (ledipasvir)	> Patients (aged ≥18 years) with a COVID-19 diagnosis based on positive RT-PCR testing for SARS-CoV-2 NP swab	> Confirmed viral clearance by serial RT-PCR testing on NP swab	> Mortality > ICU admission > Development of serious adverse events

Trial report, trial identifier(s) enrollment, location	Intervention(s) and comparator	Patient characteristics	Primary (efficacy) endpoint(s)	Secondary endpoint(s)
Rocco *et al*. 2021[97] Rocco *et al.* 2021 nitazoxanide NCT04552483 08/06/2020-20/08/2021 Brazil	> Nitazoxanide: Oral administration, 500 mg (20 mg/mL, 25 mL) taken three times a day for 5 days > Placebo: Oral administration, color-matched, 25 mL three times daily	> Consecutive adult patients (aged ≥18 years) who presented with clinical symptoms of COVID-19 (defined for the purposes of this trial as dry cough, fever and/or fatigue) of no longer than 3 days' duration	> Complete symptom resolution after 5 days	> Reduction in viral load on NP swab specimens > Improvement in laboratory parameters > Incidence of hospital admission > Adverse events
Mehdat *et al.* 2022 nitazoxanide and sofobuvir/ledipasvir NCT04498936 07/2020-10/2021 Egypt	daily, plus SCT, for 14 days > Nitazoxanide plus SCT: Oral administration, 500 mg four times daily, plus SCT, for 14 days > SCT: Oral administration for 14 days			

BID: twice daily; COVID-19: Coronavirus 2019; FLUPro: InFLUenza Patient-Reported Outcome; ICU: intensive care unit; mg: milligram; mL: milliliter; NP: nasopharyngeal; PaO2/FiO2: the ratio of arterial oxygen partial pressure to fractional inspired oxygen; RT-PCR: reverse transcription-polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SCT: standard care treatment; SpO_2: peripheral capillary oxygen saturation; TSR: time to sustained response; US: United States.

Table 34. Patients baseline characteristics for RCTs for antiparasitic (nitazoxanide)

Author and year, trial identifier(s)	Number randomized	Age (years)	Sex	Time to symptom onset
Rocco *et al*. 2021[97] Rocco *et al.* 2021 nitazoxanide NCT04552483	> Nitazoxanide: 238 > Placebo: 237	n (%) > Nitazoxanide: o 18-39 years: 115 (59) o 40-59 years: 68 (35) o 60-77 years: 11 (6) > Placebo: o 18-39 years: 113 (57) o 40-59 years: 74 (37) o 60-77 years: 11 (6)	Male, n (%) > Nitazoxanide: 101 (52) > Placebo: 83 (42)	Median (IQR), days > Nitazoxanide: 5 (4-5) > Placebo: 5 (4-5)
Rossignol *et al*. 2021[98] Rossignol *et al.* 2021 nitazoxanide NCT04486313 **Rossignol *et al*. 2022[99]** Rossignol *et al.* 2022 nitazoxanide NCT04486313	> Overall: 379 > Nitazoxanide: 184 > Placebo: 195	Median (IQR) > Overall: 40.0 (27.0-51.0) > Nitazoxanide: 38.0 (26.0-50.5) > Placebo: 42.0 (29.0-51.0)	Male, n (%) > Overall: 165 (43.5) > Nitazoxanide: 83 (45.1) > Placebo: 82 (42.1)	Mean (SD), hours > Overall: 43.6 (15.56) > Nitazoxanide: 42.7 (15.25) > Placebo: 44.6 (15.83)
Mehdat *et al*. 2022[100] Mehdat *et al.* 2022 nitazoxanide and sofobuvir/ledipasvir NCT04498936	> Sofosbuvir/ledipasvir plus SCT: 70 > Nitazoxanide plus SCT: 77 > SCT: 73	Mean (SD) > Sofosbuvir/ledipasvir plus SCT: 45.04 (8.14) > Nitazoxanide plus SCT: 44.32 (8.43) > SCT: 45.35 (5.59)	Male, female, n (%) > Sofosbuvir/ledipasvir plus SCT: 32 (45.7), 38 (54.3) > Nitazoxanide plus SCT: 27 (35.1), 50 (64.9) > SCT: 41 (56.2), 32 (43.8)	NR

IQR: Interquartile range; SCT: standard care treatment; SD: Standard deviation.

