



## Vanda Pharmaceuticals CEO's Proposal on Clinical Trial Data Sharing, COVID-19 and Remdesivir

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WASHINGTON, May 20, 2020 /PRNewswire/ -- Vanda Pharmaceuticals Inc. (Vanda) (Nasdaq: VNDA) today released a letter (below) from Mihael H. Polymeropoulos, M.D., President and CEO of Vanda Pharmaceuticals, proposing an approach to Clinical Trial Data Sharing in order to facilitate discovery and clinical utility of COVID-19 therapeutics. Vanda is also involved in the development of therapeutic solutions for COVID-19 and currently in Phase III studies with tradipitant for the treatment of Acute Respiratory Distress Syndrome (ARDS) associated with COVID-19.

### Clinical Trial Data Sharing, COVID-19 and Remdesivir

Mihael H. Polymeropoulos, M.D.

The COVID-19 pandemic has created an urgent need for scientific solutions to this deadly virus. The pandemic surprised the world with a new strain of coronavirus never encountered before, which, like its predecessor, has the capacity to infect humans with severe and deadly consequences. While this pandemic has stunned the world's populations, we are more prepared than ever to respond with a rich scientific armamentarium of tools that can be deployed in the war against this new virus resulting from the extraordinary advances in medical discoveries and treatments in the twenty years since the first full sequencing of the human genome.

While the reaction to the 1918 world epidemic was mostly one of quarantine and restrictions in movement, the world today can do better. In 1918, the world did not know the identity of the organism that was killing so many, nor did it know what a virus was, as viruses had not yet been discovered. Now equipped with the knowledge of over a century of research and tremendous advances in science and therapeutics, we stand in front of this challenge well equipped and ready to respond. In many ways, our response has been similar to the 1918 epidemic, with mitigation measures that include closing of public places and reducing opportunities for contact, while monitoring the curves of new cases and mortality rates. Vaccines and therapeutics are on the drawing board but how and when they may be of value is uncertain. The urgency and mobilization of the scientific community across the globe is impressive. The collective scientific understanding of the workings of the virus, the clinical course of the infection and the therapeutic approaches are mounting on a daily basis.

Although this is great news, the pandemic has imposed an extremely demanding pace on the timetable for the pursuit of scientific answers and solutions. The ability of developing therapeutic solutions does not just depend on the availability of research tools and ideas. The ideas must leverage scientific tools and then they must be tested. Testing of potential therapeutics happens in human volunteers that have been infected with the COVID-19 virus. One of these programs is the development of antivirals that are intended to slow down or block replication of the virus.

The U.S. National Institute for Allergy and Infectious Diseases (NIAID) and Gilead Sciences brought forward the testing of one of these antivirals, remdesivir, a nucleoside analog that induces errors in the copying machinery of the virus, thereby slowing down replication. Remdesivir has been recently studied in two types of programs, a placebo-controlled study and an open label program. The NIAID remdesivir placebo-controlled study was concluded and topline results were reported on April 29, 2020. The topline results were communicated during a brief meeting at the White House by the Director of NIAID and advisor to the President, Dr. Anthony Fauci. The communication was verbal, short, and conveyed that the study had shown that remdesivir reduced hospital stay by 4 days for remdesivir treated patients as compared to placebo, but it did not significantly reduce mortality. No other data were presented in any other scientific or media forum. Dr. Fauci acknowledged that his preference would have been to present this data at a scientific meeting but that the situation required a more immediate communication and that the data would be submitted for a peer review publication in the near future. Two days later, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) approval of remdesivir in treating patients with severe COVID-19 infection.<sup>1</sup> The prescribing information presented by the FDA included the same summary information that was reported at the White House two days earlier, but no additional information on the efficacy trial was given.<sup>2</sup> Similarly, the FDA in its cover letter suggested that it had reviewed the topline data and based on that deemed it appropriate to issue an EUA.

The paucity of information around this critical therapeutic development for COVID-19 is troubling. The NIH, the FDA and Gilead Sciences could simply provide the raw data from the clinical trials to the public immediately. Such a concept of sharing of clinical trial data is not new, instead, it is highly encouraged by the scientific community and data sharing disclosures are now required by most scientific journals according to the recommendations of the International Committee of Medical Journal Editors.<sup>3</sup> The reason for sharing of clinical data includes allowing the scientific community to independently form their own conclusions from their own analyses, develop new insights from the data, and accelerate discoveries in the field by not having to repeat the same experiments. In the case of remdesivir and COVID-19, this degree of data sharing is even more urgent given the finite amount of time within which a study can be conducted in the face of a declining number of new cases. There are a number of questions that could be answered by the existing remdesivir NIAID study that remain unanswered by the complete unavailability of the data. For example: Is there a subgroup of patients that performed better than others? Is this subgroup of a certain characteristic, such as age, sex, race, genetic makeup, time since infection, severity of disease, viral load, medication, underlying condition? And there are many others to be answered.

