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August 4, 2020

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Delivered by email

Dear Mr. O'Day, Dr. Hahn, Dr. Disbrow, Dr. Collins, and Dr. Fauci:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, and the undersigned scientists are writing to strongly urge Gilead Sciences, Inc. and relevant agencies within the U.S. Department of Health and Human Services to either work collaboratively to promptly pursue the development of the experimental antiviral drug GS-441524 (molecular formula $C_{12}H_{13}N_5O_4^1$) as a treatment for coronavirus disease 2019 (COVID-19) or publicly provide evidence why it is not scientifically or medically feasible to develop this drug in parallel with its close analogue, remdesivir.

GS-441524 — a simpler prodrug with activity against a broad range of viruses that was established in collaboration between Gilead and federally-funded scientists — is very similar in

¹ IUPAC name: (2*R*,3*R*,4*S*,5*R*)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)oxolane-2-carbonitrile

chemical structure and activity to remdesivir,² which is the only antiviral drug demonstrated to have efficacy for the treatment of COVID-19 in a phase 3 clinical trial. Importantly, **GS-441524 is converted in mammalian (including human) cells to the same active antiviral nucleotide triphosphate as is remdesivir**, thereby making them equivalent in their mechanism of action.

As you know, however, remdesivir is being pursued aggressively as a COVID-19 treatment in clinical trials, whereas GS-441524 has been neglected or overlooked.^{3,4} Although remdesivir is the first drug to have demonstrated efficacy in the treatment of patients hospitalized with serious COVID-19, publicly available evidence suggests that GS-441524 may offer significant advantages over remdesivir, given the following considerations:

- GS-441524 has demonstrated marked efficacy and safety in the treatment of a deadly coronavirus infection in cats.
- GS-441524 has shown *in vitro* antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the novel virus leading to COVID-19) that appears to be similar or superior to that of remdesivir at levels that can be achieved in the body with low toxicity.
- GS-441524 enters the lung cells and is metabolized to its triphosphate form, which halts SARS-CoV-2 viral transcription.
- GS-441524 has a lower molecular weight and is more water soluble than remdesivir. These characteristics might facilitate the use of inhaled or oral formulations of GS-441524 to treat pulmonary SARS-CoV-2 infection either therapeutically or prophylactically, thus contrasting it favorably to remdesivir, which currently is limited to intravenous use.
- GS-441524 is substantially easier to manufacture than remdesivir.

It is unclear why Gilead and federal scientists have not been pursuing GS-441524 as aggressively as remdesivir, but we cannot help but note that there are significant financial incentives tied to Gilead's current patent holdings. Specifically, Gilead holds patents on both agents, but the earliest patent approval date on remdesivir is 2015⁵ whereas the earliest on GS-441524 is 2010.⁶ Thus, Gilead's monopoly power over remdesivir may have at least five additional years of enforceability beyond that of GS-441524.

Below we review the evidence, summarized above, in more detail for why GS-441524 may offer significant advantages over remdesivir as a candidate treatment for COVID-19.

² PubChem. National Library of Medicine. CID 44468216. <https://pubchem.ncbi.nlm.nih.gov/compound/44468216>. Accessed July 27, 2020.

³ Yan V, Muller F. Advantages of the parent nucleoside GS-441524 over remdesivir for Covid-19 treatment. *ACS Med Chem Lett*. 2020;11(7):1361-1366.

⁴ Westgate J. Vet science 'being ignored' in quest for COVID-19 drug. *Vet Times*. May 07, 2020. <https://www.vettimes.co.uk/news/vet-science-being-ignored-in-quest-for-covid-19-drug/>. Accessed July 27, 2020.

⁵ PubChem. National Library of Medicine. Methods for treating Filoviridae virus infection. <https://pubchem.ncbi.nlm.nih.gov/patent/US9724360>. Accessed July 27, 2020.

⁶ PubChem. National Library of Medicine. 1??-substituted carba-nucleoside analogs for antiviral treatment. <https://pubchem.ncbi.nlm.nih.gov/patent/US8008264>. Accessed July 27, 2020.