Table 35. Results from RCTs assessing antiparasitic (nitazoxanide)

Trial report, trial identifier(s)	Primary efficacy outcome(s)	Safety outcome(s)
Rocco *et al*. 2021[97] Rocco *et al.* 2021 nitazoxanide NCT04552483	Rate of complete resolution of symptoms (dry cough, fever, and fatigue) did not significantly differ between the nitazoxanide and placebo after 5 days of therapy (p=0.277) Proportion of patients with complete symptom resolution (dry cough, fever, and fatigue) after 5 days of therapy > Nitazoxanide: 135 > Placebo: 146 > p=0.277; no statistical difference NP swab RT-PCR viral load log_{10} copies/mL > Nitazoxanide: 3.63 > Placebo: 4.13 > p=0.006; patients with nitazoxanide had significantly lower viral load than patients with placebo	Patients who experienced an AE, n (%) > Nitazoxanide arm: 60 (30.9) > Placebo arm: 60 (30.3) > p=0.913; no significant difference Patients who experienced a SAE, n (%) > Nitazoxanide arm: 1 (0.5) > Placebo arm: 1 (0.5) > p=0.999; no significant difference
Rossignol *et al*. 2021[98] Rossignol *et al.* 2021 nitazoxanide NCT04486313 **Rossignol *et al*. 2022[99]** Rossignol *et al.* 2022 nitazoxanide NCT04486313	Time (days) from the first dose to sustained response in all patients, median (IQR) > Nitazoxanide: 13.28 (6.26 to >21) > Placebo: 12.35 (7.18 to >21) > p=0.88; no statistical difference Time (days) from the first dose to sustained response with nitazoxanide in the mild subgroup, median (IQR) > Nitazoxanide: 10.3 (6.2 to >21) > Placebo: 13.4 (7.4 to >21) > p=0.10; no statistical difference *[Note: Endpoints for hospitalization or death are also available in the DEF]*	Patients who experienced an AE, n (%) > Nitazoxanide: 63 (13.3) > Placebo: 75 (16.2) Patients who experienced a SAE, n > Nitazoxanide: 2 > Placebo: 7
Mehdat *et al.* 2022[100] Mehdat *et al.* 2022 nitazoxanide and sofobuvir/ledipasvir NCT04498936	Proportion of patients with confirmed viral clearance at Days 5, 8, 11, 14, % > Sofosbuvir/ledipasvir plus SCT: 42.90, 70.00, 80.00, 85.71 > Nitazoxanide plus SCT: 0.00, 2.60, 32.47, 36.63 > SCT: 0.00, 1.37, 15.07, 16.44	NR

AE: adverse event; DEF: data extraction form; IQR: interquartile range; mL: milliliter; NP: nasopharyngeal; NR: not reported; RT-PCR: reverse transcription-polymerase chain reaction; SAE: serious adverse event; SCT: standard care treatment.

Bias assessment
The quality of each publication included in the SLR was assessed using the Cochrane risk of bias assessment tool (RoB2) for randomized trials.84 A total of 86 publications were assessed for bias.

別添 6：QOL 値の詳細
Health-related quality-of-life studies

Vignettes utilised in the *de novo* utility study

Description S1: Baseline (pre-infection)

- The patient **does not have COVID-19**.
- The patient has an **underlying health condition** that makes them more likely to get severely ill from COVID-19. You do not need to consider the impact of this underlying health condition on the patient's health, only that this condition makes the patient more likely to get severely ill from COVID-19.

