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WAMJ

World Asian Medical Journal

Inspirational Asian Healthcare Leader

JOANNE LIU

International President of Médecins Sans Frontières (MSF)

SPECIAL REPORT
In Memory of Dr. Waun Ki Hong, the Physician-Scientist Who Transformed and Redefined Cancer Treatment

BIOPHARMA REPORT I
Both AbbVie's Orilissa and Myovant's Relugolix Expected to Face Similar Payer Scrutiny in Uterine Fibroids

BIOPHARMA REPORT II
Novartis' Zolgensma Has First-Line Potential in Spinal Muscular Atrophy (SMA)

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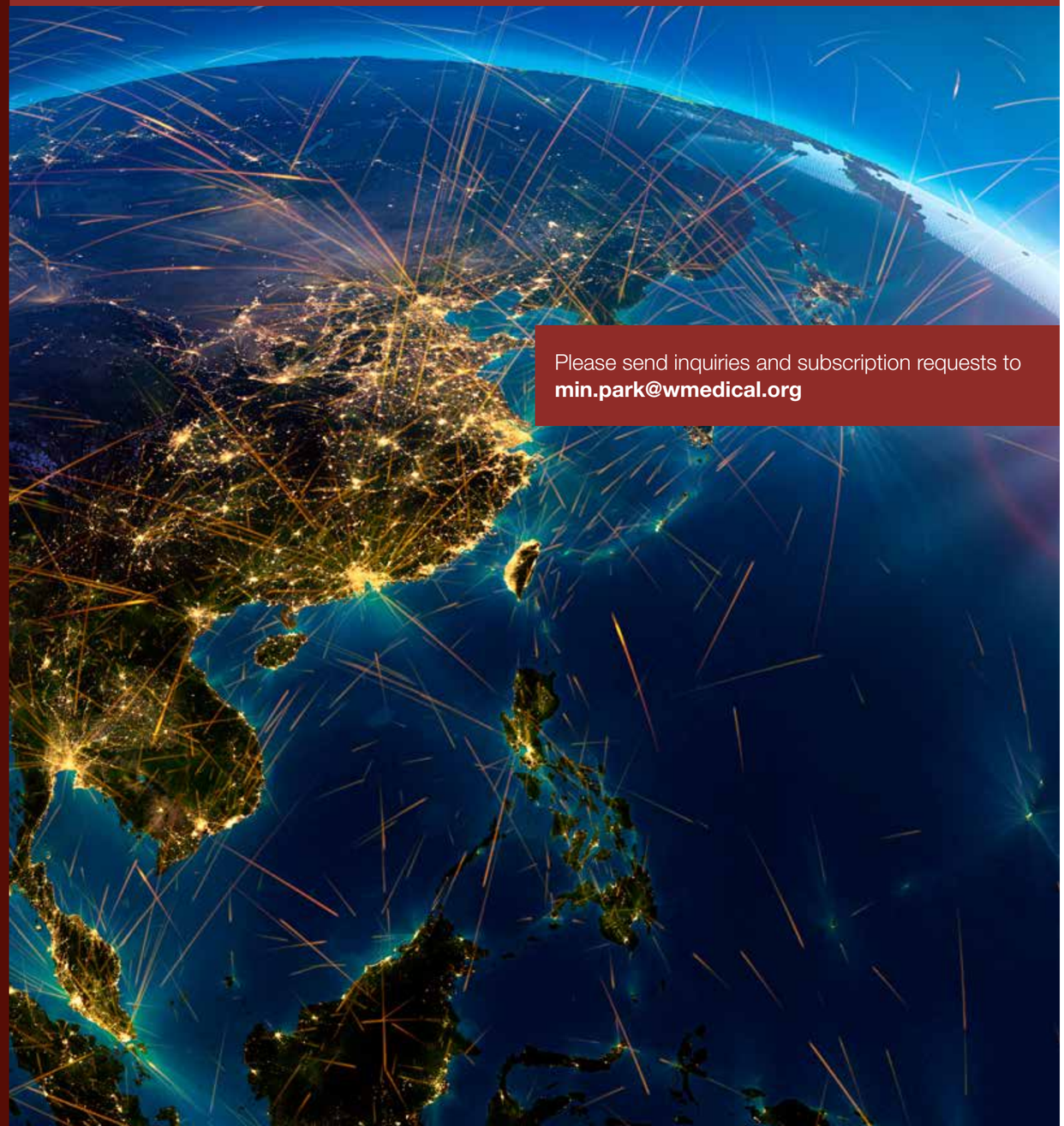

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From the Publisher

Welcome to the inaugural edition of the World Asian Medical Journal (WAMJ)! I am immensely delighted that WAMJ has finally come into fruition, and am very proud of the editorial board and staff members who have made this launch possible.

Last March marked five years since the first publication of the World Korean Medical Journal (WKMJ) back in 2014. Over the span of 18 issues, the magazine has become a platform for Korean healthcare professionals across the globe. While WKMJ has focused on the growth and competitive nature of Korea as a medical hub, we have witnessed the larger region of Asia emerge as the world's newest healthcare block. As such, we have decided to reflect this significant wave of change into our publication by expanding our coverage and republishing the magazine as the World Asian Medical Journal (WAMJ).

Our new expansion does not only reflect changes in our regional coverage, but it also incorporates newly added contents and values. In WAMJ's upcoming editions, the publication will address sustainability, community, and justice, building upon our original themes regarding innovation and advancements made in the therapeutic world.

As the Cover Story of our inaugural edition, we feature an exemplary and inspiring leader in the medical arena, Dr. Joanne Liu, International President of the non-profit organization, Médecins Sans Frontières (MSF) also known as Doctors Without Borders. MSF is an independent, international humanitarian organization whose mission is to provide medical assistance to populations affected by conflicts, epidemics, disasters, or exclusion from healthcare. In this issue, Dr. Liu shares the importance of healthcare professionals' engagement with underserved regions and populations. Her words show the stark reality of several ongoing crises we face today, but she also demonstrates the determination that we all need in order to contribute to the betterment of our world.

In this edition's Special Report, we devote an article remembering the late Dr. Waun Ki Hong and his contributions, titled: "In Memory of Dr. Waun Ki Hong, the Physician-Scientist who Transformed and Redefined Cancer Treatment." Last January, the cancer medicine field and the medical community at large lost Dr. Hong, a legacy and past President of the American Association of Cancer Research (AACR), who passed away at the age of 76. With this issue's Special Report, we hope to give our readers a look into the great achievements of one of our predecessors in the field of medicine.

In preparation for WAMJ's launch, we have also composed a new editorial board which includes 23 eminent physicians, industry executives, and other well-respected healthcare professionals to fulfill our mission. With that, I conclude this letter with a warm wish that WAMJ will continue to be informative, inspiring, and amusing to our readers.

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

From the Editor-in-Chief

Welcome to the inaugural issue of the World Asian Medical Journal, the successor to the World Korean Medical Journal. Just as the WKMJ provided a forum for Korean health care professionals and those of Korean descent, the WAMJ aims to do the same for professionals from all East Asian nations. After all, W Medical Strategy Group has long benefited its clients with its special knowledge and contacts not just in Korea, but throughout East Asia. Hence, the WAMJ is a logical extension of the WMKJ. This evolution is apparent even in this, WAMJ's first issue, which continues the WMKJ tradition of profiling prominent physicians and industry leaders.

Somalia. Afghanistan. Syria. These are among the world's most underserved and dangerous countries. They are also among the 70 nations that, throughout its history, Médecins Sans Frontières (MSF; Doctors Without Borders) has assisted, sending urgently needed doctors, nurses, medicines, food, and supplies to places from which some of their personnel, sadly, never return.

In this issue, we interview Joanne Liu, M.D., C.M., the pediatric emergency physician now completing her term as President of MSF. She continues her field work, alongside other providers both from MSF and from the communities served. Dr. Liu describes some of the desperate conditions her organization faces in areas where disease is rampant, but care is scarce, not least because, too often, belligerents kill indiscriminately. Even apart from live fire, the countries MSF serves often face abject poverty, unsafe water, and severe malnutrition. Death can come quickly. MSF overcomes challenges that most health professionals never face. MSF and Dr. Liu's story is inspiring.

As we read in Ecclesiastes, however, there is a time to be born and a time to die. In this issue, we mourn the loss earlier this year of Waun Ki Hong, M.D., past division Head and Professor at the University of Texas MD Anderson Cancer Center, past President of the American Association of Cancer Research (AACR), and a Samsung Distinguished University Chair in Cancer Medicine. Dr. Hong's extraordinary achievements are a model to all those privileged to care for the sick.

Readers of our predecessor journal, the World Korean Medical Journal, will remember the story we did on Dr. Hong in its 12th edition. It would be difficult to name a better choice, then or now, for a profile in a publication such as ours. It is only fitting, then, that we note his passing and remind ourselves what we can accomplish when we draw on the best within us, as Dr. Hong did throughout his exemplary life.

We hope you will enjoy this and all subsequent issues of WAMJ.