A. GS-441524 trials in cats infected with a deadly coronavirus

Recent studies using GS-441524 to treat a coronavirus disease known as feline infectious peritonitis (FIP) have demonstrated marked and apparent life-saving results. Specifically, in two published studies, the first with 31 cats⁷ and the second with four,⁸ GS-441524 demonstrated a combined long-term survival rate of 80% (i.e., 28 of 35 animals recovered). These results, though not yet confirmed with randomized controlled trials, are notable because untreated FIP results in over 95% mortality within a few days to months of diagnosis.⁹ The potential applicability of these findings to the treatment of human COVID-19 has been noted by the researchers who conducted these studies.¹⁰ For reasons not fully explained, Gilead has refused to pursue FDA approval of GS-441524 as an animal drug for treating FIP.¹¹

B. Similar or superior anti-viral activity against SARS-CoV-2 in cultured cells

A critical reason why consideration should be given to pursuing GS-441524 further as a potential treatment for COVID-19 is that it has demonstrated anti-viral activity against SARS-CoV-2 in cultured human and monkey cells that appears to be similar or superior to that of remdesivir.

Very recently, Puijssers et al., among whom were Gilead researchers, published a paper in the peer-reviewed journal *Cell Reports* that unambiguously demonstrates that both remdesivir and GS-441524 ('524) potentially inhibit SARS-CoV-2 replication in cultured human lung (Calu3) and monkey kidney (VeroE6) cells, with similar effective concentration (EC) curves for the two drugs in both cell lines.¹² Figures D and H below, which are taken directly from figure 2 of the Puijssers et al. paper, demonstrate not only that both drugs substantially inhibit viral replication at low dose concentrations, but also that both demonstrate near-zero toxicity on the infected cells at those same doses. Importantly, Figures D and H also show that the ECs that lead to 90% inhibition of viral replication are slightly or markedly lower for GS-441524 than for remdesivir. Not shown are other results from Puijssers et al. that demonstrate GS-441524's comparative advantage over remdesivir to reduce viral load.

⁷ Pedersen NC, Perron M, Bannasch M, et al. Efficacy and safety of the nucleoside analog GS-441524 for treatment of cats with naturally occurring feline infectious peritonitis. *J Feline Med Surg.* 2019;21(4):271-281.

⁸ Dickinson PJ, Bannasch M, Thomasy SM, et al. Antiviral treatment using the adenosine nucleoside analogue GS-441524 in cats with clinically diagnosed neurological feline infectious peritonitis. *J Vet Intern Med.* 2020 May 22; doi: 10.1111/jvim.15780. Online ahead of print.

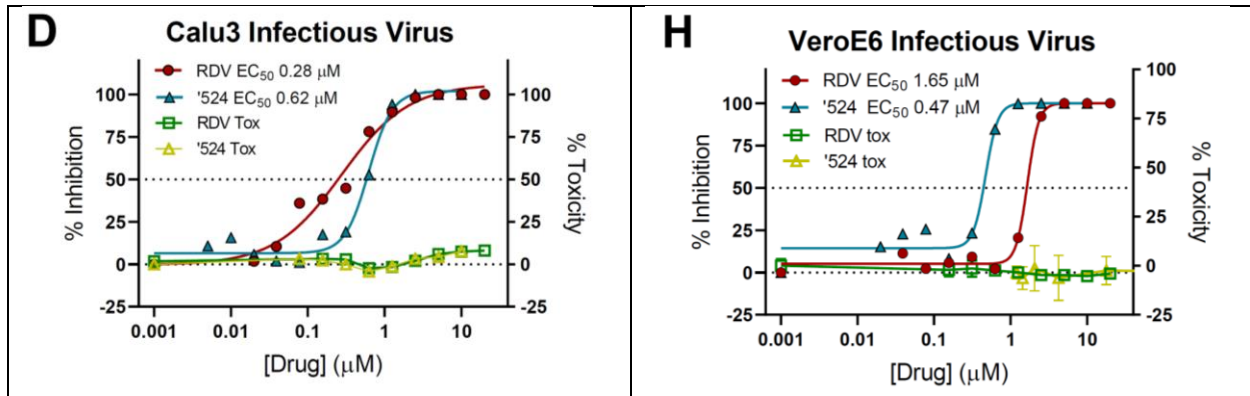
⁹ *Ibid.*

¹⁰ Westgate J. Vet science 'being ignored' in quest for COVID-19 drug. *Vet Times.* May 07, 2020.

