

## **Remdesivir: A review of its discovery and development leading to human clinical trials for treatment of COVID-19**

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## ***Abstract***

The global pandemic of SARS-CoV-2, the causative viral pathogen of COVID-19, has driven the biomedical community to action – to uncover and develop anti-viral interventions. One potential therapeutic approach currently being evaluated in numerous clinical trials is the agent remdesivir, which has endured a long and winding developmental path. Remdesivir is a nucleotide analog prodrug that perturbs viral replication, originally evaluated in clinical trials to thwart the Ebola outbreak in 2014. Subsequent evaluation by numerous virology laboratories demonstrated the ability of remdesivir to inhibit coronavirus replication, including SARS-CoV-2. Here, we provide an overview of its mechanism of action, discovery, and the current studies exploring its clinical effectiveness.

## Introduction

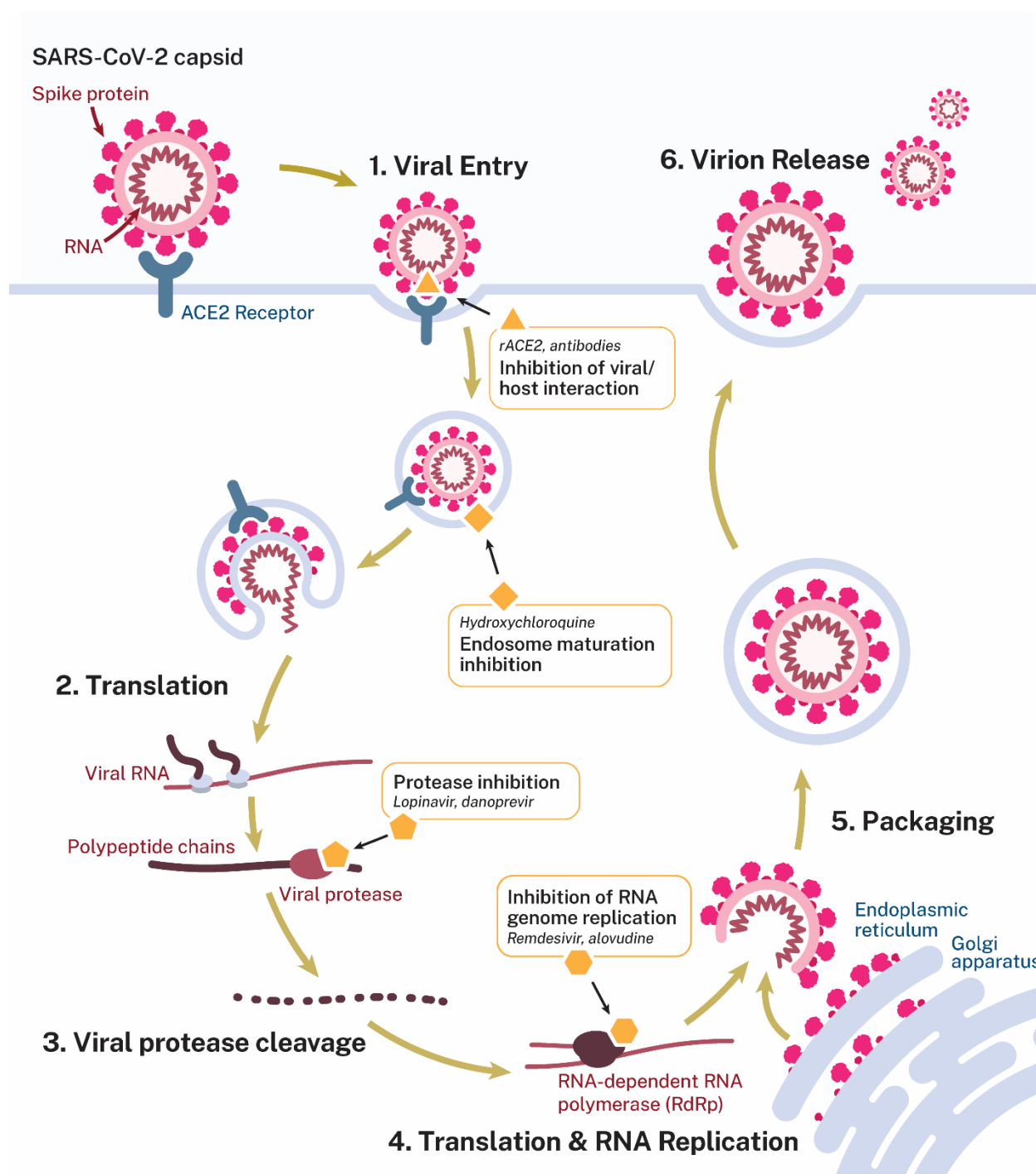
Coronaviruses are a family of enveloped viruses with a positive-sense single-stranded RNA genome that infect animal species and humans. Amongst coronavirus members are those responsible for the common cold, severe acute respiratory syndrome coronavirus (SARS), Middle East respiratory syndrome-related coronavirus (MERS) and the recently emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the causative pathogen of the disease COVID-19<sup>1</sup>.

Coronaviruses primarily cause respiratory and intestinal infections in animals and humans<sup>2</sup>. Discovered in the 1960s, they were originally thought only responsible for mild disease, with members such as HCoV 229E and HCoV OC43 responsible for the common cold<sup>3</sup>. That changed in 2003 with the SARS pandemic and in 2012 with the outbreak of MERS, both zoonotic infections that resulted in mortality rates greater than 10% and 35%, respectively<sup>4</sup>. On December 31, 2019, China reported to the World Health Organization (WHO) cases of pathogenic viral pneumonia in Wuhan, Hubei Province, China caused by SARS-CoV-2. Subsequent spread has led to a global pandemic, officially declared by the WHO on March 11, 2020<sup>5</sup>.

