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WAMJ

World Asian Medical Journal

Inspirational Asian Healthcare Leader

JEROME KIM

Director General, International Vaccine Institute (IVI)

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OUR EDITORIAL BOARDS

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From the Publisher

The life sciences industry's response to the current global COVID-19 pandemic has highlighted the importance of innovation and drug development in the space of vaccines. It has also underscored our industry's ability to come together and share resources, across borders, during a time of extreme need.

Since COVID-19 was first reported, scientists from all over the world have worked with remarkable speed to understand the virus and share findings and knowledge. Dr. Jerome Kim, the Director General of International Vaccine Institute (IVI), is one of the dedicated leaders who put enormous efforts into the battle with the pandemic. For this edition of the WAMJ, we interviewed Dr. Kim for the cover story.

IVI is a non-profit international organization that was founded to discover, develop, and deliver safe, effective, and affordable vaccines to children in any country in need. However, even IVI is currently disrupted by COVID-19 and many of the planned vaccination campaigns have been put on hold, as well as other mass campaigns and childhood vaccination programs.

Dr. Kim emphasized that we need to come together to combat this immediate threat in the world so that he and his organization can go back to providing more focused support to the population most suffering from shortage of vaccines for vaccine-preventable diseases. Throughout the interview, we were inspired by his passion and affection towards saving the lives of children by providing essential medical measures.

In addition to the cover story, new trends and current issues of the bio-health industry are featured in the biopharmaceutical reports and articles. In the articles by BioPharm Insight and BioSpace, writers examined the contemporary issues in the life sciences arena which have garnered increased attention.

WAMJ has made major progress over the past couple of years and is celebrating the completion and publication of the 22nd edition. We truly thank our readers for your continuous support.

I hope that you enjoy our selection of articles and find them inspiring. Stay strong against COVID-19!

DoHyun Cho, PhD
Publisher
President & CEO of W Medical Strategy Group
Chairman of New York Health Forum

From the Editor-in-Chief

We are proud to present this 22nd issue of the World Asian Medical Journal, and its cover story on Jerome Kim, M.D. Over the years, WAMJ has had the good fortune to meet, interview, and publish stories on a gratifyingly wide array of leaders in medicine and biomedical sciences. All of these individuals have made noteworthy contributions to human health and knowledge; many are truly world-renowned and justifiably so. However, only a few have achieved more than this issue's featured Dr. Kim.

Among all the advances of public health, with the possible exception of improved water sanitation, nothing has done more good for people than vaccines. In fact, the only disease mankind can claim to have conquered was eliminated because Edward Jenner, a courageous 18th century physician, noticed that patients infected with cowpox somehow avoided infection with smallpox. That observation and the decision to deliberately inoculate a young boy with pus from cowpox blisters led nearly two centuries later to the eradication of what had once been a human scourge. No one is sick with smallpox today; with any luck at all, no one ever will be again. Smallpox vaccination is truly mankind's triumph over a dread disease.

Dr. Jenner's heritage lives. Our interviewee is an international expert on the evaluation and development of vaccines. His titles and distinctions are legion. He currently serves as the Director General of the International Vaccine Institute in Seoul, South Korea. In his remarks, Dr. Kim enlightens us about the Institute and its uniquely valuable role in vaccine development and distribution.

Dr. Kim's remarks about the invaluable role the military has played in vaccinology are equally edifying. He is a veteran himself and an adjunct professor of medicine at the Uniformed Services University of the Health Sciences. He served both as the principal deputy and later chief at the Laboratory of Molecular Virology and Pathogenesis at the Military HIV Research Program and as the project manager for the HIV Vaccines and Advanced Concepts Evaluation Project Management Offices. Dr. Kim led the Army's Phase III HIV vaccine trial (RV144), the first demonstration that an HIV vaccine could protect against infection. During an era in which far too many fail to understand and recognize the debt we owe to our armed forces, Dr. Kim's words should be treasured as a source of insight and wisdom.

It is an honor to have had the chance to speak with Dr. Kim, and we are confident you will find inspiration in his thoughts.

Joseph P. McMenamin, MD, JD, FCLM
Editor in Chief
EVP of W Medical Strategy Group

WAMJ Recap of the Last Issue

COVER STORY
Patrick Soon-Shiong, M.D., Chairman and Chief Executive Officer, NantWorks

Dr. Patrick Soon-Shiong is a physician, surgeon, professor, researcher, philanthropist, and billionaire entrepreneur. He is the Chairman and CEO of NantWorks, a health technology company based in Culver City, California, and has devoted himself to understanding the fundamental biology of life-threatening diseases and translating these insights into medical innovations with global impact. Over the course of his career, Dr. Soon-Shiong has pioneered innovative treatments in diabetes and cancer, including the drug Abraxane which received FDA approval for the treatment of metastatic breast cancer, lung cancer, and advanced pancreatic cancer. Also, as a philanthropist, he established the Chan Soon-Shiong Family Foundation and the Chan Soon-Shiong Institute for Advanced Health to help the underserved population in aspects beyond healthcare. To learn more about Dr. Soon-Shiong, please read issue 21 of WAMJ.

ENTREPRENEUR INTERVIEW
Stanley Kim, J.D., Chief Executive Officer, WinSanTor

Stanley Kim, J.D., CEO of WinSanTor, is a seasoned entrepreneur and the founder of companies in diverse industries, including pharmaceutical/biotechnology, medical device, and software. He co-founded SoftMax and Emotient, which were acquired by Qualcomm and Apple, respectively. WinSanTor, his current affiliation, is a biotechnology company focused on the development of treatments for peripheral neuropathies (PN). WinSanTor is now active in trials to reverse the biological and functional symptoms and to improve the quality of life for the millions affected, envisioning a world where no one suffers from PN. To learn more about his philosophy and his career story, please read issue 21 of WAMJ.

BIOPHARMACEUTICAL REPORT I
Hidden Consequences of COVID-19: Why Small Biotechs Can't Just Wait This One Out

The COVID-19 has taken a harsh toll on small biotech companies, many of which have encountered a mixed bag of experiences. Many clinical trials have been halted due to travel restrictions, financing rounds have been interrupted, and major conferences and in-person meetings have been cancelled, severely affecting the chances of building an essential business network. To read more about the hidden consequences of COVID-19 and their impact on the future operations of small biotechs, please read issue 21 of WAMJ.

BIOPHARMACEUTICAL REPORT III
Evofem's Amphora Requires 12-Month Data to Convince Experts of Contraceptive Efficacy

Amphora is a viscous and bioadhesive contraceptive, packaged in a prefilled applicator that resembles a tampon applicator. This contraceptive has been developed not only to provide solutions for women who want hormone-free birth control but also to prevent sexually transmitted diseases. Amphora is under FDA review for approval, but the lack of 12-month data determining the contraceptive efficacy and safety has made some experts difficult to estimate its approval chances or even degree of use if approved. To learn more about Evofem's Amphora, please read issue 21 of WAMJ.

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Dr. Kim in Ethiopia during a preventive campaign against endemic cholera in 2015 (Credit: IVI)

Inspirational Asian Healthcare Leader

Jerome Kim, M.D.

Director General, International Vaccine Institute (IVI)

1. Dr. Jerome Kim, our readers know that you are a renowned physician and a recognized leader in vaccine research and development, especially in HIV. What motivated you to attend medical school and become a physician? Also, what events in your career or in life led you to HIV/vaccine research?

- My interest in biology and the medical field started in high school, and I was especially fascinated by the field of regeneration. In my AP Biology class, we were given an assignment to write an extensive research paper on regeneration, and then a paper on bronchopulmonary dysplasia, which made me want to work on regeneration. After high school, I went to the University of Hawaii and expressed interest in wanting to work on regeneration.

After graduation, I wanted to attend medical school outside of Hawaii, so I applied to Yale School of Medicine and was accepted. However, my parents made it clear that I should get a scholarship to attend medical school. Upon searching, I found that the military was offering a scholarship program for medical students in exchange for a service commitment, the program still being offered today. Students were required to serve in the military as medical officers after obtaining their medical degrees and had to go through residency in the military in most instances. I signed up for the Air Force scholarship, and the Air Force paid a stipend as well as tuition and books. Towards the end of medical school, I asked to defer my military service to do my residency outside of the military, and they approved. Therefore, I completed my internship, residency, and fellowship at Duke University. During my fellowship in infectious diseases, I worked with Dr. Warner Greene, who is now at the University of California San Francisco, on HIV.

In 1989, I became a faculty member at Duke University Medical Center and received a Pfizer postdoctoral fellowship grant and an NIH grant. Even though I wanted to defer my service for another five years, the first Gulf War had started, and I was activated. I was sent to "back-fill" a vacancy at one of the major air force hospitals. In the military, I was assigned to the Walter Reed Army Institute of Research to work on HIV vaccine research with the Army, and that is how I ended up in the field of HIV vaccine research. My first boss in the Department of Retroviral Research was Dr. Robert Redfield, now Director of the CDC, whom I later joined at the Institute for Human Virology at the University of Maryland after fulfilling my Air Force commitment. After two years of working, Dr. Deborah Birx, the current

Dr. Kim delivering an oral cholera vaccine to a child in Ethiopia in 2015 (Credit: IVI)

coordinator of the White House Coronavirus Task Force, reached out to me and invited me to join the Army and do more work on HIV vaccine research. I accepted her invitation and was asked to help with the RV144 Phase III HIV vaccine trial in Thailand, which remains the only vaccine trial that has shown protection against HIV infection. In 2015, I was eligible to retire from the military, and I was asked to join the International Vaccine Institute (IVI) as the Director General.

2. We understand that the International Vaccine Institute (IVI) is an international organization devoted to vaccine development and delivery for the developing world. Can you please tell our readers more about IVI's identity and mission?

- IVI is a non-profit international organization that was founded in 1997 as an initiative of the United Nations Development Programme (UNDP). The UNDP saw the need for an institute that develops vaccines for global health to fill the gap between the availability of vaccines for developing countries and developed countries. The major vaccine companies are great at making vaccines for diseases found in high-income countries, but not for diseases in developing countries. For many diseases found predominantly in developing countries, there were no vaccines because companies did not find sufficient profit incentive to develop them. Thus, IVI was founded as the brainchild of UNDP to develop vaccines to fill this gap.

IVI is an international research organization. Similar to the WHO, we have signatory countries and state funders.

More than twenty five percent of our funding comes from our state funders, which include the Republic of Korea, Sweden, India, and Finland, and the rest comes from grants by organizations such as the Gates Foundation, the Wellcome Trust, and the European Union.

IVI's operating model is that we identify diseases that have gaps in vaccine development, create a vaccine in our laboratory, work to get funding for the technology transfer of the vaccine to a developing country vaccine manufacturer, test the vaccine in Phase I – III trials, and then work with the manufacturer to get local, and ultimately WHO's approval. WHO approval, called "prequalification" (PQ) is necessary for vaccines to be purchased by UN agencies and is a further assurance of quality. We can also work with companies interested in doing clinical trials in low and middle-income countries. For example, we are working with Bharat Biotech, a major Indian vaccine manufacturer, to do Phase II/III testing of their chikungunya vaccine in Panama, Colombia, and Thailand.