Description S2: Outpatient (mild)

- The patient has COVID-19.
- The patient is not in hospital.
- The patient is not using any devices that supply extra oxygen to the lungs.
- The patient has a normal breathing rate and is not out of breath.
- The patient has a normal heart rate at rest.
- The patient has a fever – their body temperature is over 38°C. They feel hotter than usual (particularly on their chest and back), have chills and are shivery.
- The patient has a dry cough and is coughing more than they usually do.
- The patient feels extremely tired and finds daily activities (such as walking up the stairs, getting out of bed, daily chores) difficult.
- The patient has a headache that is moderately to severely painful, feels 'pulsing', 'pressing', or 'stabbing', occurs across both sides of the head and lasts more than three days.
- The patient's muscles are sore, particularly their shoulders and legs. The area feels sore to the touch and can prevent the patient from carrying out daily tasks without pain.
- The patient has lost their sense of smell, they are unable to smell as they usually would, including strongly scented things like coffee or flowers.
- The patient has a blocked, stuffy, or bunged-up feeling in their nose.
- The patient has an underlying health condition that makes them more likely to get severely ill from COVID-19. You do not need to consider the impact of this underlying health condition on the patient's health, only that this condition makes the patient more likely to get severely ill from COVID-19.

Description S3: Outpatient (moderate)

- The patient has COVID-19.
- The patient is not in hospital.
- The patient is not using any devices that supply extra oxygen to the lungs.
- The patient experiences shortness of breath on exertion, for example, when walking up the stairs.
- The patient has a high heart rate at rest.
- The patient has a fever – their body temperature is over 38°C. They feel hotter than usual (particularly on their chest and back), have chills and are shivery.
- The patient has a dry cough and is coughing more than they usually do.

- The patient feels extremely tired and finds daily activities (such as walking up the stairs, getting out of bed, daily chores) difficult.
- The patient has a headache that is moderately to severely painful, feels 'pulsing', 'pressing', or 'stabbing', occurs across both sides of the head and lasts more than three days.
- The patient's muscles are sore, particularly their shoulders and legs. The area feels sore to the touch and can prevent the patient from carrying out daily tasks without pain.
- The patient has lost their sense of smell, they are unable to smell as they usually would, including strongly scented things like coffee or flowers.
- The patient has a blocked, stuffy, or bunged-up feeling in their nose.
- The patient has an underlying health condition that makes them more likely to get severely ill from COVID-19. You do not need to consider the impact of this underlying health condition on the patient's health, only that this condition makes the patient more likely to get severely ill from COVID-19.

Description S4: General hospital ward (severe)

- The patient has COVID-19.
- The patient is in hospital on a general ward.
- The patient is using a device in which oxygen is delivered through a tube through the nose, allowing the air into their lungs.
- The patient is short of breath at rest.
- The patient's heart rate is very high.
- The patient has a fever – their body temperature is over 38°C. They feel hotter than usual (particularly on their chest and back), have chills and are shivery.
- The patient has a dry cough and is coughing more than they usually do.
- The patient feels extremely tired and finds daily activities (such as walking up the stairs, getting out of bed, daily chores) difficult.
- The patient is withdrawn and less responsive to the world around them, they forget to go to the toilet when they need to and stop eating and drinking.
- The patient's muscles are sore, particularly their shoulders and legs. The area feels sore to the touch and can prevent the patient from carrying out daily tasks without pain.
- The patient has an underlying health condition that makes them more likely to get severely ill from COVID-19. You do not need to consider the impact of this underlying health condition on the patient's health, only that this condition makes the patient more likely to get severely ill from COVID-19.

Description S5: High dependency unit (severe)

- The patient has COVID-19.
- The patient is using supplemental oxygen through a face mask.
- The patient is in a high dependency unit of a hospital, where patients are cared for more extensively than a general ward, but not to the point of intensive care.
- The patient is short of breath at rest.
- The patient's heart rate is very high.

- The patient has a fever – their body temperature is over 38°C. They feel hotter than usual (particularly on their chest and back), have chills and are shivery.
- The patient has a dry cough and is coughing more than they usually do.
- The patient feels extremely tired and finds daily activities (such as walking up the stairs, getting out of bed, daily chores) difficult.
- The patient is withdrawn and less responsive to the world around them, they forget to go to the toilet when they need to and stop eating and drinking.
- The patient's muscles are sore, particularly their shoulders and legs. The area feels sore to the touch and can prevent the patient from carrying out daily tasks without pain.
- The patient has an underlying health condition that makes them more likely to get severely ill from COVID-19. You do not need to consider the impact of this underlying health condition on the patient's health, only that this condition makes the patient more likely to get severely ill from COVID-19.

