Emerging small molecule antivirals may fit neatly into COVID-19 treatment

Caroline Fenton1 · Susan J. Keam1

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Abstract
Numerous treatments exist for COVID-19, the illness caused by SARS-CoV-2 virus, although most are not well established; among these are several small molecule antiviral agents. Intravenous remdesivir is an established treatment worldwide for inpatients and in some countries is also available for use in non-hospitalised high risk patients to prevent progression to severe disease and hospitalization. Oral molnupiravir and oral nirmatrelvir-ritonavir are also available in several countries to prevent progression to severe disease and hospitalization for high-risk outpatients. Many other antiviral small molecules that may have therapeutic potential are under investigation in clinical trials. This article provides a summary of key molecular targets, pharmacology and preliminary data on the efficacy and safety of small molecule antiviral agents being investigated for the treatment of COVID-19.

Prevention better than COVID-19 cure
Much has been learned in the months since the severe acute respiratory syndrome (SARS)-CoV-2 coronavirus, which causes COVID-19, overwhelmed an unprepared world; however, pharmacological treatment options are still very limited [1, 2]. Despite the preferred preventative approach via vaccines, COVID-19 cases still abound [3]. Most cases are mild or asymptomatic, although still contagious [4]. For those more severely affected, COVID-19 treatment aims to reduce viral load and manage and dampen the overexuberant inflammatory response that causes the often fatal acute respiratory distress syndrome (ARDS) and myocarditis [1, 5].

Essential pharmacological treatment options include antiviral agents (to reduce viral load) as well as immunomodulators and biologics [2], particularly as it is the inflammatory response and release of proinflammatory cytokines (the “cytokine storm” characteristic of ARDS) rather than SARS-CoV-2 infection per se that is fatal [5]. Of interest, some antiviral agents also act as immunomodulators [1, 6].

The COVID-19 treatment pipeline includes both “repurposed” agents already approved or developed for other indications and new compounds [1]. Benefits of the former include known adverse drug events and ready availability, but the efficacy of most in COVID-19 has been lacklustre [2, 7].

Small molecules more accessible, if supply chain works
In a pandemic setting, reliable bulk manufacture of pharmacological agents is vital; however, it is likely that supply chain issues will arise [8]. Both small molecules and biologics are being studied in COVID-19 [3]. Overall, small molecules tend to be more accessible than biologics due to stability, oral formulation and lower cost (Table 1) [8–10].

This article reviews emerging small molecule antiviral (according to WHO ATC code or EPhMRA code) COVID-19 treatments up to mid-January 2022, with a focus on those furthest along the regulatory pathway. Discussion of the role of other small molecule classes, biologics and older immunomodulators like corticosteroids in the treatment of COVID-19 is outside the scope of this article.
Look at viral family resemblances and proteins...

Applying decades of knowledge of other coronaviruses to identify relevant, readily available drugs is seen as the fastest way to develop potential SARS-CoV-2 therapeutics [1]. The need for speed, however, should not overwhelm the need for evidence of good efficacy and safety [11]. SARS-CoV-2 is a large-genome, enveloped, positive-sense RNA virus of the genus Betacoronavirus and is closely related are SARS-CoV (for which SARS is named) and Middle East respiratory syndrome (MERS)-CoV [1, 12]. Both of these emerged in the twenty-first century to cause fatal human respiratory illness [1], but they mostly spread via nosocomial, not community, routes and pandemics were avoided [5]. SARS-CoV-2 also shares some features with unrelated viruses, e.g. HIV [13].

The SARS-CoV-2 genome codes for 4 structural proteins and 16 non-structural proteins (nsp [14]), all of which provide potential pharmaceutical antiviral targets (Table 2). Structural proteins are the three surface proteins [spike (S), membrane (M) and envelope (E)] and the two-domain, multifunctional nucleocapsid (N) protein [14]. The S protein, which has a glycan shield of uncertain significance, has S1 and S2 subunits and has been closely studied during vaccine development. The N protein, involved in RNA binding, is needed for effective viral replication [14]. Recent E protein studies indicate that its ability to affect cell polarity may correlate with viral virulence. Nsps 3-16 are similar across most coronaviruses, but nsp1 is not [15]. Some SARS-CoV-2 structural and non-structural proteins have a high degree of sequence similarity to those of SARS-CoV and MERS-CoV [1].

... and modify its lifecycle and immune effects

Like other viruses, SARS-CoV-2 infects humans cells by taking over host cell functions ranging from cell entry (to effect viral replication and assembly) to release from host cells (Table 2, [1, 13]). Small molecule antiviral treatments targeting these processes are accordingly broadly grouped into viral entry, replication and release inhibitors (Tables 2 and 3) [1], although the last are so far largely experimental in SARS-CoV-2 [1].

Most treatment aims to prevent or treat severe COVID-19 in high-risk patients. These include people who are older, obese or pregnant, as well as those with cancer (especially leukaemia or lymphoma), diabetes, or respiratory, cardiovascular and other comorbidities [6].

Investigations show that cytokines that drive the most severe illness include interleukins (ILs) 2, 6, 7 and 8, tumour

Table 1  Comparison of the properties of small molecules and biologics, as reviewed by Ledford [ ] and Makurvet [ ]

| Property                          | Small molecules | Biologics                                      |
|-----------------------------------|-----------------|------------------------------------------------|
| Typical size of molecule (kDa)    | 0.1–1.0         | > 1.0                                          |
| Manufacturing and logistics       | Mostly fairly simple, with active ingredient manufactured from chemical compounds | Mostly complex, derived from living bacteria, yeasts, mammalian tissues or cells, requiring cell cultures, multiplication and manipulation |
| Drug is stabilised and packaged in tablets or vials, subject to supply chain issues | Less stable, although mAbs are an exception |
| Formulation/administration        | Normally oral   | Normally IV, not orally available              |
| Able to cross BBB                 | Yes, if < 600 Da, can act on CNS | No                                             |
| Therapeutic targets               | Many intracellular and extracellular enzymes and proteins, with specific inhibitors “nibs” | Specific parts of the immune system |
| Drug interactions                 | Can be significant, due to renal or hepatic metabolism | Relatively few, as they are metabolised much like endogenous molecules and have more specific targets |
| ADEs                              | Not immunogenic | Immunogenic, and rarely, but devastatingly, trigger cytokine release |
| Logistics                         | More affordable and easily stored, usually easier to mass manufacture | Expensive, ≥ 22x small molecule cost, need refrigeration |
| Examples                          | Antiviral agents: e.g. nucleoside analogues (remdesivir, favipiravir, molnupiravir) and protease inhibitors (nirmatrelvir-ritonavir) | Monoclonal antibodies: e.g. tocilizumab, casirivimab/imdevimab |
|                                   | Tyrosine kinase inhibitors: e.g. baricitinib, bempencitinib |                                |
|                                   | Other small molecules: e.g. nitazoxanide |                                |