Our main goal is to generate vaccines for global health, so our priority is to have the vaccines pre-qualified. In other words, we aim to move vaccines along a development pathway with the end being prequalification, use, and reduction in the burden of disease. IVI also can be viewed as a development organization because we work along the entire spectrum of vaccine R&D; we work not only with vaccines that are being developed, but with vaccines that have been approved to increase their uptake and to generate data in the "real world" that will help to generate good policy. In such efforts, we work with organizations such as WHO and Gavi, the Vaccine Alliance to create stockpiles and recommendations for the use of vaccines because many countries are not aware how significant the burden of these diseases is. In that sense, IVI also helps to generate demand for such vaccines—to get vaccines used to reduce the burden of disease.

> "We develop novel strategies on new vaccines that help children in any country receive vaccines for vaccine-preventable diseases"

(Right to left) Dr. Kim with Ban Ki-moon, 8th UN Secretary-General, Minwon Lee, Director General, Center for Public Health Emergency Preparedness and Response at the KCDC; and Ki-Hwan Kweon, Director General, International Organizations Bureau of MOFA Korea, at the IVI State Forum 2019 (Credit: IVI)

IVI's mission is to discover, develop, and deliver safe, effective, and affordable vaccines for global health. We develop novel strategies on new vaccines that help children in any country receive vaccines for vaccine-preventable diseases.

No other organizations occupy the same niche, and we are often asked how IVI is different from Gavi or the Global Fund. The difference is that Gavi and the Global Fund are funders, whereas we are executors or enablers. In our strategy, we choose vaccines based on burden of disease, whether the development is feasible and funding is available, and then assess the impact of having the vaccine available. This strategy has been working; it has created sustainable value for companies and impact for people around the world. This makes us relevant to stakeholders. Also, it means a lot for us to maintain enough capability to function like a small biotech—to have people in the lab for discovery, others to manage clinical development, policy, vaccine delivery, and effectiveness trials for licensed vaccines. Thus, we have to maintain our key capabilities, which means that we have to work in different stages of a vaccine's life cycle with different diseases of importance to global health.

IVI commemorating the institute's 22nd anniversary in 2019 (Credit: IVI)

3. What are the major vaccines that IVI has been working on?

- Our first prequalified vaccine is the oral cholera vaccine, and the second is the typhoid conjugate vaccine which currently is in Phase III testing. What we call "Vaccine #3" could be a multivalent non-typhoidal vaccine against *Salmonella* or *Shigella*. We will be involved in the testing of vaccines for chikungunya, COVID-19, and HPV, in collaboration with Bharat Biotech in India, Inovio Pharmaceuticals in the U.S., and the Ministry of Public Health in Thailand, respectively. We do not develop vaccines made by large companies that are well-funded and making significant investments, such as the respiratory syncytial virus (RSV) vaccine. Instead, we focus on vaccines that are neglected by the major companies.

In 2000, IVI received a letter from Bill Gates Sr., who recently passed away. His message was written on a single letter that (paraphrasing) said, "We think that IVI is right about the diseases of the most impoverished, here's $40 million. Please work on vaccines and inform us every now and then about the progress." It was an incredible grant that jump-started IVI's work.

IVI began its work by exploring the diseases that bring significant burdens in the developing world, and how we can start to make vaccine solutions against them. Later, IVI received another grant that allowed us to work on a cholera vaccine that was being made by a Vietnamese biotech, called Vabiotech. The vaccine wasn't at the level to be approved for use by the WHO. Therefore, IVI brought the vaccine in-house, reformulated it to meet the international standards, then transferred it back to Vabiotech and to Shantha Biotechnics. By 2011, the vaccine had not only been approved in India, but it was also pre-qualified by the WHO. This meant that UNICEF could purchase the vaccine and provide it to Gavi, the Vaccine Alliance, with the goals of increasing access to immunization in developing countries and global distribution.

In fact, that was only the beginning. Shantha was not making enough oral cholera vaccine, so we transferred the vaccine to a small Korean company, EuBiologics. Now, this company is the world's largest supplier of oral cholera vaccine, making up over 80% of the current stockpile. The demand is still skyrocketing because the WHO announced a plan to reduce cholera deaths by 90% and eliminate cholera in as many as 20 countries by 2030.

Dr. Kim with Kang Kyung-Wha, South Korean Foreign Minister discussing the COVID-19 pandemic and equitable access to vaccines in June 2020 (Credit: MOFA Korea)

4. You formerly served in the U.S. Military as Deputy Director and Chief, Laboratory of Molecular Virology and Pathogenesis at the U.S. Military HIV Research Program and as the HIV Vaccines Project Manager with the U.S. Army Medical Materiel Development Activity. Could you please share your thoughts on this experience? How did your service affect your professional philosophy?

- Something that is not very well-known about the U.S. military is that it is helping the primary development and/or the invention of eight different licensed vaccines, and many fall into the "unincentivized" category. In fact, several major vaccines that are used today originated in or were tested by the military. Examples include the meningitis vaccine, the testing of the hepatitis A and Japanese encephalitis vaccines. Moreover, the vaccine against adenovirus types 4 and 7 was developed by the military because it was causing a critical problem in the military population, particularly among the new recruits. The viruses made a large number of recruits sick and resulted in the death of a few recruits every year, so the vaccine was developed and is still being used today. Also, the famous GSK malaria vaccine started in the Army; more specifically, both the development of the antigen and the adjuvant, which makes the vaccine so effective, originated in the Army through a co-development agreement with GSK.

Thus, the Army's involvement in vaccine development revolves around neglected diseases, such as dengue, malaria, or HIV; and this closely resembles the work we do at IVI. In developing vaccines such as HIV vaccines that do not have big commercial partners attached to it, the Army model is similar to IVI's.

IVI finds funding to develop a vaccine and helps to create the use case for it, essentially creating supply and demand. For the Army, that funding comes from the U.S. government and increasingly from outside sources. In the case of IVI, the funding comes from the Gates Foundation or governments of Sweden, India, Finland, and Korea.

The Army's work is incredibly significant because it's difficult to get the big companies engaged in neglected diseases. In fact, the Army's HIV vaccine trial, RV144, showed signs of protection against HIV, but no companies were interested in further trials in Thailand anymore. Therefore, we worked with a small company to find a mechanism to manufacture the vaccine in Thailand; we were not successful in that effort, but it did make me think about the obstacles surrounding vaccines for global health. The Army's contribution to vaccine development is remarkable, but it is not very well-known.

5. During the current COVID-19 pandemic, many major health organizations around the world are making enormous efforts to develop vaccines. What efforts, if any, has IVI made to help manage the pandemic?

- Currently, IVI is also occupied by COVID-19. Some of our vaccine trials were put on hold because of the lockdown. Governments delayed mass vaccination campaigns and childhood vaccination programs that Gavi is funding all around the world. In fact, the pandemic has also impaired the activities in cholera vaccination.

As for COVID-19, by February 2020, many different companies and research groups had already become interested in developing new vaccines. Therefore, rather than pursue an IVI vaccine, we decided that we would help any company or organization that had a vaccine and needed IVI's support. I believe that was the right decision.

> "Our priority is to have vaccines as quickly as possible, and that is exactly what IVI is doing"

The companies that requested our support were usually smaller companies, and they asked for our assistance in different areas of vaccine development. We were asked to help with animal immunogenicity studies to learn if the vaccine was creating the right immune responses, challenge studies in hamsters or mice, or to help them execute trials in Korea or elsewhere. We gladly accepted those requests, and that has been our approach—we have set up IVI to be an honest facilitator, providing services to support moving many companies' products more quickly and efficiently.

By not pursuing our own vaccine, IVI chose a product-agnostic approach to COVID-19 vaccine development. Our priority is to have vaccines as quickly as possible, and that is exactly what IVI is doing.

6. As a trusted expert in the field of vaccines, what are your expectations and concerns regarding COVID-19 vaccine development?

- In my opinion, if the current round of COVID-19 vaccine development succeeds, meaning it is shown to be safe and effective against the virus, we should have

First Lady Kim Jung-sook of South Korea with Dr. Kim and Prof. Sang Chul Park during the award ceremony at 'Shared Future, Global Solidarity' event at IVI headquarters in Seoul

the initial interim read-outs in November or December of this year.

However, just because the vaccines have proven to be safe and effective, it does not mean that COVID-19 is put away for good. In fact, the questions that arise on the day after efficacy would be, "who will make this vaccine in sufficient quantity and when will those quantities be available?" The second question would be, "how are we going to utilize the vaccine?" For instance, Operation Warp Speed, initiated by the White House to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, is designed to take care of U.S. citizens, but what about the rest of the world? Operation Warp Speed has pre-purchased hundreds of millions of doses for the U.S., but where is the commitment for other countries?

Logistics and delivery of vaccines will be a major issue. Do we have the facilities to distribute vaccines that have to be kept at -20°C or -70°C, which is the necessary temperature for RNA vaccine storage? Not only that, how are we going to distribute a vaccine that may be more than 60-70% of the United States population has to take? These days, not that many vaccines are given to adults in the U.S.—maybe the flu vaccines, but not everyone takes them. Thus, even absent vaccine hesitancy, it may be more difficult to deliver vaccines to the adult population than to children.

The countries around the world, typically the high-income countries, have started to purchase large amounts of vaccines for their own populations. For other countries, COVAX, the vaccines pillar of the Access to COVID-19

Tools (ACT) Accelerator, is aiming to provide vaccines. It currently plans to have 2 billion doses by the end of 2021—roughly 20% of the anticipated need. COVAX is important to this, but countries need to step up and provide funding for it. Agreements need to be executed with 190+ countries that have potentially signed on to COVAX, and vaccines need to be purchased, delivered, and given to populations in all countries.

Then, there will be questions around safety. We will know the vaccines are efficacious if they are approved for emergency use, and we will know the safety profile over a short term, such as 6 or 9 months. However, it is crucial that we know their safety over a much longer period, especially in people who were vaccinated early or outside of the U.S. Also, we need to know if the capabilities to identify long term safety exists—the capability to review safety information, to guarantee safety, and to track adverse events related to vaccination. If not, such systems need to be strengthened around the world so that we are aware of unusual developments related to safety, enhanced disease, or worsening of the disease in the third year after vaccination. In fact, these kinds of additional data are necessary because we did not have the luxury to take time to collect the data, conduct trials, or study COVID-19 in depth in just 9 months.

Thus, many pressing questions will arise about the day after efficacy, and they will eventually need to be addressed. In addition, the final question will be around effectiveness, real world evidence, which leads to the question around herd immunity, a concept that occurs when enough people in the community become immune and reduces the spread of the disease.

7. As a respected physician and scientist with decades of experience, what do you see as the major changes in medicine, vaccines, or HIV studies in the next 10 years? How does this projection affect your work?

