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December 21, 2021

Dr. John Witcher, M.D.
111 Oakridge Trail
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Subject: **Toxicological Analysis Pertaining to the Use of Remdesivir or Ivermectin for the Treatment of COVID-19 SARS COV-2 Infection and Sequelae**

Dear Dr. Witcher,

This letter is drafted in support of your decision to withdraw your SARS-COV-2 (COVID-19) patients from remdesivir treatment, in favor of using ivermectin in conjunction with other medicines, in the course of your contracted work at Baptist Yazoo Hospital. Please find attached, a toxicology evaluation that compares and contrasts the safety and efficacy of the two drugs towards the treatment of SARS-COV-2.

Remdesivir is an anti-viral that has a singular mechanism of action and was granted emergency use authorization (EUA) based on a single study which has since faced multiple criticisms as to design and interpretation of results. Subsequent clinical trials and studies have not demonstrated its effectiveness in treating SARS-COV-2 towards lessening morbidity and mortality from the disease. In fact, in these studies, remdesivir was either found to have no effect at all, or its use increased morbidity and mortality in subjects treated with the drug. In light of this, as early as November of 2020, the World Health Organization (WHO) recommended AGAINST using this drug to treat COVID-19, due to its lack of efficacy towards these endpoints.

Moreover, remdesivir has been demonstrated to be UNSAFE, in that it is a known kidney and liver toxicant in both humans and in animal studies in monkeys and in rats, causing kidney injury and toxicity, sometimes lethal, far above the estimated margin of acceptable risk/reward therapeutic benefit. A pharmacovigilance study which was conducted in April of 2021 "Remdesivir and Acute Renal Failure: A Potential Safety Signal From Disproportionality Analysis of the WHO Safety Database", reported a statistically significant safety signal related to "acute renal failure" and "remdesivir" with 138 observed cases instead of the 9 expected, a 20-fold increase in AKI from what was expected. A second pharmacovigilance study of over 5,000 reports done in May of 2021, of adverse drug reactions reported to the WHO's VigiBase confirmed that kidney disorders, including acute kidney injury (AKI), is associated with remdesivir use at an odds ratio of 7.2. This kidney injury, ultimately leads to the worsening of pulmonary endpoints—the very symptom that drug is being used to ameliorate. The vehicle for remdesivir, the oligosaccharide SBECD, is also associated with renal and liver toxicity causing obstruction of renal tubules and frank hepatic cellular necrosis.

As a pulmonary toxicologist with multiple publications in the field I can assure you that a drug formulation with such demonstrated primary renal and hepatic toxicity impacts and secondary, pulmonary toxicity effects, should not be used to treat a pulmonary disease, for obvious reasons.

The prescribing guide notes that the drug can be toxic to the liver as well and also warns that ***"the available data from published case reports and compassionate use of remdesivir in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes"***. Further the prescribing guide notes that animal studies have demonstrated that the drug causes reproductive toxicity as follows: ***"Reproductive toxicity, including decreases in corpora lutea, numbers of implantation sites, and viable embryos, was seen when remdesivir was administered by daily intravenous administration at a systemically toxic dose (10 mg/kg) in female rats 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD"*** The safety and efficacy of the drug has also not been tested in breastfeeding women or in children under 12. No carcinogenicity studies have been done on the drug.

Ivermectin on the other hand, is a drug with a decades old safety record as an anti-parasitic, and more recently has been found to have potent anti-viral effects against SARS-COV-2 and multiple other viruses, with multiple mechanisms of action against viral binding, viral replication, and viral-induced inflammation. Ivermectin has been proven both safe and effective towards SARS-COV-2, with 69 controlled studies demonstrating its efficacy in the prophylaxis and prevention of the contraction of SARS-COV-2, in *out-patient* early treatment of SARS COV-2 to stop replication of the virus and prevent hospitalization; and in hospitalized patients to decrease *in-hospital* mortality and morbidity. In fact the weight of the scientific literature base weighs strongly in favor of ivermectin for the treatment of SARS-COV-2 and against remdesivir.

Ivermectin is listed by the National Institutes of Health under their "Characteristics of Antiviral Agents That Are Approved or Under Evaluation for the Treatment of COVID-19" as the second agent under remdesivir for use against COVID-19. This is also baffling, in light of its virtual ban by the AMA, hospitals and pharmacies for the treatment of the disease.

Much ado has been about the safety of ivermectin however, the typical high-end treatment dose for SARS COV-2 with ivermectin, is 0.6 mg/kg which for most people is less than 60 mg/day. The toxicology literature notes that a 16 month old ingesting 7-9 mg/kg developed nausea, vomiting and pallor, tachycardia and sleepiness which resolved in 3 days with no residual effects. An adult female ingested 1000 mg and experienced a coma from which she recovered over 9 days with no residual effects noted. Millions of people—men women and children have been treated with the drug world-wide on a regular bases for the treatments and prevention of parasitic disease to rare ill effect. Therefore, it is difficult to make the argument that ivermectin is unsafe for use in COVID patients.

The fact that Dr. Fauci and perhaps other safety and regulatory body members have financial interests in the company that manufactures remdesivir, a drug they have authorized as the only approved treatment for SARS-COV-2, in addition to the fact that hospitals are reimbursed financially for utilizing this treatment as well as for putting patients on ventilators, is another sincere concern. It is patently immoral and unethical to allow monetary interests to drive medical decision making in the treatment of patients and to take doctors out of the medical decision making process towards their patients. This should especially not result in the sidelined or even banned use of another drug such as ivermectin, which has been historically characterized as both safe and effective, but which being cheap and out of patent, neither the hospitals, the drug companies, nor the "investors" stand to make much of a profit off its' use.

The WHO has issued statements against the use of remdesivir in the treatment of COVID and the NIH still lists ivermectin as its second treatment drug for SARS-COV-2. Yet the hospitals and pharmacies in apparent collusion with big pharma, the AMA and government officials, are banning its use nationwide,

in favor of a drug that is causing countless deaths due to kidney and liver toxicity, worsening of pulmonary symptoms and ineffectiveness towards treating COVID-19. These same hospitals are firing learned staff like Dr. John Witcher, M.D. who is desperately trying to save his patients' lives based on his extensive medical knowledge and experience and his review of the scientific and medical studies surrounding treatment options. Pharmacies and pharmacists are actively taking part in denying lifesaving treatments to patients, acting as physicians, practicing medicine and refusing to fill doctor-written prescriptions based on administrative guidance from corporate officials whom should not have the right to order this. This in a single instance is outrageous….this collectively, is criminal behavior! When people are afraid to go to the hospital for fear they will be killed by dangerous and profit-driven hospital protocols and this fear is openly discussed on multiple platforms, it is time for change. We can no longer actively comply with these morally and ethically-bereft agendas. We expect more of our hospitals and more of our safety and regulatory officials. We expect that all those involved will participate in allowing for the treatment of patients with the best treatments available and not to participate in questionable treatments solely for profit, at the expense of the precious lives of the patients who trust hospitals, doctors and pharmacists to make lifesaving medical decisions for them.

We, the undersigned believe that there is overwhelming data in favor of treating patients with the proven safe and effective antiviral agent ivermectin, in combination with other standard measures of care given to control common features of the disease, such as coagulopathy, inflammation, pulmonary congestion and viral replication. We believe this should be done early and aggressively to prevent *in-hospital* admissions and when *in-hospital* admission is inevitable, these agents should be used to treat the disease in lieu of the unsafe and ineffective drug, remdesivir.

We stand behind Dr. Witcher in his decision to practice medicine according to long-standing principles of science and those of moral and ethical treatment towards the patient.

Sincerely,

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Subject: Toxicological Analysis Pertaining to the Use of Remdesivir or Ivermectin for the Treatment of COVID-19 SARS COV-2 Infection and Sequelae

Dear Dr. Witcher,

This toxicological assessment was compiled in support of your wish to treat your patients with ivermectin in conjunction with other treatment modalities and to withdraw treatment with remdesivir. You have asked for a preliminary toxicological assessment and opinion(s) with regards to the use of the drugs remdesivir and ivermectin in COVID-19 patients. Specifically, this report outlines the evidence from the scientific and medical literature base with respect to the safety and efficacy of these two drugs in the standardly recommended dosages, for the treatment of SARS COV-2 infection in "***in-hospital***" as well as "***out-patient***" patient early treatment settings.

Professional Qualifications

My name is Dr. Janci Lindsay, PhD. I have spent most of my career as a research scientist, and have more than 30 years of scientific experience, primarily in the area of toxicology. I hold a doctorate in Molecular Biology & Biochemistry from the University of Texas, Graduate School of Biomedical Sciences, M.D. Anderson Cancer Center. Biochemistry is the basis of toxicology as a discipline. I am a full member of the Society of Toxicology. I have authored and co-authored multiple scientific publications and have presented my research at national and international scientific meetings. My work has included investigating exposures to chemicals, drugs, and particulates, and assessing health risks, and potential for chemical contribution to disease and impairment based upon the dose-response relationship, and the known toxicological properties of the chemicals involved. I am routinely asked to interpret and evaluate the toxicological potential of various drugs and chemicals, on the human body. I am also asked to opine on the mechanism of action of various drugs towards particular molecular pathways involved in disease. My

academic training, doctoral degree, work experience in forensic and general toxicology, pulmonology and biochemistry along with my professional affiliations and published scientific publications qualify me as an expert in molecular biology and toxicology. Appended for your information is a copy of my Curriculum Vitae (***Appendix E***). My opinions in this case are based upon the known toxicology of remdesivir and ivermectin the peer-reviewed scientific literature, my professional qualifications and work experience, and my knowledge of toxicology, pharmacokinetics, and related fields.

Background

Since the widespread emergence of the SARS-COV-2 virus in the United Sates, the only approved, authorized and administered treatments for the infection under emergency use authorization, have been the genetic Covid vaccines which only lessen severity of infection but still allow contraction and transmission, treatment with the mixture of two monoclonal antibodies to differing regions of the original viral spike protein (Regeneron), or the utilization of the repurposed HIV and Ebola drug, remdesivir (*in-hospital*).

The genetic vaccines are best described as a treatment given their limitations to prevent infection and the monoclonal antibodies have limited efficacy in treating latter stages of the disease as well as treating some of the variants, against which the antibodies are not effective.

Ivermectin is a drug which found efficacy against SARS-COV-2 early on and which has been widely used as anti-parasitic since the early 1980's, for which the Nobel Prize in Medicine was awarded. Inexplicably, ivermectin has been determined quite suddenly to be "*dangerous*" and "*ineffective*" and "*not backed by science*". I have found statements such as this to be perplexing as ivermectin has been in use globally since 1984 and has a proven record of safety and efficacy in all ages.[1,2] The WHO lists ivermectin on its essential list of medicines and a review of the uses for which ivermectin is recommended includes use in children under 5.[3] It's hard to imagine that a drug which is so "un-safe" could be routinely recommended for children in this age group. Ivermectin has been found to also be effective as a broad-acting anti-viral for which there are many studies of its use in both prophylaxis and treatment against SARS-COV-2.