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

WAMJ Recap of the Last Issue

COVER STORY
Terry Kim, MD, Vice President and President-Elect of American Society of Cataract and Refractive Surgery (ASCRS)

Dr. Terry Kim is a Professor of Ophthalmology at Duke University School of Medicine and serves as Chief of the Cornea and External Disease Division and Director of the Refractive Surgery Service at Duke University Eye Center. His academic accomplishments include over 300 peer-reviewed journal articles, textbook chapters, and scientific abstracts as well as 4 well-respected textbooks on corneal diseases, corneal transplantation, and cataract surgery. Dr. Kim serves on the Executive Committee of ASCRS and other renowned medical societies. Today, he serves as the Consultant to the Ophthalmic Devices Panel of the FDA, Consultant Ophthalmologist for the Duke Men's Basketball Team, and Consultant to numerous ophthalmic companies. To learn more about Dr. Kim, please refer to issue 18 of WKMJ.

SPECIAL REPORT
New York Health Forum at a Glance

The New York Health Forum (NYHF) is a quarter-yearly, one-day event that attracts innovators from all areas of the global medical and life sciences industry for discussions that examine the most pressing issues and concerns facing the healthcare industry. With its most recent 12th forum back in May 2019, what began as an audience of 50 has quickly grown to about 200. With a continuously growing number of prominent attendees, the NYHF places special emphasis on the quality of its panel discussions, carefully assembling its programs of guest speakers. To find out more about the New York Health Forum, please read issue 18 of WKMJ.

BIOPHARMACEUTICAL REPORT I
Aldeyra's Reproxalap Has Experts Mixed on Seasonal Allergic Conjunctivitis Focus in Phase III

Aldeyra Therapeutics' Reproxalap faces mixed opinions surrounding its Phase III study in allergic conjunctivitis. While some experts believe Reproxalap's Phase III trial will be a success, some believe otherwise due to their uncertainty in the previous Phase IIb study. In a press release announced in June 2017 regarding the Phase IIb study, the data showed Reproxalap to be well-tolerated with no significant side effect. However, it left some doubt due to Phase IIb's flaw in proving its statistical significance and due to its inability to show long-term and chronic-use safety. To read more about Aldeyra Therapeutics' Reproxalap studies, please refer to issue 18 of WKMJ.

BIOPHARMACEUTICAL REPORT II
Aclaris' Phase II Result for ATI-502 and ATI-501 in Alopecia May Lack Cosmetic Significance

Aclaris Therapeutics' Phase II ATI-502 for alopecia areata (AA) and Phase II for ATI-501 for AA, alopecia universalis (AU) and alopecia totalis (AT) may lack cosmetic significance due to their primary endpoints. Experts claim the ATI-501 and ATI-502 trials' endpoints using the Severity of Alopecia Tool (SALT) are inadequate to gauge cosmetic significance because SALT is a tool used to measure hair loss, not growth. Thus, although the SALT measurement determined clinical significance in the trials, there was no hard evidence for any cosmetic significance, which is more important for the patients. To find out more about Aclaris Therapeutics' Phase II studies for ATI-502 and ATI-501 in Alopecia, please read issue 18 of WKMJ.

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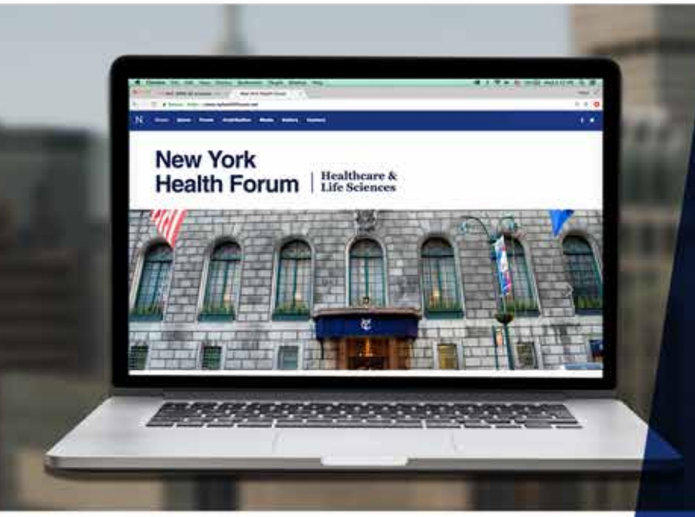

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Inspirational Asian Healthcare Leader

Dr. Joanne Liu, M.D., C.M., FRCPC,
International President of
Médecins Sans Frontières

1. Dr. Joanne Liu, you have served as International President of Médecins Sans Frontières (MSF) since 2013 and have been involved with the organization since 1996. Could you please explain to our readers about MSF as a global humanitarian organization and how it operates?

- Simply put, MSF operates on one core principle: to work in areas that demonstrate need for medical humanitarian help. Many people from all over the world lack access to healthcare for a range of reasons. MSF works to help these populations situated in conflict zones, protected crises, epidemics, natural disasters, and those who are stigmatized and marginalized. In the past, for example, we have provided assistance to women in Afghanistan.
Currently, we are working with populations that suffer from neglected tropical diseases or NTDs such as Leishmaniasis. These are the kinds of events we are witnessing.

Dr. Liu posing with an Ebola survivor at the Ebola treatment center in Butembo, DR Congo (Photo by: Laurie Bonnaud/MSF)

For MSF, there is one stark event, what I call a black day in our history that occurred in Kunduz, a city in northeastern Afghanistan. Back in October 3rd of 2015, the Kunduz Trauma Center operated by our team was bombed by not one, but by five air strikes within the span of an hour and 10 minutes, and 42 people lost their lives. It is one thing when one air strike happens; it is another when five precise air strikes hit the central building of our trauma center. This is what I call a precise mistake. This event alongside the others I've mentioned earlier demonstrate a change in the way wars are being waged today.

One of the things we did during my two mandates is that MSF sought after political reaffirmations that hospitals would remain a safe space for both patients and medical staffs, whether in Kunduz, Afghanistan; Sana'a, Yemen; or Montreal, Canada. This was reiterated with the Resolution 2286 on May 3rd, 2016. In reality however, although it was voted unanimously with 80 countries backing up the resolution, the fact remains that the resolution did not change much of this problem. This represents that change in how wars are waged is related to the change in the world's multilateral platform and brings up the question, "What power do they really have?"

The other thing that has really changed, and I think we need to emphasize, is the criminalization of migrants, or people who are fleeing for their lives. Right now, refugees placed in Libyan migrant detention centers are stripped of their basic human rights. The fact that we are also criminalizing those bringing aid to migrants or refugees crossing the Mediterranean Sea, and the fact that saving lives in the Mediterranean Sea is illegal - these are things I never thought that I would witness in my life.

2. Could you describe some of the major changes and improvements you have witnessed in the world during your time at MSF?

- I think the present issue is that the way in which people wage wars has changed. Civilians are not spared, and we powerlessly witness this in Syria as well as in Yemen. Bombs are being dropped in residential and public spaces, and last year an airstrike hit a school bus in Yemen that killed 40 children. This is quite distressing, if not scandalous.

Moreover, hospitals are not being spared. While I don't have a benchmark number of hospitals targeted in the past, the reality today is that hospitals are being bombed over and over again and more so than ever. We know that more than 50 percent of the hospitals in Yemen have been partly or fully destroyed due to the ongoing war.

> “In 2019, we were able to deploy new tools to fight Ebola, signaling that when we have the political will, we can get things done”

We are all in a very difficult moment in human history, and a moment of uncertainty as a world. However, I believe there are also positive changes, and the evolution of the Ebola crisis is exemplary of some of the improvements. Back when I began my mandate in 2013, the start of the Ebola epidemics in West Africa shortly followed just a few months in. I recall us begging to obtain the needed vaccines and therapeutic solutions to care for the people affected by Ebola. Fast forwarding to last year and this year, we have been able to scale up vaccinations for both the people affected by the disease and the workers on the frontlines in providing care. As a result, we have vaccinated more than 160,000 people. Additionally, we are now conducting trials for four therapeutic solutions in North Kivu of the Democratic Republic of Congo (DRC), which will soon conclude as we are close to reaching over 500 participants in these trials. If we were to have taken the normal rate of discovery in research and development, these improvements would not have come to fruition just few years after the outbreak in West Africa. Yet in 2018 and 2019, we were able to deploy several new tools to fight Ebola, signaling that when we have the political will, we can get things done.

Dr. Liu addressing a special session of the United Nations Security Council (Photo by: Paulo Filgueiras)

3. MSF responds to an array of humanitarian crises: wars, natural disasters of any kind, epidemics, pandemics, forcibly displaced refugees, and famines. You have indicated that a lot of the obstacles you faced were political in nature. Are there other obstacles MSF had to encounter in order to reach those in need of medical attention? What are some measures MSF is taking to address them?

- If I were to summarize our key challenges in terms of deployment, it is access. There are challenges in MSF’s access to populations in need, the populations’ access to our healthcare facilities, and people’s access to medicine in general.

It is always difficult to access populations when they are in remote areas, where we have to cross several checkpoints just to reach them. In some places, if we do not have the means to airlift our team members, it is unlikely that we will reach these remote populations.