- The last HIV vaccine efficacy trial, conducted by the HIV Vaccine Trials Network (HVTN), was stopped because it was not able to show protection, as opposed to previous HVTN trials which were stopped because of excess infections in the vaccine group. There is a trial on-going with a Johnson & Johnson HIV vaccine

Dr. Kim with his family

using its Ad26 vector, and I hope that will show some signs of protection. However, what the company plans to do with the vaccines in low and middle-income countries is an open question. There is a tremendous need for HIV vaccines around the world, but many companies are not interested in vaccines purely for use outside of high-income countries. Thus, there is a need for organizations to move forward. Maybe they can consider IVI's operating model involving developing country manufacturers to make global health vaccines available at a much lower cost and to minimize risk to the larger pharmaceutical companies.

HIV medicine/HIV prevention is changing. We now have longer acting prophylactic medication that people can take, which makes it easier to prevent HIV around the world through the use of drugs. There are also novel methods of delivery and broadly neutralizing monoclonal antibodies for new ways to prevent HIV. In fact, monoclonal antibodies have been a remarkable advance in medicine, but their cost is high—tens of thousands of dollars per dose. The challenge is moving this forward in global health because we need vaccines that cost $1 or $2 per dose or are priced according to the cost of HIV care. For that, companies need to be able to manufacture monoclonal antibodies at a lower cost.

Thus, the HIV field is definitely changing, and the non-vaccine strategies are showing promise. However, for all the millions of HIV infected people in this world and for all the infections that are prevented by prophylactic treatment, we have to move forward with whatever works.

Dr. Kim with with IVI's typhoid surveillance and vaccine effectiveness teams in Antananarivo, Madagascar in 2019 (Credit: IVI)

8. Dr. Kim, your experience will be a true inspiration to our readers and many in the healthcare industry. Could you please share a message for future physicians and healthcare professionals that wish to pursue careers in medicine?

- I think that future physicians and people who want to be physicians should never stop trying to improve the quality of people's lives, either by treating patients directly under their care or through research in preventing illness or death. For me, research is what always interested me about medicine. I wanted to be in something where I was on the cutting edge, thinking about problems that are able to bring solutions forward, and not everyone wants to do that. As COVID-19 emphasizes, we have hundreds of thousands of dedicated healthcare professionals around the world doing what they do best, which is saving the lives of those who are suffering. We desperately need people who are willing to do that, and we also need people who are willing to come up with the innovative solutions to move forward. IVI's mission of discovery, development and delivery may enable the world's most vulnerable people to lead full and productive lives by accelerating R&D for vaccines that confer freedom from vaccine preventable illnesses. That is what motivates the people who work at IVI. W

Jerome Kim, M.D.

Director General, International Vaccine Institute (IVI)

Jerome Kim, M.D., an international expert on the evaluation and development of vaccines, currently serves as the Director General of the International Vaccine Institute in Seoul, South Korea. He is also an adjunct professor of medicine at the Uniformed Services University of the Health Sciences and a fellow of the American College of Physicians and the Infectious Diseases Society of America. Dr. Kim received his B.A. from the University of Hawaii and his M.D. from the Yale University School of Medicine. Formerly, he was the principal deputy and chief at the Laboratory of Molecular Virology and Pathogenesis at the Military HIV Research Program. Dr. Kim also served as project manager for the HIV Vaccines and Advanced Concepts Evaluation Project Management Offices. He led the Army's Phase III HIV vaccine trial (RV144), the first demonstration that an HIV vaccine could protect against infection. Throughout his career to date, Dr. Kim has authored over 250 publications and received the John Maher Award for Research Excellence from the Uniformed Services University of the Health Sciences in 2013.

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Biopharma Report

Aurinia's Voclosporin Has Nephrotoxicity Concerns That Could Minimize First-Line Potential for Lupus Nephritis Patients

Aurinia Pharmaceutical's (NASDAQ:AUPH) voclosporin has potential long-term nephrotoxicity concerns that could preclude widespread first-line use in lupus nephritis (LN) until extended safety data becomes available, most experts said. The mode of action, though, means there is first-line treatment potential for patients with elevated proteinuria risk, which typically occurs in more severe LN, some said.

However, a Phase III investigator countered this view, noting the mechanism of action (MOA) means there will be no significant nephrotoxicity concerns. Voclosporin will most likely serve as a second-line treatment for patients unsuccessful on current standards of care (SOCs), this investigator added.

After demonstrating statistically significant improvement in the primary endpoint of complete renal response over placebo in the 52-week Phase III AURORA trial (NCT03021499), voclosporin has a high likelihood of becoming the first FDA-approved LN treatment, experts agreed. The drug's regulatory chances are bolstered by the study's heavy taper of corticosteroids, which carry a multitude of side effects in high doses. In addition, the study found no apparent added toxicity over SOC.

Nevertheless, nephrologists are typically more concerned with sustained renal remission and nephrotoxicity concerns over at least several years, rather than the primary endpoint, most experts said. As a result, nephrologists could be hesitant to prescribe voclosporin, a calcineurin inhibitor (CNI), first-line to patients with an elevated risk of nephrotoxicity until more extended safety data and additional pharmacokinetic analyses of kidney biopsies of treated patients become available, they added.

The CNI class has been prone to nephrotoxicity concerns in the kidney transplant indication. As a result, most experts said they are unclear whether voclosporin, which offers a more stable metabolic profile than the first generation of CNIs, poses similar concerns.

The FDA granted voclosporin a PDUFA date of 22 January 2021, according to a 21 July company press release. According to a one analyst report, voclosporin in LN has expected peak sales of USD 2.13bn in 2034. Aurinia did not respond to a request for comment. Aurinia has a market cap of USD 1.96bn.

Lack of extended safety data hampers placement

Though there are no FDA-approved treatments for LN, mycophenolate mofetil (MMF) or cyclophosphamide are widely considered to be the two SOC first-line treatment options for LN alongside corticosteroid use. In AURORA, patients on voclosporin and MMF together had greater complete renal response and no apparent added toxicity over monotherapy MMF, which experts said will most likely mean FDA approval.

Though the rate of renal remission and safety profile demonstrated in AURORA are encouraging from a regulatory and clinical perspective, nephrologists are typically most concerned with sustained renal remission and nephrotoxicity concerns over at least two to three years, agreed a LN researcher and AURORA investigator Dr Brad Rovin, nephrologist, Wexner Medical Center, University of Ohio. As a CNI, voclosporin could cause nephrotoxicity or kidney fibrosis, which is more likely to occur at least two years after diagnosis, they said. Similar concerns are present in first-generation CNIs and in their use for kidney transplant patients.

As a result, the lack of extended safety data will likely preclude many nephrologists from considering voclosporin as a first-line therapy until this data becomes available, agreed Rovin, the LN researcher and Dr Joan Merrill, professor of medicine, University of Oklahoma Health Sciences Center, Oklahoma City. As a result, both Rovin and the LN researcher said it was unlikely any LN patients with pre-existing impaired kidney function or more susceptible to profibrotic risk would be prescribed voclosporin, particularly as a first-line therapy.

> "Still, most nephrologists would only prescribe this treatment to patients with high levels of proteinuria who are not at a high risk of nephrotoxicity"

However, voclosporin's more stable metabolic profile compared to the previous class of CNIs likely means nephrotoxicity will not be a significant concern, AURORA principal investigator Dr Mary Anne Dooley said. As a result, voclosporin could be an effective later-line treatment option for patients who are not successful on cyclophosphamide or monotherapy MMF initially, said Dooley, rheumatology specialist, Raleigh Neurology Associates, North Carolina.

When compared to cyclosporine, a CNI sometimes used as a later-line LN treatment, voclosporin binds more tightly to the site of activity, uses smaller doses, and does not require constant dose adjustments. These all will likely significantly reduce nephrotoxicity concerns, Dooley added.

Still, the LN researcher said initial signs of nephrotoxicity are often delayed and subclinical, meaning they may not appear during the study's one-year time period. Additionally, because the voclosporin dosage is fixed and does not require consistent metabolic data monitoring to adjust doses, initial clinical signs of nephrotoxicity could be harder to detect, he added.

Rovin agreed with the LN researcher, adding that his lab and several others were histologically examining tissues from kidney biopsies done in some AURORA patients before and after the study in both treatment groups. Additionally, a three-year extension safety study (NCT03597464) is underway for AURORA patients, though neither these results nor data from the biopsy examinations are likely to be available prior to voclosporin's PDUFA date, he said.

MOA beneficial for high-risk proteinuria patients

As a CNI, voclosporin counteracts LN by targeting T cells, which in turn helps stabilize podocytes and

reduces proteinuria and inflammation, Rovin and the LN researcher said. As a result, LN patients with high levels of proteinuria could gain a more pronounced benefit from using voclosporin, making them candidates for-first line use of voclosporin and MMF, they said.

Still, most nephrologists would only prescribe this treatment to patients with high levels of proteinuria who are not at a high risk of nephrotoxicity and do not have significant pre-existing kidney damage, they said. Though the heterogeneity of the LN population makes it difficult to predict the number of patients who could benefit from first-line voclosporin use, the LN researcher predicted 10–40% of the patient population.

Positive results in AURORA are a strong indicator of voclosporin's ability to counteract proteinuria, as urine protein/creatinine ratio (UPCR) was used in part to define complete renal response, Rovin and the LN researcher said. In AURORA, the study's primary endpoint of complete renal remission was defined as UPCR of ≤0.5 mg/mg, estimated glomerular filtration rate (eGFR) ≥60 mL/min, or no decrease from baseline in eGFR of > 20% (Arriens, et al. *Annals of the Rheumatic Diseases* 2020; 79: pp. 172-173).

Strong efficacy, safety in trial support approval likelihood

Because AURORA demonstrated efficacy on top of MMF without any apparent added toxicity, FDA approval is likely, said Rovin. In the 367-patient AURORA study, 40.8% of patients receiving 23.7mg of voclosporin twice a day with 2g of MMF daily had a complete renal response, compared to 22.5% of patients taking only MMF ($p<0.001$), according to the aforementioned paper.

While both immunosuppressors are known to cause side effects, including infection, the lack of increased toxicity in combining voclosporin with the most commonly accepted SOC will be important for regulators, agreed Dr George Tsokos, immunology faculty member, Beth Israel Deaconess Medical Center, Boston, Massachusetts. Severe adverse events (SAEs) were largely consistent in both groups, occurring in 20.8% of patients in the treatment arm, including one death, and 21.3% of patients in the placebo arm, including five deaths. The most commonly occurring SAE was infection, which occurred in 10.1% of voclosporin patients and 11.2% of placebo patients, and no significant changes in eGFR, blood pressure, lipids, or glucose in the voclosporin arm, according to the paper.

Because of the steroid taper, voclosporin demonstrated efficacy against a low placebo response, increasing confidence in the voclosporin's ability to immediately help patients during the study's one-year timeframe from a regulatory standpoint, said Merrill.

Further, in line with a growing movement in nephrology to lower steroid use in light of their many side effects, which include increased blood pressure and bone damage, the steroid taper adds to voclosporin's attractiveness from a clinical standpoint, agreed Merrill and AURORA investigator Dr Cristina Arriens, clinical assistant member, Arthritis & Clinical Immunology Research Program, University of Oklahoma Health Sciences Center. Additionally, despite being only one small molecular change from cyclosporine, voclosporin does not cause hypertension and does not require constant metabolic data monitoring and dose adjusting, Merrill and Rovin said.