ADE adverse drug event, BBB blood-brain barrier, CNS central nervous system, IV intravenous, (k)Da kilodaltons, mAbs monoclonal antibodies
necrosis factor (TNF)-α and interferon (INF)-γ [5, 6]; for some of these cytokines, antagonists already exist [5]. Granulocyte-colony stimulating factor, INF-γ-inducible protein 10, macrophage inflammatory protein 1-α (MIP-1α), and monocyte chemoattractant protein-1 (MCP-1) are also of interest [5]. Clinical trials indicate that a low level of type 1 IFN is also a poor prognostic factor, as are elevated C-reactive protein and D-dimer levels [5, 16].

### Mutating genes, resistance and safety matter

The potential for drug resistance, particularly for those to be used as monotherapy, needs to be considered when developing antivirals for the treatment of COVID-19. The propensity of SARS-CoV-2 for drug resistance is inversely proportional to its genetic stability [1]. Although its structural proteins are very stable [14], the mutations that do occur in the S1 subunit explain some of the increased infectivity of the α, δ and omicron SARS-CoV-2 variants [13, 17]. Despite this, experience with SARS-CoV suggests resistance may not be a significant problem for viral entry inhibitors [1]. Resistance is also less of an issue with agents that directly target host cell, rather than viral, factors (Table 2). These agents may, helpfully, also reduce ARDS via immune modulation (Table 2). Nevertheless, resistance to remdesivir (an RdRp inhibitor) has been reported after emergence of an E802D mutation during treatment of an immune-deficient patient with COVID-19 (Table 3) [18].

The choice of antiviral agent may depend on the potential for drug–drug interactions, particularly in patients who are being treated for underlying health issues and therefore may be at high risk of developing severe COVID-19 [19, 20]. Among the small molecule antivirals that are currently available for the treatment of COVID-19, nirmatrelvir-ritonavir [21–23] has numerous and complex drug–drug interactions (including with over-the-counter medicines and herbal supplements) because of the ritonavir component, which is required to achieve effective nirmatrelvir concentrations (Tables 3 and 4). For clinicians who are not experienced in prescribing ritonavir-boosted therapies, consultation with an expert should be considered [24]. In contrast, remdesivir [25, 26] and molnupiravir [27, 28] and their active metabolites do not inhibit or induce major drug metabolising enzymes and are not inhibitors of major drug transporters, so interaction with concomitant medications is unlikely (Tables 3 and 4).

### Don’t gloss over gaps in pharmacology

Pharmacological features of several approved or almost-approved COVID-19 therapies are still being elucidated (Table 3), with ideal dosages sometimes unclear [4, 29, 30]. Investigations into several repurposed antivirals, such as favipiravir [4, 29, 30], suggest the plasma and lung concentrations needed to treat COVID-19 may be higher than

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**Table 2** SARS-CoV-2 infective life cycle and key small molecule pharmacological targets, as reviewed by Scudellari [13] and Laws [12]

| Viral life stage and key mediators | Key small molecule targets | Types: examples of small molecule antiviral therapies |
|------------------------------------|---------------------------|--------------------------------------------------|
| Viral entry via cell membrane binding, fusion and release of viral genome | Viral S protein, Host ACE2, AXL receptors, Host proteases: TMPRSS2, cathepsin L, furin | AXL kinase inhibitor: bemcentinib, Non-steroidal antiandrogen that ↓ TMPRSS2 +/− ACE2: proxalutamide 
| Viral replication and assembly in the host cell | Host cell components, including proteins, enzymes (e.g. eIF-2α kinase, SK2) and cytoskeleton | CK2 inhibitor: silmitasertib, ↑ eIF-2α kinase phosphorylation: nitazoxanide SK inhibitor: opaganib 
| Viral exit from host cell | Viral S and E proteins, Host calcium-ion channel and furin | None with significant development in COVID-19 |

ACE2 angiotensin converting enzyme-2, CK2 casein kinase 2, 3C prO 3-chymotrypsin like protease, E envelope, eIF-2α eukaryotic initiation factor 2 alpha, M membrane, M pro main protease, N nucleocapsid, niRAN nidovirus RdRp-associated nucleotidyltransferase, nsp non-structural protein, PL prO papain-like protease, RdRp RNA-dependent RNA polymerase p, S spike, SK sphingosine kinase, TMPRSS2 transmembrane protease serine 2, ↓ decrease(s)/downregulates, ↑ increase(s)/upregulates 