Access is also an issue in terms of populations coming to us for help. We have seen it in Yemen everyday since the beginning of the country’s conflict. MSF, for example, has 2,200 staff in Yemen who are providing direct support to more than a dozen hospitals and another 15 remotely. The reality is, however, that not all people are able to come to our centers, and the reasons include roadblocks as well as their inaccessibility to fuel that will allow them to make the journey to these hospitals. This issue with access is truly devastating: over the past year and a half, there were 600 people who arrived with a slim chance of survival, many being children and newborn. We are not talking about the people wounded from war; we are talking about the general, civilian populations seeking care. A journey that should only take 30 minutes to arrive to a hospital can end up taking hours, if not days, because of these roadblocks, fuel insecurities, and checkpoints.

Dr. Liu and medical team at the MSF Trauma Center in Afghanistan (Photo by: Kim Clausen/MSF)

The last aspect of access is our access to medicine. I think we have seen it in the ongoing HIV/AIDS epidemic where despite the development of new forms of treatment, they remain inaccessible due to their inflated prices. Meaning, even when the right tools are materially available, people who cannot afford it will still die from a treatable condition. This was the big battle in the beginning of the millennium. Fortunately, there is now accessibility to generic medicine for the general population. The cost of antiretroviral treatments (ARVs) went from more than $10,000 to less than $200 within a year’s time, and this was a huge achievement. In essence, access to medicine is a real issue. We have seen it in the U.S. with epinephrine a year and a half ago. This concern as to how we will continue to maintain access to new treatment discoveries at an affordable price is one that pertains to everybody.

As I have stated earlier, even if we may have a medical breakthrough, if people cannot afford it, there is no use. As I always say, if you have a vaccine, it is only useful not in the freezer, but in the arms of the person who needs it. This is what we have been trying to do at MSF, and this is why the Access Campaign that was put together in 1999. The idea in the message is very clear: if the best available medicine and tests are accessible to those who need them, many more lives would be saved. This was clear to us early on, and this is what MSF tries to promote at all times. If we are to be available as a provider of medical services, we need to see what we can do about the intellectual property of medicine, where we can treat it as a public good rather than a private one. This was a highly challenging legal fight. I think people today, however, better see the role of generics, and this helps bring accessibility to those who need it the most.

4. Despite various organizations’ goal and effort to relieve global humanitarian crises, many of them face limited budgetary and human resources. What aspects drive MSF to carry out its mission without facing such issues?

- As an organization, we are very fortunate. We are an organization today with an approximately $1.6 billion incoming operational budget and a global workforce of 68,000 headcounts on a yearly basis working in 72 countries. We have the immense privilege to be funded

by 6.5 million individual donors and private institutions. This is a real privilege. By having private donors, we have an agenda that is stripped of any political bias from institutional or state donors. This allows us to invest in things that might not always be successful, but can make a difference. For instance, nobody believed in the Access Campaign in 1999. I remember back then, we invested the money that we had received from the Nobel Peace Prize into launching our Access Campaign for medicine. Today, we have invested in the discovery of a new molecule to conduct trials for Hepatitis C treatment. Instead of having a 12-week treatment costing over $60,000, it is projected to be less than $300 soon. Our independence allows us to invest in solutions that, although are still in their infancy and outside the radar of others, can make a huge difference in people's lives.

> "If we are able to harness the best of our diversity, we will be much further in terms of the quality of our response, innovation, and enacted inclusion"

Moreover, MSF brings value as an independent, neutral organization. Because we have the robustness, independence, and the means of reaching remote populations, more than 60 percent of the countries we intervene in are war zones. South Sudan, for example, is a war zone and its population can be difficult to provide medical services to. People cannot use the roads because they are too dangerous. Because MSF is equipped with our own planes, we use them to fly our teams in and out regularly of what would otherwise be a difficult area to reach. If one does not have the financial robustness to do that, they cannot work as freely and as independently as MSF fortunately can.

5. MSF is a global organization that consists of 24 independent sections worldwide. How do you, as the International President, lead and sustain a sense of cohesion among these sections?

- MSF is a movement with 24 sections and more than 48 offices scattered throughout the world. It is a real challenge to keep all MSF members aligned behind a common mission and foster unity with purpose. With that being said, I truly believe that there is a real added value in being a global multipolar organization because it allows us to have a very true approach to the different challenges we face. Because we have the perspectives of different cultures and countries, and eyes from other points of view, I believe this removes some of our blind spots. When reading a situation or making a decision, the outlook from the eyes of someone coming from Africa may be completely different from that of the eyes of a Canadian. There will be different interpretations and there will be different priorities. However, if we are able to harness the best of our diversity, we will be much further in terms of the quality of our response, innovation, and enacted inclusion.

Dr. Liu voting during a motion session at the 2018 International General Assembly in Barcelona (Photo by: Bueno De Cock/MSF)

6. As your term as International President nears its end, you have had the benefit of multiple years of experience and are now in a position to offer advice. What advice would you offer to your successor? What do you envision for the future of MSF?

- I will be leaving this position at the beginning of September, and my successor has been identified and elected fairly recently. I would like to wish him good luck. That being said, my advice would be that as we are growing into a bigger, multipolar, and loosely federated organization, it is key that we do not lose track of what is our primary goal and what is our raison d'être (reason of being). Our raison d'être is about the patients. It is about bringing care to the underserved populations in the world, those who are affected by conflicts, natural disasters, epidemics, or stigmatization. In regards to everything we do as MSF, we always need to think of the patient first. Patients are always in the center of decision making. It is very easy for a growing organization to allow its survival as an institution to take over that of the patient and their survival. We should not be blind to that as this can be a real risk. My advice is to put the patients first; keep your eyes on the core social mission of MSF which is, in essence, caring for the people in need in times of crisis.

In terms of what I see for the future, I may loop in something from the beginning of our conversation, which is that we are all working in a world that is changing. We will have to clearly articulate ourselves in a world where those bringing aid to the "unwanted" populations are criminalized. When MSF was conducting search and rescue operations in the Mediterranean, we were attacked. We were made to feel intimidated and we were dragged into court for our activities. How are we to continue to care for people and their lives lawfully in that context? Are we to continue to care for people that are living in areas or zones controlled by opposition groups such as Al-Shabaab or Al Qaeda, whom the government labels as terrorists? Are we to continue to care for these populations knowing that there is a huge narrative about counter-organizations? MSF should strive to deliver a message that a patient is a patient, even a combatant patient.

7. As we come to a close, the World Asian Medical Journal, otherwise known as WAMJ is a medical publication that highlights the contributions of various healthcare professionals of Asian heritage. While many Asians pursue medicine in one way or another, relatively fewer are involved in non-profit, humanitarian organizations such as MSF. For readers of the journal who wish to enter this area of healthcare but are unsure as to where and how to start, can you recommend some steps they might take to follow a path resembling yours?

- I am not sure if I would strongly advise them to follow my footsteps exactly. That being said, I must be very honest. Being a first-generation born in Canada, which many people call CBC for Canadian-born Chinese, my parents to this day always ask: "When will you be getting a real job?" That is a common experience for many Asians following non-conventional career paths. Although I found my last job to be very tough, I counted my blessings everyday because it is about doing something meaningful. If going into medical humanitarian care is meaningful for you, then I would say go into it. The best way to prepare yourself is to have something that is exportable and brings value.

In MSF, out of the 68,000 people working within the organization, doctors only represent between 20 to 25 percent. There is a full scope of different professionals, including nurses, logisticians, and administrative staff, who help make humanitarian work possible. If you were to make a difference, you would have to understand that not everyone is meant to work on the forefront of medical crises, such as in Yemen or at the Ebola center in North Kivu of the DRC; and that is okay. That might not be your fit, but you can contribute otherwise. We are always looking for great staff members to help carry on MSF's mission. If you do not want to be on the very frontlines of MSF's services but still would like to contribute as a team member, join our telemedicine project. It is the basic tool that brings expertise advice to the bedside of every one of our patients. You can contribute from your living room and be one of MSF's experts on our telemedicine platform. We have more than 600 experts around the world, and everyday they answer questions to patients who may be in remote areas, such as South Sudan or the DRC.

Dr. Liu visiting the Ebola treatment center in Butembo, DR Conco (Photo by: Alexander Wade/MSF)

For me, being involved in humanitarian work is to help build a better world. The fundamental approach starts with not being indifferent to the crises going on in the world, and maybe by simply talking about it. In Libyan detention centers, people are being stripped of their basic human rights just because they fled their homes to save their lives or to look for a better future. The world could be in a better place if everybody addresses such issues and say “this doesn’t make sense”, instead of turning a blind eye. Right now, we need people who will not denounce matters that are outrageously unfair, inequitable, and cruel, but who will instead bring these issues into light for discourse and action.