Description S6: ICU (critical)

- The patient has COVID-19, they cannot breathe on their own and will die if not treated.
- The patient is in an intensive care unit in a hospital.
- The patient has a breathing tube inserted into their windpipe to allow a machine to breathe for them.
- The patient is unable to breathe on their own.
- The patient has multi-organ dysfunction/failure of more than 1 of the following organ systems: respiratory (lungs), cardiovascular (heart and blood vessels), kidney, liver, and/or central nervous systems (brain and spinal cord) and requires organ support.
- The patient is unconscious.
- The patient has an underlying health condition that makes them more likely to get severely ill from COVID-19. You do not need to consider the impact of this underlying health condition on the patient's health, only that this condition makes the patient more likely to get severely ill from COVID-19.

Description S7: Recovered (no long-term sequelae)

- The patient has had COVID-19 and has now recovered without any long-term health issues.
- The patient has an underlying health condition that makes them more likely to get severely ill from COVID-19. You do not need to consider the impact of this underlying health condition on the patient's health, only that this condition makes the patient more likely to get severely ill from COVID-19.

Description S8: Recovered (long-term sequelae)

- The patient has had COVID-19 and is now suffering from long-term health issues as a result.
- The patient has an underlying health condition that makes them more likely to get severely ill from COVID-19. You do not need to consider the impact of this underlying health condition on the patient's health, only that this condition makes the patient more likely to get severely ill from COVID-19.

- The patient feels extremely tired and finds daily activities (such as walking up the stairs, getting out of bed, daily chores) difficult.
- The patient is short of breath and feels as though they cannot get enough air in their lungs. They find it difficult to inhale and exhale. They have a tight chest.
- The patient's muscles and/or joints are sore, particularly their shoulders and legs. The area feels sore to the touch and can prevent the patient from carrying out daily tasks without pain.

Table 36. Proportion of participants reporting each level of the EQ-5D-5L for each domain

Domain	Level	Health state							
		S1	S2	S3	S4	S5	S6	S7	S8
Mobility	No problems								
	Slight problems								
	Moderate problems								
	Severe problems								
	Unable to walk about								
Self-care	No problems								
	Slight problems								
	Moderate problems								
	Severe problems								
	Unable to wash or dress								
Usual activities	No problems								
	Slight problems								
	Moderate problems								
	Severe problems								
	Unable to do usual activities								
Pain/discomfort	No pain/discomfort								
	Slight pain/discomfort								
	Moderate pain/discomfort								
	Severe pain/discomfort								
	Extreme pain/discomfort								
Anxiety/depression	Not anxious/depressed								
	Slightly anxious/depressed								
	Moderately anxious/depressed								
	Severely anxious/depressed								
	Extremely anxious/depressed								

Footnotes: The health states were as follows: S1, Baseline (pre-infection); S2, Outpatient (mild); S3, Outpatient (moderate); S4, General hospital ward (severe); S5, High dependency unit (severe); S6, ICU (critical); S7, Recovered (no long-term sequelae); S8, Recovered (long-term sequelae). The blue highlighting indicates the level that was most commonly reported by participants for each domain.

Table 37. Summary of EQ-5D-5L utility scores of vignettes by prior COVID-19 infection status (N = [redacted])*

Health state	Prior COVID-19 infection, mean (SD)		p-value**
	Yes (n=[redacted])	No (n=[redacted])	
S1: Baseline (pre-infection)	[redacted]		
S2: Outpatient (mild)			
S3: Outpatient (moderate)			
S4: General hospital ward (severe)			
S5: High dependency unit (severe)			
S6: ICU (critical)			
S7: Recovered (no long-term sequelae)			
S8: Recovered (long-term sequelae)			

Footnotes: *One participant reported 'Prefer not to say' and was removed from this analysis. **Significance was calculated using independent t-test or Wilcoxon rank sum test.

Abbreviations: ICU: intensive care unit; N: total number of respondents; n: subset number of respondents; SD: standard deviation.