COVID-19 disease appears to be a spectrum of clinical presentations ranging from asymptomatic to severe respiratory failure. Common symptomology at the onset of illness are fever, cough and general myalgia, with less common symptoms including sputum production, headache and diarrhea<sup>6-8</sup>. A case analysis study from China through mid-February found 14% of cases were associated with severe disease (dyspnea, respiratory frequency  $\geq 30/\text{min}$ , blood oxygen saturation  $\leq 93\%$ , partial pressure of arterial oxygen to fraction of inspired oxygen ratio  $< 300$ , and/or lung infiltrates  $> 50\%$  within 24 to 48 hours), and 5% of cases were critical (i.e., respiratory failure, septic shock, and/or multiple organ dysfunction or failure<sup>9</sup>. Disease progression to acute respiratory distress syndrome, typically occurred in older patients (over 63), often with underlying medical conditions such as hypertension or diabetes<sup>10</sup>; elevated risk of mortality was associated with advanced age, sepsis, blood clotting deficiencies<sup>11,12</sup>. Other symptoms, including neurologic symptoms, have been reported in a portion of infected individuals<sup>13-16</sup>.

As a new disease, SARS-CoV-2 does not have any clinically proven therapeutics. Furthermore, a significant amount of pre-clinical research was reported in the search for therapeutic treatments for SARS and MERS. As SARS and MERS outbreaks did not persist, no therapeutic or vaccine development programs were completed. The consequence is that drug repositioning and repurposing has received a significant amount of attention<sup>17</sup>, and approved agents including chloroquine, azithromycin, ritonavir, ruxolitinib, and camostat have entered clinical trials to address the current SARS-CoV-2 pandemic (**Figure 1**)<sup>18-20</sup>.

One of the first clinical candidates that has received attention is remdesivir, a pre-existing drug candidate developed by Gilead Sciences. It was originally authorized for compassionate use and has now entered controlled clinical trials. Like all other therapeutic approaches for patients with COVID-19, remdesivir was not developed specifically to treat COVID-19, and here we review its mode of action and discovery.

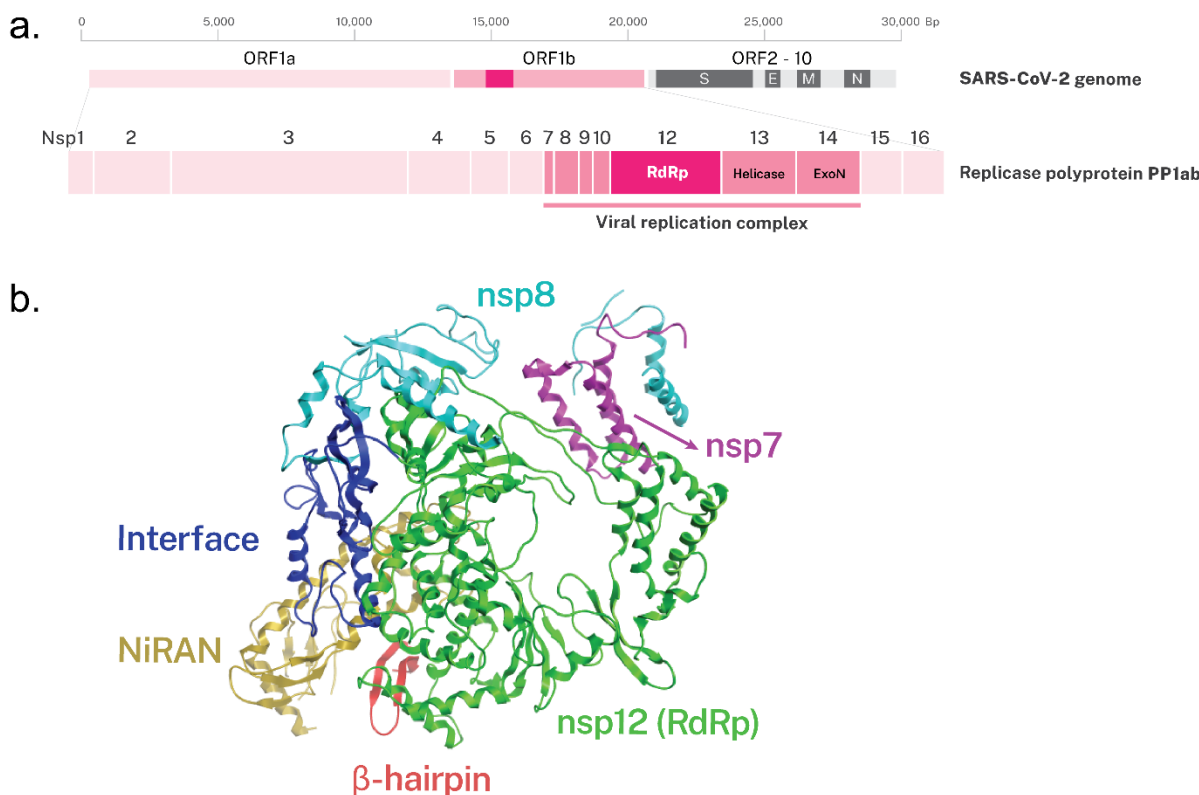


**Figure 1.** Life cycle of SARS-CoV-2 in host cells. SARS-CoV-2 enter target cells through the endosomal pathway via direct binding of the viral S protein to the cellular receptor angiotensin-converting enzyme 2 (ACE2). Following entry of the virus into the host cell the virus complex is then translocated to endosome, where endosomal acid proteases cleave the S protein mediating membrane fusion. The viral genome is released and translated into the viral replicase polyproteins PP1a and PP1ab, which are cleaved into functional proteins by viral proteases. Sub-genomic templates for mRNA synthesis and translation of the viral structural proteins occur through discontinuous transcription<sup>2</sup>. Viral genome replication is mediated by the viral replication

complex. Viral nucleocapsids are assembled from the packaged viral genomes and translated viral structural proteins. Infectious virions are then released from the cell through exocytosis. Potential targets and postulated mechanism of action for antiviral interventions are shown: blocking virus/host cell interaction through the use of antibodies/nanobodies (and convalescent plasma therapy) or recombinant ACE2 protein; use of hydroxychloroquine to inhibit endosome maturation; use of protease inhibitors to inhibit viral/endosome membrane fusion or viral polypeptide maturation; nucleoside/nucleotide analogs to inhibit viral genome replication.