*a Dual effect, also acts as host cell immunomodulator or anti-inflammatory*
| Parameter                                             | Key information                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Remdesivir (Veklury®, Redyx™, GS-5734™, Captisol-enabled GS 5734/remdesivir); Gilead Sciences [25, 26] | **Formulation** IV injection or infusion (available as either a 100 mg lyophilized powder to be reconstituted as a 5 mg/mL solution or a 100 mg/20 mL solution for dilution) [25, 26], other formulations including inhaled options being investigated [31]  
**Drug class/background** Broad-spectrum nucleoside analogue effective against RNA viruses, studied in influenza, Ebola, MERS, Marburg and others  
**Mechanism of action** ↓ viral replication by RdRp inhibition, via metabolite remdesivir triphosphate [25, 26]  
**Pharmacological properties** EC<sub>50</sub> = 0.77 μM, CC<sub>50</sub> > 100 μM, SI > 129.87 in Vero cells, MOI 0.05 [33]. In vitro activity maintained against SARS-CoV-2 Omicron variant [34]. Several resistance mutations (NSP12 E802D and E802A mutants and NSP6 I168T mutant) identified in vitro [35]; an E802D mutation has emerged in a patient [18]  
Absorbed and rapidly metabolised in humans; peak concentration of remdesivir and metabolites in ≤ 2 h  
Substrate for CYP3A4, metabolite 50% excreted in urine [25, 26]  
Inhaled formulations of remdesivir have aerosol characteristics consistent with good pulmonary delivery properties in vitro [36–38] and achieve effective pulmonary drug concentrations in animal models [36–38]. A phase 1/2 study of inhaled remdesivir 31 or 62 mg in early stage COVID-19 infection has completed (NCT04539262). A phase 1 study of an inhaled nanoparticle formulation of remdesivir in healthy volunteers is underway (NCT04480333) |
| Favipiravir (Avifavar®, Avigan®, FabiFlu®, Reeqonus™, T705, T705a); Fujifilm Toyama Chemicals [39, 40] | **Formulation** Oral 200, 400 or 800 mg tablets  
**Drug class/background** Pyrazinecarboxamide derivative and nucleoside analogue studied in Ebola, influenza and other viruses and originally approved in Japan for resistant influenza infections. Prodrug requiring phosphorylation in tissues to T-705-RTP, the active form of the drug  
**Mechanism of action** ↓ viral replication by RdRp inhibition, mutagenic in viral, but apparently not host cells [4, 41]  
**Pharmacological properties** In vitro SARS-CoV-2 EC<sub>50</sub> = 61.88 μM, CC<sub>50</sub> > 400 μM, SI > 6.46, MOI 0.05 [42]  
Complex pharmacokinetics; no clear correlation between favipiravir plasma concentrations and clinical efficacy [29]  
Long half-life of active metabolite FAVI-RTP results in adequate intracellular levels despite fast clearance [30] |
| Molnupiravir (Lagavrio, MK-4482, EIDD-2801); Merck/Ridgeback Biotherapeutics [27, 28, 43] | **Formulation** Oral 200 mg capsules  
**Drug class/background** Prodrug of rNHC with broad antiviral activity, studied in Ebola, influenza, MERS and others [44]  
**Mechanism of action** ↓ viral replication by RdRp inhibition, via second metabolite NHC triphosphate that causes mutations during viral replication [41] and which, at high dosages, is also mutagenic to host cells [41]  
**Pharmacological properties** EC<sub>50</sub> 0.32-2.03 μM in Vero cells; IC<sub>50</sub> 1.32-1.77 μM [45]; NHC had similar activity against SARS-CoV-2 variants B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta) [EC<sub>50</sub> 1.59, 1.77 and 1.32 and 1.68 μM, respectively] [43]; CC<sub>50</sub> > 20 in Vero E6 cells [46]; MOI ≈ 0.1 for key SARS-CoV-2 variants [44] In vitro activity maintained against SARS-CoV-2 Omicron variant [34]  
Rapidly absorbed in humans and metabolised to NHC with linear dose-proportional pharmacokinetics, not plasma bound; minimal renal excretion (3%) and likely minor hepatic excretion [27, 28, 43] |
| Nirmatrelvir (PF-07321332)-ritonavir (PAXLOVID™); Pfizer [21–23, 47–50] | **Formulation** Oral 150 mg (nirmatrelvir) and 100 mg (ritonavir) co-packaged tablets  
**Drug Class/background** Protease inhibitor. Coadministered with low-dose ritonavir to maintain effective nirmatrelvir plasma concentrations  
**Mechanism of action** Viral replication inhibitor via ↓ viral 3CLPRO protease [21–23, 47–50]  
**Pharmacological properties** EC<sub>50</sub> 74.5 nM in Vero cells with EI (to inhibit P-gp mediated efflux; EC<sub>50</sub> 4.48 μM with no EI); EC<sub>30</sub> = 317 nM in cytopathic effect assays, CC<sub>50</sub> > 100 μM, [47] In vitro activity maintained against SARS-CoV-2 variants of concern, including Omicron [34, 51, 52]  
Phase 1 trial: drug exposure over 10 d at 5× the level predicted to inhibit SARS-CoV-2 viral replication [47]  
Nirmatrelvir is a CYP3A4 substrate and is mainly eliminated via the kidneys. Coadministration with ritonavir slows metabolism of nirmatrelvir to achieve higher drug concentrations [22, 23] |
for influenza or HIV and perhaps closer to those required for Ebola treatment [4, 29]. Inhaled formulations of drugs used to treat COVID-19 infection can deliver the drug directly to the site of activity, avoid first-pass metabolism and have less systemic toxicity, so may be of benefit [31].

Clinically, the best constant plasma drug concentration may be at least the identified in vitro EC90; combinations of antivirals are also often preferred [30]. From a safety perspective, the ideal antiviral has an effective or inhibitory trough concentration (EC50 or IC50) well below the half-cytotoxic concentration (CC50) [4] and will not cause serious adverse drug events at the highest clinically effective dose (Table 4). Both the in vitro selectivity index and, especially for oral agents that will be used mostly at home, the clinical therapeutic index [4] are important. At this stage, clinical results (Table 4) are driving many decisions [11, 32].

**Endpoints evolving in “learn-as-we-go” trials**

Currently, the most prominent small molecule antivirals in clinical use are remdesivir [58], which has full approval for COVID-19 treatment in a number of countries (Tables 3 and 4) and molnupiravir and nirmatrelvir-ritonavir, which have either conditional approval or are in the regulatory pre-registration or emergency use authorisation (EUA) phase of approval (Tables 3 and 4) [20]. Along with dexamethasone, remdesivir is often now the “standard of care” (SOC) comparator in clinical trials (Table 4). Lopinavir/ritonavir or hydroxychloroquine were common early SOCs [59], but newer meta-analyses and reviews do not support their use in COVID-19 [60–62].