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[1] Morris-Jones R. Oral ivermectin for infants and children under 15 kg appears to be a safe and effective treatment for scabies. Br J Dermatol. 2020 Apr;182(4):835-836. doi: 10.1111/bjd.18788. Epub 2019 Dec 29. PMID: 31885077.

[2] Levy M, Martin L, Bursztejn AC, Chiaverini C, Miquel J, Mahé E, Maruani A, Boralevi F; Groupe de Recherche de la Société Française de Dermatologie Pédiatrique. Ivermectin safety in infants and children under 15 kg treated for scabies: a multicentric observational study. Br J Dermatol. 2020 Apr;182(4):1003-1006. doi: 10.1111/bjd.18369. Epub 2019 Sep 29. PMID: 31344258.

[3] https://list.essentialmeds.org/medicines/58

Analysis

Toxicology of Ivermectin

Ivermectin is a semi-synthetic derivative of abamectin a member of the avermectin family of macrolide antibiotics produced by *Streptomyces avermitilis.* It has been used as an anti-helminth in both human and veterinary medicine since 1984. A single oral 12 mg dose given to 12 healthy men resulted in peak plasma ivermectin levels averaging 46 ug/L at 3.6 hours. A dose of 30 mg given to 11-12 healthy adults produced plasma levels of 85 ug/L at 4.3 hours in a fasting state and 261 ug/L at 4.6 hours in a fed state. Elimination half-lives in these two studies averaged 20 and 15 hours respectively.[4] Adverse effects experienced during ivermectin therapy include abdominal pain, nausea, vomiting, diarrhea, anorexia, fatigue, dizziness, headache skin rash, edema and lymph node enlargement. In terms of potential to overdose on this medication, a 16-month old child who ingested 7-9 mg.kg of the drug developed pallor, vomiting, tachycardia, hypotension, hypothermia, and sleepiness that resolved within 3 days. A woman who ingested 1000 mg fell into a coma followed by weakness, dizziness and agitation, but recovered over a period of 9 days. A typical dose to treat COVID is no greater than 0.6 mg/kg for 5 days and so for most persons does not exceed a 100 mg single dose.

Ivermectin Mechanisms of Action as an Anti-Viral

Ivermectin has been found to be useful as an antiviral agent for many viral infections and has been shown to inhibit the replication of West-Nile, Zika, Dengue, Influenza, and most recently SARS-CoV-2. [5,6,7,8,9,10,11,12] Ivermectin has been shown *in-vitro* to inhibit the replication of many viruses including those in Flaviviridae, Circoviridae and Coronaviridae families. Cell culture experiments have shown robust antiviral action towards HIV-1, dengue, Zika and West Nile Virus, Venezuelan

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[4] *Ivermectin* Disposition of Toxic Drugs and Chemicals in Man. Randall C. Baselt. 9th Ed.

[5] Atkinson SC, Audsley MD, Lieu KG, et al. Recognition by host nuclear transport proteins drives disorder-to-order transition in Hendra virus V. *Sci Rep*. 2018;8(1):358. Published 2018 Jan 10. doi:10.1038/s41598-017-18742-8.

[6] Yang, S. N. , Atkinson, S. C. , Wang, C. , Lee, A. , Bogoyevitch, M. A. , Borg, N. A. & Jans, D. A. (2020). Antiviral Research, 177 , 104760. doi: 10.1016/j.antiviral.2020.104760.

[7] Lv, C. , Liu, W. , Wang, B. , Dang, R. , Qiu, L. , Ren, J. , Yan, C. , Yang, Z. & Wang, X. (2018). Antiviral Research, 159 , 55-62. doi: 10.1016/j.antiviral.2018.09.010.

[8] Mastrangelo, E. , Pezzullo, M. , De Burghgraeve, T. , Kaptein, S. , Pastorino, B. , Dallmeier, K. , de Lamballerie, X. , Neyts, J. , Hanson, A. M. , Frick, D. N. , Bolognesi, M. & Milani, M. (2012). Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity. Journal of Antimicrobial Chemotherapy, 67 (8), 1884-1894. doi: 10.1093/jac/dks147.

[9] Tay, M. Y. , Fraser, J. E. , Chan, W. K. , Moreland, N. J. , Rathore, A. P. , Wang, C. , Vasudevan, S. G. & Jans, D. A. (2013). Antiviral Research, 99 (3), 301-306. doi: 10.1016/j.antiviral.2013.06.002.

[10] King CR, Tessier TM, Dodge MJ, Weinberg JB, Mymryk JS. Inhibition of Human Adenovirus Replication by the Importin α/β1 Nuclear Import Inhibitor Ivermectin. J Virol. 2020 Aug 31;94(18):e00710-20. doi: 10.1128/JVI.00710-20. PMID: 32641484; PMCID: PMC7459547.

[11] Jans DA, Wagstaff KM. The broad spectrum host-directed agent ivermectin as an antiviral for SARS-CoV-2 ?. *Biochem Biophys Res Commun*. 2021;538:163-172. doi:10.1016/j.bbrc.2020.10.042

[12] Rakedzon S, Neuberger A, Domb AJ, Petersiel N, Schwartz E. From hydroxychloroquine to ivermectin: what are the anti-viral properties of anti-parasitic drugs to combat SARS-CoV-2? J Travel Med. 2021 Feb 23;28(2):taab005. doi: 10.1093/jtm/taab005. PMID: 33480414; PMCID: PMC7928734.

equine encephalitis virus, Chikungunya, pseudorabies virus, adenovirus, and SARS-CoV-2 (COVID-19). Ivermectin works in multiple ways as an antiviral in SARS COV-2 infection, blocking the binding of the spike protein to the ACE-2 receptor, preventing replication through the importin α/β1 nuclear import inhibitor and dampening NS3 helicase activity as well as preventing the nuclear translocation of viral proteins.[13]

Controlled Clinical Trials Using Ivermectin

Ivermectin has been tested for its efficacy against SARS-COV-2 in 69 controlled clinical trials with 49,914 patients, 31 of these trials were randomized control trials. Ivermectin has shown an 85% improvement in 15 prophylaxis trials, a 66% improvement in 29 early treatment trials, a 37% improvement in 25 late treatment trials and a 56% improvement in 30 mortality studies.[14] Seven meta-analyses of the clinical trial data on ivermectin reported a total of 31 deaths amongst 1101 subjects in ivermectin treatment groups and 91 deaths amongst 1064 control subjects from eleven randomized clinical trials, which resulted in a 67% reduction in mortality. In the RCT that used the highest dose of ivermectin at 400 ug/kg on days 1-4, there were 2 versus 24 deaths in the treatment group versus the control group.[15] A meta-analysis of 15 trials found that ivermectin reduced the risk of death compared with no ivermectin and ivermectin prophylaxis reduced the Covid infection by 86%.[16] A meta-analysis of 69 studies using the most serious outcome reported shows 66% [53-76%] and 85% [75-91%] improvement for early treatment and prophylaxis. A table outlining these studies can be found in **Appendix A**

Epidemiological Evidence Utilizing Ivermectin

The Indian state of Uttar Pradesh with a population of 241 million persons has effectively eradicated COVID via the widespread use of ivermectin in both prevention and early treatment.[17]

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[13] Kinobe RT, Owens L. A systematic review of experimental evidence for antiviral effects of ivermectin and an in silico analysis of ivermectin's possible mode of action against SARS-CoV-2. Fundam Clin Pharmacol. 2021 Apr;35(2):260-276. doi: 10.1111/fcp.12644. Epub 2021 Jan 28. PMID: 33427370; PMCID: PMC8013482.

[14] www.C19ivermectin.com

[15] Santin AD, Scheim DE, McCullough PA, Yagisawa M, Borody TJ. Ivermectin: a multifaceted drug of Nobel prize-honoured distinction with indicated efficacy against a new global scourge, COVID-19. New Microbes New Infect. 2021 Aug 3;43:100924. doi: 10.1016/j.nmni.2021.100924. PMID: 34466270; PMCID: PMC8383101.

[16] Bryant A, Lawrie TA, Dowswell T, Fordham EJ, Mitchell S, Hill SR, Tham TC. Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines. Am J Ther. 2021 Jun 21;28(4):e434-e460. doi: 10.1097/MJT.0000000000001402. PMID: 34145166; PMCID: PMC8248252.

[17] https://www.thegatewaypundit.com/2021/09/huge-uttar-pradesh-india-announces-state-covid-19-free-proving-effectiveness-deworming-drug
ivermectin/?utm_source=Twitter&utm_medium=PostTopSharingButtons&utm_campaign=websitesharingbuttons

In Peru, the government approved ivermectin use in May of 2020, and death rates in 8 states were reduced by 64% and 91% over a two month period.[18] Peruvian provinces that used ivermectin had lower COVID-19 case fatality rates that regions which did not use ivermectin.[19] In Mexico City, they reduced the number of hospitalizations by 75% with a test and treat protocol.[20] In Argentina they showed significant reductions in mortality in Misiones and La Pampas with ivermectin use.[21]

The following are summary points that were taken directly from the FLCCC Alliance white paper on the "Summary of the Evidence for Ivermectin in Covid-19".[22] The white paper with searchable reference links is attached as **Appendix B**.

- "Mexico City – The IMSSS Health Agency compared over 50,000 patients treated early with ivermectin to over 70,000 not treated and found up to a 75% reduction in need for hospitalization.

- Peru – A nationwide mass-distribution program called "Mega-Operación Tayta" (MOT), initiated at various times across 25 states of Peru in May 2020, led to a 74% drop in regional excess deaths within a month, with each drop beginning 11 days after each MOT region's varied start times.

- La Pampas, Argentina – Health Ministry compared over 2,000 patients they treated early with ivermectin to over 12,000 without treatment and found a 40% reduction in hospitalization and 35% less ICU or death in older patients

- La Misiones, Argentina – Health Ministry just analyzed the first 800 of 4,000 ivermectin treated patients and compared to the rest of the population over the same time period, they found a 75% reduction in need for hospital and an 88% reduction in death.

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[18] http://www.pagina16.com.ar/ivermectina-brindan-resultados-parciales-de-monitoreo-en-el-uso-ampliado-en-pacientes-positivos/

[19] Chamie-Quintero, Juan and Hibberd, Jennifer and Scheim, David, Sharp Reductions in COVID-19 Case Fatalities and Excess Deaths in Peru in Close Time Conjunction, State-By-State, with Ivermectin Treatments (January 12, 2021). Available at SSRN: https://ssrn.com/abstract=3765018 or http://dx.doi.org/10.2139/ssrn.3765018

[20] Merino, J., Borja, V. H., Lopez, O., Ochoa, J. A., Clark, E., Petersen, L., & Caballero, S. (2021, May 4). Ivermectin and the odds of hospitalization due to COVID-19: evidence from a quasi-experimental analysis based on a public intervention in Mexico City. https://doi.org/10.31235/osf.io/r93g4

[21] http://www.pagina16.com.ar/ivermectina-brindan-resultados-parciales-de-monitoreo-en-el-uso-ampliado-en-pacientes-positivos/

[22] www.FLCCC.net

- Uttar Pradesh, India – Used a strategy of close surveillance combined with both ivermectin treatment of all positive cases and preventive treatment of all family contacts. On September 10, 2021, only 11 cases with no deaths were recorded in a population of 241 million. As of August 31, of the previous 187,638 tests performed, only 21 were positive, an essentially zero positive rate or .01%."