### ***Remdesivir mode of action***

Antiviral chemotherapeutic interventions often target specific viral enzymes or attack a weak point of viral replication within the host. One proven approach for the latter is demonstrated through the use of the nucleoside analogue ribavirin for the treatment of Hepatitis C<sup>21</sup>. Ribavirin targets the viral reliance on an RNA-dependent RNA polymerase (RdRp) to catalyze the replication of the RNA genome from the original RNA template (**Figure 2**). RdRps have a higher error rate (between  $10^{-4}$ - $10^{-6}$  errors/nucleotide/replication) compared to DNA polymerases, stemming from a reduced proofreading activity<sup>22</sup>. This higher mutation rate contributes to the rapid evolution of RNA viruses and adaptability to new environments, facilitating the ability of coronaviruses to jump from animals to humans. This high error rate also makes RNA viruses, and specifically SARS-CoV-2, susceptible to error catastrophe. In a seminal paper, Crotty *et al.* demonstrated that the RNA virus poliovirus exists on the edge of viability, due to the proportion of virus particles with deleterious mutations. Furthermore, treatment with concentrations of ribavirin that caused a 9.7-fold increase in mutations was sufficient to induce “error catastrophe,” in effect lethally mutating the poliovirus, reducing infectivity by 99.3%<sup>23</sup>.

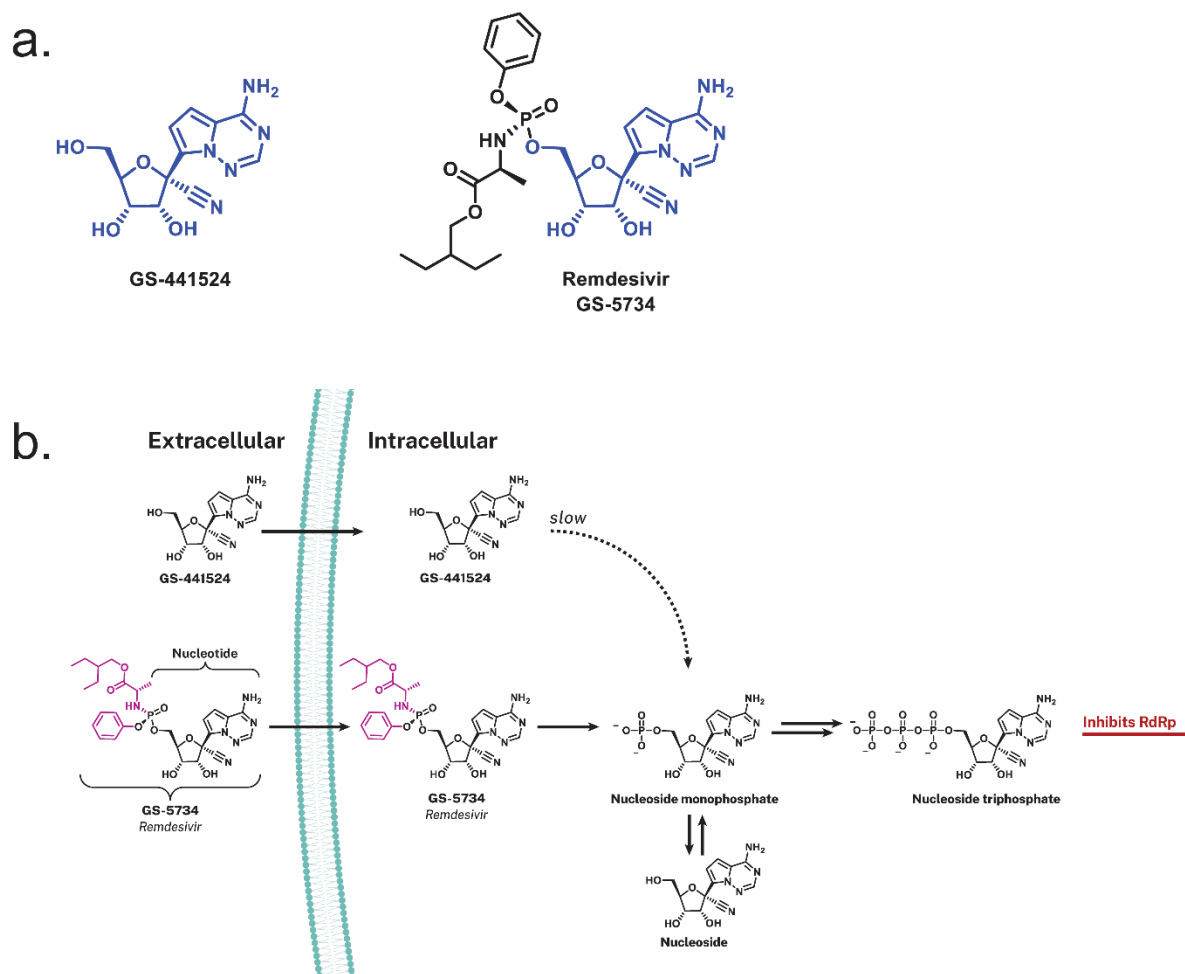


**FIGURE 2.** SARS-CoV-2 genome and RNA-dependent RNA polymerase structure. **a)** Representation of the SARS-CoV-2 RNA genome. As SARS-CoV-2 is a positive sense RNA virus, the genome serves as a direct template for protein translation. After translation by the host ribosome into polyprotein PP1ab, open reading frame 1 (ORF1), which encodes most of the non-structural proteins of the virus, is processed by a viral protease to produce functional viral proteins. These include the seven proteins that putatively form the viral replication complex, among these are the RNA-dependent RNA polymerase (RdRp), helicase and exonucleaseN proteins. **b)** Domain organization of the SARS-CoV-2 RdRp (encoded by nsp12) domains bound to cofactors nsp7 and dimers of nsp8, that serve as essential cofactors that increase polymerase activity. The rendering was based on the cryo-EM structure at a resolution of 2.9-Å, published by Gao et al, 2020 (PDB code is 6M71). The nsp12 RdRp domain is shown in green, nsp7 in purple, nsp8 in cyan, nidovirus RdRp-associated nucleotidyltransferase (NiRAN) domain in yellow, interface in blue, and a newly identified  $\beta$ -hairpin domain is shown in red<sup>24</sup>.