Joanne Liu, M.D., C.M., FRCPC

International President, Médecins Sans Frontières (MSF)
Pediatric Emergency Physician, Associate Professor at CHU Sainte-Justine, Université de Montréal

Joanne Liu, M.D., C.M., FRCPC, is a pediatric emergency physician, associate professor at the Université de Montréal (University of Montreal), and the International President of Médecins Sans Frontières (MSF), also known as Doctors Without Borders. Born in Quebec City, Canada, Dr. Liu trained at McGill University School of Medicine, specializing in pediatrics at Montreal’s CHU Sainte-Justine Hospital. In 2013, she received the Teasdale-Corti Humanitarian Award from Royal College of Physicians and Surgeons of Canada. Her time with MSF started in 1996, when she worked with Malian refugees in Mauritania. Since then, she has provided support after the tsunami in Indonesia, assisted people affected by the earthquake and cholera epidemic in Haiti, and worked with Somali refugees in Kenya. In MSF, Dr. Liu also helped create the telemedicine project, which connects MSF physicians in 150 remote sites with a pool of more than 300 medical specialists across the globe. She also helped develop one of the first programs offering comprehensive medical care for survivors of sexual violence in Republic of Congo. Dr. Liu has worked in many other conflict zones, including in Palestine, Central African Republic, and Sudan’s Darfur region.

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In Memory of Dr. Waun Ki Hong, the Physician-Scientist Who Transformed and Redefined Cancer Treatment

In January of this year, the cancer medicine field and the medical community at large lost a legacy. Dr. Waun Ki Hong, past division Head and Professor at The University of Texas MD Anderson Cancer Center, past President of the American Association of Cancer Research (AACR), and a Samsung Distinguished University Chair in Cancer Medicine lived a full and accomplished life before passing in the close presence of family. He was 76.

It was a great honor to have interviewed Dr. Hong and have shared his story with our readers in the 12th issue of the World Korean Medical Journal (WKMJ). In this first issue of WAMJ, we would like to commemorate Dr. Hong's lifelong contributions that have inspired not only Asian-American healthcare professionals, but also those across the globe to further the healthcare field.

Waun Ki Hong was born on August 13, 1942 in South Korea, and grew up amidst World War II and the ensuing Korean War. By enduring such a tumultuous time in his home country, he learned to develop resilience and perseverance very early on. In 1967, Dr. Hong received his medical degree at the Yonsei University School of Medicine, and soon after served as a flight surgeon in the Vietnam War. There, he practiced a high sense of duty that he would continue to carry throughout his medical career and personal life. After marrying whom would be his lifelong partner, Mi Hwa in 1969, Dr. Hong and his then pregnant wife immigrated to the United States with two things: $451 and their determination to seize better opportunities for the family and Dr. Hong's career.

As a foreign medical intern at the Bronx/Lebanon Hospital in New York City, Dr. Hong faced language and cultural barriers, as well as challenges that came along with his new parenthood. However, with tenacity and patience, Dr. Hong completed his internship and afterwards, a medical residency at the Boston Veterans Affairs (VA) Medical Center. Upon completion of his two-year medical oncology fellowship at the Memorial Sloan Kettering Cancer Center in New York, Dr. Hong returned to the Boston VA Medical Center as Chief of Medical Oncology.

During his time there, Dr. Hong transformed the hospital's treatment of laryngeal cancer by moving beyond the disease-centered model and into patient-centered care. Dr. Hong's research alongside Dr. Gregory Wolf revealed that chemo- and radiotherapy combination treatment would result in the same survival rate as surgical removal of a patient's voice box, which was the prevailing method of treatment at the time. Since Dr. Hong's discovery, patients have been able to combat cancer without compromising their ability to speak, and in 1991, the study was published in the *New England Journal of Medicine*. What followed was an improved standard of care for laryngeal cancer patients in hospitals across the nation.

Dr. Waun Ki Hong also emphasized preventative measures in cancer treatment. After joining the MD Anderson Cancer Center as Chief of Head and Neck Oncology in 1984, Dr. Hong established the concept of chemoprevention. Rather than treating patients already diagnosed with a form of cancer, he demonstrated how a high dosage of retinoic acid had the capacity to reverse oral premalignant lesions, and furthermore prevent the development of cancer in high-risk patients. The then novel approach was recognized by Nobel Laureate Dr. Elizabeth Blackburn, and received positive reception that sparked dialogue and efforts to make prevention a part of regular cancer treatment.

Dr. Hong would go on to accomplish further milestones in cancer research and medicine, one of which was in lung cancer treatment. The implementation of the BATTLE clinical trial (Biomarker-based Approaches of Targeted Therapy for Lung Cancer Elimination) informed the development of other newly targeted therapies for cancer. With such major breakthroughs, Dr. Hong played a vital role in establishing MD Anderson as what AARC Chief Executive Officer Maragret Foti described as "arguably one of the most important clinical and translational cancer research and care centers in the world."

The list of Dr. Hong's remarkable accomplishments is endless. He had published over 660 scientific publications, edited 11

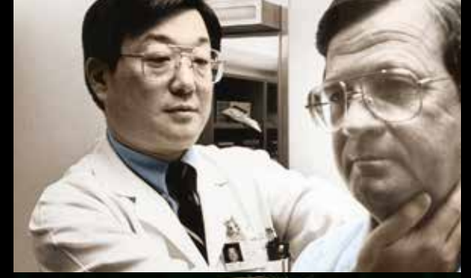

Photo by AACR (American Association for Cancer Research)

major books, acted as an editorial board member for 17 scientific journals, and served in numerous science and policy committees, including those for Stand Up to Cancer (SU2C), the American Association for Cancer Research (AACR), the U.S. Food and Drug Administration (FDA), the National Cancer Institute, the National Cancer Advisory Board, the President's Cancer Panel under George W. Bush, and several international committees. Additionally, Dr. Hong was the recipient of many awards from the AACR, the American Cancer Society, the American Society of Cancer Oncology, as well as the Ho-Am Prize in Medicine from the Samsung Foundation.

Dr. Waun Ki Hong's remarkable character, however, extended beyond his contributions as a physician-scientist and researcher. He was a proactive mentor and professor to clinical and postdoctoral fellows, and according to his close colleagues, derived great fulfillment in educating the younger generations of physician-scientists and basic researchers. Dr. Waun Ki Hong often cited his oldest brother, Dr. Suk Ki Hong, M.D., Ph.D. as his life-long role model and supporter, and sought to provide the same mentorship to his students and mentees whom he envisioned would advance the field of oncology.

While Dr. Waun Ki Hong leaves behind his legacy in medicine, he was first and foremost a husband, father, and grandfather who immensely valued his relationships with his family. Moreover, Dr. Hong was a person of duty and service to not only the health profession at large, but also to the individual people he encountered and developed strong relationships with.

The WAMJ community remembers Dr. Waun Ki Hong for his scientific advancements, proactive guidance, as well as his people and patient-oriented character that always sought to better the lives of others. His contributions and words have resonated and will continue to remain with us. W

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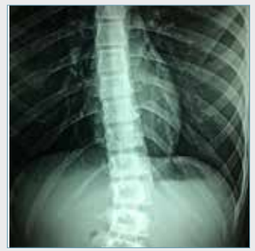
Biopharma Report

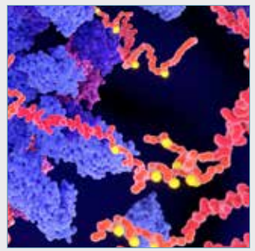
BIOPHARMACEUTICAL REPORT I

BOTH ABBVIE'S ORILISSA AND MYOVANT'S RELUGOLIX EXPECTED TO FACE SIMILAR PAYER SCRUTINY IN UTERINE FIBROIDS



BIOPHARMACEUTICAL REPORT II

NOVARTIS' ZOLGENSMA HAS FIRST-LINE POTENTIAL IN SPINAL MUSCULAR ATROPHY (SMA)



BIOPHARMACEUTICAL REPORT III

IS TAU THE NEW AMYLOID?

Both AbbVie's Orilissa and Myovant's Relugolix Expected to Face Similar Payer Scrutiny in Uterine Fibroids

The reimbursement experience physicians are having with **AbbVie's** (NYSE:ABBV) Orilissa (elagolix) in endometriosis-related pain is likely to spill over to **Myovant Sciences**' (NYSE:MYOV) relugolix and both drugs' use to control menstrual bleeding in uterine fibroids if approved, noted physicians and reimbursement experts.

To prescribe Orilissa beyond the specified limit on its label, a physician letter stating the need and the drug's effectiveness has been required, experts said. While interviewed physicians expected access after such a process, it was not a uniform experience for all doctors, they noted.

Insurance coverage is a major obstacle for Orilissa's adoption, one analyst noted, adding AbbVie has stated approximately 70% of patients taking Orilissa have access to the drug through their insurance plans and the rest are offered the drug for free.

The challenge of proving adequate evidence for the reimbursement of prolonged gonadotropin-releasing hormone (GnRH) antagonist treatments like Orilissa and relugolix will likely extend to other indications like uterine fibroids, said experts. This may be even more obvious since treatment is driven by patients, and endometriosis-related symptoms are more distressing than those in uterine fibroids, two experts noted.