Aside from some doubtful SOCs, comparing different agents is complex, as primary endpoints vary and have evolved with emerging understanding of COVID-19 [68]. In early trials, virological cure, preferably measured with the reverse transcription polymerase chain reaction (RT-PCR), was often the primary endpoint, but it was seldom achieved [60, 62]. Clinical primary endpoints are now more
### Table 4 Preliminary data on efficacy and tolerability of small molecule antivirals approved/with EUA in COVID-19 and/or other indications

| Parameter | Key information |
|-----------|----------------|
| **Remdesivir (Veklury® Redyx™), viral replication inhibitor approved in COVID-19 [25, 26, 63]** | |
| **Recommended COVID-19 dosage (all IV)** | USA [26, 63]: Adults and paediatric pts (aged ≥ 12 y and ≥ 40 kg): 200 mg d 1 then 100 mg for ≤ 4 d if not on MV, or ≤ 9 d if on MV/no response or for 3 d in adults and paediatric pts ≥ 40 kg not requiring supplemental oxygen who are at increased risk of progressing to severe COVID-19; paediatric pts weighing 3.5 to < 40.0 kg: 5 mg/kg d 1 then 2.5 mg/kg for ≤ 4 d if not on MV, or ≤ 9 d if on MV |
| **COVID-19 approvals and EUAs** | EU [25]: Adults and adolescents ≥ 40 kg: 200 mg d 1 then 100 mg for ≥ 5 d but < 10 d if requiring supplemental oxygen or for 3 d in adults not requiring supplemental oxygen who are at increased risk of progressing to severe COVID-19 (treatment commenced as soon as possible and within 7 d of symptom onset) |
| **Efficacy in mild-moderate COVID-19** | P3 PL-controlled trial (GS-US-540-9012; NCT04501952) using a 3 d course in moderate COVID-19 in 562 symptomatic high-risk pts [64] |
| PE achieved: ↓ hospitalisation or death by d 28 with remdesivir vs PL [0.7% vs 5.3% (HR 0.134; 95% CI 0.031–0.586; p = 0.0076)]; 0 deaths in either arm by d 28 [64] |
| **Efficacy in other severity COVID-19** | Moderate-severe COVID-19: P3 trials in 584 and 4891 pts achieved PE of improvement in clinical status vs SOC with remdesivir 5 d course, but no extra benefit from 10 d course [65, 66] |
| Large WHO Solidarity trial [67] found no ACM benefit in hospitalised pts | |
| Systematic review [61] and a meta-analysis [62] found improved hospital discharge times | |
| Severe COVID-19: P3 (ACCT-1) trial in 1062 pts, ≈ 90% with severe COVID-19 [68] achieved PE of d 29 TTR: median 10 vs 15 d with remdesivir for ≤ 10 d vs PL (p < 0.001); smaller trial found no benefit [69] |
| Adding bemcentinib improved median TTR (7 vs 8 d, p = 0.03) in a follow-on study [70] and the combination ↓ MV and improved discharge rates in a large meta-analysis [71] |
| **Tolerability and safety** | Mild-moderate ADEs: pyrexia, nausea and abnormal laboratory parameters including ↓ GFR, Hb and/or lymphocytes, ↑ creatinine and/or blood glucose, ↑ ALT, AST and prothrombin time in ≥ 5% |
| Severe ADEs: seizure, rash, ↑ heart rate all ≤ 2% [26] | |
| Precautions and drug interactions: monitor hepatic function for ↑ enzymes; coadministration with HCQ or chloroquine is not recommended due to cytochrome P450 3A4 metabolism [26] | |
| Special pt populations: limited data suggests remdesivir safe in pregnancy and poor oral absorption may allow safe breastfeeding [26] | |
| Not recommended if ClCr < 30 mL/min (adults and adolescents) [26] or sCr ≥ 1 mg/dL in neonates aged 7d to ≤ 28 d [63] | |
| **Pending P3 COVID-19 trials** | Numerous studies recruiting or active, including NCT 04431453 pharmacokinetics in children [72] |
| **Favipiravir (Avifavir®, Avigan®, FabiFlu®, Reeqonus™), viral replication inhibitor, approved in influenza** | |
| **Recommended COVID-19 dosage (oral)** | 1800 mg bid d 1 then 800 mg bid for ≤ 13 d in recent trials [4] |
| New analysis suggests 1600 mg d 1 then 800 mg × 3 d or 1200 mg × 9 d may be effective [73] | |
| **COVID-19 approvals and EUAs** | Approved in Russia; EUA in Latin America, India and Asia [74] for mild-severe COVID-19 |
| **Efficacy in mild-moderate COVID-19** | P3 trial composite PE including VC was not achieved, but meta-analysis found a d 7 and weaker d 14 VC benefit [75], as did another trial [76] and a large (n = 940) retrospective review [74] |
| Consistent benefit in time to ↓ fever vs PL or SOC (e.g. HCQ, lopinavir/ritonavir) [59, 76, 77] | |
| Varied chest imaging, oxygen saturations, and cough results in clinical trials and reviews [59, 61, 77] | |
| **Efficacy in other severity COVID-19** | Asymptomatic and other mild COVID-19: ↓ CRP in recurrent cases, tendency to better VC [78, 79] |
| Moderately severe-critical COVID-19: no clear benefit vs HCQ [80] | |
### Table 4 (continued)