National Institutes of Health (NIH) COVID-19 Treatment Guidelines

The National Institutes of Health actually recommends Ivermectin. On the NIH website, *Table 2e. Characteristics of Antiviral Agents That Are Approved or Under Evaluation for the Treatment of COVID-19 (Last Updated: July 8, 2021)* lists 3 treatments for COVID-19. The first listed is Remdesivir, second is Ivermectin, and third is Nitazoxanide.[21] With Ivermectin as one of the three treatments recommended by the NIH, there should be no question as to why a provider has prescribed the treatment. Each patient's family and personal health history, comorbidities, and response to medication is different, so physician's must use their knowledge and clinical judgement in prescribing, monitoring, and terminating treatment.

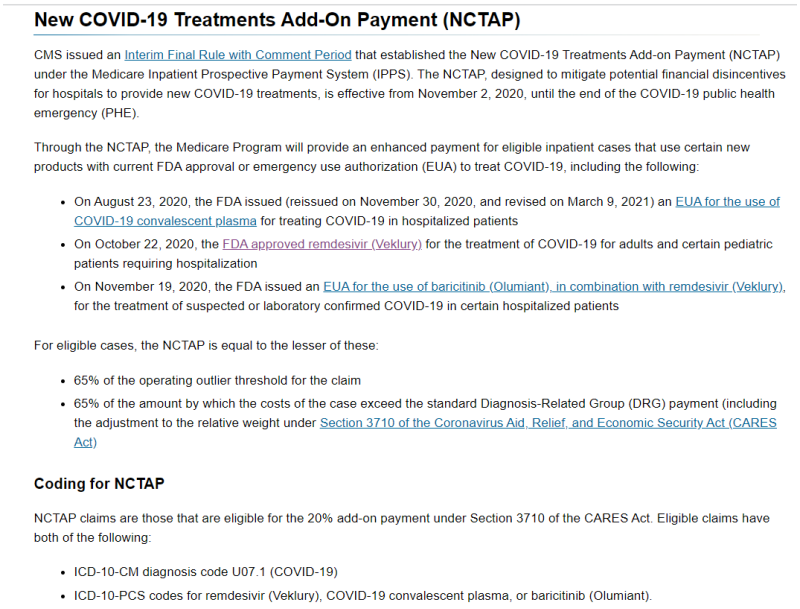
The NIH table 2e, **Appendix D,** also recommends monitoring parameters while the patient is on treatment. For Remdesivir they include:

- *Infusion reactions*
- *Renal function and hepatic function should be monitored before and during treatment as clinically indicated.*
- *In the FDA product information, RDV **is not recommended** when eGFR is <30 mL/min. See the Remdesivir section for a discussion on using RDV in people with renal insufficiency.*
- *RDV may need to be discontinued if ALT level increases to >10 times ULN and should be discontinued if there is an increase in ALT level and signs or symptoms of liver inflammation are observed.* For Ivermectin they include: *Monitor for potential AEs.*

Hospitals are Being Paid Differentially to Prescribe Remdesivir over Ivermectin: CMS' New COVID-19 Treatments Add-on Payment

CMS established the New COVID-19 Treatments Add-on Payment (NCTAP) until the end of the COVID-19 public health emergency.[23] Under this program (text below), CMS will provide, "an enhanced payment for eligible inpatient cases that use certain new products with current FDA approval or emergency use authorization (EUA) to treat COVID-19)." This only includes Convalescent Plasma, Remdesivir, and Baricitinib with Remdesivir. So, hospitals received an addition 20% add-on payment when they use the ICD codes for COVID19 and Remdesivir to the exclusion of the Ivermectin and Nitazoxanide, which are also on the recommended NIH list.

[23] https://www.cms.gov/medicare/covid-19/new-covid-19-treatments-add-payment-nctap [Accessed 12/8/21]



New COVID-19 Treatments Add-On Payment (NCTAP)

CMS issued an Interim Final Rule with Comment Period that established the New COVID-19 Treatments Add-on Payment (NCTAP) under the Medicare Inpatient Prospective Payment System (IPPS). The NCTAP, designed to mitigate potential financial disincentives for hospitals to provide new COVID-19 treatments, is effective from November 2, 2020, until the end of the COVID-19 public health emergency (PHE).

Through the NCTAP, the Medicare Program will provide an enhanced payment for eligible inpatient cases that use certain new products with current FDA approval or emergency use authorization (EUA) to treat COVID-19, including the following:

- On August 23, 2020, the FDA issued (reissued on November 30, 2020, and revised on March 9, 2021) an EUA for the use of COVID-19 convalescent plasma for treating COVID-19 in hospitalized patients
- On October 22, 2020, the FDA approved remdesivir (Veklury) for the treatment of COVID-19 for adults and certain pediatric patients requiring hospitalization
- On November 19, 2020, the FDA issued an EUA for the use of baricitinib (Olumiant), in combination with remdesivir (Veklury), for the treatment of suspected or laboratory confirmed COVID-19 in certain hospitalized patients

For eligible cases, the NCTAP is equal to the lesser of these:

- 65% of the operating outlier threshold for the claim
- 65% of the amount by which the costs of the case exceed the standard Diagnosis-Related Group (DRG) payment (including the adjustment to the relative weight under Section 3710 of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act)

Coding for NCTAP

NCTAP claims are those that are eligible for the 20% add-on payment under Section 3710 of the CARES Act. Eligible claims have both of the following:

- ICD-10-CM diagnosis code U07.1 (COVID-19)
- ICD-10-PCS codes for remdesivir (Veklury), COVID-19 convalescent plasma, or baricitinib (Olumiant).

AAPS Drafts Letter to AMA Questioning the Rationale of Banning Ivermectin use for Covid

The Association of American Physicians and Surgeons has recently drafted a letter to the American Medical Association in September of 2021 querying as to why the AMA has told physicians to stop prescribing and pharmacies to quit dispensing ivermectin for Covid treatment.[24] They relay that this is unprecedented given ivermectin' s successful record above other treatments in 63 clinical trials, the fact that it is recommended for use in other countries such as Japan and that is has been safely prescribed since 1981 with billions of doses written, globally and 88,000 prescriptions per week being written in the US.

Toxicology of Remdesivir

Remdesivir is an adenosine-like nucleotide analogue RNA polymerase inhibitor and on May 1, 2020 received emergency use authorization (EUA) for SARS-COV-2 coronavirus disease (COVID-19). Remdesivir displays linear pharmacokinetics and a prolonged intracellular half-life (>35 hours for the active parent triphosphate). The recommended dosage is 200 mg IV on the first day, followed by 100 mg intravenously once daily. 5–10 days total, depending on disease severity and ventilation.[23,24] Data regarding volume distribution and clearance is not available. It has an elimination half-life of one hour following a single 30 IV infusion. There is no data on overdoses of Remdesivir.[25] Adverse events include hypersensitivity including anaphylactic reaction, transaminase elevations, nausea, increased ALT and AST, decreased creatinine clearance, increased creatinine, decreased eGFR. increased glucose, decreased hemoglobin, decreased lymphocytes, and increased prothrombin time. Drug-drug interaction (DDI) information is limited and not well understood.[26,27]

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[24] https://aapsonline.org/aaps-letter-to-ama-re-ivermectin-and-covid/
[25] https://pubchem.ncbi.nlm.nih.gov/compound/Remdesivir#section=Absorption-Distribution-and-Excretion
[26] https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf

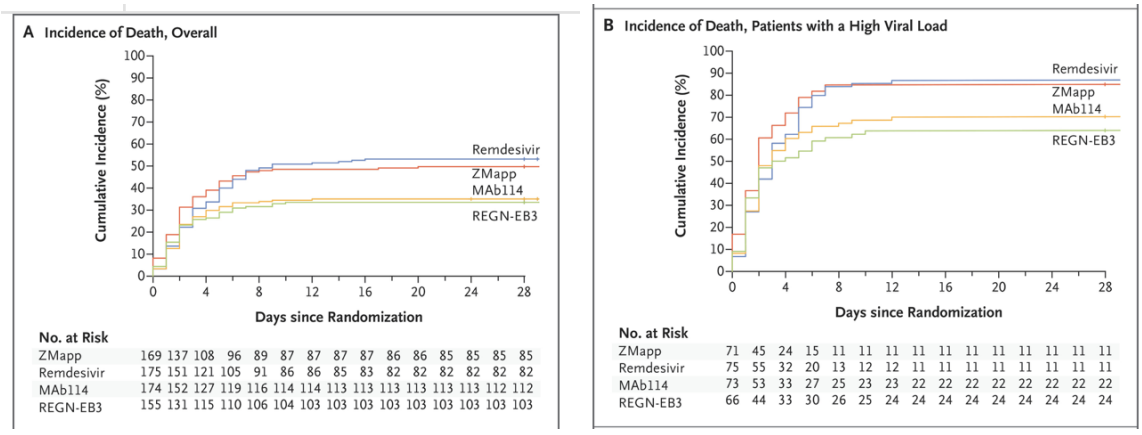
Remdesivir's Utility as an Anti-viral is Limited to a Single Mechanism of Action

Remdesivir is described is an antiviral medication that "*acts to inhibit the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication—and thus creation of virions that circulate in the body*" by the manufacturer.[27] Remdesivir's *in-vitro* antiviral activity has been demonstrated against members of the Filoviridae, Paramyxoviridae, Pneumoviridae, and Coronaviridae and also has activity against SARS-like and MERS-like bat coronaviruses.[30]

Remdesivir did not Meet Early Safety and Efficacy Endpoints in the Treatment of Ebola

Remdesivir was initially developed for the treatment of Ebola virus (EBOV), but it did not meet efficacy endpoints nor reduce mortality in a randomized control trial that was conducted during the Ebola outbreaking Africa as shown in **Figures A-C.** Over 53% (93/175) of those treated with Remdesivir died, compared to 49% for the triple monoclonal antibody ZMapp (the control), 35% for single monoclonal antibody MAb114, and 33% for triple monoclonal antibody REGN-EB3.[28] **Assignment to treatment with remdesivir and Z-Mapp was also terminated partway through the study as there was a clear excess mortality safety signal for remdesivir and Z-Mapp as opposed to the other treatments.**

Figures A, B



[27] https://www.vekluryhcp.com/about/about-moa.php

[28] Mulangu S et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N Engl J Med*. 2019 Dec 12;381(24):2293-2303. doi: 10.1056/NEJMoa1910993. Epub 2019 Nov 27. PMID: 31774950.