AbbVie plans to file a New Drug Application (NDA) for Orilissa to address menstrual bleeding with uterine fibroids in mid-2019 based on topline data from two trials, according to a 14 November 2018 announcement. Myovant announced data from one trial in May, and plans an NDA in 4Q pending positive results from a second Phase III trial, as per a 14 May press release. **ObsEva** (NASDAQ:OBSV) also has a Phase III GnRH antagonist, linzagolix, with results expected in mid-2019. As a likely third-to-market asset, the impact of ObsEva's efforts to differentiate linzagolix from Orilissa and relugolix by offering dosing flexibility remains unclear, this news service reported on 31 January.

Individual analysts estimated revenues for Orilissa, relugolix and linzagolix to be USD 1.58bn in 2027, USD 1bn in 2028 and USD 992.6m in 2028, respectively, for endometriosis-related pain. Sales for their use to address bleeding with uterine fibroids are anticipated to be USD 985m in 2027, USD 700m in 2028 and USD 600m in 2028, respectively. The market caps for AbbVie, Myovant and ObsEva are USD 107.83bn, USD 785m and USD 489m, respectively. Orilissa was approved for endometriosis-related pain in June 2018 and launched at a list price of USD 10,000 per year.

AbbVie and Myovant did not respond to a request for comment.

Extrapolation of Orilissa experience across women's health

Initial reimbursement challenges with Orilissa use for endometriosis-related pain will likely carry over to Orilissa's and relugolix's use in patients with uterine fibroids, noted Dr. Richard Stefanacci, chief medical director, Managed Markets, Eversana, Pennsylvania. Since long-term evidence is lacking in women's health, these drugs will likely face the same issues with payers requiring additional information to cover using the drugs for longer than what is noted on their labels, said R. Brett McQueen, PhD, assistant professor, Center for Pharmaceutical Outcomes Research, University of Colorado Anschutz Medical Campus.

> "The prevalence of endometriosis is probably underestimated given its poor diagnosis history, so as more drugs become available, it could have a major impact on healthcare budgets"

It is quite common to consider prescribing Orilissa beyond the time period approved, given the lack of new and effective treatment options, said interviewed experts. Orilissa is indicated at either 150mg once daily for two years or 200mg twice daily for up to six months. The relugolix Phase III program is testing the drug for six months of use.

However, in both uterine fibroids and endometriosis, the need for therapy is dictated by the patient, unlike in blood pressure medications where test data drives treatment, said Stefanacci. It will be surprising if the drugs are very successful in treating bleeding associated with uterine fibroids where symptoms are not as debilitating as those in endometriosis, since symptomatically women deal better with fibroids than endometriosis, said Dr. Charles Ascher-Walsh, director of Gynecology, Urogynecology, MIS Mount Sinai School of Medicine, New York. Moreover, the side-effect tradeoff is clearer for endometriosis compared to uterine fibroids, he noted.

However, Dr. Tatiana Burnett, consultant, Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, disagreed about whether women are more likely to seek care for endometriosis-related pain as opposed to heavy menstrual bleeding related to fibroids. Even women with endometriosis have an average eight-year delay from symptoms to diagnosis, some of which is due to the normalization of symptoms either by family, friends or physicians, she added.

The prevalence of endometriosis is probably underestimated given its poor diagnosis history, so as more drugs become available, it could have a major impact on healthcare budgets, said McQueen. Gynecologists are familiar with identifying symptoms, but drug approvals and advertisements may result in more patients speaking out about their symptoms, said Ascher-Walsh.

Payer pushback over Orilissa in endometriosis-related pain

The reimbursement experience for Orilissa in endometriosis-related pain, including the need for prior authorization or outcomes-based contracts, has been variable depending on an individual patient's insurance, said Burnett and Ascher-Walsh. While she has not been denied coverage for her patients, Burnett noted she has heard about rejections from her colleagues.

Although it is not straightforward, insurance companies can be convinced to pay for Orilissa with a letter from the physician, said Ascher-Walsh, based on his experience. In general, physicians will need to write an appeal based on the literature to support continued use, and the vast majority of written appeals are successful, agreed Stefanacci.

Based on its approved label, Orilissa is under the cost-effectiveness threshold the Institute for Clinical and Economic Review (ICER) used in its analysis, said McQueen, who was part of the ICER report group that published its findings in August 2018. However, during the ICER panel, gynecologists said they would continue treatment for longer periods of time if it worked, and that is where the cost-effectiveness estimate dropped, he added.

An AbbVie-sponsored analysis looked at Orilissa treatment for up to two years and found it to be cost effective, noted Scott Johnson, PhD, a health economist who worked on this analysis and principal, Medicus Economics, Boston. The analysis compared Orilissa to Lupron (leuprolide acetate) instead of placebo, as done by ICER. Lupron is indicated for the management of endometriosis, including pain relief and reduction of endometriotic lesions.

The AbbVie analysis indicated if a plan covers Lupron, it should also cover Orilissa, said Johnson. US payers are increasingly using cost-effectiveness analyses, which is partly driven by the need for value-based plan designs, he added. Payers may explore outcomes-based contracts to allow continued access to the drug if effective, said McQueen and Johnson. Such contracts would involve financial rebates where the manufacturer is required to pay back the cost of the drug if the patient does not respond, said McQueen.

Nonetheless, long-term use also comes with safety questions like the higher risk of bone mineral density loss, said Burnett. However, the one to two year time period used to determine cost effectiveness may be inadequate to capture any adverse event changes, noted Johnson.

While Orilissa is currently the only approved GnRH antagonist, relugolix is in two Phase III studies for patients with endometriosis-related pain, with completion dates in December. As more drugs get approved for endometriosis-related pain, companies may provide additional rebates to retain a drug's position on a formulary tier, but list prices would be unlikely to change, said McQueen. Factors like bone loss leading to fractures would be a consideration for providers and payers alike, but any differentiation between multiple drugs on that front will have to be significant, and it will not be substantial if it is a class effect or based on just one trial, noted Stefanacci.

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.

Happy smile and hope after pain

D.K. Lee has related to It's A Wig that she will promote to cancer patients about the beauty classes and healing programs she attended. The beauty classes are held at Kyung Hee Medical Center and it is for cancer patients to help them feel more womanly during their hard times. She would like to thank all the people who gave her hope. "Thank you for giving me a second chance to live as a woman. With the hopes and gifts that I have received, it encourages me to work harder to volunteer my time for the people who are fighting against cancer."

Kyung Hee Medical Center patient
D. K. Lee

Cancer-free D.K. Lee

D.K. Lee attending
beauty classes while chemotherapy treatment

Novartis' Zolgensma Has First-Line Potential in Spinal Muscular Atrophy (SMA)

Novartis' (SIX:NOVN) Zolgensma (onasemnogene abeparvovec-xioi) has strong potential to be used as a first-line treatment in spinal muscular atrophy (SMA), but it is unclear how durable it will be despite being designed as a one-time treatment, experts said. Second-line options including **Biogen's** (NASDAQ:BIBB) Spinraza (nusinersen) are being considered, but lack of clinical data attesting to post-Zolgensma use could cause payer resistance.

Analyst reports suggest strong uptake sentiment for IV Zolgensma due to its broad label, but some experts interviewed by this news service noted there are still unaddressed efficacy questions for Zolgensma, as pivotal data fails to account for older patients that fall within the label. While ongoing and upcoming trials seek to address some of those efficacy shortcomings, including use in older patients or patients with neutralizing antibodies, there is no guarantee of success in those trials.

This news service reported on 28 June that Novartis has plans for a 2020 Phase I trial in SMA infants who present neutralizing antibodies. At the recent American Academy of Neurology (AAN) annual meeting in May, Novartis announced positive interim data from its Phase I STRONG trial (NCT03381729) testing intrathecal Zolgensma delivery in older patients, and trial completion is expected in September 2020. The company also presented results from the STR1VE, SPRINT and STRONG trials at the recently concluded Cure SMA conference, although details have not been publicly released.

Analysts' impressions of Zolgensma include optimism about its intrathecal formulation. Zolgensma's projected 2023 sales are USD 1.4bn, and Novartis has a market cap of CHF 228bn (USD 229bn).

Novartis did not respond to a request for comment.

Second-line options desirable but likely restricted

While patients who are diagnosed with SMA early will likely be recommended Zolgensma in the first line, there is no guarantee that they will not need any other treatments as they age, despite Zolgensma being designed as a one-time treatment, experts agreed. This has led physicians to wonder about second-line treatments in case of a failure, said a pediatric neurologist.

There are concerns that the effects of the therapy, which are nonintegrating, might dilute with increasing age or that it might spontaneously shut off, said Dr. Darryl De Vivo, professor of neurology, Columbia University, New York. Data over 10 years would help answer those concerns, but at least current trends are promising, as some type 1 patients from the 15-patient Phase I START trial (NCT02122952) were followed for over four years and have needed no other intervention, the pediatric neurologist noted. The fact these patients are still thriving represents a big achievement, as type 1 SMA patients typically do not live beyond two years and require lifelong ventilation, he added.

However, another neurologist pointed out that some patients from the START trial had already gone back to a combination therapy, casting doubts on its durability. AAN data showed that three of the 10 patients who enrolled in START's follow-up resumed combination therapy at parental and physician discretion, but not due to loss of motor function. The other seven patients did not have any other treatment intervention, and none of the 10 needed ventilation support. START was a safety trial exploring tolerability, while STR1VE measured developmental milestones as a primary efficacy endpoint.