Remdesivir (GS-5734), a prodrug, is metabolized within cells into the adenosine nucleotide analog GS-441524. Nucleotide analogs such as GS-441524 are not highly cell permeable, and once in the cell they require di-, and then tri-phosphorylation to produce the nucleoside triphosphate (NTP) that can be utilized by the viral RNA-dependent polymerases for genome replication. As such, NTPs, can then be mis-integrated into viral RNA by the viral RNA-dependent RNA polymerase (RdRp; **Figure 2**). The initial phosphorylation of nucleosides, into the monophosphate form, is considered to be the rate-limiting step<sup>25</sup>, but as the monophosphate form is highly polar, it does not diffuse back across the cell membrane (and so is essentially trapped in the cell). Given that the initial phosphorylation step of nucleosides is slow in cells, monophosphorylated nucleosides should be more potent antiviral agents, but they are not cell permeable. To address this, an

approach to antiviral drug design evolved the utilization of phosphoramidate prodrugs (ProTides, inferred as prodrugs of nucleotides)<sup>26,27</sup>. Protides are composed of a nucleoside monophosphate with an aryl group and an amino acid ester (a phosphoramidate). Following diffusion into the cell, the phosphoramidate prodrug is presumed to metabolize in a sequence of hydrolytic steps that starts with esterase-mediated ester hydrolysis to a carboxylate that cyclizes internally to the phosphonate ejecting the phenoxide; the resultant unstable cyclic anhydride is hydrolyzed open by water to an alanine derivative whose P-N bond is hydrolyzed by a phosphoramidase-type enzyme. This final step liberates the nucleoside monophosphate, which is then processed to the triphosphorylated form (TNP analog) and able to act as a substrate for RdRP (**Figure 3**). The approach has been successfully applied to a number of FDA-approved antiviral drugs including the Gilead products sofosbuvir (for treating HCV) and tenofovir alafenamide (first approved for treating HIV)<sup>26</sup>.

Remdesivir's antiviral activity was demonstrated against coronaviruses (SARS, MERS, contemporary human CoV and bat-CoVs), supporting remdesivir's broad antiviral activity at inhibiting RdRp activity<sup>28</sup>. Remdesivir was also shown to perturb pan-CoV RdRp function by inhibiting viral replication of SARS, MERS, and the model  $\beta$ -coronavirus murine hepatitis virus (MHV), even in settings with intact exonuclease proofreading activity<sup>29</sup>. Biochemical data from recombinant respiratory syncytial virus (RSV) RdRp suggested the primary mechanism of action was through delayed chain termination, or the inhibition of RNA synthesis a few residues distal to the incorporated inhibitor<sup>30-32</sup>. Importantly, remdesivir inhibits viral replication (demonstrated with both Ebola and RSV) in cell-based assays with IC<sub>50</sub> values of approximately 100 nM, whereas human RNA Polymerase (RNAP) II and human mitochondrial RNAP are not inhibited in the presence of compound<sup>32</sup>, providing approximately 500-fold selectivity. Interestingly, *in vitro* assays demonstrate that the triphosphate form of the inhibitor was incorporated at increased rates compared to natural nucleotide pools<sup>33</sup>, likely adding to strong antiviral potency of remdesivir through premature RNA synthesis termination.



**FIGURE 3.** Remdesivir and its intracellular conversion. **a)** Chemical structures of GS-441524 that composes the nucleoside analog core (blue) of remdesivir (GS-5734). **b)** Intracellular processing of the pro-drug remdesivir (GS-5734), the phosphoramidate (purple) form of GS-441524. Upon diffusion of remdesivir into the cell, it is metabolized into the nucleoside monophosphate form. The nucleoside monophosphate is routed to further phosphorylation events (hijacking the endogenous phosphorylation pathway) yielding the active nucleoside triphosphate analog form that is utilized by the viral RNA-dependent RNA polymerase (RdRp). Utilization of the GS-441524 nucleoside triphosphate analog by RdRp inhibits viral replication through inducing delayed chain termination. While the nucleoside analog core of remdesivir, GS-441524, can diffuse into cells, the initial phosphorylation step for nucleosides is rate-limiting (slow), which is believed to account for the reduced anti-viral activity of GS-441524 compared to remdesivir.

### Development of remdesivir

Remdesivir (GS-5734) was developed by Gilead Sciences and emerged from a collaboration between Gilead, the US Centers for Disease Control and Prevention (CDC) and the US Army Medical Research Institute of Infectious Diseases (USAMRIID). They sought to identify therapeutic agents for treating RNA-based viruses that maintained global pandemic potential, such as those that indeed emerged following the initiation of the program, such as Ebola virus (EBOV)



and the *Coronaviridae* family viruses exemplified by Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).