[29] Deb S, Reeves AA, Hopefl R, Bejusca R. ADME and Pharmacokinetic Properties of Remdesivir: Its Drug Interaction Potential. *Pharmaceuticals (Basel)*. 2021;14(7):655. Published 2021 Jul 8. doi:10.3390/ph14070655

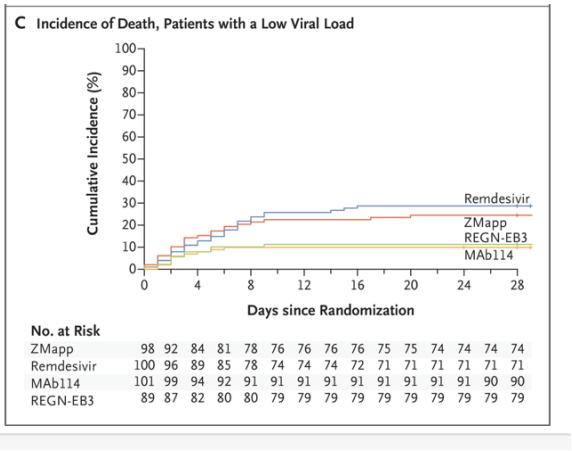


Figure C.

Preclinical Assumptions and Evaluations May have been Overestimated for Remdesivir

A review came out by Yan et al. in 2021 which proposed that the data for remdesivir's safety and efficacy was overestimated based on *in-vitro* and *in-vivo* studies in model systems that were not appropriate for comparison. They proposed that cell culture protocols should have been revised to better reflect the prodrug's pharmacokinetics and species differences in drug metabolism should have been considered based on what they observed in terms of the drug's lack of clinical efficacy in humans.[29]

Wang *et al.* conducted a randomized, double-blind, placebo-controlled, multi-center study of 237 patients between February 6-March 12, 2020, in China.[30] This study was the primary study relied upon to grant the EAU for the drug to be used preferentially in the treatment of COVID-19. In the study, patients were enrolled and randomly assigned to a treatment group (158 to remdesivir and 79 to placebo). Remdesivir use was not associated overall with a difference in time to clinical improvement. The study found a non-statistically significant faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less. Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) of the 158 remdesivir patients versus four placebo (5%). Overall, remdesivir was not associated with statistically significant clinical benefits against COVID-19 in their study and a majority of the remdesivir patients suffered adverse effects that were greater than those in the placebo group. The authors also noted that remdesivir did not result in significant reductions in SARS-CoV-2 RNA loads or detectability in upper respiratory tract or sputum specimens, despite showing strong antiviral effects in preclinical models of infection with coronaviruses. Additionally, the authors also noted that there were limitations of their study which included sufficient power to detect assumed differences in clinical

[30] Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial [published correction appears in Lancet. 2020 May 30;395(10238):1694]. *Lancet*. 2020;395(10236):1569-1578. doi:10.1016/S0140-6736(20)31022-9

outcomes and the initiation of remdesivir treatment quite late in COVID-19. There was also no data on infectious virus recovery or on possible emergence of reduced susceptibility to remdesivir in viral isolates from these patients.

Yan and group found that remdesivir was not associated with statistically significant clinical benefits. The authors noted that several subsequent clinical trials resulted similarly such as the Wang study. In an analysis of the preclinical work on remdesivir, the authors summarize:

"*For both COVID-19 and Ebola, significant discordance between the robust preclinical data and remdesivir's lackluster clinical performance have left many puzzled. Here, we critically evaluate the assumptions of the models underlying remdesivir's promising preclinical data and show that such assumptions overpredict efficacy and minimize toxicity of remdesivir in humans. Had the limitations of in vitro drug efficacy testing and species differences in drug metabolism been considered, the underwhelming clinical performance of remdesivir for both COVID-19 and Ebola would have been fully anticipated."*[31]

Remdesivir Emergency Use Approval was Based on only a Single Completed Study

The number of studies used to base approval of currently accepted drugs for use in the Covid-19 pandemic are listed below. As can be seen, Remdesivir was approved based upon a single study (Table 1).

Table 1.

Evidence base used for other COVID-19 approvals			
Medication	Studies	Patients	Improvement
Molnupiravir (UK)	1	775	50%
Budesonide (UK)	1	1,779	17%
Remdesivir (USA EUA)	1	1,063	31%
Casirivimab/i.. (USA EUA)	1	799	66%
Ivermectin evidence	69	49,914	66% [58-73%]

On May 1, 2020, Remdesivir was given an Emergency Use Authorization (EUA) by the FDA

[31] Yan VC, Muller FL. Why Remdesivir Failed: Preclinical Assumptions Overestimate the Clinical Efficacy of Remdesivir for COVID-19 and Ebola. *Antimicrob Agents Chemother*. 2021;65(10):e0111721. doi:10.1128/AAC.01117-21

citing just 2 studies, 1 of which was not completed at the time the EAU was granted[32]:

"Results are available from two randomized, double-blind, placebo-controlled trials that are discussed below. Patient-level data have not been submitted or reviewed for either trial.

- *An analysis report is available from a large definitive trial sponsored by the National Institute of Allergy and Infectious Disease (clinicaltrials.gov identifier NCT04280705).*

- *A published article [Wang et al., 2020, The Lancet, https://doi.org/10.1016/S0140 6736(20)31022-9] is available for a smaller trial conducted in China in patients hospitalized with severe COVID-19 (clinicaltrials.gov identifier NCT04257656)."*

The first NIAID study was not completed at the time of issuance of the EUA for remdesivir. The seconf study, the Wang et al study, found the following: In a study of 237 patients whom were treated between Feb 6, 2020, and March 12, 2020, patients were enrolled and randomly assigned to a treatment group (158 to remdesivir and 79 to placebo); one patient in the placebo group withdrew and was not included. The results showed that remdesivir use was not associated with a significantly significant difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo if they started treatment before 10 days of symptoms (hazard ratio 1·52 [0·95–2·43]). Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early.
In this study, adverse events were reported in 102 (66%) of the 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. The final interpretation of this study was that adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits.

The first study conducted by the NIAID according to clinicaltrials.gov completed on May 21, 2020, **so the EUA was issued before the study was completed**. And the second study listed conducted in China was the study referenced above that demonstrated **no clinical benefit.** The clear question is then: How was this drug given preference over ivermectin or hydroxychloroquine, both of which had far more data supporting their safe and effective use towards the treatment of COVID-19?

The EUA further states:

> *Top line results are also available from a Gilead-sponsored trial that compared 5-day and 10-day remdesivir durations in patients with severe COVID-19 (clinicaltrials.gov identifier NCT04292899).*

[32] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/EUA%20Review%20Remdesivir_050120.pdf

However, this Gilead study did not conclude until June 30, 2020 according to clinicaltrials.gov.

According to the reissuance of the EUA on October 16, 2020, the authorization was based on *review of the data from the randomized, double-blinded, placebo-controlled trial conducted by NIAID (NCT04280705), from the Gilead-sponsored open-label trial that evaluated different durations of Veklury (NCT04292899), and from the Gilead-sponsored open-label trial that evaluated different durations of Veklury as compared to standard of care (NCT04292730).* [33]

In the randomized, double-blinded, placebo-controlled trial conducted by NIAID (NCT04280705), a total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo). The study group concluded that the data demonstrated that:

"remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection."[33]

The Gilead-sponsored open-label trial that evaluated different durations of Veklury (remdesivir) (NCT04292899), had a total n of 397 who were randomized (200 patients receiving remdesivir for 5 days and 197 patients for 10 days). They concluded:

"In patients with severe Covid-19 not requiring mechanical ventilation, our trial did not show a significant difference between a 5-day course and a 10-day course of remdesivir. With no placebo control, <u>however, the magnitude of benefit cannot be determined</u>."[35]

In the third study mentioned, the Gilead-sponsored open-label trial that evaluated different durations of Veklury as compared to standard of care (NCT04292730), randomized patients in a 1:1:1 ratio to receive a 10-day course of remdesivir (n = 197), a 5-day course of remdesivir (n = 199), or standard care (n = 200), for a total n of 596. This was the first study to evaluate moderate COVID-19. The authors concluded:

"***Among patients with moderate COVID-19, those randomized to a 10-day course of remdesivir <u>did not have a statistically significant difference in clinical status compared with standard care</u> at 11 days after initiation of treatment. Patients randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard care, <u>but the difference was of uncertain clinical importance</u>."***[35]

In that updated EUA in October, it was foot noted that the, "*Prior to the reissuance of the EUA on August 28, 2020* [which expanded the EUA of the drug by not limiting its use to just patients with severe disease] *and pursuant to the conditions of authorization, Gilead had requested, and FDA*

[33] https://www.fda.gov/media/143188/download [Accessed 12/8/21]
[34]Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764
[35] https://www.fda.gov/media/143188/download [Accessed 12/8/21]

had concurred with, other changes to the Fact Sheets, including but not limited to: (1) clarified dosing and administration recommendations; (2) added sponsor's recommended formula to be used in calculating eGFR (this formula was removed in the August 28, 2020, reissuance)…" [36] It is to notable that assessing kidney functioning was taken out but then later added back in and dosing recommendation were made on the above summarized studies.[32]

Remdesivir Causes Kidney and Liver Toxicity

In clinical trials and case studies, acute kidney injury (AKI), including renal replacement, has been frequently reported with remdesivir use. A pharmacovigilance retrospective study which was conducted in April of 2021, **"Remdesivir and Acute Renal Failure: A Potential Safety Signal From Disproportionality Analysis of the WHO Safety Database",** found a statistically significant safety signal related to "acute renal failure" and "remdesivir" with 138 observed cases instead of the 9 expected. These authors reported that the odds ratio of acute renal failure from remdesivir use was 20-fold what was expected.[37]

A second pharmacovigilance study of reports registered from January 1st through August 30, 2020 in the World Health Organization's VigiBase reported that 5,532 were from patients with COVID-19. Of those 5,532 reports regarding COVID-19, 434 cases were related to kidney disorders, including 327 who had been treated with remdesivir. In the overwhelming majority of cases (316 [96.6%]), no other drug was suspected in the onset of kidney disorders. Reactions were serious in 301 (92.0%) cases, with a fatal outcome for 15 (4.6%) patients; acute kidney injury (AKI) comprised 295 cases. Compared with the use of chloroquine, hydroxychloroquine, dexamethasone, sarilumab, or tocilizumab, the use of remdesivir was associated with an increased reporting of kidney disorders (reporting odds ratio, 7.2; 95% confidence interval, 5.7–9.0). This analysis indicates that kidney disorders, primarily AKI, represent a serious, early, and potentially fatal adverse drug reaction of remdesivir.[38] The prescribing guide for remdesivir (Veklury) also warns of liver toxicity and recommends monitoring liver enzyme levels throughout treatment and before initiating treatment.[39] The vehicle for remdesivir, the oligosaccharide SBECD, is also associated with renal and liver toxicity causing obstruction of renal tubules and frank hepatic cellular necrosis in animal studies.