As Spinraza, which was approved in 2016, has been shown to improve symptoms across all SMA types, many physicians are considering the drug as an additional line of treatment, the second neurologist said. However, the lack of data on Spinraza use following Zolgensma's failure will further arm payers to restrict access as they are both expensive, she added.

Spinraza has a list price of about USD 750,000 for the first year of treatment and USD 375,000 annually for maintenance thereafter, while Zolgensma is slated to cost over USD 2m, according to prices obtained online.

Ongoing trials closely watched for much needed additional evidence

There are ongoing and upcoming efforts to address unanswered efficacy questions, but Zolgensma's previous successes are no guarantee ongoing trials will succeed, said Dr. Alexander Fay, assistant professor of neurology, University of California, San Francisco. These questions include how patients of ages six months to two years might fare with intravenous Zolgensma, as the FDA has approved it for these patients, but registrational data only examined type 1 patients up to six months, he noted. Zolgensma was approved on 24 May based on data from the 20-patient Phase III trial STR1VE (NCT03306277) for patients who were under two years old with bi-allelic mutations in the survival motor neuron 1 gene.

Type 1 patients tend to have symptom onset at around six months of age, and the disease progresses rapidly and aggressively within months, leading to a significant amount of motor neuron loss even at one year old, experts said. Similarly, while type 2 and type 3 SMA patients have a later symptom onset, neuronal degeneration could already have occurred even at two years old, they added.

The pediatric neurologist pointed out that the ongoing STRONG study, which is examining type 2 patients from ages six months up to 60 months, would help answer efficacy questions in older patients. STRONG is examining an intrathecal administration of Zolgensma. Mechanistically, while an intrathecal administration allows more direct access to the motor neurons than intravenous delivery, older patients might have already lost a significant amount of motor neurons, De Vivo noted.

An intrathecal administration could lead to fewer side effects, as less vector might be required, Fay said. Although the intrathecal delivery could mitigate some of the liver abnormalities that were observed with the IV treatment, these abnormalities were transient and easily controlled with corticosteroids in past trials and are thus of low concern, the second neurologist noted.

The upcoming 2020 Phase I trial could help address patients who were excluded from previous clinical trials due to having neutralizing antibodies, but current confidence for success stems from preclinical data, the pediatric neurologist said. Approximately 5–10% of patients might present neutralizing antibodies, he added.

Shuan Sim
Reporter, New York

Shuan Sim has a Bachelors degree in linguistics and journalism from New York University. He had previously worked in various trade publications covering technology, precious metals and diamond trade and more. Shuan has worked as a breaking news reporter covering Asia and an international reporter in the Czech Republic. He's also fluent in Mandarin and proficient in Japanese.

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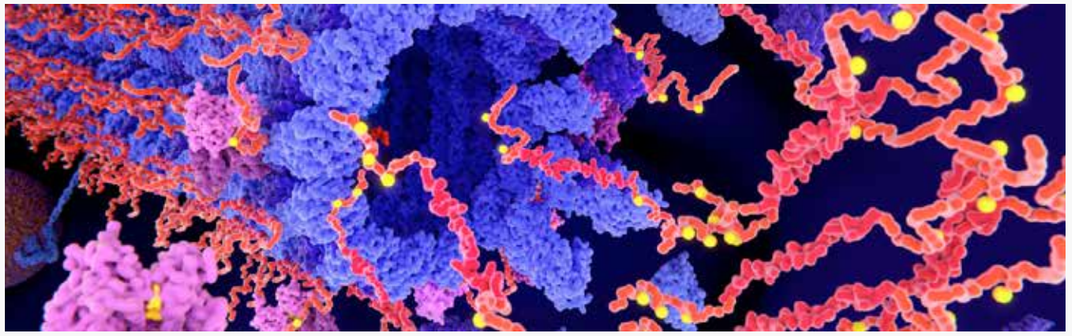

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PRODUCT DEVELOPMENT

Is tau the new amyloid?

BY SELINA KOCH, SENIOR EDITOR

After finally getting the message that they need to look beyond amyloid to treat Alzheimer's disease, pharmas are lining up behind tau as the next big target. The question is whether they can pick out the lessons from the amyloid saga to avoid following the same storied path.

At least four Phase II readouts of anti-tau antibodies are on the horizon. But there remain a number of questions, from the target's biology to how best to translate that biology, plus the beginnings of a lemming effect, that serve as warning echoes (see "How the Amyloid Hypothesis Holds its Grip").

The amyloid hypothesis was rooted in multiple lines of genetic data pointing to β amyloid as a causative agent in AD. In contrast, tau mutations are not found in AD patients, though they do occur in frontotemporal dementia (FTD), another neurodegenerative disease that leads to cognitive decline.

But tau is an obvious choice as the next-best chance for the disease because its aggregation in neurons — in neurofibrillary tangles — is one of the two major pathological hallmarks found in patient brains, the other being the extracellular deposits of β amyloid in plaques.

And there's good reason to think tau could be a better target than β amyloid — the timing and location of tau aggregation correlate much better with the onset and nature of patients' symptoms. Tau builds up closer to clinical onset, and in the right places to explain early cognitive deficits, suggesting a role in progression to clinical disease. Amyloid accumulates decades before symptoms arise, and in a wide variety of brain regions, not specifically the areas that drive symptoms.

"Tau has really emerged as the leading target in Alzheimer's," Husseini Manji, global therapeutic area head for neuroscience at Johnson & Johnson's Janssen Pharmaceuticals unit, told BioCentury.

Janssen is gearing up to run a Phase II study of its anti-tau mAb JNJ-63733657. Ahead of that is a small molecule from TauRx Pharmaceuticals Ltc. and the four anti-tau mAbs already in Phase II testing. A host of tau-targeted molecules trail it, including vaccine and antisense oligonucleotide therapies in clinical development, as well as small molecules and other therapies in preclinical testing (see Figure: "Tau in the Clinic").

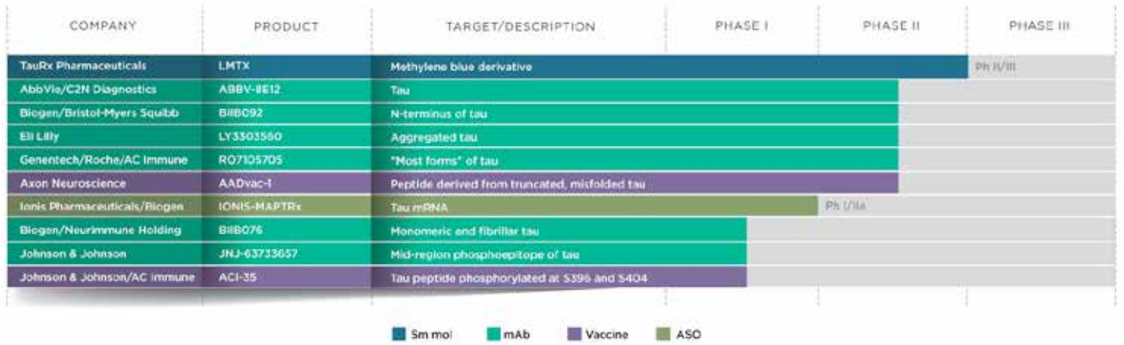
This piling of companies onto the same target in the absence of any clinical proof of concept is reminiscent of amyloid, as is the focus on a single aggregation-prone protein. That should set off some alarm bells, as the disease has many such proteins, plus dysfunctional immune cells, vascular abnormalities and other features (see "After Amyloid").

Tau in the clinic

At least 10 compounds targeting tau are in clinical testing to treat Alzheimer's disease. Six of them are mAbs designed to intercept tau as it spreads extracellularly from neuron to neuron, with the goal of slowing disease progression. Because the mAbs target different forms of tau, they could shed light on which of its various species are toxic.

Other programs are testing the tau hypothesis in different ways. The two vaccines in the clinic, from **Axon Neuroscience SE** and partners **Johnson & Johnson** (NYSE:JNJ) and **AC Immune S.A.** (NASDAQ:ACIU), induce immune responses to different forms of tau. IONIS-MAPTRx, an antisense oligonucleotide (ASO) from **Ionis Pharmaceuticals Inc.** (NASDAQ:IONS), targets tau's mRNA to block production of all tau species, lowering their levels both intracellularly and extracellularly. **Biogen Inc.** (NASDAQ:BIIB) has an option to IONIS-MAPTRx.

The first small molecule to reach the clinic, LMTX from **TauRx Pharmaceuticals Ltd.**, failed to meet its primary endpoints in two Phase II/III trials and is in a third trial based on the idea that it could work at a lower dose in patients not taking standard-of-care therapies. *Source: BCIQ: BioCentury online intelligence; company websites; ClinicalTrials.gov.*



The good news is that the Alzheimer's field has more experience and better biomarkers than it had when it started testing anti-amyloid agents, suggesting it can avoid repeating some of its early mistakes. The risk is that the major players get tied up for another decade or two on a single target, iterating compounds and trial designs rather than casting a wide net (see "Amyloid: How Did We Get Here and What Can We Learn?").