As a starting point for discovery, a library of ~1,000 small molecules focused around nucleoside analogs was compiled, based on prior knowledge of effective antiviral compounds targeting RNA viruses. Nucleosides are poorly cell-permeable (and therefore have a low hit rate in cell-based screens such as antiviral screens), so modified nucleosides such as monophosphate, ester, and phosphoramidate pro-drugs composed a significant portion of the library. Such prodrugs are typically more permeable and metabolized to liberate the nucleoside or phosphorylated nucleoside within cells (*vide infra*)<sup>34-36</sup>. While the data from the original full screen does not appear to have been disclosed, a 1'-CN modified adenosine C-nucleoside hit (GS-441524), along with a pro-drug form of GS-441524 (GS-5734, later renamed as remdesivir) was found to be highly potent (Structures shown in **Figure 3**)<sup>37</sup>. GS-441524 and its *S*-acyl-2-thioethyl prodrug had previously been reported in 2012 as potent leads from a series of 10-substituted 4-aza-7,9-dideazaadenosine C-nucleosides, with broad activity against a panel of RNA viruses: yellow fever virus (YFV), Dengue virus type 2 (DENV-2), Influenza A, Parainfluenza 3, and SARS<sup>38</sup>. The primary assay used was the cytoprotection effect (CPE) assay, in which live virus is incubated with a target cell line and the antiviral activity is inferred by the ability of a test agent to rescue cell death, measured using a standard cell viability reagent<sup>39</sup>. In a 2012 study, GS-5734 showed CPE activity against SARS strain Toronto 2 (IC<sub>50</sub> = 2.2  $\mu$ M) without causing cytotoxicity toward the host Vero African green monkey kidney epithelial cells used in the CPE assay (note that different target cells were utilized in viral CPE assays).

When the Ebola outbreak occurred in 2014, the assembled library was utilized to identify and prioritize compounds with efficacy against EBOV. The study by Madelain *et al.* found that GS-5734 reduced EBOV replication in HeLa cells with an IC<sub>50</sub> ~ 100 nM, and it retained potency in *in vivo* non-human primate EBOV infection models, while GS-441524 was inactive<sup>29,40</sup>. In addition to demonstrating activity against EBOV, Warren *et al.*, showed that remdesivir also had antiviral activity against several other viruses, including the coronavirus MERS, with an IC<sub>50</sub> of 340 nM *in vitro*.

With the demonstration that GS-5734 (remdesivir) possessed broad activity against RNA viruses, multiple groups assessed antiviral activity both *in vitro* and *in vivo*<sup>25,39,41,42</sup>, validating its activity against coronaviruses. Antiviral activity was confirmed against SARS, MERS zoonotic coronaviruses<sup>25,43</sup>, as well as the circulating human coronaviruses HCoV-OC43 and HCoV-229E, causative agents of the common cold<sup>44</sup>. Furthermore, de Wit *et al.* demonstrated that remdesivir had both prophylactic and therapeutic activity against MERS in a nonhuman primate *in vivo* model<sup>45</sup>.

The pharmacokinetics of remdesivir have been summarized in compassionate use documentation published by the European Medicines Agency (EMA, 2020). Remdesivir is administered via an intravenous injection (IV) with a loading dose on day 1 (200 mg in adults, adjusted for body weight in pediatric patients) followed by a daily maintenance dose (100 mg in adults) for up to 10 days. In non-human primates daily administration of 10 mg/kg of remdesivir yielded a short plasma half-life of the prodrug ( $t_{1/2}$  = 0.39 hr), but sustained intracellular levels of the triphosphate form<sup>29</sup>.

*In vitro* and pre-clinical *in vivo* animal models supported the effectiveness of remdesivir against SARS-CoV-2 and related coronaviruses. These include a recent *in vitro* study of remdesivir assessing antiviral activity against SARS-CoV-2 (previously known as 2019-nCov, strain nCoV-2019BetaCoV/Wuhan/WIV04/2019) using qRT-PCR quantification of viral copy number in infected Vero E6 cells. This study demonstrated an IC<sub>50</sub> of 770 nM and an IC<sub>90</sub> equal to 1,760 nM (with cytotoxic concentration >100 mM)<sup>47</sup>. In addition, works by Sheahan *et al.* and de Wit *et al.* demonstrated *in vivo* efficacy of remdesivir at inhibiting viral replication and reducing viral related pathology against related coronaviruses<sup>43,45</sup>. These findings, along with the safety profile of remdesivir in the clinical trial assessment against EBOV<sup>48</sup>, support the evaluation of remdesivir as a potential therapeutic drug for repurposing against the SARS-CoV-2 pandemic.

Driven by the EBOV outbreak in 2014 and based on *in vitro* and animal model *in vivo* efficacy against EBOV<sup>29</sup>, Gilead Sciences initiated clinical evaluation of remdesivir for EBOV. Gilead pursued FDA evaluation under the FDA's Animal Rule, permitting the reliance on efficacy findings from animal studies for drugs in which it is not feasible or ethical to conduct human trials. As such, remdesivir was included in a randomized, controlled trial of Ebola virus therapeutics in patients within the Democratic Republic of the Congo (NCT02818582), however, mid-study primary analyses found remdesivir inferior to the antibody based therapeutics MAb114 and REGN-EB3, with respect to mortality, and the remdesivir intervention arm was terminated<sup>48</sup>. Mulangu *et al.* reported one serious adverse event related to remdesivir, an instance of hypotension, along with elevated creatinine and aspartate aminotransferase plasma levels in remdesivir-treated patients compared to either antibody based therapeutic arms. Although, remdesivir was inferior against EBOV based on efficacy compared to antibody therapy, the study arm did provide an initial insight into the safety profile in patients.

### ***Clinical studies for COVID-19***

With the COVID-19 outbreak increasing in size and a lack of alternative therapeutics, two clinical trials were designed and initiated in China. On February 5th, a phase 3 randomized, quadruple-blind, placebo-controlled clinical trial was registered at Capital Medical University, with the goal to determine safety and efficacy of remdesivir in patients with mild to moderate SARS-CoV-2 infection (NCT04252664, since suspended)<sup>49</sup>. A day later, a second trial (NCT04257656, since terminated) was registered at the same location, focused on patients with advanced COVID-19 respiratory disease<sup>50</sup>. Both trials had planned to track the primary outcome as time to clinical improvement, up to 28 days; normalization of fever, oxygen saturation, and respiratory rate, and alleviation of cough which is sustained for 72 hours. Both trials delivered remdesivir as a 200 mg loading dose on the first day, with 9 subsequent days of maintenance dosing at 100 mg - this regime is identical to that utilized in the previous NCT03719586 Ebola trial, which appears to be the model for all subsequent trials involving remdesivir (discussed below; **Figure 4** and **Table 1**, registered trials of remdesivir).