In the 265-patient Phase II AURA-LV (NCT02141672) study, patients taking the lower-dose of voclosporin, which was used in the AURORA trial, had complete renal response in 32.6% of patients compared to 19.3% of patients in the placebo group after 24 weeks. Like AURORA, patients in all AURA-LV trial arms underwent background MMF therapy and an aggressive steroid taper (Rovin, et al. *Kidney International* 2019; 95(1): pp. 219-231). Experts said the strong efficacy in the Phase II trial further bolsters voclosporin's regulatory chances. W

William Newton

Reporter, Texas

William Newton is a healthcare reporter for GlobalData focusing on central nervous system diseases and ophthalmology. Previously, he worked at the healthcare information firm Close Concerns, where he covered breaking news in diabetes therapeutics and technology for the company's industry-facing publication, and at the digital health startup Fitscript, where he assisted in researching digital health and lifestyle intervention approaches to treating diabetes. He graduated Williams College with a BA in Economics and Spanish and worked as a News Editor, Executive Editor, and Managing Editor of the Williams Record.

Fate and Celyad's CAR Therapies Offer Potential to Amplify Efficacy With Multiple Doses

Fate Therapeutics' (NASDAQ:FATE) and **Celyad's** (NASDAQ:CYAD) natural killer (NK) cell biology-focused cell therapies could overcome cell persistence challenges and consequent efficacy concerns with redosing strategies, experts said.

One of Fate's lead products, FT596, is an allogeneic, multitargeted, chimeric antigen receptor (CAR) NK cell product. Celyad's autologous CYAD-01 and CYAD-02 and allogeneic CYAD-101 are CAR T cell products using NK cell specificity to target T-cells. One analyst considered the potential to redose allogeneic products as a key item to consider while assessing clinical potential. While clinical data establishing the additive efficacy advantages of giving multiple doses is still preliminary, redosing allogeneic products could increase their expansion and persistence, experts said. Autologous therapies carry source constraints, so the ability to manufacture and administer allogeneic therapies is an advantage, they said.

While past NK cell therapy data has been mixed, experts saw potential in CAR NKs like FT596 or CAR T-cell products engineered to express NKG2D like CYAD-101, given the advancements in cell production.

Phase I FT596 results in B-cell lymphomas/ CLL are expected at either the American Society of Hematology (ASH) meeting in December or an investor meet in early 2021, as per a second analyst report. Phase I data for CYAD-01 and CYAD-02 in relapsed/refractory (r/r) acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are expected by YE20, as per the company's August corporate presentation. Celyad's allogeneic CYAD-101 is being tested in a Phase I alloSHRINK trial (NCT03692429) in metastatic colorectal cancer (CRC), which has a primary completion date of November 2020.

FT596's sales are expected to reach USD 136m in 2026, according to a GlobalData Consensus forecast. Celyad did not respond to a request for comment.

Redosing carries potential efficacy advantages

Increasing the persistence of cell therapies once they are infused into a patient has been a challenge, especially with NK cell-based therapies, experts said. The issue of persistence and consequent efficacy is significant because the potential efficacy with Celyad and Fate's platforms remains largely unknown, they added.

Because the immune system can recognize foreign cells, cell products would not last for more than a few weeks, said Dr Marco Davila, medical oncologist, in the Department of Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, Florida. With CAR T-cell therapies, the expansion and persistence of CAR cells is said to correlate with the durability of response, said Dr David Sallman, assistant member, Department of Malignant Hematology, Moffitt Cancer Center.

Strategies involving multiple doses of cell therapies could maximize the total dose, improve duration, and increase efficacy magnitude with both autologous and allogeneic cell therapies, said Dr Tara Lin, associate professor of medicine, University of Kansas Medical Center, Kansas City. Multiple infusions of a therapy could also potentially lead to a complete remission, said Sallman. In Fate's Phase I FT500 (NCT03841110) study, patients had been given up to six doses of the therapy, which was not found to be toxic, according to Fate CEO Scott Wolchko. Redosing has the potential to offer multiple infusions as a maintenance therapy, said Dr Jeffrey Miller, professor of Medicine, Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis.

"Strategies involving multiple doses of cell therapies could maximize the total dose, improve duration, and increase efficacy magnitude with both autologous and allogeneic cell therapies"

The persistence of allogeneic therapies is not well understood, and it is unknown how long cells need to persist to be effective or whether persisting cells confer durability of response, said Wolchko. Giving multiple doses is one way to overcome the lack of persistence, if it is an important factor for efficacy, he said. In a 4Q19 call, the FDA said it was allowing the dose to be repeated on a patient-by-patient basis, Wolchko said. In the alloSHRINK study, CYAD-101 is administered three times with a two-week interval between each administration in metastatic CRC, as per ClinicalTrials.gov.

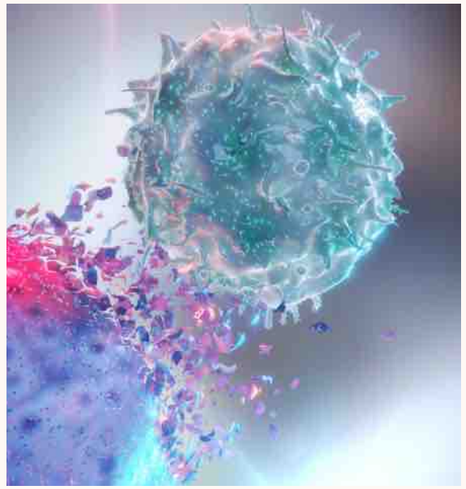
However, even if the engineered cells do not persist in the body, the response rate and ability to eradicate the disease should not be limited, said Davila. With a limited lifespan, allogeneic cell therapies would dissipate as the patient's immune system recovers, said Dan Kaufman. With the incorporation of interleukin (IL)-12 or IL-15 into the cell product, the cell therapy could persist without exogenous cytokines, said Kaufman. The FT596 construct contains a IL-15 fusion protein.

Experts cited the data from a Phase I/II (NCT03056339) investigator-led effort at MD Anderson Cancer Center using cord blood-derived anti-CD19 CAR NK cells as an example of an effective CAR NK therapy. The study by Rezvani and colleagues showed a persistence challenge did not seem to hamper the response, because once a critical threshold for cell expansion is crossed, activity can be mediated, Davila said. Eleven r/r patients with CD19-positive cancers, such as non-Hodgkin's lymphoma or CLL, were treated with a single infusion; eight had a response, including seven with a complete remission (Rezvani et al. [2020] *N Engl J Med*, 382, pp. 545–553). Even if the cells do not persist, they expand to sufficient levels to eradicate the disease before they are lost, Davila added.

In the Phase I THINK (NCT03018405) CYAD-01 data, decreased bone marrow blasts were observed in eight patients, including five objective responses and one stable disease for three or more months, as per the company presentation. Responding patients did have blast clearances, but some of the remissions were short-lived and the cells did not persist in the system, said Sallman. However, the short hairpin (sh) ribonucleic acid (RNA) technology employed CYAD-02, which could increase persistence and expansion, said Sallman (Fontaine et al., [2019] *Blood*, 134[Suppl 1], p. 3931). The shRNA technology allows T cell engineering without the need for gene editing to inhibit alloreactivity and increase persistence, according to Celyad.

Ongoing research on improving preconditioning regimens by combining additional drugs could also help with the persistence of allogeneic products, said Davila. It is not known whether every dose needs a conditioning regimen, but since conditioning regimens can suppress a patient's immune system for several months, it may not be necessary before every therapy infusion, he added.

Patients will not have to receive a preconditioning regimen before every cell infusion, said Wolchko, adding redosing FT500 was found to be safe. Celyad's protocol does not specify the preconditioning strategy for redosing. No predictive biomarkers are available to explain why some patients respond well and others do not, said Sallman, adding it is critical to identify potential responders. Nonetheless, there is no way to predict clinical efficacy based only on preclinical data, so data is still needed, said Miller.

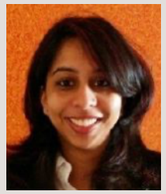


Potential advantages over existing autologous CAR T-cell products

The economic advantage to developing off-the-shelf therapies has driven interest in NK-cell based platforms, said Miller and Davila. If a quick treatment is needed, then an allogeneic NK cell therapy would be better than an autologous therapy, which may take up to six weeks to manufacture, said Sallman. While the results with autologous CAR T-cell therapies have been significant, their scale up and costs are challenging, said Kaufman.

The ability to use induced pluripotent stem cell (iPSCs) or cord blood cells as a source would help scale up the cell manufacture and allow effective results, said Kaufman. iPSCs provide an advancement in expansion protocols, which can provide multiple doses, Miller added. Fate has an iPSC-derived NK cell franchise. Also, since T cell therapies require donor apheresis to collect cells in a process lasting four to five hours, it is not feasible to keep going back to the same donor, said Miller.

Moreover, newer platforms are expected to improve on past NK cell therapy trials, specifically those showing mixed efficacy. Past studies had feasibility limitations in getting the required number of cells, said Miller. Those small studies were conducted at a time when cell isolation and production systems were not as advanced as they are now, said Davila. W



Manasi Vaidya

Reporter, New York

Manasi Vaidya joined as a reporter in New York in February 2015 and has covered the drug development space across a number of therapeutic areas, and built an expertise in writing about oncology. While focusing on analysis pieces about ongoing clinical trials, her coverage has also branched out to regulatory issues, pricing and reimbursement and patent litigation. She has covered practice-changing developments from high profile conferences like ASCO and SABC, in addition to FDA regulatory meetings. She previously covered the Asian biotechnology industry for BioSpectrum, a monthly magazine in India, for two years. She has a Masters degree in Science, Health and Environmental Reporting from New York University, and a Masters degree in Biotechnology from Dr. D. Y. Patil University. Her work has appeared in Nature Medicine, Nautilus and Technology Review India.

ATLANTIC RESEARCH GROUP

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Jane's Journey: The Rare Disease Landscape From a Mother's Perspective

When Jane discovered that her 15-month-old son had the autoimmune disorder Histiocytosis, suddenly she was forced to navigate the complex and unfamiliar terrain of what she called "rare disease land."

She began her journey with questions. The answers were not straightforward. Jane needed compassionate experts to translate the complex clinical language and guide her family through the steps. Fortunately, she connected with doctors who didn't define her son by his disease, as well as with advocates who provided resources for understanding and navigating the clinical landscape.

Over time, Jane became part of the support network, and now serves as a board member of the Histiocytosis Association, helping others who seek guidance for their own journeys.

At Atlantic Research Group, we have seen great things happen when passionate people like Jane combine their strengths to make things better. Together with our Sponsors and Partners around the world, we create smart, feasible studies that account for the challenges faced by people with rare diseases.