Over 50,000 Alzheimer's patients have been or are being treated with amyloid-lowering compounds. So far, for tau, the tally is closer to 2,700.

Already one anti-tau agent, the small molecule LMTX from TauRx, has failed to meet its primary endpoints in two Phase II/III trials, and the company is trying again with a new dose. But other stakeholders dismiss the compound as a poor test case.

More specific tests of the hypothesis could come when results from the mAbs start rolling in, which should be by the middle of next year, according to ClinicalTrials.gov.

Not the same story

Despite parallels between tau and β amyloid, proponents of the tau hypothesis point to several advantages over the amyloid hypothesis (see Figure: "Tau vs. Amyloid").

"In Alzheimer's disease, tau is the one thing that correlates really beautifully with disease progression, much more so than Aβ [β amyloid] or any other markers that are out there," Holly Kordasiewicz, executive director of neuroscience drug discovery at Ionis Pharmaceuticals Inc., told BioCentury.

Ionis has an antisense oligo therapy against tau, IONIS-MAPTRx, in a Phase I/IIa trial in AD.

Tau accumulates first in the hippocampus and other brain regions whose dysfunction is thought to drive early cognitive symptoms in patients, and then begins to aggregate in other regions, mirroring disease progression.

"That really strong correlation between tau pathology, tau spreading and disease progression suggest that this might be one of the underlying molecular causes of the disease," said Kordasiewicz.

Despite the fact there have been many more studies on amyloid than tau, more is known about tau's endogenous functions and how it might drive toxicity, she added.

For example, tau is an axonal protein that regulates the stability and flexibility of microtubules, as well as transport of cargo along them. Excessive phosphorylation of tau can cause it to detach from the microtubules, leading to loss of that function. Hyperphosphorylated tau also ends up in synapses, where it is thought to cause toxicity by a gain of function mechanism.

Tau is also prone to misfolding, and one concept — under debate — is that the misfolded protein passes from neuron to neuron, similar to

prion proteins, accounting for the way the disease progresses from one brain region to another.

That provides at least two mechanistic footholds for companies to translate the biology into disease-modifying therapies — targeting different forms of the protein, and preventing its spread. Arguably, this puts tau a step ahead of the β amyloid field, which converged on the central hypothesis that reducing the amount of aggregated β amyloid would lead to cognitive improvement, despite the fact that no solid mechanistic connection has yet explained why that should be the case.

Spreading dispute

The fact that tau progressively spreads throughout the brain is not in dispute. At issue is how it spreads, which has implications for the best way to drug it, and how important tau spreading is in the disease process.

Antibodies directed against tau, which represent the largest class of clinical compounds against the target, are based on the idea that tau spreads extracellularly.

"Our core therapeutic hypothesis is that we can intercept the cell-to-cell spreading of tau in the brain to reduce the progression of disease," Casper Hoogenraad, senior director and staff scientist at Roche's Genentech Inc. unit, told BioCentury. Genentech and partner AC Immune S/A have the anti-tau mAb RO7105705 in two Phase II trials.

There are also differences among those who think tau spreads this way. One theory is that extracellular tau gets trapped in exosomes or other protected compartments, meaning the target won't be accessible to antibodies. Some researchers have suggested microglia — the brain's phagocytic cells — ingest tau aggregates when they phagocytose dying synapses, then spread tau through the brain by releasing it in exosomes (see "Microglia Strike Again").

Compounds that act intracellularly, such as small molecules and antisense oligos, would bypass these issues.

According to Manji, J&J is developing a preclinical small molecule inhibitor. AC Immune has a preclinical small molecule tau inhibitor partnered with Eli Lilly and Co.

"More people have focused on the spread of tau, and I think there's good reason for that. But ultimately the toxicity is intracellular and can you target that with a small molecule," said Manji.

Genentech's Hoogenraad is not concerned about using mAbs, because he thinks release of free tau is more common. "While there is cell culture data that suggests that some extracellular tau might be found in a membrane-bound component, those studies suggest that only a small proportion of the tau detected was found in such compartments," he said. He noted that the compartment could be an exosome or ectosome, for example, and that the proportion found in them was less than 10%.

Hoogenraad declined to say when Genentech expects topline data from its two ongoing trials, but said the blinded portion of its first one, TAURIEL, runs for 18 months and dosed its first patient in 4Q17. Its primary completion date in ClinicalTrials.gov is in June 2020.

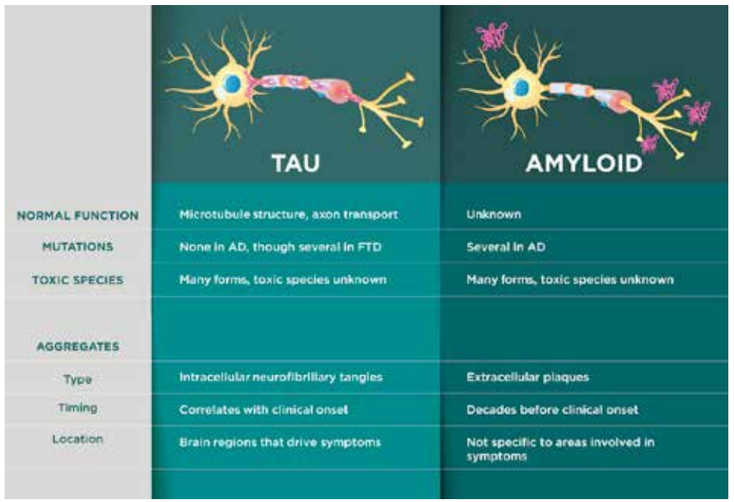
Other anti-tau mAbs in Phase II trials are LY3303560 from Lilly, BIIB092 from Biogen Inc. and partner Bristol-Myers Squibb Co., and ABBV-8E12 from AbbVie Inc. and partner C2N Diagnostics LLC. According to ClinicalTrials.gov, the first Phase II trials from all these programs have primary completion dates in 2021.

Dennis Selkoe disputes the idea that tau spreads via any extracellular mechanism, and thinks that the pattern of progression is due to the fact that tau aggregation is more toxic to some neurons and parts of the brain than others.

Selkoe — one of the originators of the amyloid hypothesis, and one of the researchers who discovered in the 1980s that tangles were made of tau — told BioCentury the extracellular

Tau vs. amyloid

As companies look beyond amyloid for treating Alzheimer's disease, tau is shaping up to be the next big bet, with at least 10 tau-targeting therapies in clinical trials. The two targets differ on a variety of parameters, which underlie the relative strengths and weaknesses of the hypotheses.



BIOCENTURY

"TAU HAS REALLY EMERGED AS THE LEADING TARGET IN ALZHEIMER'S."

HUSSEINI MANJI, JOHNSON & JOHNSON

spreading hypothesis "is probably not correct." If neurons are leaking or spitting out misfolded tau, then it is hard to explain why, "even after 20 years of clinical disease, some neurons have tangles, and neurons right next door are spared."

"People who believe this say there must be some kind of receptor. But, usually, the more complicated you make your model, the less likely it is to be right," said Selkoe, who is a professor of neurologic diseases at Harvard Medical School and co-director of the Center for Neurologic Diseases at Brigham and Women's Hospital.

Form factor

The use of different modalities could tease apart which forms of tau drive toxicity, a goal that was not achieved for β amyloid.

Like amyloid, tau comes in different sizes, conformations and aggregation states, from small soluble oligomers to large insoluble aggregates. Tau is even more complicated, because its many phosphorylation sites increase the number of distinct states it can assume.

Hoogenraad said Genentech's mAb "was selected to bind most forms of tau, since there is not yet conclusive evidence about which forms of tau are pathological."

Janssen's Manji said his company's Phase I mAb JNJ-63733657 binds "a mid-region phosphoepitope, in contrast to most of our competitors who are targeting whole tau and terminal epitopes."

Manji said the decision was based on extracting misfolded tau from postmortem brain tissue and finding "seeds" that are capable of inducing tau pathology in cell culture "fully retain the mid-region epitopes; whereas some of the N-terminal epitopes are cleaved, and so we thought that the mid-region phospho-tau is the more germane pathogenic form."

Lilly declined to say which part of tau LY3303560 binds to, but told BioCentury the mAb has demonstrated about 1,000-fold higher selectivity for aggregated tau over tau monomers in preclinical studies.

Ionis' Kordasiewicz noted that because her company's antisense oligo targets tau's mRNA, it does not depend on which form of the target drives toxicity. Nor does it depend on extracellular spread of the protein — a benefit it shares with small molecules.

"By stopping the production of tau we're preventing the cells from ever having to deal with it in the first place, and we're getting rid of all the toxic species," she said.

Biogen has an option to develop and commercialize the Ionis compound, making Biogen one of several companies attacking tau via multiple modalities. In addition to its BMS-partnered mAb, Biogen has a Phase I anti-tau mAb from Neurimmune Holding AG. BIIB092 from BMS targets the N-teriminus of tau and truncated forms of tau containing the terminus, according to published studies. Neurimmune declined to disclose the tau epitope targeted by BIIB076, and Biogen did not respond to interview requests.