Contemporaneous to the development of the Chinese trials, the first cases of COVID-19 were emerging in the USA. On January 20<sup>th</sup>, a patient reported to urgent care in Snohomish County, Washington with subjective fever and a 4-day history of cough, later to be confirmed as the first positive case of COVID-19 in the USA<sup>51</sup>. On the seventh day of hospitalization and after worsening clinical status, the patient was given IV remdesivir under compassionate use access

(Gilead Sciences), with no adverse events observed on infusion<sup>51</sup>. The patient's clinical condition improved the next day, though concurrent treatment with acetaminophen, ibuprofen, guaifenesin, vancomycin, cefepime, and supplemental oxygen confound the direct interpretation of remdesivir's impact.

Subsequently, twelve patients were confirmed to be infected with SARS-CoV-2 between January 20–February 5, 2020<sup>52</sup>. Of these twelve patients, seven were hospitalized and three received remdesivir (compassionate use access; Gilead Sciences) upon worsening clinical disease. Treatment was continued for 4-10 days with 200 mg IV on the first day and 100 mg each following day. Following the initial dose, all patients experienced “transient gastrointestinal symptoms, including nausea, vomiting, gastroparesis, or rectal bleeding,” though treatment was continued until improvement in respiratory symptoms, with all twelve patients reporting symptom resolution by February 22<sup>52</sup>. The small sample size and lack of controlled randomization preclude analysis of clinical efficacy or safety.

The National Institute of Allergies and Infectious Diseases (NIAID), NIH initiated the Adaptive COVID-19 Treatment Trial (ACTT), a double-blind, randomized, placebo-controlled phase 3 trial to evaluate the safety and efficacy of remdesivir compared with a remdesivir placebo-control (NCT04280705)<sup>53</sup>. NIAID developed this study in part based on the existing Chinese clinical trials in addition to consulting with the WHO<sup>54</sup>. This study is currently recruiting patients, tracking the primary outcome of patient status severity on an 8-point ordinal scale, with multiple secondary outcomes of interest. 75 clinical sites are anticipated to participate in the study, with distribution across the United States, and an estimated primary completion date of April 2023.

Subsequently, Gilead Sciences initiated two clinical trials that began in mid-March, comparing remdesivir to standard of care in patients with moderate or severe coronavirus disease (COVID-19) in an open-label, randomized trial, NCT04292899<sup>55</sup>. This trial will explore the safety and efficacy of remdesivir in combination with standard of care to compare study arms of five- or ten-day remdesivir dosing on the primary outcome of fever and oxygen saturation. NCT04292730 maintains three study arms to compare remdesivir provided over five or ten days, to standard of care alone, with the primary outcome being the proportion of patients discharged by the fourteenth day<sup>56</sup>.

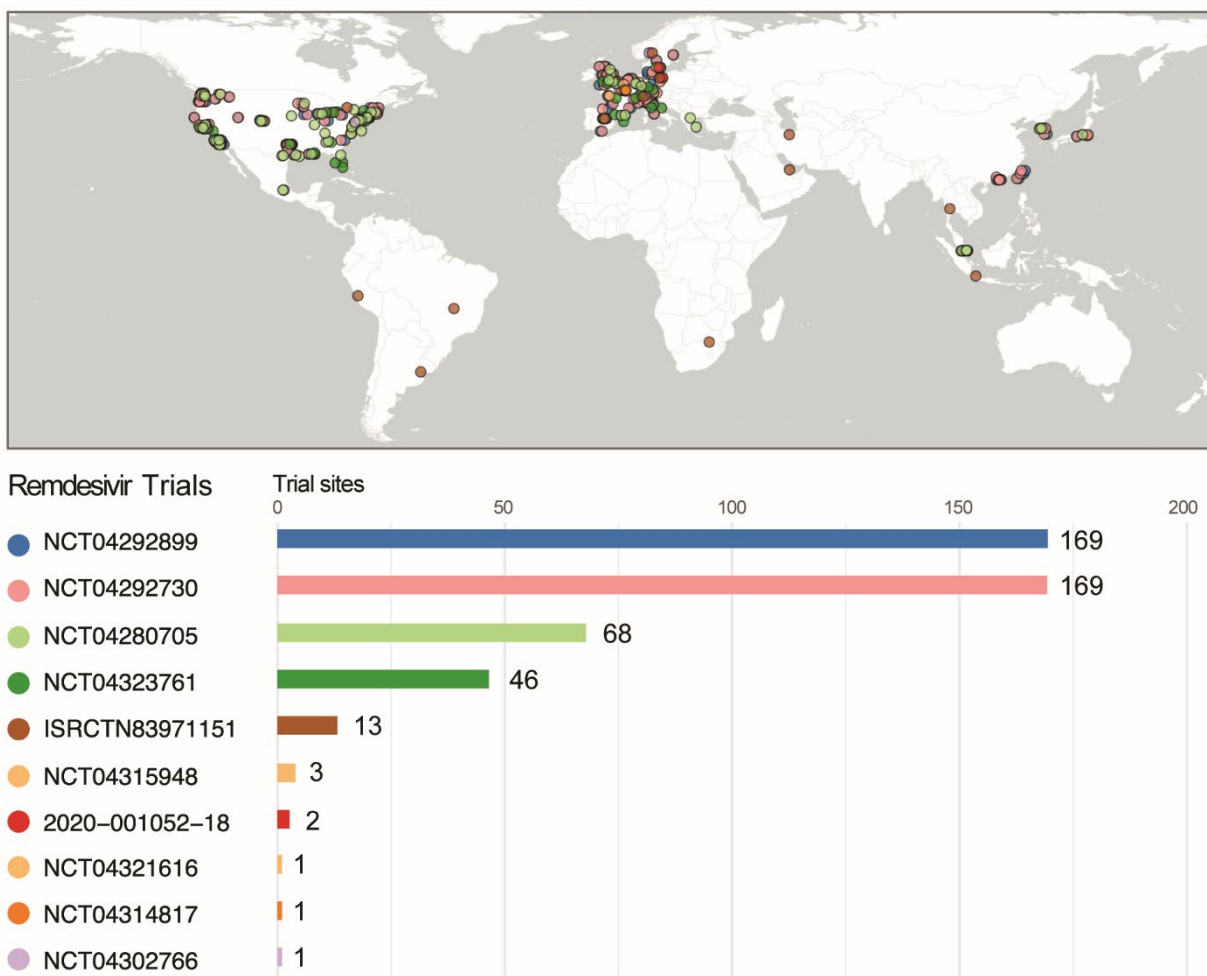
To determine the most effective treatments for COVID-19 and ensure sufficient power to observe definitive results, the WHO announced the SOLIDARITY clinical trial, a four-arm trial comparing remdesivir, lopinavir/ritonavir, lopinavir/ritonavir with Interferon- $\beta$ 1a, and chloroquine or hydroxychloroquine (ISRCTN83971151). With the goal of reducing trial design time and start-up, the WHO seeks to rapidly facilitate comparison of treatments on a worldwide scale. Data will be analyzed on an interim basis by an independent group of experts, the Global Data and Safety Monitoring Committee<sup>57</sup>, enabling the modification of study design if particular treatments show early promise. As of March 27, over 70 countries had committed to participating.