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[36] Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324(11):1048-1057. doi:10.1001/jama.2020.16349

[37] Gérard AO, Laurain A, Fresse A, Parassol N, Muzzone M, Rocher F, Esnault VLM, Drici MD. Remdesivir and Acute Renal Failure: A Potential Safety Signal From Disproportionality Analysis of the WHO Safety Database. Clin Pharmacol Ther. 2021 Apr;109(4):1021-1024. doi: 10.1002/cpt.2145. Epub 2021 Jan 16. PMID: 33340409

[38] Chouchana L, Preta LH, Tisseyre M, Terrier B, Treluyer JM, Montastruc F. Kidney disorders as serious adverse drug reactions of remdesivir in coronavirus disease 2019: a retrospective case-noncase study. *Kidney Int*. 2021;99(5):1235-1236. doi:10.1016/j.kint.2021.02.015

[39] https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf

Remdesivir can Cause Reproductive Injury in Animal Test Models and human Data Towards this and Cancer Endpoints are Lacking

The prescribing guide for Veklury (remdesivir) warns that ***"the available data from published case reports and compassionate use of remdesivir in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes."*** Further the prescribing guide notes that animal studies have demonstrated that the drug causes reproductive toxicity as follows: ***"Reproductive toxicity, including decreases in corpora lutea, numbers of implantation sites, and viable embryos, was seen when remdesivir was administered by daily intravenous administration at a systemically toxic dose (10 mg/kg) in female rats 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD"*** The safety and efficacy of the drug has also not been tested in breastfeeding women or in children under 12. No carcinogenicity studies have been done on the drug.

Subsequent Studies on Remdesivir

Randomized clinical trials have reported conflicting results and conclusions about the effects of remdesivir therapy on mortality and length of hospital stay among people with COVID-19. So, researchers conducted a retrospective cohort study using data from the Veterans Health Administration (VHA) in 123 VHA hospitals who had a first hospitalization with laboratory-confirmed COVID-19. After propensity score matching, the analysis included 1172 patients who received remdesivir and matched controls on age, sex, dexamethasone use, admission to ICU, and mechanical ventilation. Remdesivir recipients had a longer median time to hospital discharge compared with matched controls. The findings suggest that routine use of remdesivir is associated with longer median time to hospital discharge compared with matched controls and did not improve in survival rate.[40]

In a retrospective multicenter study, medical records of 3372 patients discharged between 1 March 2020 and 30 March 2021 were reviewed. Patients had laboratory confirmed COVID-19 in the Mount Sinai Health System and were treated with steroids. Of the 3372 eligible patients, 1336 (39.6%) received remdesivir. After 1:1 propensity score matching (N = 999 pairs), in-hospital mortality was similar between those with and without remdesivir (21.4% versus 21.6%, respectively, P = 0.96). Remdesivir was not significantly associated with in-hospital mortality regardless of endotracheal intubation or COVID-19 antibody status.[41]

Methodological and analytical issues exists in many of the Remdesivir studies, but a full analyses

[40] Ohl ME, Miller DR, Lund BC, et al. Association of Remdesivir Treatment With Survival and Length of Hospital Stay Among US Veterans Hospitalized With COVID-19. *JAMA Netw Open.* 2021;4(7):e2114741. doi:10.1001/jamanetworkopen.2021.14741

[41] Kuno T, Miyamoto Y, Iwagami M, Ishimaru M, Takahashi M, Egorova NN. The association of remdesivir and in-hospital outcomes for COVID-19 patients treated with steroids. *J Antimicrob Chemother*. 2021;76(10):2690-2696. doi:10.1093/jac/dkab256

of all studies and results can be found in **Appendix C.** In the seven randomized control trials conducted on remsidivir in patients with COVID-19, the total improvement with remdsivir overall was only 8% over controls. In the 18 peer-reviewed studies, improvement was only 13% over controls. In the three COVID-19 studies on hospital results, the control group's improvement was 36% greater than remdesivir. And the one viral clearance studies demosntrated 0% effect.[42]

The WHO Recommends Against the Use of Remdesivir for Covid-19

Even the World Health Organization recommended against the use of Remdesivir (WHO).

"The WHO has issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of disease severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients. This recommendation, released on 20 November, is part of a living guideline on clinical care for COVID-19. It was developed by an international guideline development group, which includes 28 clinical care experts, 4 patient-partners and one ethicist.

The guidelines were developed in collaboration with the non-profit Magic Evidence Ecosystem Foundation (MAGIC), which provided methodologic support. The guidelines are an innovation, matching scientific standards with the speed required to respond to an ongoing pandemic. Work on this began on 15 October when the WHO Solidarity Trial published its interim results. Data reviewed by the panel included results from this trial, as well as 3 other randomized controlled trials. In all, data from over 7000 patients across the 4 trials were considered.

The evidence suggested no important effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient-important outcomes. The guideline development group recognized that more research is needed, especially to provide higher certainty of evidence for specific groups of patients. They supported continued enrollment in trials evaluating remdesivir.

Updated 20 November 2020

** "A conditional recommendation is issued when the evidence around the benefits and risks of an intervention are less certain. In this case, there is a conditional recommendation against the use of remdesivir.* ***This means that there isn't enough evidence to support its use."*** [43,44]

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[42] www.c19rmd.com/

[43] https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19patients#:~:text=WHO%20has%20issued%20a%20conditional%20recommendation%20against%20the,a%20living%20guideline%20on%20clinical%20care%20for%20COVID-19.

[44] A living WHO guideline on drugs for covid-19.BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m3379. BMJ 2020;370:m3379

Conclusions

After reviewing the case evidence provided to us, we offer the following opinions and conclusions to a reasonable degree of toxicological and scientific certainty:

1. There is a large scientific and medical literature base supporting that ivermectin is effective towards the prophylaxis and treatment of SARS-COV-2 with 69 controlled clinical trials with 49,914 patients, 31 of these trials were randomized control trials. Ivermectin has shown an 85% improvement in 15 prophylaxis trials, a 66% improvement in 29 early treatment trials, a 37% improvement in 25 late treatment trials and a 56% improvement in 30 mortality studies.

2. There is a large scientific and medical literature base supporting that ivermectin is effective towards the treatment of *in-hospital* patients infected with SARS-COV-2 and even the NIH lists it as one of the three therapies for use against SARS-COV-2. Therefore, there is no rationale to use other drugs like remdesivir where the efficacy profile is poor and the safety profile is poor to uncertain.

3. Remdesivir was granted emergency approval for the treatment of SARS-COV-2 based upon a single completed study. The overwhelming majority of the scientific literature base supports that remdesivir is ineffective for the treatment of SARS-COV-2 viral infection and even the WHO advises ***against*** using the drug in these patients. Therefore the rationale for the continued use of remdesivir, rather than other more effective treatments, such as ivermectin, is not supported.

4. Remdesivir formulations can have toxic effects on the kidneys and the liver which are observed at standard treatment doses. This would exclude its safe use in COVID-19 as these impacts could further compromise pulmonary function already impacted by the respiratory viral disease.

5. Financial incentives towards providing certain standards of medical care that are not supported by the scientific and medical literature base, above others that are, are not morally or ethically acceptable practices within medicine for self-obvious reasons.

Janci Chunn Lindsay, Ph.D.
Director of Toxicology and Molecular Biology
Toxicology Support Services, LLC.

Appendix A
Ivermectin Covid-19 Studies

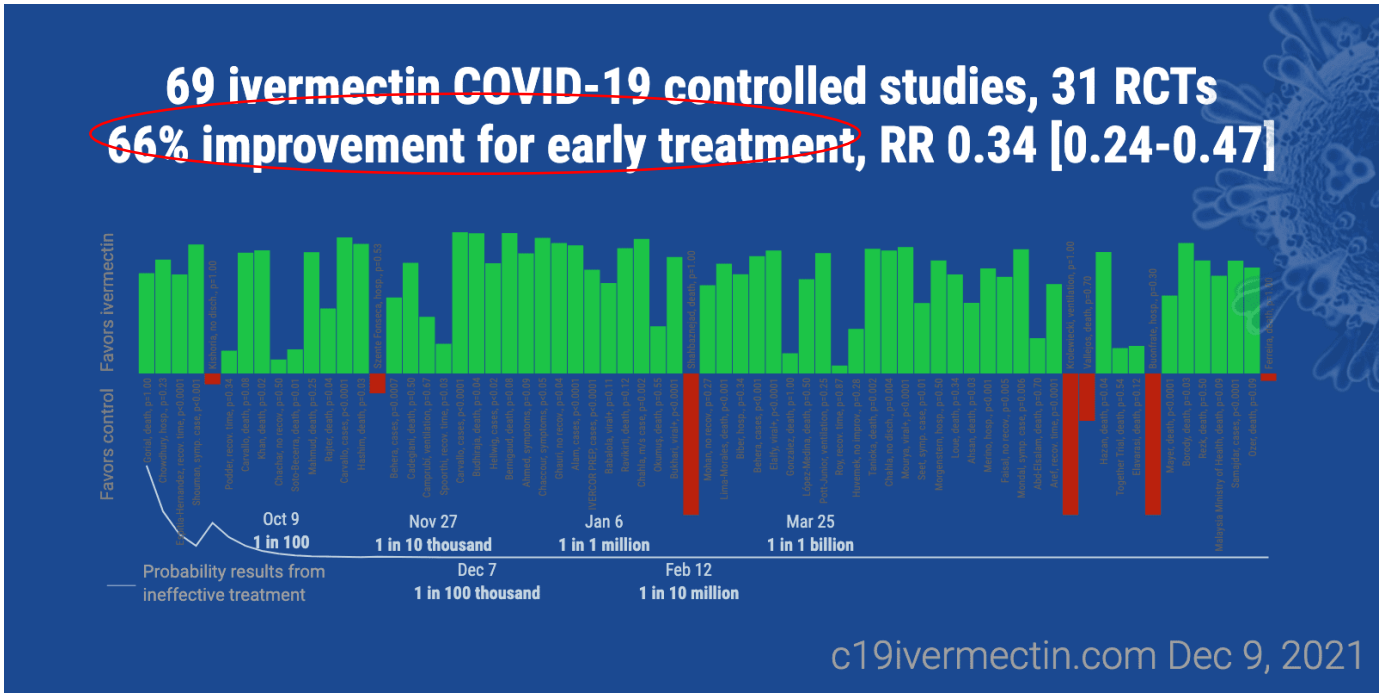
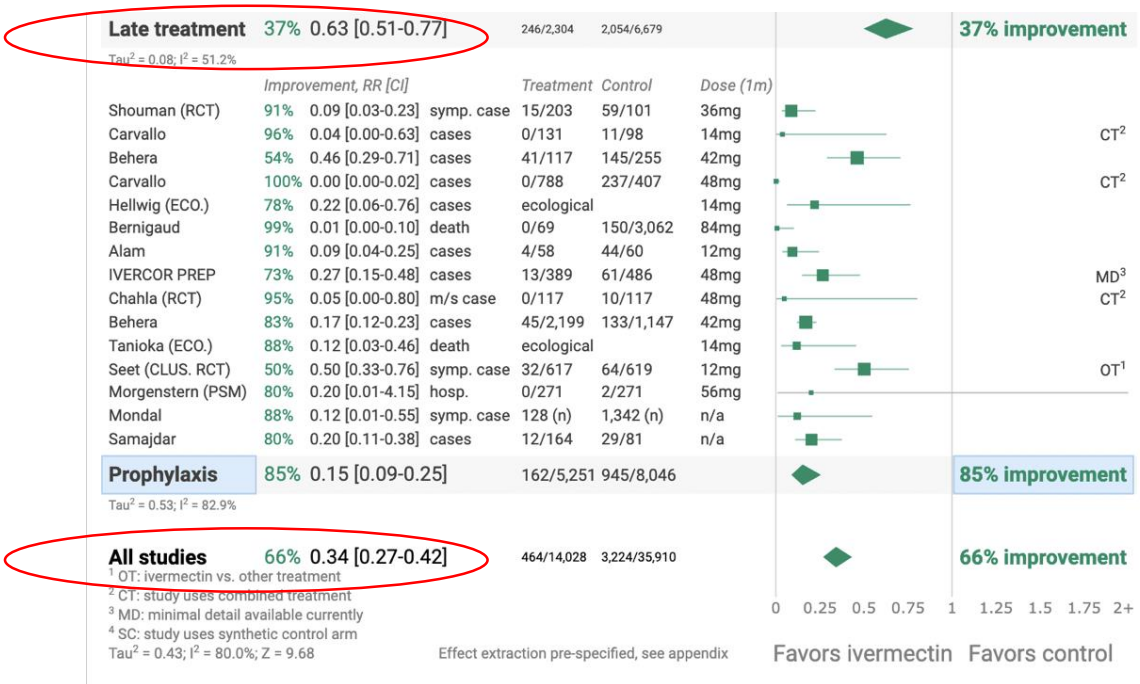