<https://www.vettimes.co.uk/news/vet-science-being-ignored-in-quest-for-covid-19-drug/>. Accessed July 24, 2020.

¹¹ Zhang S. A much-hyped COVID-19 drug is almost identical to a black-market cat cure. *The Atlantic.* May 8, 2020. <https://www.theatlantic.com/science/archive/2020/05/remdesivir-cats/611341/>. Accessed July 27, 2020.

¹² Puijssers AJ, George AS, Schäfer A, et al. Remdesivir potentially inhibits SARS-CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice. *Cell Rep.* 2020;32(3):107940. doi.org/10.1016/j.celrep.2020.107940.



Results of an earlier study by Agostini et al. in 2018 similarly found that both remdesivir and GS-441524 potently inhibit severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in cultured human airway epithelial cells at concentrations that are projected to be therapeutically sustainable and far below those that cause cellular toxicity.^{13,14}

C. Pharmacology and biochemistry

Remdesivir and GS-441524 are highly similar in chemical structure and identical in the way they are believed to inhibit replication of SARS-CoV-2 in infected human cells. Figure 3 below, which is excerpted with modifications (insertion of the red text box and arrows highlighting two misleading assumptions) from a publication by federal scientists Eastman et al., demonstrates these points.¹⁵

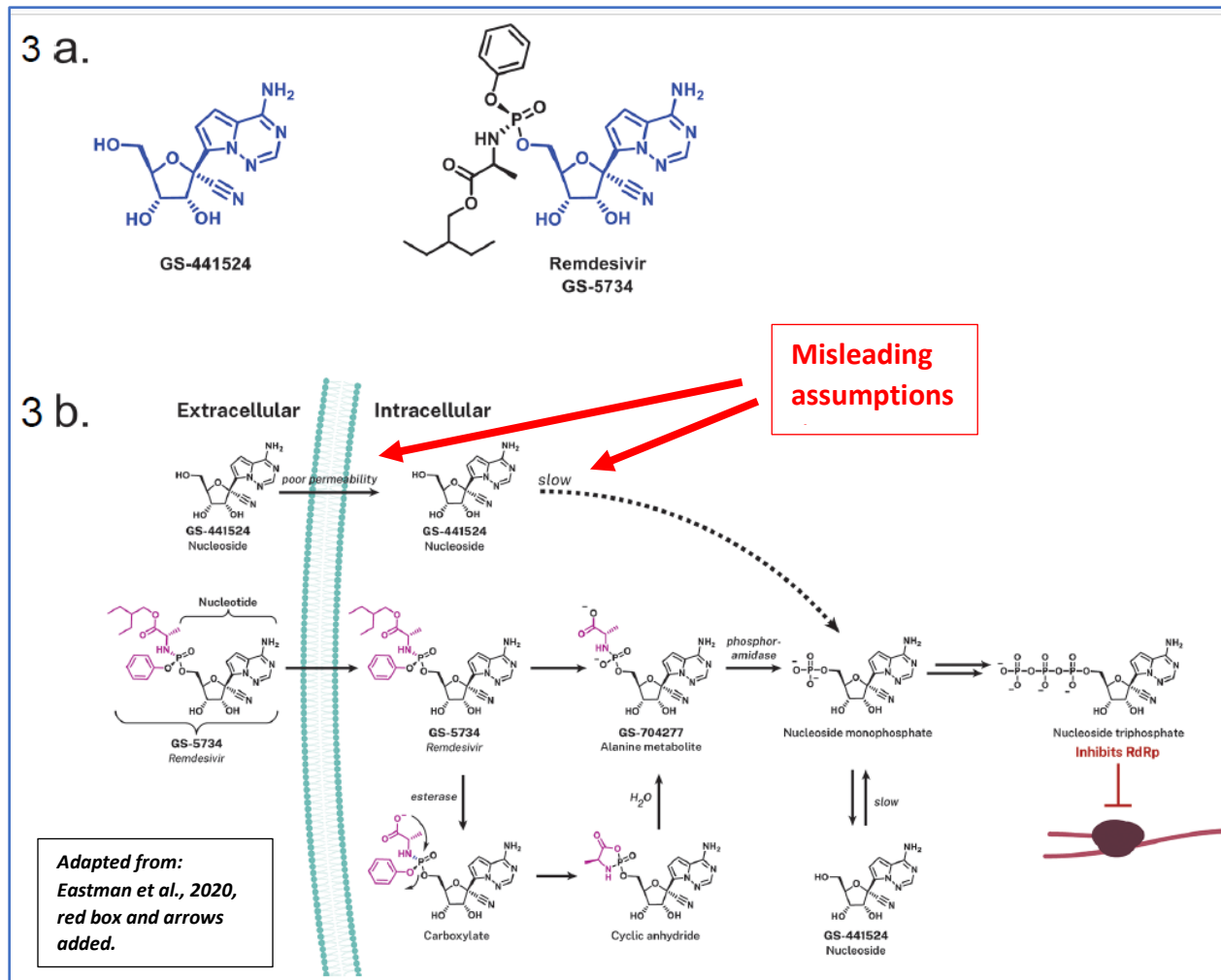
First, figure 3a shows that the chemical structure of GS-441524 completely overlaps with that of remdesivir except that one hydrogen atom is replaced by a phosphoramidate group.