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Lessons From Bergamo: Halting the Complement Cascade May Stop COVID-19 in Its Tracks

Treatments for COVID-19 may be focusing on at the wrong elements of the disease, according to physicians analyzing results from Bergamo, Italy, the epicenter of the pandemic in Europe. They realized, as they combed through the data, that COVID-19 is an endothelia injury rather than a pulmonary event and that stopping the complement cascade can have a significant effect on the escalation of symptoms during a patient's illness.

Making that case at a recent Demy-Colton Virtual Salon, Jeffrey Conrad Lawrence, M.D., professor of medicine at **Cornell Medical College**, noted immunohistochemistry analysis of pulmonary autopsy tissue showed "striking depositions of C5b-9 in the microvasculature of the interalveolar septa, including areas of normal appearing lung, which is suggestive of systemic complement activation." C4 and MASP2 deposition also were seen in the septa.

"This was the first time we showed clotting in the small blood vessels, leading to lung damage. Chinese researchers also found it in the kidneys, and we've found it in the skin, which shows the deposition of MASP2 is a systemic problem," Lawrence said. The presence of MASP2 activates the inflammatory system and clotting and, with D-dimers, involves complement, coagulation, and inflammation.

Research showed co-deposition of virus spike points along with complement in the damaged vessels, which leads to activation of MASP2. Consequently, "The virus can directly activate MASP2. This is a very important finding," Lawrence stressed, because it emphasizes the role of complement in COVID-19.

That importance also was indicated in studies of mice. They showed that the survival of infected mice, with 1 million copies per milliliter of the SARS-CoV-2 virus in their bloodstream, hinged on the presence or absence of complement. "Knocking out the complement made the difference," he said.

In severe cases of COVID-19, heparin (a blood thinner) often is administered either prophylactically or therapeutically, but it offers only one avenue of attack. MASP2 activation, however, affects complement and initiates anticoagulation and anti-inflammatory responses. To halt the cascade, Lawrence said, "You need to attack all the processes."

The effects of interrupting the MASP2 cascade are evident in acute thrombotic microangiopathy (TMA). That condition correlates closely with COVID-19. In both conditions, MASP2 levels are very high. In TMA studies, drug narsoplimab was administered. Narsoplimab blocks the activation of caspase 8 – "the first thing activated when killing a macrovascular endothelial cell, Lawrence said –" thus has potential as a COVID-19 treatment by blocking the complement cascade.

"Narsoplimab is an investigational, fully human IgG4 monoclonal antibody (mAb) that binds to MASP2 (the effector enzyme of the lectin pathway of complement), leaves the classical pathway function fully intact, and blocks MASP-2-mediated coagulation," Miguel-Angel Perales, M.D., chief of the adult bone marrow transplantation service at Memorial Sloan Kettering Cancer Center, explained during the virtual salon.

Perales launched a Phase II trial of narsoplimab in TMA patients, which was converted to a pivotal trial after receiving FDA breakthrough therapy designation. Patients were treated once weekly for four weeks. Of the 28 patients in the study, 54% had a complete response rate. Of the 23 who were treated for four weeks or more, 65% (15 patients) had a complete response rate. Of those 15, 93% survived at least 100 days. "These are high response rates," Perales pointed out, "and are supportive of COVID patients who also received narsoplimab."

> "In all, we had clinical resolution of the dramatic respiratory failure and evidence that the hypercoagulation could be downregulated by the treatment with narsoplimab"

These results underscore the importance of blocking the MASP2-mediated complement cascade. "Once the cascade is in motion, taking away the original insult doesn't solve the problem," Perales said.

In Bergamo, Professor Alessandro Rambaldi, professor of hematology at the University of Milan and head of hematology and oncology at Papa Giovanni XXIII Hospital, found himself in the COVID-19 fight soon after the outbreak occurred. "My colleagues called from infectious disease, intensive care, and other departments, asking why their patients had thrombosis. This was unexpected," he recalled, during the virtual salon.

Launching an investigation, he found severe, extensive thrombotic events in the lungs, hearts, and brains of COVID-19 patients as endothelial cells were released into the bloodstream. He began searching for biological markers.

"The parallels between COVID-19 and TMA were strikingly similar," Rambaldi said, reiterating the point Perales made. Both involved endothelial damage that activated the lectin pathway, MASP2 activation, and multi-organ TMA.

In a small trial, Rambaldi administered narsoplimab to six COVID-19 patients who had received continuous airway pressure for less than 48 hours. "Their clinical condition improved rapidly," Rambaldi reported. "The levels of endothelial cells in the blood dropped after

two, four, and six administrations of narsoplimab but in one patient rose again," he continued. One additional administration returned cell levels to normal. Serum levels of LDH, CRP, IL-6, and IL-8 also dropped throughout treatment. Ultimately, all six patients were discharged from the hospital. D-dimer also dropped during treatment and normalized after 25 days. "In all, we had clinical resolution of the dramatic respiratory failure and evidence that the hypercoagulation could be downregulated by the treatment with narsoplimab," Rambaldi said.

The research of these three physicians suggests COVID-19 is an endothelial injury event and that narsoplimab, because of its ability to interrupt the MASP2-mediated cascade, may be an effective treatment for COVID-19. More extensive trials are needed, of course, before it can be authorized for use but, early results appear promising.

by Gail Dutton, BioSpace

BIOPHARMA REPORT IV

Prepping for COVID-19's Next Wave: Is the Glass Half Full or Half Empty?

COVID-19 didn't disappear with summer temperatures, it just shifted locations and demographics. Now, with both autumn and flu season fast approaching, nearly everyone is wondering whether we will endure another round of illnesses that will rival that of last spring.

There is a lot of good news to temper the bad.

"We know a lot more about the disease and how to treat it than we did in March so, reactively, we're better," Chris Ehlinger, CEO of ValhallaMED, told BioSpace.

For example, physicians are realizing COVID-19 may be a disease of the microvascular system rather than a pulmonary disease, according to speakers at the Demy-Colton Virtual Salon, "Lessons from Bergamo." This could be why so many of the therapies that have been tried have had relatively low effects. The good news is that we now know more about what doesn't work and why.

Physicians also are developing a list of sequela, helping them more accurately diagnose cases that last spring may not have been recognized as COVID-19, enabling earlier treatment.

For hospitals, Ehlinger pointed out, "The FDA has been working feverishly to authorize ventilator alternatives. There are 77 to date and 11 dual patient circuits." The federal government also is replenishing emergency supplies of personal protective equipment.

In terms of prevention, the New York Times Vaccine Tracker reports 38 vaccines are in clinical trials for COVID-19, with three approved for limited or early use. More than 120 are in development globally. One already is being administered in Russia.

With so many vaccines in development using multiple different approaches, the halt of Astra Zeneca's Phase III COVID trial is not a major setback. It is still possible for a vaccine for COVID-19 to become available for at least first line responders and the vulnerable by the end of the year.

Populations are better prepared, too. People generally are wearing masks and are accustomed to social distancing to slow the spread of the virus.

Globally, as well as in the U.S., the curve is flattening, as fewer people contract the disease each day.

There will be fluctuations, of course. Just-released projections from the PolicyLab at Children's Hospital of Philadelphia suggest there will be upticks during the next four weeks in the Mid-Atlantic and Sun Belt states. The effect on transmission rates of opening college campuses appears mixed. Some institutions have opened with few outbreaks while others have experienced significant incidents.

Meanwhile, the possibility of herd immunity is growing. So far, approximately 28 million people globally already have had confirmed cases of COVID-19. Of those, about 906,000 have died. That's a mortality rate of 3.2%

The U.S., despite having the most confirmed cases (6,327,009), has a case mortality rate of 3.0%, on par with Australia and significantly lower than that of Italy (12.7%), the UK (11.7%), France (8.2%), Sweden and Canada (6.2% each), and Finland (4.0%), according to Johns Hopkins University of Medicine. Mortality rates depend upon multiple factors, however, and can't be consider alone. For example, as more people are tested, mortality rates decline because less severe cases are discovered.

Unlike last spring, diagnostic tests are now generally available. By September 9, the U.S. Food & Drug Administration (FDA) had authorized 244 COVID-19 tests under emergency use authorizations (EUAs). Of those, 196 were molecular tests, 44 were antibody tests and 4 were antigen tests. This provides a wide range

of testing options from lab PCR tests to point of care assays that deliver results within minutes. This has enabled the U.S. to perform more COVID-19 tests than any nation other than China. In the U.S., 149 tests per 100,000 people are performed daily, dropping the positivity rate from 9% to 8.8% in the course of two days.

Population surveys of antibodies suggest many others have developed cases that were so mild they didn't realize that had contracted the virus. To better track the actual infection rate, the Centers for Disease Control and Prevention (CDC) is performing serology tests in the hardest hit regions of the U.S. It already has results from Connecticut, Louisiana, Minnesota, Missouri, the New York City metropolitan area, Philadelphia, the San Francisco Bay area, South Florida, Utah and Western Washington state. According the survey, the New York City area has the highest seroprevalance rate, at nearly 20%. Missouri had the lowest at 0.8%. Washington, where the outbreak was first noticed, had a seroprevalance rate of nearly 4%.

There's no consensus, yet, on whether having the antibodies from the virus confers immunity, but the theory has held true in other viral outbreaks.

Given what has been learned about SARS-CoV-2 in just the past nine months, the warp speed response of the pharmaceutical industry, and the immediate actions of the federal government to remove needless choke points in the drug and vaccine approval process, we've made substantial progress.

While the nation isn't fully prepared – no vaccines or therapeutics have yet been approved, even under EUAs – there is reason to believe the anticipated next wave may not be as debilitating as the first onslaught last spring. In terms of preparation, we're more than halfway there.

by Gail Dutton, BioSpace

FOLLOW THE JOURNEY OF VIREAD

COMPLETE RESPONSE RESULTS AT YEAR 1...

#1 **Prescribed oral antiviral** according to US prescription data for treatment of CHB[1a]

AT YEAR 1
The primary endpoint—complete response*—was evaluated in Studies 102 and 103[2]

THROUGH YEAR 8
Resistance was evaluated as a secondary endpoint[2,3]

In Study 102 (HBeAg–, n=375) and Study 103 (HBeAg+, n=266), a combined total of 641 adult patients with chronic hepatitis B (CHB) and compensated liver disease who were primarily nucleoside treatment naïve entered a 48-week, randomized, double-blind, active-controlled treatment period comparing VIREAD 300 mg to adefovir dipivoxil 10 mg. Subjects who completed double-blind treatment at Week 48 were eligible to roll over with no interruption in treatment to open-label VIREAD. Of 641 patients enrolled in the initial trials, 412 (64%) completed 384 weeks of treatment.[2]

***The primary endpoint in Studies 102 and 103 was complete response to treatment at 48 weeks as defined by HBV DNA <400 copies/mL (69 IU/mL) + histological response (Knodell necroinflammatory score improvement of ≥2 points without worsening in Knodell fibrosis score). Annual evaluation of resistance was a prespecified secondary endpoint. Cumulative VIREAD genotypic resistance was evaluated annually for up to 384 weeks in Studies 102, 103, 106, 108, and 121.[2,3]**

71% of HBeAg– VIREAD patients vs **49%** of adefovir dipivoxil patients.[2-4]

67% of HBeAg+ VIREAD patients vs **12%** of adefovir dipivoxil patients.[2,3,5]

INDICATION AND USAGE

VIREAD® (tenofovir disoproxil fumarate) is indicated for the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older.