Figure A



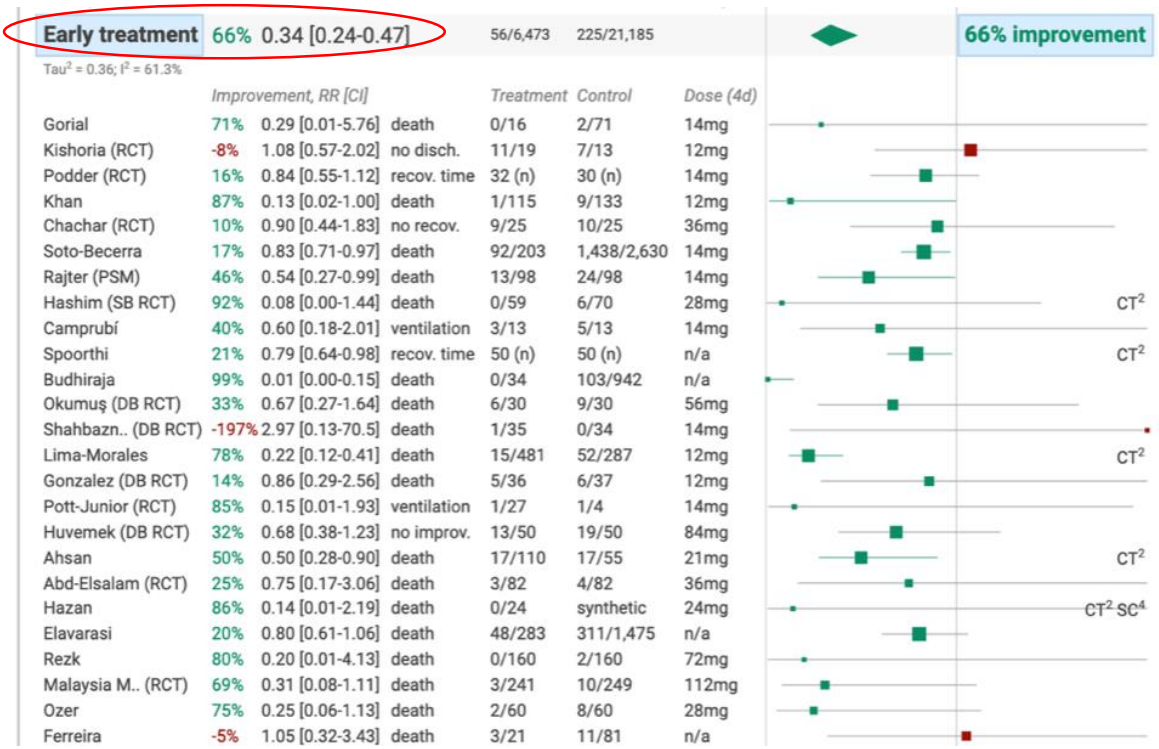
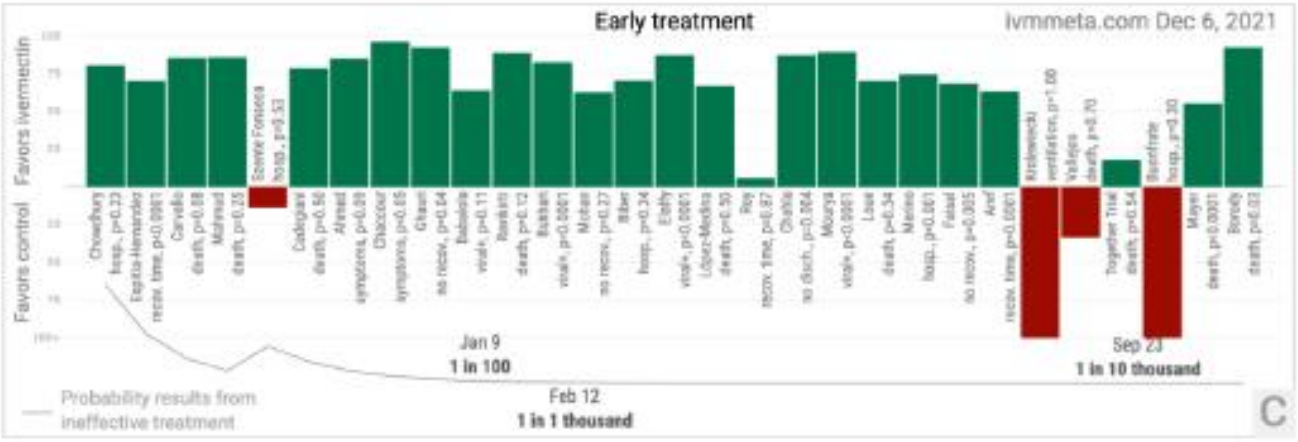
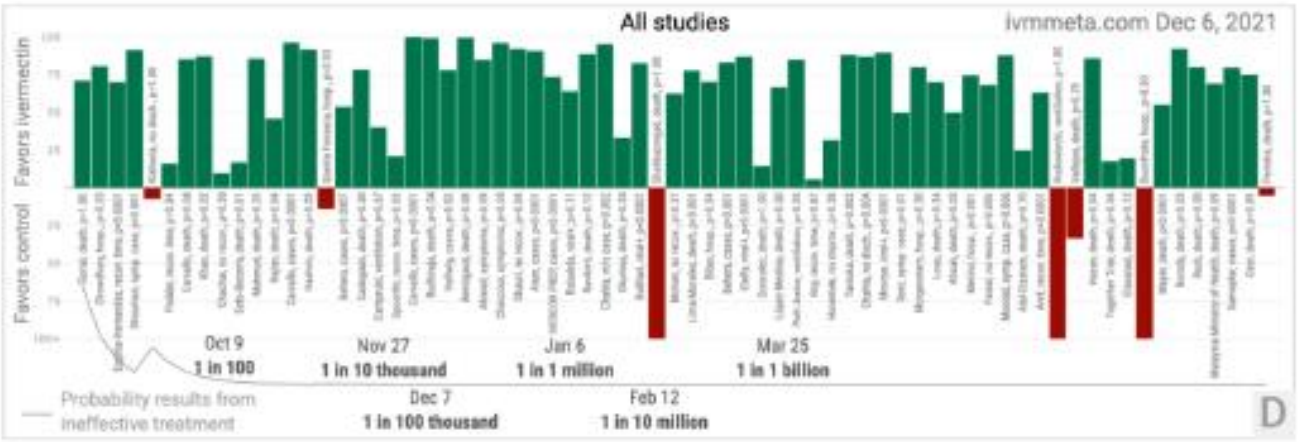

Early treatment 66% 0.34 [0.24-0.47] 56/6,473 225/21,185 66% improvement
Tau² = 0.36; I² = 61.3%
Improvement, RR [CI] Treatment Control Dose (4d)
Gorial 71% 0.29 [0.01-5.76] death 0/16 2/71 14mg
Kishoria (RCT) -8% 1.08 [0.57-2.02] no disch. 11/19 7/13 12mg
Podder (RCT) 16% 0.84 [0.55-1.12] recov. time 32 (n) 30 (n) 14mg
Khan 87% 0.13 [0.02-1.00] death 1/115 9/133 12mg
Chachar (RCT) 10% 0.90 [0.44-1.83] no recov. 9/25 10/25 36mg
Soto-Becerra 17% 0.83 [0.71-0.97] death 92/203 1,438/2,630 14mg
Rajter (PSM) 46% 0.54 [0.27-0.99] death 13/98 24/98 14mg
Hashim (SB RCT) 92% 0.08 [0.00-1.44] death 0/59 6/70 28mg CT²
Camprubí 40% 0.60 [0.18-2.01] ventilation 3/13 5/13 14mg
Spoorthi 21% 0.79 [0.64-0.98] recov. time 50 (n) 50 (n) n/a CT²
Budhiraja 99% 0.01 [0.00-0.15] death 0/34 103/942 n/a
Okumuş (DB RCT) 33% 0.67 [0.27-1.64] death 6/30 9/30 56mg
Shahbazn.. (DB RCT) -197% 2.97 [0.13-70.5] death 1/35 0/34 14mg
Lima-Morales 78% 0.22 [0.12-0.41] death 15/481 52/287 12mg CT²
Gonzalez (DB RCT) 14% 0.86 [0.29-2.56] death 5/36 6/37 12mg
Pott-Junior (RCT) 85% 0.15 [0.01-1.93] ventilation 1/27 1/4 14mg
Huvemek (DB RCT) 32% 0.68 [0.38-1.23] no improv. 13/50 19/50 84mg
Ahsan 50% 0.50 [0.28-0.90] death 17/110 17/55 21mg CT²
Abd-Elsalam (RCT) 25% 0.75 [0.17-3.06] death 3/82 4/82 36mg
Hazan 86% 0.14 [0.01-2.19] death 0/24 synthetic 24mg CT² SC⁴
Elavarasi 20% 0.80 [0.61-1.06] death 48/283 311/1,475 n/a
Rezk 80% 0.20 [0.01-4.13] death 0/160 2/160 72mg
Malaysia M.. (RCT) 69% 0.31 [0.08-1.11] death 3/241 10/249 112mg
Ozer 75% 0.25 [0.06-1.13] death 2/60 8/60 28mg
Ferreira -5% 1.05 [0.32-3.43] death 3/21 11/81 n/a