In a trial sponsored by the Oslo University Hospital, the WHO NOR (Norwegian)-COVID 19 study is a multi-center, adaptive, randomized, open label study to evaluate the safety and efficacy of hydroxychloroquine, remdesivir and current standard of care (NCT04321616, 2020-001052-18)<sup>58</sup>. The comparative arms of the study are daily remdesivir, hydroxychloroquine loading dose

of 800 mg x 2 followed by 400 mg x 2 daily for a total of 10 days, or the standard of care. Primary outcome is all cause in-hospital mortality, with secondary measures of duration of mechanical ventilation, ICU duration, 28-day mortality, viral clearance, readmittance, occurrence of co-infections and organ dysfunction. Inclusion criteria include confirmed SARS-CoV-2 infection by PCR, 18 years of age, and admittance to the hospital ward or ICU. Importantly, exclusion criteria include prolonged QT interval ( $> 450\text{ms}$ ) due to the known toxicity issues associated with hydroxychloroquine.

An observational study sponsored by the Groupe Hospitalier Pitie-Salpetriere, with collaborator CMC Ambroise Paré, was initiated to investigate adverse events in COVID-19 treatment (NCT04314817)<sup>59</sup>. The study will consider events as classified by the international classification of disease ICD-10, and track lopinavir/ritonavir, chloroquine, azithromycin, remdesivir and Interferon- $\beta 1a$ , potentially expanding the scope in the future prior to the primary completion date in January 2021.

The DisCoVeRy trial is an adaptive, open-label, randomized interventional trial which includes five treatment modalities (NCT04315948); standard of care alone or standard of care plus the following: remdesivir, hydroxychloroquine, lopinavir and ritonavir, or lopinavir, ritonavir and Interferon- $\beta 1a$ <sup>60</sup>. The remdesivir dose regime is identical to existing trials, with maintenance dosing continuing up to 10 days. Lopinavir and ritonavir tablets are to be administered every 12 hours for 14 days (400 lopinavir mg/100 mg ritonavir). In combination with the lopinavir/ritonavir schedule, Interferon- $\beta 1a$  will be administered subcutaneously at a dose of 44  $\mu\text{g}$ , for three doses in six days (day 1, day 3, day 6). Hydroxychloroquine will be given 400 mg, twice on the first day, followed by 400 mg once daily for 9 days. Initially the study will include five French hospitals (Paris – Hôpital Bichat-AP-HP, Lille, Nantes, Strasbourg, Lyon) with potential expansion to other participating sites<sup>61</sup>. Primary outcome is the reported disease severity on a 7-point ordinal scale, assessed on the 15th day, with secondary outcomes tracking various physiological and clinical metrics.



**Figure 4.** Remdesivir global clinical trials. Shown are the locations of the clinical study sites for the ongoing clinical studies of remdesivir for SARS-CoV-2/COVID-19. Number of sites participating for each respective study, if no specific information was given, shown are the countries participating (e.g. ISRCTN83971151). Listed are the number of sites participating for each respective study, if no detailed information was provided, shown are the number of countries participating. NCT04302766 is an expanded access trial with no specific sites listed in the registration. Figure created with R<sup>62</sup>, utilizing the packages rnatrualearth<sup>63</sup>, sf<sup>64</sup>, and ggplot2<sup>65</sup>.

### Expanded Access

With the overwhelming influx of compassionate use requests, on March 23<sup>rd</sup> Gilead Sciences suspended compassionate use access to remdesivir for all cases save children and pregnant women, shifting their focus to support mounting clinical trials and establish a system of expanded access, wherein hospitals or physicians can request emergency use of remdesivir for multiple patients at one time<sup>66</sup>. In an open letter to the public on March 28<sup>th</sup>, Gilead CEO reported that they had provided over 1,000 doses of remdesivir through compassionate use requests<sup>67</sup>. To date, the FDA has granted expanded access treatment protocols for remdesivir, sponsored by the U.S. Army Medical Research and Development Command (NCT04302766)<sup>66</sup> and Gilead Sciences (NCT04323761)<sup>68</sup>. The primary objective of these studies is the provision of expanded access to



remdesivir for the treatment of SARS-CoV2 infections. Gilead Sciences have acknowledged that production of remdesivir is an involved process, and this is being scaled up to meet demand.