The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- The indication in adults is based on data from treatment of subjects who were nucleoside–treatment-naïve and treatment-experienced with documented resistance to lamivudine. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease
- VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease
- The numbers of subjects in clinical trials who had adefovir resistance-associated substitutions at baseline were too small to reach conclusions of efficacy

IMPORTANT SAFETY INFORMATION

BOXED WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals**
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted**

[a]Healthcare Analytics Monthly data, August 2014-June 2015.

Please see Brief Summary of full Prescribing Information including **BOXED WARNING** on the following pages.

GILEAD IS COMMITTED TO THE EDUCATION AND TREATMENT OF CHRONIC HEPATITIS B.

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Not an actual patient, but is representative of a real patient type. Models are used for illustrative purposes only.

...AT 8 YEARS: NO RESISTANCE WAS DETECTED AT YEAR 1 THROUGH YEAR 8

Annual evaluation of resistance was a prespecified secondary endpoint for Studies 102 and 103 in HBeAg- and HBeAg+ chronic hepatitis B patients[3]; no evidence of resistance was found. Cumulative VIREAD genotypic resistance was evaluated annually for up to 384 weeks in Studies 102, 103, 106, 108, and 121.[2,4,5]

- In the nucleotide-naïve population from Studies 102 and 103, HBeAg+ subjects had a higher baseline viral load than HBeAg– subjects and a significantly higher proportion of the subjects remained viremic at their last time point on VIREAD monotherapy (15% vs 5%, respectively)[2]
- HBV isolates from these subjects who remained viremic showed treatment-emergent substitutions; however, no specific substitutions occurred at a sufficient frequency to be associated with resistance to VIREAD (genotypic and phenotypic analyses)[2]

0%

NO HBV RESISTANCE DEVELOPED
YEAR 1 through YEAR 8
in clinical trials (Studies 102 and 103)[2,3]*

*Data for Years 2 through 8 are from the open-label phase.[6]

- There was a 64% (412/641) retention rate at Year 8: 266/426 patients given VIREAD→VIREAD; 146/215 patients given adefovir dipivoxil→VIREAD[2,6]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

- **New onset or worsening renal impairment:** Cases of acute renal failure and Fanconi syndrome have been reported with the use of VIREAD. In all patients, assess estimated creatinine clearance (CrCl) prior to initiating and during therapy. In patients at risk for renal dysfunction, including those who previously experienced renal events while receiving adefovir dipivoxil, additionally monitor serum phosphorus, urine glucose, and urine protein. In patients with CrCl <50 mL/min, adjust dosing interval and closely monitor renal function. Avoid concurrent or recent use with a nephrotoxic agent. Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after initiation of high dose or multiple NSAIDs in HIV-infected patients with risk factors for renal dysfunction; consider alternatives to NSAIDs in these patients. Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function
- **Coadministration with other products:**
  – Do not use in combination with other products containing tenofovir disoproxil fumarate
  – Do not administer in combination with adefovir dipivoxil
- **Patients coinfected with HIV-1 and HBV:** Due to the risk of development of HIV-1 resistance, VIREAD should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen. HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD
- **Bone effects:** Decreases in bone mineral density (BMD) and mineralization defects, including osteomalacia, have been seen in patients treated with VIREAD. Consider assessment of BMD in adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for bone loss. In a clinical trial conducted in pediatric subjects 12 to <18 years of age with chronic hepatitis B, total body BMD gain was less in VIREAD-treated subjects as compared to the control group. In patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms, hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered

ADVERSE REACTIONS

- **In HBV-infected subjects with compensated liver disease:** Most common adverse reaction (all grades) was nausea (9%). Other treatment-emergent adverse reactions reported in >5% of patients treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash
- **In HBV-infected subjects with decompensated liver disease:** Most common adverse reactions (all grades) reported in ≥10% of patients treated with VIREAD were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%)

DRUG INTERACTIONS

- **Didanosine:** Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy). Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. In patients weighing >60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with VIREAD and in patients weighing <60kg, the didanosine dose should be reduced to 200 mg once daily when coadministered with VIREAD

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS (cont'd)

- **HIV-1 protease inhibitors:** Coadministration decreases atazanavir concentrations and increases tenofovir concentrations; use atazanavir given with ritonavir. Coadministration of VIREAD with atazanavir and ritonavir, darunavir and ritonavir, or lopinavir/ritonavir increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity
- **Drugs affecting renal function:** Coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir

DOSAGE AND ADMINISTRATION

- Recommended dose, in adults and pediatric patients ≥12 years of age (≥35 kg), for the treatment of chronic hepatitis B: one 300 mg tablet, once daily, taken orally, without regard to food
- In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown
- Safety and efficacy in pediatric patients <12 years of age or weighing <35kg with chronic hepatitis B have not been established
- The dosing interval of VIREAD should be adjusted (using recommendations in the table below) and renal function closely monitored in patients with baseline creatinine clearance <50 mL/min

DOSAGE ADJUSTMENT FOR PATIENTS WITH ALTERED CREATININE CLEARANCE

	Creatinine clearance (mL/min)[a]			Hemodialysis patients
	≥50	30-49	10-29	
Recommended 300 mg dosing interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

[a]Calculated using ideal (lean) body weight.

[b]Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

- The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients
- No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50-80 mL/min). Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in these patients
- No data are available to make dose recommendations in pediatric patients with renal impairment

Please see Brief Summary of full Prescribing Information including **BOXED WARNING** on the following pages.

References: 1. Data on file, Gilead Sciences, Inc. Healthcare Analytics. **2.** VIREAD [package insert]. Foster City, CA: Gilead Sciences, Inc.; May 2015. **3.** Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med.* 2008;359(23):2442-2455. **4.** Data on file, Gilead Sciences, Inc. Study 102 CSR. **5.** Data on file, Gilead Sciences, Inc. Study 103 CSR. **6.** Marcellin P, Gane EJ, Flisiak R, et al. Long term treatment with tenofovir disoproxil fumarate for chronic hepatitis B infection is safe and well tolerated and associated with durable virologic response with no detectable resistance: 8 year results from two phase 3 trials [AASLD abstract 229]. *Hepatology.* 2014;60(4)(suppl):313A-314A.

Viread® 300 mg tablets
tenofovir disoproxil fumarate

VIREAD® (tenofovir disoproxil fumarate) tablets

Brief summary of full Prescribing Information. Please see full Prescribing Information including Boxed WARNING. Rx only

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT EXACERBATION OF HEPATITIS

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals *(See Warnings and Precautions)***
- **Severe acute exacerbations of hepatitis have been reported in HBV-infected patients who have discontinued anti-hepatitis therapy, including VIREAD. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy, including VIREAD. If appropriate, resumption of anti-hepatitis B therapy may be warranted *(See Warnings and Precautions)***

INDICATIONS AND USAGE: VIREAD is indicated for the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older.

The following points should be considered when initiating therapy with VIREAD for the treatment of HBV infection:

- The indication in adults is based on safety and efficacy data from treatment of subjects who were nucleoside-treatment-naïve and subjects who were treatment-experienced with documented resistance to lamivudine. Subjects were adults with HBeAg-positive and HBeAg-negative chronic hepatitis B with compensated liver disease *(See Adverse Reactions)*
- VIREAD was evaluated in a limited number of subjects with chronic hepatitis B and decompensated liver disease *(See Adverse Reactions)*
- The numbers of subjects in clinical trials who had adefovir resistance-associated substitutions at baseline were too small to reach conclusions of efficacy

DOSAGE AND ADMINISTRATION: For the treatment of chronic hepatitis B the recommended dose, in adults and pediatric patients ≥12 years of age (≥35 kg), is one 300 mg tablet, once daily, taken orally, without regard to food. In the treatment of chronic hepatitis B, the optimal duration of treatment is unknown. Safety and efficacy in pediatric patients <12 years of age with chronic hepatitis B weighing <35 kg have not been established. **Dose Adjustment for Renal Impairment in Adults:** Significantly increased drug exposures occurred when VIREAD was administered to subjects with moderate to severe renal impairment. Therefore, the dosing interval of VIREAD tablets 300 mg should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease (ESRD) requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients *(See Warnings and Precautions)*. No dose adjustment of VIREAD tablets 300 mg is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance, serum phosphorus, urine glucose and urine protein should be performed in patients with mild renal impairment *(See Warnings and Precautions)*.

Dosage Adjustment for Adult Patients with Altered Creatinine Clearance

	Creatinine clearance (mL/min)[a]			Hemodialysis patients
	≥50	30-49	10-29	
Recommended 300 mg dosing interval	Every 24 hours	Every 48 hours	Every 72 to 96 hours	Every 7 days or after a total of approximately 12 hours of dialysis[b]

a. Calculated using ideal (lean) body weight.
b. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients. No data are available to make dose recommendations in pediatric patients with renal impairment.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). **Exacerbation of Hepatitis after Discontinuation of Treatment:** Discontinuation of anti-HBV therapy, including VIREAD, may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue VIREAD should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. **New Onset or Worsening Renal Impairment:** Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD *(See Adverse Reactions)*. It is recommended that estimated creatinine clearance be assessed in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving adefovir dipivoxil, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of VIREAD, and periodically during VIREAD therapy. Dosing interval adjustment of VIREAD and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min *(See Dosage and Administration)*. No safety or efficacy data are available in patients with renal impairment who received VIREAD using these dosing guidelines, so the potential benefit of VIREAD therapy should be assessed against the potential risk of renal toxicity. VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) *(See Drug Interactions)*. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir DF. Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction. Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients. **Coadministration with Other Products:** VIREAD should not be used in combination with the fixed-dose combination products ATRIPLA®, COMPLERA®, STRIBILD® or TRUVADA® since tenofovir disoproxil fumarate is a component of these products. VIREAD should not be administered in combination with adefovir dipivoxil *(See Drug Interactions)*. **Patients Coinfected with HIV-1 and HBV:** Due to the risk of development of HIV-1 resistance, VIREAD should only be used in HIV-1 and HBV coinfected patients as part of an appropriate antiretroviral combination regimen. HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with VIREAD. It is also recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B before initiating treatment with VIREAD.

Bone Effects

Bone Mineral Density: In clinical trials in HIV-1 infected adults, VIREAD was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving VIREAD *(See Adverse Reactions)*.

Clinical trials evaluating VIREAD in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the VIREAD-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected *(See Adverse Reactions)*.

The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects: Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of VIREAD *(See Adverse Reactions)*. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF *(See Warnings and Precautions)*.