| Parameter | Key information |
|-----------|-----------------|
| **Tolerability and safety** | Mild-moderate ADEs: diarrhoea, pyrexia, nausea (< 5%) [59, 75, 79] and abnormal laboratory parameters including hyperuricaemia, ↑ blood uric acid (30–40%) ↑ ALT, triglycerides (≤ 15%), AST, hepatic function (5–10%) ↑ neutrophils [59, 75, 79] |
| | Serious, possibly drug-related ADEs: cardiac arrest, cerebral infarction, liver disorder, pneumonia [39] |
| | Precautions and drug interactions: gout and hyperuricaemia, coadministration with pyrazinamide, repaglinide, theophylline, sulindac [39] |
| | Contraindications: pregnancy and breastfeeding although no mutagenic effects detected in vitro [79] |
| **Pending P3 COVID-19 trials** | Four completed, no results posted: NCT04349241, NCT04981379, NCT04303299, NCT04351295 19 others in progress |
| **Molnupiravir (Lagevrio), viral replication inhibitor [27, 28, 43]** | |
| **Recommended COVID-19 dosage (oral)** | 800 mg bid × 5 d, as soon as possible and within 5 d of symptom onset |
| **COVID-19 approvals and EUAs** | Conditional approval in the UK [27] and EUA in the EU [43] and in the USA [28] for mild-to-moderate COVID-19 in adult pts who are at risk of developing severe COVID-19; seeking EUAs elsewhere |
| **Efficacy in mild-moderate COVID-19** | P3 component of the P2/3 MOVe-OUT PL-controlled trial (n = 1433) in mild-moderate COVID-19 in symptomatic high-risk pts [81] 
PE achieved: ↓ hospitalisation or all-cause death through day 29 with molnupiravir vs PL [interim analysis (n = 762) 7.3% vs 14.1%; p = 0.0012; final analysis (n = 1408) 6.8% vs 9.7%]; 1 molnupiravir- and 9 PL-group COVID-19-related deaths through d 29 [81]. Results confirmed those of the P2 component in 302 pts [82] |
| **Efficacy in other severity COVID-19** | MOVe-OUT subgroup analysis in 40% of pts showed efficacy against γ, δ, and μ variants [44] 
P2 component of the P2/3 MOVe-IN (n = 304) showed that in pts hospitalized with COVID-19 molnupiravir 200–800 mg bid for 5 d provided no clinical benefit vs PL [83] |
| **Tolerability and safety** | Mild-moderate ADEs: diarrhoea, headache, nausea, dizziness (< 5% of pts) Serious ADEs: 1 rash causing withdrawal from trial [84] |
| | Precautions and drug interactions: reproductive toxicity in animals, no drug interactions predicted [27, 28, 43] |
| | Contraindications: pregnancy and breastfeeding. Not authorized for use in pts aged < 18 y because MOL may affect bone and cartilage growth [27, 28, 43] |
| | Special pt populations: no dose adjustment in kidney or liver impairment [27, 28, 43] |
| **Pending P3 COVID-19 trial** | NCT04939428 (MOVe-AHEAD) PE: non-infection in adults living with someone with COVID-19 |
| **Nirmatrelvir (PF-07321332)-ritonavir (PAXLOVID™) protease inhibitor [21–23]** | |
| **Recommended COVID-19 dosage (oral)** | 300 mg + 100 mg bid for 5 d as soon as possible and within 5 d of symptom onset |
| **COVID-19 approvals and EUAs** | Conditional approval in the UK [22] and the EU [21] and EUA in the USA [23] in pts with mild-to-moderate COVID-19 at risk of progression to severe COVID-19. Seeking EUAs in other countries |
| **Efficacy in mild high-risk COVID-19** | PE met in P 2/3 EPIC-HR trial in non-hospitalized pts with high risk of progressing to severe COVID-19 in interim analysis (n = 780) [89.1% reduction in risk of hospitalization or death with nirmatrelvir-ritonavir vs PL when administered within 3 d of symptom onset (0.8% vs 7%; p < 0.0001)] significant reduction in risk vs PL when administered within 5 d of symptom onset as well (p < 0.0001). No deaths through d 28 nirmatrelvir-ritonavir arm vs 10 deaths in PL arm [21–23, 50]. Final analysis (n = 2246) confirmed 89% reduction in risk of hospitalization or death vs PL when administered within 3 d of symptom onset (0.7% vs 6.5%; p < 0.0001). No deaths through d 28 in nirmatrelvir-ritonavir arm vs 12 deaths in PL arm [50] |
| **Efficacy in standard-risk COVID-19** | PE (self-reported, sustained alleviation of symptoms for 4 consecutive d with nirmatrelvir-ritonavir vs PL) not met in interim analysis of EPIC-SR (at 45% of planned enrolment). 0.6% vs 2.4% of pts were hospitalized (no deaths in either treatment arm) [50] |
### Table 4 (continued)