Second, as shown in figure 3b below, inside the cell, GS-441524 and remdesivir follow metabolic pathways that converge to become exactly the same triphosphate nucleoside molecule that inhibits viral RNA transcription. Figure 3b further notes key assumptions, regarding relatively lower permeability and slower rate of phosphorylation, which to date have led some researchers to incorrectly conclude that remdesivir may be superior to GS-441524. In fact, existing evidence, including results from cell culture studies noted in section B above, demonstrates otherwise.

¹³ Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *MBio*. 2018;9(2):e00221-18.

¹⁴ European Medicines Agency. Summary on compassionate use: Remdesivir, Gilead. April 3, 2020. https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf. Accessed July 27, 2020.

¹⁵ Eastman RT, Roth JS, Brimacombe KR, et al. Remdesivir: A review of its discovery and development leading to emergency use authorization for treatment of COVID-19. *ACS Cent Sci*. 2020;6(5):672-683.



Additionally, data from studies in monkeys show that remdesivir is rapidly (in less than one hour) metabolized in plasma to GS-441524, resulting in concentrations of GS-441524 that are 100 to 1,000 times higher than those seen with remdesivir.^{16,17} Likewise, a pharmacokinetic study in two COVID-19 patients treated with intravenous remdesivir revealed that at one hour after administration, remdesivir had decreased by approximately 97% from peak blood levels seen immediately post-injection and were undetectable at 24 hours post-injection, whereas GS-441524 blood levels peaked at one hour post-injection and subsequently decreased by only 35% to 50% at 24 hours post-injection.¹⁸ These results suggest that following administration of remdesivir, GS-441524 is the predominant molecule that enters lung cells and provides cell-specific antiviral therapeutic effects in that critical target organ. The plausibility of GS-441524 efficiently entering cells of the lung and other organs is further supported by the existence of

¹⁶ Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature*. 2016;531(7594):381-385.

¹⁷ Williamson BN, Feldmann F, Schwarz B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature*. 2020 June 9. doi: 10.1038/s41586-020-2423-5. Online ahead of print.