The FDA has authorized remdesivir for all people with severe COVID-19 infection, but there may not be enough supply for all eligible patients at this time. How are doctors supposed to choose who should receive it? The prevailing rationale, which would suggest that it be administered to the most severely ill first, may be misguided and not supported by the data. What if analysis of the existing data showed that remdesivir works better when given to less severe patients or very early after the infection? In this example, providing the currently limited supply of remdesivir to severe patients may be wasteful and may deprive patients who could benefit from it instead. Another reason for sharing the raw data is that there is no other large dataset of patients with COVID-19 infection and thus there is not a good guide how to optimally design any therapeutic programs. The question of whether viral load is associated with response is also of critical importance. Imagine a scenario where the drug's effect was dependent not on disease severity but rather on viral load, so that severely ill patients with low viral load respond to the drug, but severely ill patients with high viral load do not. What if some patients have zero viral load but nonetheless have a severe infection, would they be candidates for treatment? Even in a more complex scenario, what if patients had no decrease in viral load but the infectivity of the virus post remdesivir treatment was decreased? What is the cause of mortality and how does it differ between remdesivir and placebo?

Unfortunately, so far there has been little to no discussion about data transparency and data availability for remdesivir. Dr. Fauci's statement that the results will be submitted for peer review is not enough. On the face of it, it appears that this is consistent with the well-established approach to validate scientific findings. During this process, a scientific report is submitted to a journal and the editorial board appoints two or more reviewers to independently critique the paper and advise whether the conclusions are supported by the data presented. This process is well-intentioned, and has served us well, but in and of itself it is grossly inadequate for the task in hand. The American public is comforted that expert scientists opine on the validity of a potential treatment but they would likely prefer that the data are also fully and transparently available to the public for inspection and analysis for both verifying and learning.

Reliance upon just the ordinary peer review of scientific reports is not sufficient in this case. Dr. Fauci's suggestion that worries about "leaks" or "ethical concerns" prompted this style of announcement is not an acceptable explanation either. Most of the American public is not concerned with the reasons that compelled the verbal announcement of the results from a White House office on April 29. The American public is interested in seeing the data and having the data available for all to examine and learn from. The speed of the FDA decision in issuing an EUA for remdesivir needs to be commended but the absence of any available detailed information is of great concern. The EUA was granted based on the information presented to the FDA. The data which the FDA used to make its decision must become immediately available to the public. If the FDA deems that it needs more information to grant a full approval, it can request this information in due course. Until then, the FDA should provide to the public the information that the FDA scientists used to make its decision.

If the NIAID, the FDA and Gilead Sciences decided to follow this recommendation and share the data, could they do it quickly? The process that the NIAID scientists used to analyze the available data is as follows: anonymized patient data are collected throughout the study, they are tabulated as raw data, and then certain parameters are derived. These data are stored in standard format files which are of two types, the RAW and the DERIVED data files. These exact files that the NIAID analyzed and which Gilead Sciences filed with the FDA, can be shared with minimal effort and within minutes after the leaders of the NIAID, the FDA and Gilead Sciences decide to share. In summary, there is no technical hurdle for the immediate release of the underlying remdesivir clinical study data. Concerns about credit and intellectual property can easily and expediently be addressed without imposing any delay on the release of this data.

We are experiencing a historic health crisis where success is dependent on a community coming together and overcoming a tremendous challenge to humanity. Open source sharing of information has always accelerated solutions to problems, and I am confident that it will work here as well. In the scientific community, open source mentality and data sharing has served humanity well, especially recently with the Human Genome project, where genetic data were made immediately available to the scientific community for the betterment of human health. This is the time to show that pharmaceutical companies and government agencies put patients first. If indeed the interest of patients is front and center, which it should be, then the NIAID, Gilead Sciences and the FDA will release ALL data from the remdesivir studies without delay.

More than ever, the American public is dependent on the competencies of its leaders, in the government and science alike. Trust in the system is conditional and temporary and is based upon transparency and truthfulness. The American public will not, and should not, blindly trust the expert. The American public should not have to wait for a handful of scientists, no matter how brilliant, to review the information and give their approval. The American public is entitled to unconditional access to all such data so that all people, and not just a few, can judge the course of affairs and make decisions. In the midst of this difficult moment for humanity, an unconditional data sharing movement may become a silver lining and the rainbow promise past the storm. The American public, scientists, and non-scientists, bonded by sharing and trust, will overcome this new challenge. Let us remove from the vocabulary of our democracy the "trust me I am an expert" mentality and replace it with "transparency for all."

#### References

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#### About Vanda Pharmaceuticals Inc.

Vanda is a leading global biopharmaceutical company focused on the development and commercialization of innovative therapies to address high unmet medical needs and improve the lives of patients. For more on Vanda Pharmaceuticals Inc., please visit [www.vandapharma.com](http://www.vandapharma.com) and follow us on Vanda's Twitter and LinkedIn.

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