| Parameter                                      | Key information                                                                                                                                                                                                 |
|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Tolerability and safety**                    | TEAEs mostly mild and comparable to PL (19% vs 21%); few SAEs (1.7% vs 6.6%) and treatment discontinuations due to AEs (2.1% vs 4.1%) [50]                                                                 |
| Precautions and drug interactions: hepatotoxicity, potential for developing resistance to HIV protease inhibitors in pts with uncontrolled/undiagnosed HIV-1 infection. Numerous drug interactions identified (because of coadministration with ritonavir, which is predominantly metabolized by CYP3A) [21–23] |                                                                                                                                                                                                                    |
| Contraindications: co-administration with drugs highly dependent on CYP3A for clearance where high levels of those drugs are associated with serious/life-threatening ADEs; coadministration with drugs that are potent CYP3A inducers and therefore reduce plasma levels of nirmatrelvir or ritonavir, which may lead to loss of virological response and the potential for drug resistance [21–23] |                                                                                                                                                                                                                    |
| Special pt populations: dose reductions in moderate kidney impairment; not recommended in severe kidney or liver impairment [21–23] |                                                                                                                                                                                                                    |
| **Pending P2/3 COVID-19 trials**                | NCT05047601 (EPIC-PEP) P2/3 nirmatrelvir-ritonavir bid × 5/10 d, PE: post-exposure prophylaxis in household contacts of symptomatic COVID-19 case; NCT05011513 (EPIC-SR) final results. P2/3 mild COVID-19, low-risk pts, nirmatrelvir-ritonavir bid × 5 d, PE: TTR |                                                                                                                                                                                                                    |
| **Proxalutamide (GT-0918), viral replication inhibitor and immune modulator** |                                                                                                                                                                                                                    |
| COVID-19 dosage used in trials (oral/IV)       | Mild-moderate oral 200 mg od or bid; in severe or critically ill patients oral or IV 300mg od                                                                                                                                                                               |
| COVID-19 approvals and EUAs                    | EUA in Paraguay for hospitalised pts [85]                                                                                                                                                                                                                                   |
| Efficacy in mild-moderate COVID-19             | Statistical significance not achieved in interim analysis of P3 trial (NCT04870606) in non-hospitalized pts with mild COVID-19 (n = 348) who received proxalutamide 200 mg or PL bid within 5 d of symptom onset for 14 d [53] |
| Efficacy in other severity COVID-19            | P3 trial in 645 hospitalised pts (North arm; NCT04728802) receiving proxalutamide 300 mg/d vs PL [86]                                                                                                                                                                      |
|                                                   | PE: d 14 TTR achieved, 81% vs 36% with proxalutamide vs PL [RR 2.28 (95% CI 1.95–2.66); p < 0.001]                                                                                                                                                                          |
|                                                   | 28 d ACM 11% vs 49%, [RR 0.16 (95% CI 0.11–0.24], 77% lower with proxalutamide vs PL [86]                                                                                                                                                                                   |
|                                                   | Combined data from North (NCT04728802) and South (NCT05126628) arm trials (n = 778); d 14 TTR 81.1% vs 36.6% [RR 2.21 (95% CI 1.92–2.56); p < 0.0001] 28 d ACM 10.6% vs 48.2% [RR 0.22 (95% CI 0.16–0.30); p < 0.001] [87] |
| Tolerability and safety                         | Mild ADEs: diarrhoea (15-20%), abdominal pain, irritability, spontaneous erection (< 5%)                                                                                                                                                                                   |
|                                                   | Severe ADEs ≤ 3% proxalutamide vs 5-41% PL recipients (notably shock and MV) [86, 87]                                                                                                                                                                                      |
| Pending P3 COVID-19 trials                      | NCT04853927 in critically ill pts, PE: ACM; NCT05009732 in hospitalised pts, PE: TTR NCT05009732 in hospitalised pts, PE: TTR NCT04853134 outpatient study in mild-moderate COVID-19, PE: non-hospitalisation NCT04869228 outpatient study in mild-moderate COVID-19, PE: change to clinical status d 11 and oxygen need d 28 |
| **Nitazoxanide (Alinia® and many others), viral replication inhibitor +/- immune modulator approved as antiparasitic agent** |                                                                                                                                                                                                                    |
| Recommended COVID-19 dosage (oral)             | 300 mg bid for 5 d, potential prophylaxis dosage 600 mg bid for 6 wks [72]                                                                                                                                                                                                  |
| COVID-19 approvals and EUAs                    | Seeking FDA EUA [57]                                                                                                                                                                                                                                                        |
| Efficacy in mild-moderate COVID-19             | PL-controlled trial in 1092 symptomatic people aged ≥ 12 y PE: time to sustained response with nitazoxanide not achieved vs PL [57]                                                                                                                                            |
| Efficacy in other severity COVID-19            | Mild COVID-19 subgroup (n = 247) had faster sustained response (10 vs 13 d) 85% ↓ (0.5% with nitazoxanide vs 3.6% with PL) in progression to severe disease including high-risk pts (0.9% vs 5.6%) Large network meta-analysis [62] found improved VC [OR 1.72 (1.20, 2.73)] [57] |

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Table 4 (continued)

| Parameter | Key information |
|-----------|----------------|
| Tolerability and safety | Mild ADEs: diarrhoea (< 5%) [57] |
| | Precautions and contraindications: may compete with other highly plasma bound agents, e.g. warfarin |
| | Special pt populations: approved in pts aged >1 y for *Giardia lamblia* and *Cryptosporidium parvum* diarrhoea |
| Pending P3 COVID-19 trial | NCT04359680: PE: non-infection in high-risk groups, e.g. healthcare, after nitazoxanide 600 mg bid × 6 wks |

Patients were eligible for SOC, usually dexamethasone and/or remdesivir in hospitalised pts, as well as specific trial interventions

*ACM* all-cause mortality, *ADE* adverse drug event, *AE* adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *bid* twice daily, *(s)Cr* (serum) creatinine, *CrCl* Cr clearance, *CRP* C-reactive protein, *d* day(s), *EMA* European Medicines Agency, *EUA* emergency use authorisation, *FDA* US Food & Drug Administration, *HCQ* hydroxychloroquine, *HR* hazard ratio, *hsCRP* high-sensitivity CRP, *IV* intravenous, *MV* mechanical ventilation, *OR* odds ratio, *P2, P3* phase 2, 3, *PE* primary endpoint, *PL* placebo, *pt(s)* patient(s), *RR* risk ratio, *SAE* serious adverse event, *SOC* standard of care, *TEAE* treatment-emergent adverse event, *TTR* time to recovery, *VC* viral clearance/cure, *wk(s)* week(s), *y* year(s), ↓ decrease(d), ↑ increase(d)

common (Table 4) and these may change during a trial (e.g. to day 29 from the original day 15 primary endpoint in the remdesivir ACCT-1 trial in severe disease [68]). Recent disappointments (e.g. for AT-527 [88] and eicosapentaenoic acid [7]) have resulted in a further rethink and/or a focus on narrower patient subgroups [89]. Drug dosages used in the treatment of patients with COVID-19 have also come under the spotlight [73, 90].

Newer COVID-19 studies are also taking place against a changing patient backdrop. Better understanding of COVID-19’s clinical course and consequent treatment protocols have contributed to significantly improved patient outcomes since the pandemic started [2, 91]. Between March 2020 and April 2021, COVID-19 mortality rates in selected US hospitals decreased from approximately 18% to 4% and length of stay from 12 to 7 days [92]. In-hospital patient demographics have also changed, with one US study reporting mild disease in almost half of those diagnosed with COVID-19 in early 2021, versus 36% during 2020 [93].