¹⁸ Tempestilli M, Caputi P, Avataneo V, et al. Pharmacokinetics of remdesivir and GS-441524 in two critically ill patients who recovered from COVID-19. *J Antimicrob Chemother*. 2020 July 1;doi:10.1093/jac/dkaa239. Online ahead of print.

similar drugs (for example, fludarabine and gemcitabine for cancer) that enter cells via passive diffusion or naturally occurring transporter proteins on the cellular membrane that facilitate such molecular entry.^{19,20}

Regarding intracellular phosphorylation of GS-441524, Pruijssers et al. specifically noted that this key metabolic step occurs, and they present data supporting that conclusion.²¹ Their data shows that both remdesivir and GS-441524 yield the active triphosphate molecule within hours of drug exposure in cultured kidney and lung cells. Finally, it is notable that, according to the Human Protein Atlas, intracellular metabolism of remdesivir within alveolar pneumocytes (lung cells that are consequential targets of SARS-CoV-2) is likely limited because of the extreme deficiency of metabolizing enzymes (CTSA, CES1), which are essential to the activation of that complex prodrug.²²

D. GS-441524 is better suited for aerosolized and oral delivery

It is evident from the chemical structures of GS-441524 and remdesivir that the former drug has a lower molecular weight and is more water soluble (see figure 3a above), characteristics that might facilitate the use of inhaled or oral formulations of GS-441524 to treat pulmonary SARS-CoV-2 infection either therapeutically or prophylactically.

Moreover, as previously noted, the enzymes that bioactivate GS-441524 are highly expressed in lung pneumocytes, whereas analogous enzymes for remdesivir are poorly expressed in that COVID-19 critical cell type.²³ Both of these characteristics could make GS-441524 especially amenable to administration via an inhaled aerosol formulation. Remdesivir's current Emergency Use Authorization that was issued by the Food and Drug Administration is limited to an intravenous formulation of the drug,²⁴ although Gilead recently announced that it has commenced testing of a nebulizer-delivered version.²⁵

¹⁹ Yan V. Fact-checking the ACS Central Science review on remdesivir. May 22, 2020.

<https://medium.com/@victoriacyanide/fact-checking-the-acscentral-science-review-on-remdesivir-44a9e1240731>. Accessed July 27, 2020.

²⁰ Kraiss JJ, De Crescenzo O, Harrison RG. Purine nucleoside phosphorylase targeted by annexin v to breast cancer vasculature for enzyme prodrug therapy. *PLoS One*. 2013;8(10): e76403.

²¹ Pruijssers AJ, George AS, Schäfer A, et al. Remdesivir potently inhibits SARS-CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice. *Cell Reports*. 32, 10740. doi.org/10.1016/j.celrep.2020.107940. Accessed July 20, 2020.

²² Yan V, Muller F. Advantages of the parent nucleoside GS-441524 over remdesivir for Covid-19 treatment. *ACS Med Chem Lett* 2020;11(7):1361-1366.

²³ *Ibid.*

²⁴ Food and Drug Administration. Letter to Gilead Sciences granting Emergency Use Authorization Approval for remdesivir to treat COVID 19. May 1, 2020. <https://www.fda.gov/media/137564/download>. Accessed July 27, 2020.

²⁵ O'Day D. An open letter from Daniel O'Day, Chairman and CEO, Gilead Sciences. June 22, 2020. <https://stories.gilead.com/articles/an-open-letter-from-daniel-oday-june-22>. Accessed July 27, 2020.

E. GS-441524 is easier to manufacture

Gilead recently disclosed that manufacturing remdesivir is a “complicated chemical process” taking six months and requiring “many, many steps.”²⁶ In fact, scientists from Gilead, the U.S. Army Medical Research Institute of Infectious Diseases, the U.S. Centers for Disease Control and Prevention, and others in 2017 jointly published an overview of the six steps necessary to synthesize remdesivir. In contrast, only the first three steps of the remdesivir-production pathway are needed to synthesize GS-441524.²⁷ As such, production of GS-441524 would be easier, faster, and thus less expensive than producing remdesivir.

Steps to advance GS-441524 to phase 1 clinical trials

One important reason why the development of remdesivir as a treatment for COVID-19 is advancing, while that of GS-441524 is not, is because only the former has undergone human testing. Clinicaltrials.gov²⁸ lists more than a dozen active, recruiting, or completed randomized clinical trials testing remdesivir as a treatment for COVID-19, whereas no clinical trials testing GS-441524 are listed.