Figure B


ivmmeta.com Dec 6, 2021
min, Q1, median, Q3, max
Early treatment
All studies
0
0.25
0.5
0.75
1
1.25
1.5
1.75
2+
Favors ivermectin
Favors control
B

Figures C, D


Early treatment
ivmmeta.com Dec 6, 2021
Favors ivermectin
Favors control
Jan 9
1 in 100
Feb 12
1 in 1 thousand
Sep 23
1 in 10 thousand
Probability results from ineffective treatment
C


All studies
ivmmeta.com Dec 6, 2021
Favors ivermectin
Favors control
Oct 9
1 in 100
Nov 27
1 in 10 thousand
Dec 7
1 in 100 thousand
Jan 6
1 in 1 million
Feb 12
1 in 10 million
Mar 25
1 in 1 billion
Probability results from ineffective treatment
D

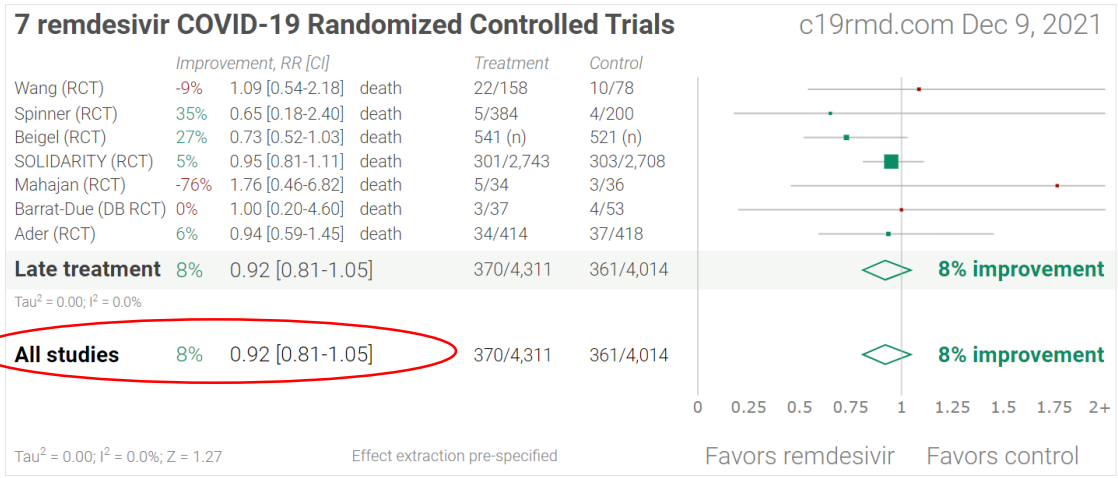
Appendix B

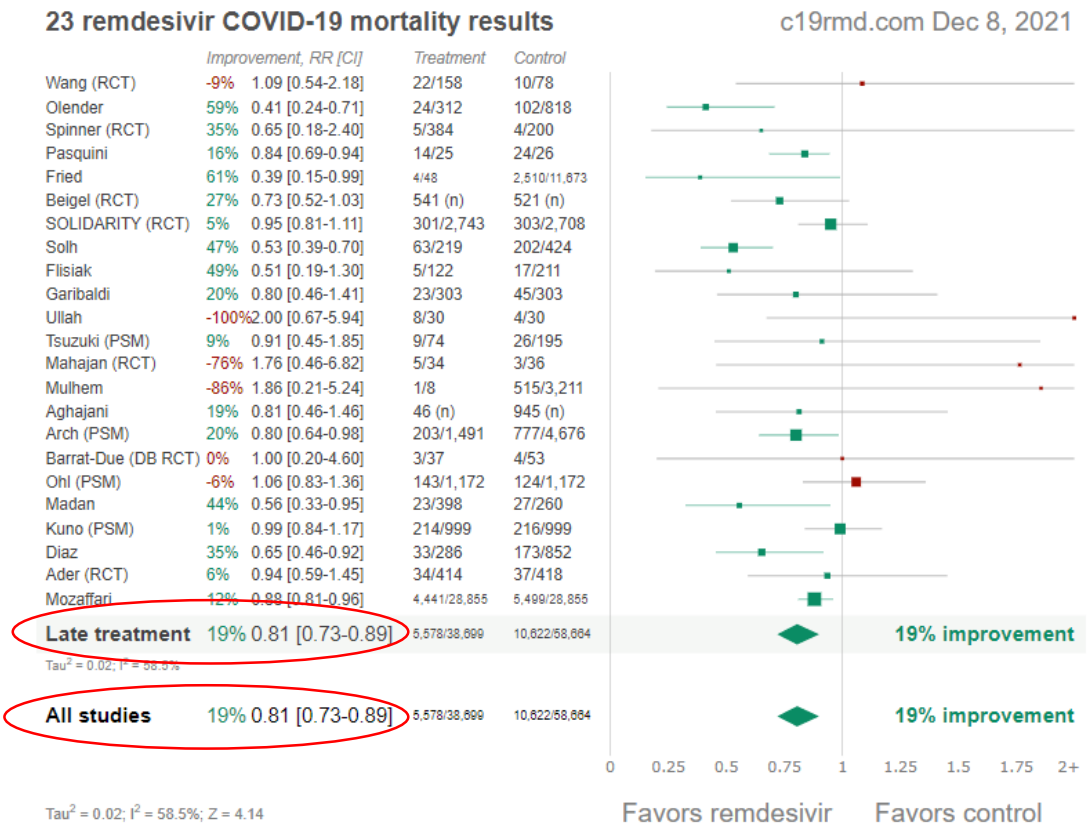
FLCC Alliance White Paper Summary of the Evidence for Ivermectin on Covid-19

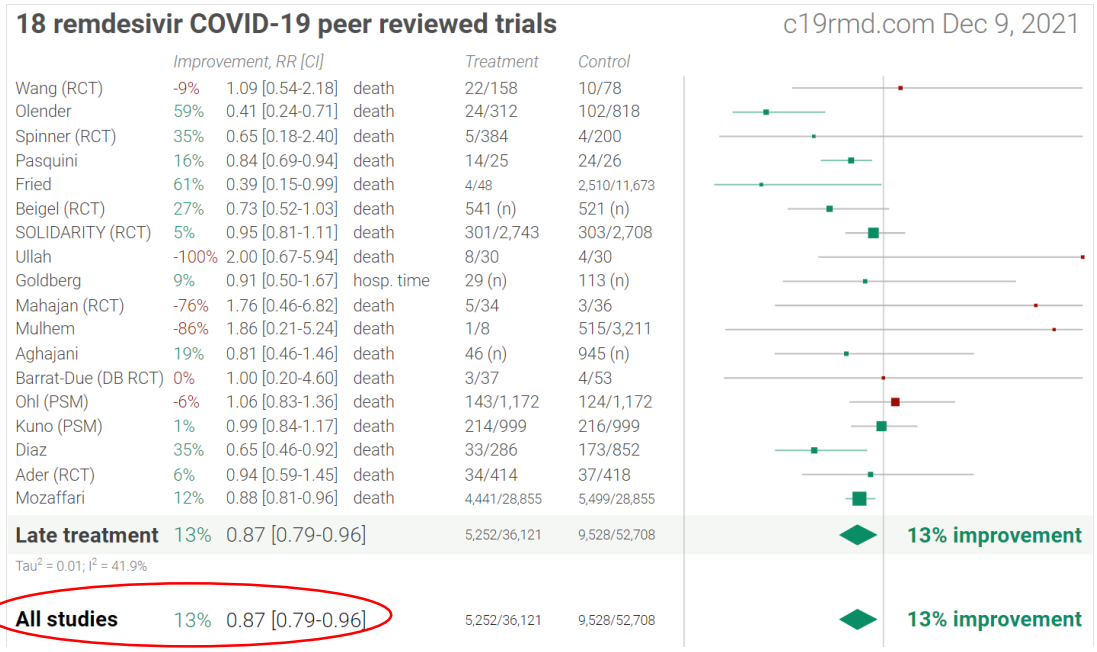
https://covid19criticalcare.com/wp-content/uploads/2021/08/SUMMARY-OF-THE-EVIDENCE-BASE-FINAL.pdf

Appendix C
Remdesivir Covid-19 Studies

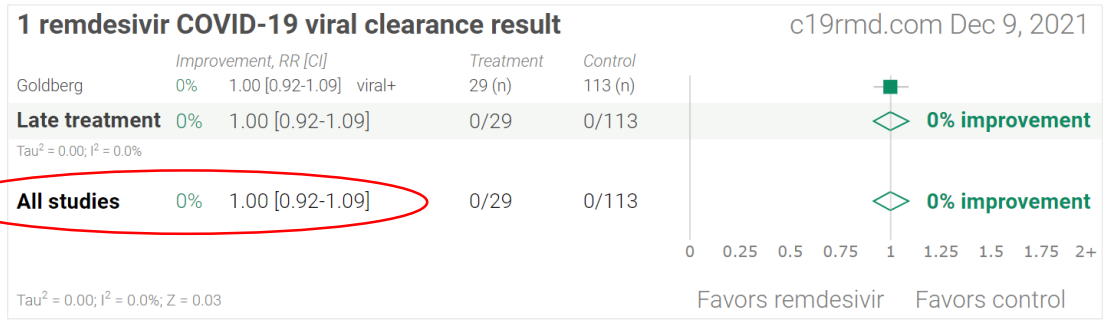
https://c19rmd.com/






18 remdesivir COVID-19 peer reviewed trials
c19rmd.com Dec 9, 2021
Improvement, RR [CI]
Treatment
Control
Wang (RCT) -9% 1.09 [0.54-2.18] death 22/158 10/78
Olender 59% 0.41 [0.24-0.71] death 24/312 102/818
Spinner (RCT) 35% 0.65 [0.18-2.40] death 5/384 4/200
Pasquini 16% 0.84 [0.69-0.94] death 14/25 24/26
Fried 61% 0.39 [0.15-0.99] death 4/48 2,510/11,673
Beigel (RCT) 27% 0.73 [0.52-1.03] death 541 (n) 521 (n)
SOLIDARITY (RCT) 5% 0.95 [0.81-1.11] death 301/2,743 303/2,708
Ullah -100% 2.00 [0.67-5.94] death 8/30 4/30
Goldberg 9% 0.91 [0.50-1.67] hosp. time 29 (n) 113 (n)
Mahajan (RCT) -76% 1.76 [0.46-6.82] death 5/34 3/36
Mulhem -86% 1.86 [0.21-5.24] death 1/8 515/3,211
Aghajani 19% 0.81 [0.46-1.46] death 46 (n) 945 (n)
Barrat-Due (DB RCT) 0% 1.00 [0.20-4.60] death 3/37 4/53
Ohl (PSM) -6% 1.06 [0.83-1.36] death 143/1,172 124/1,172
Kuno (PSM) 1% 0.99 [0.84-1.17] death 214/999 216/999
Diaz 35% 0.65 [0.46-0.92] death 33/286 173/852
Ader (RCT) 6% 0.94 [0.59-1.45] death 34/414 37/418
Mozaffari 12% 0.88 [0.81-0.96] death 4,441/28,855 5,499/28,855
Late treatment 13% 0.87 [0.79-0.96] 5,252/36,121 9,528/52,708
13% improvement
Tau² = 0.01; I² = 41.9%
All studies 13% 0.87 [0.79-0.96] 5,252/36,121 9,528/52,708
13% improvement