In terms of patient selection, criteria for mild, moderate and severe disease range from WHO and other ordinal scales to oxygen saturations (SpO₂ %) and/or clinical descriptions [68, 69, 80]. As far as possible, disease severity in Table 4 is based on outpatient or hospital status and SpO₂ as follows:

- **mild**: non-hospitalised and sometimes asymptomatic, SpO₂ ≥ 95%;
- **moderate**: hospitalised but not needing active COVID-19 therapy or oxygen, SpO₂ ≥ 94%;
- **moderate-severe**: hospitalised, on supplemental oxygen but not mechanical ventilation, SpO₂ ≥ 93%; or
- **severe-critical**: requiring mechanical ventilation, SpO₂ < 93%.

Two network meta-analyses [60, 62], which enable comparisons in the absence of head-to-head trials, assessed all-cause mortality, virological cure [60, 62], mechanical ventilation, hospital discharge and/or adverse drug events in 46 [60] and 222 [62] randomised, controlled trials reported in peer reviewed journals. Proxalutamide, nitazoxanide and remdesivir (Tables 3 and 4) improved some outcomes, as did the combination of remdesivir and baricitinib [60, 62].

**A multitude of studies, but relatively few results**

Hundreds of small molecule COVID-19 therapy studies are underway [1], with some preliminary efficacy and tolerability data now available (Table 5) and a range of registered trials in progress (Tables 4, 5 and 6).
| Parameter | Key information |
|-----------|----------------|
| **Bemcentinib (BGB 324, BGB3234, R428) [with FDA fast track status for cancer]** | Mechanism of action: Viral entry/internalisation inhibitor, antikinase immune modulator Inhibits AXL tyrosine kinase receptor and ↑ anti-viral IFN response [94]  
Efficacy and tolerability: Mild-moderate COVID-19: PE of better survival, TTR and TTW not significant with bemcentinib 400 mg × 1d then 200 mg × ≤ 14 d vs SOC in P2 trials (n = 177) [94]  
In pt subgroup with more severe COVID-19 and BL C-reactive protein ≥30 mg/mL (60% of pts): TTW better with bemcentinib than SOC [94]  
ADEs: diarrhoea, headache, pulmonary embolism and ↑ ALT, hyperglycaemia (≤ 5%)  
Serious ADEs: cardiovascular events, ↑ ALT, septic shock + acute renal failure caused treatment discontinuation [94]  
Ongoing COVID-19 trials: None, although trial in more severe pts contemplated [95] |
| **Opaganib (ABC 294640, YELIVA) [being investigated for cancer]** | Mechanism of action: Sphingosine kinase-2 inhibitor with dual viral replication inhibition and anti-inflammatory properties; ↓ levels of IL-6 and TNF-alpha in bronchoalveolar lavage fluids [96]  
Efficacy and tolerability: Moderate COVID-19: minor benefit with opaganib vs PL for oxygen needs in small P2a trial  
Severe COVID-19: PE of d 14 room air not significant for opaganib vs PL in P2/3 trial (n = 465); post hoc analysis in moderately severe COVID-19 (n = 251) showed d 14 room air achieved in 77% opaganib vs 64% PL recipients (p = 0.033), 62% ↓ ACM, and ↓ TT discharge (14 vs 10 d) [both p = 0.02] [96]  
Ongoing COVID-19 trials: None |
| **Sabizabulin (Vero-111) [being investigated for cancer]** | Mechanism of action: Viral replication inhibitor and immune modulator, via α- and β-tubulin ↓ and cytoskeleton disruption that ↓ viral intracellular transport and α- and β-tubulin colchicine site binding, ↓ microtubule polymerisation and inflammation [97]  
Efficacy and tolerability: Moderate-severe COVID-19: PE of ↓ ACM/respiratory failure not significant with sabizabulin 18 mg od × 21 d despite 81% ↓ (5.6% sabizabulin vs 30% PL) in P2 trial in hospitalised high-risk pts with COVID-19 (n = 38); ↓ ACM/respiratory failure significant pts aged > 60 y (9% vs 50%) and severe COVID-19 (11% vs 54%) and in ICU d [98]  
Ongoing COVID-19 trials: P3 NCT04842747 in 300 severe +/- high-risk hospitalised pts, 21 d sabizabulin vs PL, PE: ACM d 60 |
| **AT-527 (Drug R07496998) [prodrug of guanosine nucleotide developed for Hepatitis C]** | Mechanism of action: Viral replication inhibitor, primarily targets viral polymerase nidovirus RdRp-associated nucleotidyltransferase function [99] to ↓ viral RNA synthesis, active metabolite AT-511 [100]  
Efficacy and tolerability: Mild-moderate COVID-19: PE of ↓ d 7 viral load not achieved in P2 MOONSONG trial with AT-527 550 or 1100 mg bid vs PL; possible benefit in high-risk subgroup may lead to change in MORNINGSKY trial design [61]  
ADEs: in 20% pts, mostly gastrointestinal (5–10%), no clinically significant laboratory abnormalities [88]  
Ongoing COVID-19 trials: P3 NCT04889040 (MORNINGSKY) in mild-moderate COVID-19; AT527 550 mg bid × 5 d vs PL; PE: d 29 TTR or TT symptomatic improvement  
Observational NCT05059080 (MEADOWSPRING) 6-mo study assessing prior AT-527 in long COVID |
| **Auxora (CM 4260 Calcimedia); injectable emulsion given as IV infusion** | Mechanism of action: Immune modulator, selective inhibitor of CRAC channel, ↓ epithelial and endothelial cell injury and inflammation in lungs and other organs, ↓ proinflammatory cytokine release [101]  
Efficacy and tolerability: Severe-critical COVID-19: trial stopped at 27 pts, to move to blinded trial: MV with Auxora in 18% vs 50% with SOC, and D-dimer levels - 0.24 vs + 0.63 µg/mL  
Serious ADEs in 30% vs 50%, 2 deaths in each [16, 101]  
Ongoing COVID-19 trials: P2 NCT04345614 severe COVID-19 completed, no results, PE (revised): d to recovery from start of infusion of Auxora 2.0 mg/kg at 0 h, then 1.6 mg/kg at 24 h and 1.6 mg/kg at 48 h vs PL, both + SOC |