Though it is not trivial to engage in human testing of any drug, given the data that currently exist for both remdesivir and GS-441524 (including data from feline, monkey, human, and *in vitro* studies) there appears to be strong justification for aggressively advancing preclinical and cautiously advancing human testing of GS-441524 for the treatment of COVID-19 and other coronavirus-related diseases that may emerge in the future.

Already, GS-441524 has demonstrated safety under Good Manufacturing/Good Laboratory Practice (GMP/GLP) conditions as it is the major and prevalent hydrolysis product of remdesivir and also is remdesivir’s direct precursor in the manufacturing process. Because of this lineage, both the FDA and European Medicines Agency (EMA) reviews for remdesivir also detail much about GS-441524’s behavior and apparent safety in the human body.^{29,30}

The EMA’s Committee for Medicinal Products for Human Use describes the pharmacokinetics of remdesivir, and by direct association of GS-441524, thusly:

²⁶ Herper H. Gilead CEO: We’re going to make sure that access is not an issue with remdesivir. *STAT*. April 29, 2020. <https://www.statnews.com/2020/04/29/gilead-ceo-were-going-to-make-sure-that-access-is-not-an-issue-with-remdesivir/>. Accessed July 27, 2020.

²⁷ Siegel D, Hui HC, Doerffler E, et al. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo [2, 1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. *J Med Chem*. 2017;60(5):1648-1661.

²⁸ National Library of Medicine. National Institutes of Health. Clinicaltrials.gov. Accessed June 20, 2020.

²⁹ European Medicines Agency. Summary on compassionate use: Remdesivir, Gilead. April 3, 2020. https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf. Accessed July 27, 2020.

³⁰ Food and Drug Administration. Fact sheet for health care providers. Emergency Use Authorization (EUA) of remdesivir (GS-5734). Revised June 2020. <https://www.fda.gov/media/137566/download>. Accessed July 27, 2020.

Remdesivir (GS-5734) is a single diastereomer monophosphoramidate prodrug of a monophosphate nucleoside analog (GS-441524). The rapid decline in plasma levels of remdesivir are accompanied by the sequential appearance of the intermediate metabolite GS-704277 and the nucleoside metabolite GS-441524. Inside cells, the GS-441524 monophosphate undergoes rapid conversion to the pharmacologically active analog of adenosine triphosphate (GS-443902) that inhibits viral RNA polymerases.³¹

Accordingly, it seems urgent to expeditiously advance the development of GS-441524 as a plausible alternative to remdesivir for COVID-19 treatment. GMP/GLP conditions and phase 1 clinical trials could rapidly be achieved by Gilead in collaboration with government scientists or by other drug developers, researchers, and commercial research organizations.

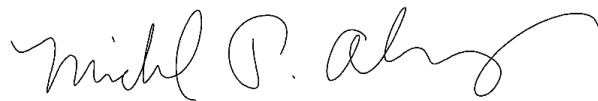
Conclusions

GS-441524 is the parental nucleoside of remdesivir that has demonstrated strong anti-coronavirus activity *in vitro* and *in vivo*. GS-441524 further demonstrates comparable or superior anti-SARS-CoV-2 activity to remdesivir *in vitro*. Against a deadly coronavirus in cats, GS-441524 has yielded exceptional cure rates. As the predominant and persistent (half-life equals 24 hours) circulating metabolite in remdesivir-treated patients, there is strong scientific justification for its further investigation in clinical trials for COVID-19.

We look forward to your prompt response to this letter with either a commitment and plan to pursue GS-441524 as a treatment for COVID-19, or supportable evidence of why it is necessary to defer development of this seemingly obvious drug candidate. Finally, if Gilead is unwilling to pursue further investigation and development of GS-441524, we request that the company immediately permit other academic and federal scientists to do so.

Thank you for your attention to this urgent public health matter.

Sincerely,

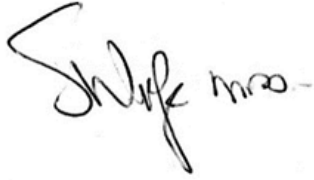


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³¹ European Medicines Agency. Summary on compassionate use: Remdesivir, Gilead. April 3, 2020.
https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf.
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*The views expressed in this letter are those of the signatories, and not necessarily those of the MD Anderson Cancer Center