Brief Summary (Cont'd)

ADVERSE REACTIONS: Clinical Trials in Adult Subjects with Chronic Hepatitis B and Compensated Liver Disease: *Treatment-Emergent Adverse Reactions:* In controlled clinical trials in subjects with chronic hepatitis B (0102 and 0103), more subjects treated with VIREAD during the 48-week double-blind period experienced nausea: 9% with VIREAD versus 2% with adefovir dipivoxil. Other treatment-emergent adverse reactions reported in >5% of subjects treated with VIREAD included: abdominal pain, diarrhea, headache, dizziness, fatigue, nasopharyngitis, back pain, and skin rash. No significant change in the tolerability profile was observed with continued treatment with VIREAD for up to 384 weeks.

Laboratory Abnormalities: in Studies 0102 and 0103 (0–48 Weeks) laboratory abnormalities (Grades 3–4) reported in ≥1% of subjects treated with Viread (n=426) and adefovir dipivoxil (n=215), respectively, were: any ≥Grade 3 laboratory abnormality (19%, 13%); creatine kinase (M: >990 U/L; F: >845 U/L) (2%, 3%); serum amylase (>175 U/L) (4%, 1%); glycosuria (≥3+) (3%, <1%); AST (M: >180 U/L; F: >170 U/L) (4%, 4%); and ALT (M: >215 U/L; F: >170 U/L) (10%, 6%). Laboratory abnormalities (Grades 3–4) were similar in subjects continuing VIREAD treatment for up to 384 weeks in these trials.

The overall incidence of on-treatment ALT flares (defined as serum ALT >2 × baseline and >10 × ULN, with or without associated symptoms) was similar between VIREAD (2.6%) and adefovir dipivoxil (2%). ALT flares generally occurred within the first 4-8 weeks of treatment and were accompanied by decreases in HBV DNA levels. No subject had evidence of decompensation. ALT flares typically resolved within 4-8 weeks without changes in study medication. The adverse reactions observed in subjects with chronic hepatitis B and lamivudine resistance who received treatment with VIREAD were consistent with those observed in other hepatitis B clinical trials in adults. *Clinical Trial in Adult Subjects with Chronic Hepatitis B and Decompensated Liver Disease:* In a small randomized, double-blind, active-controlled trial (0108), subjects with CHB and decompensated liver disease received treatment with VIREAD or other antiviral drugs for up to 48 weeks. Among the 45 subjects receiving VIREAD, the most frequently reported treatment-emergent adverse reactions of any severity were abdominal pain (22%), nausea (20%), insomnia (18%), pruritus (16%), vomiting (13%), dizziness (13%), and pyrexia (11%). Two of 45 (4%) subjects died through Week 48 of the trial due to progression of liver disease. Three of 45 (7%) subjects discontinued treatment due to an adverse event. Four of 45 (9%) subjects experienced a confirmed increase in serum creatinine of 0.5 mg/dL (1 subject also had a confirmed serum phosphorus <2 mg/dL through Week 48). Three of these subjects (each of whom had a Child-Pugh score ≥10 and MELD score ≥14 at entry) developed renal failure. Because both VIREAD and decompensated liver disease may have an impact on renal function, the contribution of VIREAD to renal impairment in this population is difficult to ascertain. One of 45 subjects experienced an on-treatment hepatic flare during the 48 week trial.

Clinical Trials in Pediatric Subjects 12 Years of Age and Older with Chronic Hepatitis B: Assessment of adverse reactions is based on one randomized study (0115) in 106 pediatric subjects (12 to less than 18 years of age) infected with chronic hepatitis B receiving treatment with VIREAD (N = 52) or placebo (N = 54) for 72 weeks. The adverse reactions observed in pediatric subjects who received treatment with VIREAD were consistent with those observed in clinical trials of VIREAD in adults. In this study, both the VIREAD and placebo treatment arms experienced an overall increase in mean lumbar spine BMD over 72 weeks, as expected for an adolescent population. The BMD gains from baseline to Week 72 in lumbar spine and total body BMD in VIREAD-treated subjects (+5% and +3%, respectively) were less than the BMD gains observed in placebo-treated subjects (+8% and +5%, respectively). Three subjects in the VIREAD group and two subjects in the placebo group had significant (greater than 4%) lumbar spine BMD loss at Week 72. At baseline, mean BMD Z-scores in subjects randomized to VIREAD were −0.43 for lumbar spine and −0.20 for total body, and mean BMD Z-scores in subjects randomized to placebo were −0.28 for lumbar spine and −0.26 for total body. In subjects receiving VIREAD for 72 weeks, the mean change in BMD Z-score was −0.05 for lumbar spine and −0.15 for total body compared to +0.07 and +0.06, respectively, in subjects receiving placebo. As observed in pediatric studies of HIV-infected patients, skeletal growth (height) appeared to be unaffected *(See Warnings and Precautions)*.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of VIREAD. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: allergic reaction, including angioedema, lactic acidosis, hypokalemia, hypophosphatemia, dyspnea, pancreatitis, increased amylase, abdominal pain, hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT), rash, rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy, acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria, asthenia. The following adverse reactions listed above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

DRUG INTERACTIONS: Didanosine: Coadministration of VIREAD and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions. When administered with VIREAD, C_{max} and AUC of didanosine increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis and neuropathy. Suppression of $CD4^+$ cell counts has been observed in patients receiving VIREAD with didanosine 400 mg daily. In patients weighing >60 kg, the didanosine dose should be reduced to 250 mg once daily when it is coadministered with VIREAD. In patients weighing <60 kg, the didanosine dose should be reduced to 200 mg once daily when it is coadministered with VIREAD. When coadministered, VIREAD and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). For additional information on coadministration of VIREAD and didanosine, please refer to the full Prescribing Information for didanosine. **HIV-1 Protease Inhibitors:** VIREAD decreases the AUC and C_{min} of atazanavir. Viread should not be coadministered with atazanavir without ritonavir. Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations. Tenofovir disoproxil fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir disoproxil fumarate is coadministered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving VIREAD concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for VIREAD-associated adverse reactions. VIREAD should be discontinued in patients who develop VIREAD-associated adverse reactions. **Drugs Affecting Renal Function:** Since tenofovir is primarily eliminated by the kidneys, coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs *(See Warnings and Precautions)*. In the treatment of chronic hepatitis B, VIREAD should not be administered in combination with adefovir dipivoxil.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Pregnancy Category B:* There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD should be used during pregnancy only if clearly needed. *Antiretroviral Pregnancy Registry:* To monitor fetal outcomes of pregnant women exposed to VIREAD, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263. *Animal Data:* Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. **Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1.** Samples of breast milk obtained from five HIV-1 infected mothers in the first post-partum week show that tenofovir is secreted in human milk. The impact of this exposure in breastfed infants is unknown. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving VIREAD. Geriatric Use:** Clinical studies of VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Patients with Impaired Renal Function:** It is recommended that the dosing interval for VIREAD be modified in patients with estimated creatinine clearance <50 mL/min or in patients with ESRD who require dialysis *(See Dosage and Administration)*.

For detailed information, please see full Prescribing Information. To learn more call 1-800-GILEAD-5 (1-800-445-3235) or visit www.VIREAD.com.

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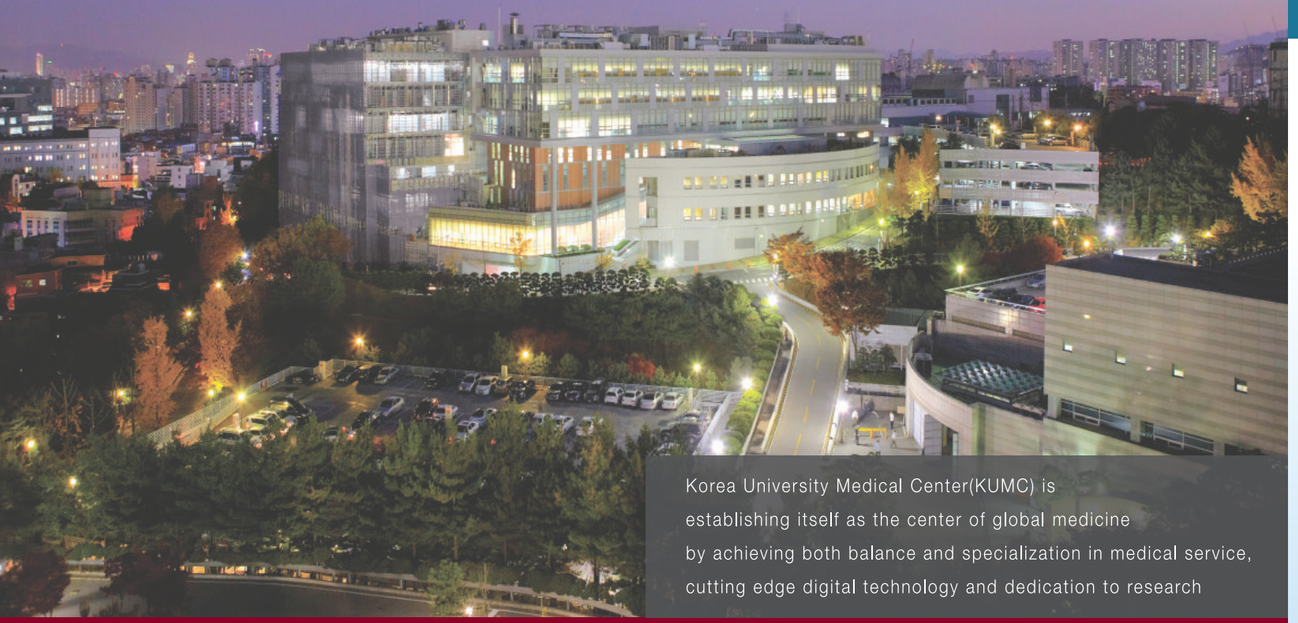

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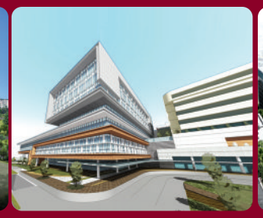

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Conference Alerts

North America

Infectious Diseases Virtual Partnering Event

December 2-4, 2020 | Virtual Conference

Website: https://virtual-partnering.com/infectious-diseases/
Contact: https://virtual-partnering.com/contact/?e=infectious-diseases-virtual-partnering

The Infectious Diseases Virtual Partnering Event is a face-to-face targeted meetings where top biotechs and biopharmaceutical companies will meet, network and partner to accelerate infectious diseases pipelines and bring new treatment options to patients worldwide. This event will leverage Inova Software and Biotechnology Innovation Organization (BIO)'s biopharma industry expertise, leading digital networking platform and years of experience organizing partnering events to connect scientific and business communities for the benefit of patients. worldwide.

62nd ASH Annual Meeting and Exposition

December 5-8, 2020 | Virtual Conference

Website: https://www.hematology.org/meetings/annual-meeting
Contact: 202-776-0544

The 62nd ASH Annual Meeting and Exposition is the the world's most comprehensive hematology event of the year for an invaluable educational experience and the opportunity to review thousands of scientific abstracts highlighting updates in the hottest topics in hematology.