### ***Other nucleoside candidates***

Remdesivir is certainly not the only nucleoside analog that is being investigated for use against SARS-CoV-2, but is the most clinically advanced. A recent publication by Sheahan *et al.* describes the ribonucleoside analog,  $\beta$ -D-N<sup>4</sup>-hydroxycytidine (NHC, EIDD-1931), that has *in vitro* activity against SARS-CoV-2 and *in vivo* against the related SARS virus<sup>69</sup>. Although in preclinical development, EIDD-1931 is orally bioavailable, a significant advantage compared to remdesivir, and has increased potency against viruses containing mutations in RdRp that conferred increased resistance to remdesivir, supporting the potential for a combination therapy to address the risk of SARS-CoV-2 becoming clinically drug resistant. Other clinically approved nucleoside/nucleotide analogs, such as the hepatitis C drug sofosbuvir and HIV drugs alovudine and zidovudine have also been shown to be active against the SARS RdRp in *in vitro* biochemical assays, and might have potential to be repurposed against COVID-19<sup>70</sup>.

### ***Conclusions***

Thus far, remdesivir has not been demonstrated to be an efficacious therapy for COVID-19. As the COVID-19 pandemic races across the globe, the scientific community, from academic and government laboratories to small biotechnology companies and multinational pharmaceutical corporations, has mobilized to develop and evaluate potential therapeutics and vaccines<sup>71-74</sup>. Repurposing or repositioning an effective small-molecule therapeutic promises the fastest therapeutic means to stem the tide of the pandemic<sup>75,76</sup>. Among the candidate drugs, remdesivir has demonstrated efficacy in both *in vitro* and *in vivo* models against coronaviruses. Recently, through a compassionate use indication, remdesivir has supportive evidence for yielding some clinical improvement in COVID-19 patients<sup>77</sup>. While remdesivir represents one compound whose consideration may yet play a role in mitigating the morbidity, mortality and strain on global healthcare systems caused by COVID-19, ongoing clinical trials will provide much-needed clarity surrounding the repurposing of approved drugs and experimental agents against SARS-CoV-2.

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### **Declaration of Conflicting Interests**

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Table 1.** Registered remdesivir trials for SARS-CoV-2/COVID-19

Study Identifier	Study Title	Start Date	Status	Sponsor	Interventions	Phase	Study Design	Expected Completion Date	Location(s)
NCT04280706*	Adaptive COVID-19 Treatment Trial (ACTT)	Feb. 21, 2020	Recruiting	National Institute of Allergy and Infectious Diseases (NIAID)	Remdesivir; Remdesivir placebo	3	Clinical Trial, Randomized Parallel Assignment Double (Participant, Investigator)	Treatment	April 1, 2023 Multiple US; Multiple Korea; Tokyo, Japan; Singapore
ISRCTN183971151*, NCT04335958	Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients	March 1, 2020	Available	World Health Organization	Remdesivir; Lopinavir/Ritonavir; Lopinavir/Ritonavir, Interferon Beta-1A; Hydroxychloroquine; Standard of care	3	Clinical Trial, Randomized	None (Open Label)	Treatment March 25, 2021 Multiple sites: countries of recruitment: Argentina, Brazil, Canada, Germany, Indonesia, Iran, Norway, Peru, Qatar, South Africa, Spain, Switzerland, Thailand
NCT04292899*	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Severe Coronavirus Disease (COVID-19)	March 6, 2020	Recruiting	Gilead Sciences	Remdesivir; Standard of Care	3	Clinical Trial, Randomized Parallel Assignment	None (Open Label)	Treatment May 1, 2020 Multiple US; Multiple Hong Kong; Multiple Italy; Multiple Korea; Multiple Singapore; Multiple Spain; Multiple Taiwan
NCT04292730*	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment	March 15, 2020	Recruiting	Gilead Sciences	Remdesivir; Standard of Care	3	Clinical Trial, Randomized Parallel Assignment	None (Open Label)	Treatment May 1, 2020 Multiple US; Multiple Hong Kong; Multiple Italy; Multiple Korea; Multiple Singapore; Multiple Spain; Multiple Taiwan
NCT04314817*	Adverse Events Related to Treatments Used Against Coronavirus Disease 2019	March 17, 2020	Recruiting	Groupe Hospitalier Pitié-Salpêtrière, CMC Ambroise Paré	Any drug used to treat Covid-19		Observational Model, Case-Only		Jan 1, 2023 AP-HP Assistance Publique Hôpitaux de Paris, Paris, France
NCT04315948*	Trial of Treatments for COVID-19 in Hospitalized Adults	March 22, 2020	Recruiting	Institut National de la Santé Et de la Recherche Médicale, France	Remdesivir; Lopinavir/Ritonavir; Interferon Beta-1A; Hydroxychloroquine; Standard of care	3	Clinical Trial, Randomized Parallel Assignment	None (Open Label)	Treatment March 1, 2023 Multiple France
NCT04321618*, 2020-00562-18*	The Efficacy of Different Anti-viral Drugs in (Severe Acute Respiratory Syndrome-Coronavirus 2) SARS-CoV-2	March 26, 2020	Not yet recruiting	Oslo University Hospital	Remdesivir; Hydroxychloroquine; Standard of Care	2, 3	Clinical Trial, Randomized Parallel Assignment	None (Open Label)	Treatment Nov. 1, 2020
2020-001052-18*	A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults		Available	Regents of the University of Minnesota	Remdesivir		Clinical Trial, Randomized Parallel Assignment Double (Participant, Investigator)	Treatment	Multiple sites: countries of recruitment: Denmark, Germany, Italy, Portugal, Spain; United Kingdom
NCT04302766*	Expanded Access Remdesivir (RDV, GS-5734)		Available	U.S. Army Medical Research and Development Command	Remdesivir		Expanded access		
NCT04323781*	Expanded Access Treatment Protocol: Remdesivir (RDV, GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection		Available	Gilead Sciences	Remdesivir		Expanded access		

\*Registered remdesivir clinical studies (as of 4/15/2020) for SARS-CoV2/COVID-19. \* Clinicaltrials.gov registered. \* ISRCTN registered (www.isrctn.com). \* Clinicaltrials.gov registered

Registered remdesivir clinical studies (as of 4/15/2020) for SARS-CoV-2/COVID-19. \* ClinicalTrials.gov registered; \*\* ISRCTN registered (www.isrctn.com); \*\*\* ClinicalTrials.gov registered



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