3 remdesivir COVID-19 hospitalization results
c19rmd.com Dec 8, 2021
Improvement, RR [CI]
Treatment
Control
Goldberg 9% 0.91 [0.50-1.67] hosp. time 29 (n) 113 (n)
Tsuzuki (PSM) -27% 1.27 [1.10-1.47] hosp. time 74 (n) 195 (n)
Ohl (PSM) -100% 2.00 [1.33-3.02] hosp. time 1,172 (n) 1,172 (n)
Late treatment -36% 1.36 [0.96-1.94] 0/1,275 0/1,480
-36% improvement
Tau² = 0.06; I² = 64.4%
All studies -36% 1.36 [0.96-1.94] 0/1,275 0/1,480
-36% improvement
0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+
Tau² = 0.06; I² = 64.4%; Z = 1.72
Favors remdesivir
Favors control


1 remdesivir COVID-19 viral clearance result
c19rmd.com Dec 9, 2021
Improvement, RR [CI]
Treatment
Control
Goldberg 0% 1.00 [0.92-1.09] viral+ 29 (n) 113 (n)
Late treatment 0% 1.00 [0.92-1.09] 0/29 0/113
0% improvement
Tau² = 0.00; I² = 0.0%
All studies 0% 1.00 [0.92-1.09] 0/29 0/113
0% improvement
0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+
Tau² = 0.00; I² = 0.0%; Z = 0.03
Favors remdesivir
Favors control

Appendix D

NIH Characteristics of Anti-viral Agents that are Approved or Under Evaluation for the Treatment of Covid -19

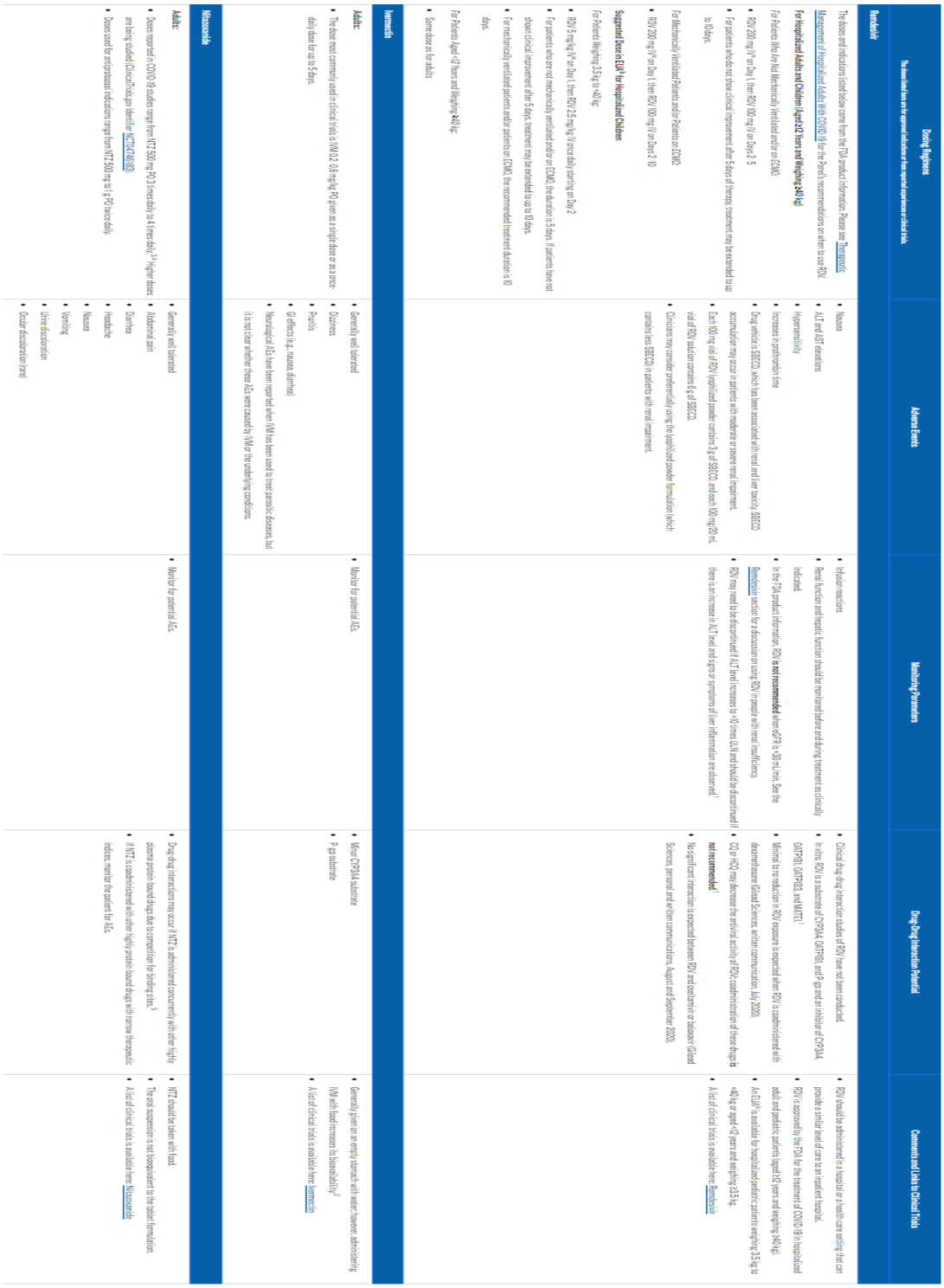


Table 2e. Characteristics of Antiviral Agents That Are Approved or Under Evaluation for the Treatment of COVID-19

Last Updated as: July 6, 2021

Dosing Regimens The dosage listed here are for approved indications or those reported in peer-reviewed clinical trials.	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Remdesivir				
The dosage and indications listed below come from the FDA product information. Please see Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on when to use RDV. **For Hospitalized Adults and Children (Aged ≥12 Years and Weighing ≥40 kg):** For Patients Who Are Not Mechanically Ventilated and/or on ECMO: • RDV 200 mg IV on Day 1, then RDV 100 mg IV on Days 2–5 • For patients who do not show clinical improvement after 5 days of therapy, treatment may be extended to up to 10 days. For Mechanically Ventilated Patients and/or Patients on ECMO: • RDV 200 mg IV on Day 1, then RDV 100 mg IV on Days 2–10 **Suggested Dose in CLN for Hospitalized Children** For Patients Weighing 3.5 kg to <40 kg: • RDV 5 mg/kg IV on Day 1, then RDV 2.5 mg/kg IV once daily starting on Day 2 • For patients who are not mechanically ventilated and/or on ECMO, the duration is 5 days. If patients have not shown clinical improvement after 5 days, treatment may be extended to up to 10 days. • For mechanically ventilated patients and/or patients on ECMO, the recommended treatment duration is 10 days. For Patients Aged <12 Years and Weighing ≥40 kg: • Same dose as for adults.	• Nausea • ALT and AST elevations • Hypersensitivity • Increases in prothrombin time • Drug vehicle is SBECD, which has been associated with renal and liver toxicity. SBECD accumulation may occur in patients with moderate or severe renal impairment. • Each 100 mg vial of RDV lyophilized powder contains 3 g of SBECD, and each 100 mg/20 mL vial of RDV solution contains 6 g of SBECD. • Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECD) in patients with renal impairment.	• Infusion reactions • Renal function and hepatic function should be monitored before and during treatment as clinically indicated. • In the FDA product information, RDV **is not recommended** when eGFR is <30 mL/min. See the Remdesivir section for a discussion on using RDV in people with renal insufficiency. • RDV may need to be discontinued if ALT level increases to >10 times ULN and should be discontinued if there is an increase in ALT level and signs or symptoms of liver inflammation are observed.	• Clinical drug-drug interaction studies of RDV have not been conducted. • In vitro, RDV is a substrate of CYP3A4, OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1. • Minimal to no reduction in RDV exposure is expected when RDV is coadministered with atazanavir/cobicistat (Gilead Sciences, written communication, July 2020). • CQ or HCQ may decrease the antiviral activity of RDV; coadministration of these drugs **is not recommended**. • No significant interaction is expected between RDV and ceritinib or baricitinib (Gilead Sciences, personal and written communications, August and September 2020).	• RDV should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital. • RDV is approved by the FDA for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). • An EUA is available for hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing <3.5 kg. • A list of clinical trials is available here: Remdesivir
Nitazoxanide				
Adults: • Doses reported in COVID-19 studies range from NTZ 500 mg PO 3 times daily to 4 times daily.[44] Higher doses are being studied (ClinicalTrials.gov Identifier NCT04746183). • Doses used for antiprotozoal indications range from NTZ 500 mg to 1 g PO twice daily.	• Generally well tolerated • Abdominal pain • Diarrhea • Headache • Nausea • Vomiting • Urine discoloration • Ocular discoloration (rare)	• Monitor for potential AEs.	• Drug-drug interactions may occur if NTZ is administered concurrently with other highly plasma protein–bound drugs due to competition for binding sites.[3] • If NTZ is coadministered with other highly protein-bound drugs with narrow therapeutic indices, monitor the patient for AEs.	• NTZ should be taken with food. • The oral suspension is not bioequivalent to the tablet formulation. • A list of clinical trials is available here: Nitazoxanide
Ivermectin				
Adults: • The dose most commonly used in clinical trials is IVM 0.2–0.6 mg/kg PO given as a single dose or as a once-daily dose for up to 5 days.	• Generally well tolerated • Dizziness • Pruritis • GI effects (e.g., nausea, diarrhea) • Neurological AEs have been reported when IVM has been used to treat parasitic diseases, but it is not clear whether these AEs were caused by IVM or the underlying conditions.	• Monitor for potential AEs.	• Minor CYP3A4 substrate • P-gp substrate	• Generally given on an empty stomach with water; however, administering IVM with food increases its bioavailability.[2] • A list of clinical trials is available here: Ivermectin

Appendix E
Cirriculum Vitae
Dr. Janci Chunn Lindsay, PhD