39th Annual J.P. Morgan Healthcare Conference

January 11-14, 2021 | Virtual Conference

Website: https://www.jpmorgan.com/solutions/cib/insights/healthcare-conference

The annual J.P. Morgan Healthcare Conference is the largest and most informative healthcare investment symposium in the industry, brining together industry leaders, emerging fast-growth companies, innovative technology creators, and members of the investment community. The hundreds of companies presenting run the gamut, from start-ups to those with more than $300 billion in market cap, and encompass the entire global healthcare landscape, including pharmaceutical firms, healthcare service providers, profit and not-for-profits, and medical device companies.

2021 Biotech Showcase

January 11-15, 2021 | Virtual Conference

Website: https://informaconnect.com/biotech-showcase/
Contact: conferences@ebdgroup.com

Biotech Showcase is an investor conference, during JPM 2020, devoted to providing private and public biotechnology and life sciences companies with an opportunity to present to, and meet with, investors and pharmaceutical executives in one place during the course of one of the industry's largest annual healthcare investor conferences.

BIO CEO & Investor Digital Conference

February 16-18, 2021 | Virtual Conference

Website: https://www.bio.org/events/bio-ceo-investor-digital-conference
Contact: info@bio.org

Now in its 22nd year, the 2021 Biotechnology Innovation Organization (BIO) CEO & Investor Conference is one of the largest independent investor conferences focused on established and emerging publicly traded and select private biotech companies. Experience the best of biotech with two days of productive partnering meetings with institutional and early-stage investors, industry analysts, and senior biotechnology executives, in one location. The virtual 2021 event will showcase the BIO perspective on the new U.S. Congressional agenda, the record setting pacing of biotech IPOs and the hottest clinical developments and industry catalysts.

12th Annual CUGH Conference

February 16-18, 2021 | Virtual Conference

Website: https://www.cugh2021.org
Contact: info@cugh.org

The theme of the 12th Annual Consortium of Universities for Global Health is "Addressing Critical Gaps in Global Health and Development." Over 1800 scientists, students and implementers from academia, NGOs, government and the private sector will present, learn and collaborate to address some of the pressing challenges our world faces. Attendees will have many opportunities to engage, learn, contribute, and collaborate in a dynamic, inspiring environment.

Europe

IMCAS World Congress 2021

January 28-30, 2021 | Paris, France

Website: https://www.imcas.com/en/attend/imcas-world-congress-2021
Contact: contact@imcas.com

IMCAS marks two decades of being at the forefront of multi-specialty conferences dedicated to aesthetic science. A record of 12,000 delegates, from dermatology, plastic surgery, and related professions, will be seizing this exceptional opportunity to explore the hottest topics related to the medical aesthetic field. The conference will be a hybrid congress with new products and activities to gain the exposure from the prominent physicians and industry players in aesthetics both physically and digitally. In addition to hundreds of the world's experts and innovators sharing their insights, IMCAS Annual World Congress will also host 250 international exhibiting companies.

DIA Europe 2021

March 15-19, 2021 | Virtual Conference

Website: https://www.diaglobal.org/Flagship/DIA-Europe-2021
Contact: https://www.diaglobal.org/en/flagship/dia-europe-2021/about/contact

DIA Europe 2021 is the largest and most forward-looking neutral healthcare conference in Europe. This annual healthcare meeting is event for all life science professionals working in drug development, from discovery to marketed use. It also reflects DIA's strategic initiatives across several Thought Leadership streams, including Clinical Development & Operations, Regulatory Science & Operations, Value and Access, Medical Affairs and many others.

Conference Alerts

Asia

13th Asia Pacific Pediatrics Congress

November 25-26, 2020 | Virtual Conference

Website: https://pediatrics.pediatricsconferences.com
Contact: asianpediatrics@globalconferences.net

Asian Pediatrics 2020 will be an innovative and informative International conference reflecting the direction of Pediatrics in the 21st century and offers a wide range of diversions to participants of all backgrounds. This Pediatric conference provides an excellent opportunity to discuss the latest developments within the field. The conference runs with the theme "Meeting the Challenges in the field of Pediatrics."

International Conference on Neurology and Neural Disorders

December 14-15, 2020 | Virtual Conference

Website: https://neurology.insightconferences.com
Contact: neuraldisorders@theexpertsmeet.com

Neurology Research Conference 2020 will join world-class professors, scientists, researchers, students, perfusionist, neurologist to discuss methodology for ailment remediation for neuro diseases and health disorders. The conference is planned to give various information that will keep helpful specialists next to each other of the issues impacting the expectations, finding and treatment of neuro diseases. It also provides the opportunity to learn the latest advances in the field of Neurology and healthcare and to exchange scientific ideas and experiences in a distinctive environment.

CPhl China 2020

December 16-18, 2020 | Shanghai, China

Website: https://www.cphi.com/china/en/home.html
Contact: +31-20-708-1637

CPhl China is a gateway to successfully grow the business at the 2nd largest pharma market in the world and the leading pharmaceutical ingredients show in China. The event presents a great opportunity to connect with China's market leaders, meet existing clients, stay on top of industry trends and regulations and more. It is a one-stop-shop platform for reaching out to the entire Chinese pharmaceutical supply chain, including every stakeholder, from beginning to end of the professional chain.

BIO Asia International Conference

March 9-10, 2021 | Tokyo, Japan

Website: https://www.bio.org/events/bio-asia-international-conference
Contact: register@bio.org

The BIO Asia International Conference brings together the global biotechnology and pharmaceutical industry to explore licensing collaborations and investor engagement in the current Asia-Pacific business and policy environments. Gain insights into the changes, challenges, and opportunities key opinion and policy leaders foresee for the Japanese biotech market and throughout the region. Companies with more than 460 therapeutic assets from more than 25 countries pursued Partnering discussions at the Tokyo conference.

LATEST HEALTHCARE INDUSTRY NEWS

SEP – NOV 2020

1. Serum Institute of India Initiates Manufacturing of Codagenix's Intranasal Live-Attenuated COVID-19 Vaccine Candidate

The Serum Institute of India, Ltd., the world's largest vaccine maker by the number of doses produced, has begun manufacturing CDX-005, the company's intranasal, live-attenuated vaccine candidate for SARS-CoV-2, the virus that causes COVID-19. Having received the necessary regulatory approval from the Review Committee on Genetic Manipulation (RCGM) of India's Department of Biotechnology (DBT), Serum Institute will initiate manufacturing for large-scale safety and efficacy studies. Codagenix is collaborating with the Serum Institute of India to develop CDX-005. Preclinical animal studies have been successfully completed, and Codagenix expects to initiate a Phase 1 first-in-human clinical trial in the UK by the end of 2020.
https://www.biospace.com/article/releases/serum-institute-of-india-initiates-manufacturing-of-codagenix-s-intranasal-live-attenuated-covid-19-vaccine-candidate/?keywords=september

2. Blueprint's Bet on Itself Pays Off With Rare Disease Drug Data

A cancer drug developed by Blueprint Medicines could help treat a rare and debilitating disease called systemic mastocytosis, based on Blueprint's results from two trials. Treatment with Ayvakit, which was approved by the FDA in January 2020, for an uncommon type of gastrointestinal tumor, significantly reduced the proliferation of mast cells throughout the body, addressing the cellular cause of the chronic and unpredictable symptoms that people with systemic mastocytosis experience. Blueprint plans to ask the FDA to expand Ayvakit's use to allow for the treatment of systemic mastocytosis, a step that would further boost the company's drug pipeline.
https://www.biopharmadive.com/news/blueprint-ayvakit-mastocytosis-study-independent/585666/

3. Gene Therapy Company Taysha Completes Sprint From First Funding to IPO

Taysha Gene Therapies announced it would sell its first publicly traded shares at $20 apiece in an upsized initial public offering in a year that has featured dozens of lucrative biotech listings. The offering was priced at the top end of its estimated range and should raise $157 million. The company's focus is on rare, mutation-driven neurodegenerative disorders and, prior to its IPO, it received $126 million in venture financing to develop a pipeline of 18 announced programs, including a therapy it bought from Abeona Therapeutics. By developing a large arsenal of experimental gene therapies, Taysha is attempting to build a sustainable company that won't be tied to the market potential of a potentially one-time treatment for a disease with few affected individuals.
https://www.biopharmadive.com/news/taysha-gene-therapy-ipo/585834/

4. White House Approves Tougher Rules for COVID-19 Vaccine Development

The White House approved tough new rules for coronavirus vaccine developers that will make it unlikely that a vaccine will be approved before the 2020 Election Day. The approval came only after the U.S. FDA published the updated guidelines on its website as part of briefing materials for outside vaccine advisers. The guidelines recommend that participants in late-stage vaccine clinical trials be followed for a median of at least two months, starting after they receive a second shot. The standards, which would be applied to an emergency-use authorization for a vaccine, are similar to the standards for a traditional approval, but the criteria are likely to delay authorization of a vaccine.
https://www.usnews.com/news/health-news/articles/2020-10-07/white-house-approves-tougher-rules-for-covid-19-vaccine-development

5. FDA Approves Regeneron Antibody Drug as First Ebola Virus Treatment

The FDA approved the first treatment for the Ebola virus, clearing an antibody drug cocktail that was shown in a landmark 2019 study to reduce the risk of dying from the lethal and feared infectious disease. The drug, now dubbed Inmazeb, was developed by a New York biotech, Regeneron, in response to a different Ebola outbreak that spread virulently throughout several West African nations between 2014 and 2016. U.S. government researchers, working together with international aid groups and investigators from the Democratic Republic of Congo, tested the drug alongside three other antiviral treatments in the trial, which was conducted last year during the recent Ebola virus outbreak in the central African country.
https://www.biopharmadive.com/news/fda-ebola-drug-regeneron-first-approval/587066/

6. Lily Wagers $135M on a Startup's Plan to Stop Neurodegeneration

Eli Lilly has reached a deal to acquire Disarm Therapeutics, a biotech startup developing treatments for neurological diseases. Lilly will pay $135 million upfront and could shell out another $1.2 billion in milestone payments, although that additional cash isn't guaranteed. The acquisition gives Lilly rights to an early portfolio of experimental medicines meant to prevent the degeneration of axons, the thin tails of nerve cells that send out electrical impulses. None of the drugs are in human testing yet. The deal is a bet by Lilly on a startup trying to prove that devastating neurological conditions like multiple sclerosis can be treated by protecting axons.
https://www.biopharmadive.com/news/eli-lilly-disarm-neurodegeneration-drug-deal/587114/

7. Gloomy COVID Drug Data Shows Why Big, Randomized Trials Matter

According to the results of the world's largest randomized clinical trial of potential COVID-19 drugs run by the WHO, Gilead's Remdesivir—an antiviral originally developed to treat Ebola—showed no benefit on survival rates. A striking factor of the results was the apparent difference to the company's own study. It showed that the treatment cut recovery time by five days compared with patients who got a placebo. In response to the data, Gilead questioned the accuracy of the WHO study, spurring a debate about what makes a trial more accurate.
https://www.reuters.com/article/us-health-coronavirus-remdesivir-trials/gloomy-covid-drug-data-shows-why-big-randomised-trials-matter-idUSKBN2712FS

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