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Table 5  (continued)

| Parameter | Key information |
|-----------|-----------------|
| **Vidofludimus calcium (IMU-838) [being investigated in Crohn’s disease, multiple sclerosis and others]** |  |
| Mechanism of action | Viral replication inhibitor and selective antikinase immune modulator, which inhibits dihydroorotate dehydrogenase and ↓ release of cytokines such as IL 17A, 17F and INF-γ [3] |
| Efficacy and tolerability | Severe COVID-19: PE and SE not met as MV required in so few pts in P2 CALVID-1[91] |
| Ongoing COVID-19 trials | P2 NCT04516915 (IONIC) recruiting (late) PE: TTI, IMU-838 as oseltamivir adjunctive therapy: IMU-838 loading dose then 22.5 mg bid + oseltamivir 75 mg bid vs oseltamivir + SOC × 14 d |

| **Silmitasertib (CX-4945) [being investigated in cancer]** |  |
| Mechanism of action | Immune modulator, via casein kinase 2 inhibition [102] |
| Efficacy and tolerability | Mild-moderate COVID-19: faster TT symptomatic recovery (6 vs 14 d; \(p < 0.02\)) with silmitasertib 1g bid vs SOC, trend to faster improvement in health-related quality of life and normalisation of COVID signs in P2 trial (\(n = 20\)) [102] |
| Ongoing COVID-19 trials | NCT04668209 P2/3, high-risk hospitalised pts; silmitasertib × 21 d; PE: ADEs, SE: clinical efficacy |

| **Abivertinib (abivertinib maleate, avitinib, AC0010, STI-5656) [originally investigated in cancer]** |  |
| Mechanism of action | Immune modulator, via epidermal growth factor receptor TK and Bruton’s TK inhibition [103] |
| Efficacy and tolerability | Moderate-severe COVID-19: PE↓ treatment failure (ACM or respiratory failure) to d 28 achieved in most severe subgroup (≈ 20% pts) in P2 trials in 480 hospitalised pts receiving abivertinib 200 mg od for ≤ 28 d or until discharge [103] |
| Ongoing COVID-19 trials | None registered, P3 study in severe COVID-19 planned |

| **Brilacidin (PMX-30063); given as IV infusion [being investigated in skin and soft tissue infections, oral stomatitis, inflammatory bowel disease]** |  |
| Mechanism of action | Virus internalisation inhibitor and immunomodulatory (non-peptidic HDP mimic); targets both viral proteins and host factors [104, 105] |
| Efficacy and tolerability | Moderate-severe COVID-19: PE of TT sustained recovery through d 29 not met in top line analysis of data from P2 trial (\(n = 120\)) of brilacidin or PL for 3-5 d plus SOC. Generally well tolerated [106] |
| Ongoing COVID-19 trials | None registered. Ongoing analysis of data to see if eligible for inclusion in larger COVID-19 platform trials [107]; compassionate use program data in critically ill patients to be analysed [108] |

*ACM all-cause mortality, ADE adverse drug event, bid twice daily, BL baseline, CRAC calcium release-activated calcium, d day(s), HDP Host Defence Proteins/Peptides, IL interleukin(s), INF interferon, IV intravenous, od once daily, P2, 2/3 phase 2, 2/3, PE primary endpoint, pt(s) patient(s), RdRp RNA-dependent RNA polymerase inhibitor, SE secondary endpoint, SOC standard of care, TK tyrosine kinase, TNF tumour necrosis factor, TT time to, TTR TT recovery, TTW TT worsening, y years, ↓ decrease(s), ↑ increase(s)*

Table 6  Small molecule antivirals with phase 2 or 2/3 COVID-19 trials in progress and/or not yet reported [72]

| Agent | Company developing | Trials in progress (including phase) |
|-------|--------------------|--------------------------------------|
| **Trials completed at 31 December 2021, but clinical results not yet reported** |  |
| Antroquinonol | Golden Biotechnology | P2 NCT04523181 |
| Asapiprant/BGE-175 | BioAge Labs | P2 NCT04705597 |
| Brequinar | Clear Creek Bio | P1/2 NCT04425252 (CRISIS) P2 NCT04527038 (CRISIS2) |

| **Trials in progress at 31 December 2021** |  |
| AddX-629 | Aldeyra Therapeutics | P2 NCT04847544 |
| ATR 002 | Atriva Therapeutics | P2 NCT04776044 |
| Emvoodstat (PTC 299) | PTC Therapeutics | P2/3 NCT 04439071, FITE19 |
| GNS 561 | Genoscience Pharma | P2 NCT04637828, NCT04333914 |
| MP 1032 | MetrioPharm AG | P2 NCT04932941, not yet recruiting |
| Pentarlandir™, UPPTA (SNB 011) | SyneuRx International (Taiwan) | P2 NCT04911777 |
| Plicidenoson | Can-Fite Biopharma | P2 NCT04333472 |
| Tafenquine (Arakoda) | 60 Degrees Pharmaceuticals | P2 NCT04533347 |
| Tempol (MBM-02) | Adamis Pharmaceuticals | P2/3 NCT04729595 |
| Upamostat | Red Hill Biopharma | P2/3 NCT04723537 RHB-107-01 |

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Take home messages

- Three small molecule antivirals, intravenous remdesivir, oral molnupiravir and oral nirmatrelvir-ritonavir are among the available COVID-19 treatments; other small molecule antivirals and immune modulators are urgently needed.
- Small molecule antiviral therapies are practical pandemic options, as they are usually more easily manufactured, stable, orally available, less costly and may be repurposed from studies or use in viruses other that COVID-19, especially those closely related to SARS-CoV-2.
- While COVID-19 treatments are a pressing need, approved medications should meet high efficacy and safety standards and there are many gaps in current knowledge.
- Many small molecule antivirals show some promise in selected groups of COVID-19 patients, but large, randomised efficacy and safety studies of both monotherapy and combined antiviral agents are needed.
- New small molecule antivirals have been designed with a high barrier for drug resistance; real-world data are required to confirm this. Combination therapy using small molecule antivirals with different mechanisms of action may be required to overcome drug resistance in the future.
- Other administration routes for small molecule antivirals, including via inhalation, are a possibility.

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