Manji said in addition to having a mAb in development and a preclinical small molecule inhibitor, J&J has partnered with AC Immune on a Phase I anti-tau vaccine.

"The vaccine is only a little behind the antibody," he said, adding that the modality would be particularly useful in developing countries. "A vaccine could help more people in more parts of the world."

AbbVie declined to be interviewed for this story.

Path to answers

At a minimum, the lessons from β amyloid mean that tau drug developers start off knowing that timing the treatment and finding the right patient population — rather than taking all comers — could dramatically increase their chance of success.

There are enough open questions around the biology of tau to suggest that the road ahead could still be long.

Because TauRx's LMTX is a derivative of methylene blue, which has a wide array of effects in cells, many in the field don't consider it a rigorous test of the tau hypothesis. TauRx argues that despite the two Phase II/III failures, a subgroup analysis supports continuing the program. The company is testing it in another Phase II/III trial as monotherapy and at a lower dose.

"If the first antibodies don't read out positively, I would caution people not to throw the baby out with the bathwater," said Manji. "A negative trial doesn't mean every tau modality is doomed to failure. They're not all the same."

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Lilly is trying to speed the process by homing in on patients at the right stage of disease. The pharma's "Goldilocks tau" trial uses PET imaging of tau to enroll patients with low to medium levels of tau pathology, and are therefore likely to progress during the timeframe of the trial, but who don't have so much tau aggregation that it's too late to intervene.

Manji said J&J has set up a consortium through the Innovative Medicines Initiative (IMI) to "thoroughly characterize" the biomarkers and cognition performance of a group of patients prior to placing them in an interventional trial.

"Sometimes one of the challenges is you don't have long enough baseline information on people. So if you already have this cohort that you've characterized well before intervention, then you're more likely to pick up a correct signal after intervention," he said.

J&J's trial will likely enroll an "early, prodromal-type population" in its Phase II trial, said Manji.

By contrast, Hoogenraad said Genentech is not making assumptions about the best disease stage to target or how much baseline tau is optimal to achieve efficacy. Genentech is tracking tau PET signals in its patients but hasn't set enrollment criteria based around the parameter. It is running two Phase II trials: one in early stage patients and the other in moderate stage.

Ionis may take a detour from AD after the safety studies, using patients with frontotemporal lobar degeneration (FTLD) who harbor tau mutations as a test case for proof of concept that the compound works. The company is still deciding if and when to run efficacy trials in AD and other tauopathies.

Kordasiewicz said the biotech believes sticking as close to the genetics as possible is the best bet for success. "That is a general principle we have."

"We went into AD first because it is a larger patient population," which makes recruitment faster, she said. "Going to the mutation carriers is just trying to give the drug the best shot for success, by getting it to the patients who are going to benefit the most."

The approach is opposite to how pharmas approached β amyloid. Early β amyloid trials took virtually all comers, and over time became more restrictive. Only now, after almost two decades of failures, are companies testing amyloid agents in mutation carriers.

Biogen too is running a trial in tau mutation carriers. In addition to its AD studies, the biotech is conducting a Phase Ib trial of BIIB092 in four tauopathies that include FTD patients with tau mutations.

Hoogenraad said Genentech is "interested" in other tau-driven dementias but is sticking with its focus on AD. "Currently, cognitive/functional outcome measures are far better understood in AD than in other tauopathies, such as FTD," he said. bc

COMPANIES AND INSTITUTIONS MENTIONED

AC Immune S/A (NASDAQ:ACIU), Lausanne, Switzerland
Biogen Inc. (NASDAQ:BIIB), Cambridge, Mass.
Brigham and Women's Hospital, Boston, Mass.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
C2N Diagnostics LLC, St. Louis, Mo.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Harvard Medical School, Boston, Mass.
Ionis Pharmaceuticals Inc. (NASDAQ:IONS), Carlsbad, Calif.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Neurimmune Holding AG, Schlieren, Switzerland
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
TauRx Pharmaceuticals Ltd., Singapore

TARGETS

Tau (MAPT; FTDP-17) - Microtubule-associated protein tau

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FOLLOW THE JOURNEY OF VIREAD

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

COMPLETE RESPONSE RESULTS AT YEAR 1...

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.

Viread® 300 mg tablets
tenofovir disoproxil fumarate

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

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]

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

DETECTED AT YEAR 1 THROUGH YEAR 8

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)

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.

For more information, visit www.viread.com/hcp

300 mg tablets
Viread®
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

Brief Summary (Cont'd)

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).*

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.

Conference Alerts

North America

PAINWeek 2019

September 3-7, 2019 | Las Vegas, Nevada, USA

Website: https://www.painweek.org/conferences/painweek
Contact: info@painweek.org

PAINWeek 2019 offers a multidisciplinary faculty and diverse curriculum in the following course concentrations: behavioral, functional, integrative, and interventional pain management, health coaching, medical/legal issues, neurology, pain and chemical dependency, physical therapy, palliative care, pharmacotherapy, and wound care. There will also be full-day programs presented by the American Pain Society, the American Society of Pain Educators, and the International Pelvic Pain Society.

Global Healthcare Conference - 2019

September 4-5, 2019 | New York, New York, USA

Website: http://www.bairdconferences.com/conference2/Index/20
Contact: jgrayson@rwbaird.com

Baird is delighted to host its annual Global Healthcare Conference. This conference brings institutional and private equity investors together with senior management from over 90 public and privately-held companies. The conference will feature companies across the following sectors: Biotechnology, Healthcare Supply Chain & Pharma Services, Healthcare Information Technology, Life Sciences & Diagnostics, Medical Technology and Facilities & Services. Each conference provides in-depth looks at the strategies leading companies are pursuing to grow their businesses and shareholder value.

AHIMA19: Health Data and Information Conference

September 14-18, 2019 | Chicago, Illinois, USA

Website: http://ahima.org/conference
Contact: info@ahima.org

The AHIMA19: Health Data and Information Conference (formerly AHIMA Convention and Exhibit) is the premier health data and information event for education and networking. Attendees can witness successes and hear how challenges were overcome through interactive sessions, roundtables, panels, town halls, and site visits. Attendees can also meet with established leaders empowered for change, foster lasting connections, and discuss strategy around the industry's newest innovations.

Medicine X | CHANGE

September 20-22, 2019 | Stanford, California, USA

Website: https://medicinex.stanford.edu/change19-program/
Contact: medicinex@stanford.edu

Medicine X | CHANGE will gather the innovators who are disrupting health care throughout the globe and highlight the emerging technologies of today and learn how they will impact the health care we deliver and receive tomorrow. This conference will explore the drivers of change through organizational leadership and creative collaboration outside of health care's traditional silos.

The 15th MedTech Conference

September 23-25, 2019 | Boston, Massachusetts, USA

Website: https://themedtechconference.com/
Contact: conferenceinfo@advamed.org

The MedTech Conference will bring together more than 3,000 attendees to network, conduct business, gain access to capital, and share insights. The MedTech Conference provides the environment to connect with medical technology professionals in one place. The conference will provide the opportunity to search for potential industry partners and attendees with similar interests, making new contacts. MedTech Innovator Showcase with 50 companies and exhibition with over 125 companies will offer attendees to learn about the latest updates on trends and the future of the industry.

BIO Investor Forum

Oct 22-23, 2019 | San Francisco, California, USA

Website: https://www.bio.org/events/bio-investor-forum
Contact: info@bio.org

The BIO Investor Forum delivers a rich program that features corporate presentations and panel debates on the sweet spots and growth challenges facing the industry. The BIO Investor Forum features public and venture-stage company presentations, expert-led panel discussions on the latest market and investment opportunities with emphasis on drug and technology development, BIO One-on-One Partnering™ meetings between biopharma executives and investors, and premier opportunity to network with industry executives and investors focused exclusively on life sciences.

12th Annual Conference on the Science of Dissemination and Implementation in Health

December 4-6, 2019 | Arlington, Virginia, USA

Website: https://www.academyhealth.org/events/site/12th-annual-conference-science-dissemination-and-implementation-health
Contact: 202.292.6700

The Annual Conference on the Science of Dissemination and Implementation in Health (D&I) helps to optimize health and health care by bridging the gap between research, practice, and policy. The event is co-hosted by the National Institutes of Health (NIH) and AcademyHealth. This year's conference theme, *Raising the Bar on the Rigor, Relevance, and Rapidity of Dissemination and Implementation Science*, is intended to help us map the way forward for improvements in the development, execution and application of D&I science.

Europe

Association for Dental Education in Europe (ADEE) Annual Meeting

August 21-23, 2019 | Berlin, Germany

Website: http://www.adee.org/meetings/berlin2019/index.html
Contact: +353-1-612-7287 or 7235

Every year, the ADEE invites its members from all over Europe to attend our Annual Meeting. This year ADEE meeting will be held at the Dental Faculty, Charité - Universitätsmedizin Berlin, Germany and the theme will be 'Equipping our students to be dentists of the future'. The meeting features on keeping abreast of developments and new techniques in Dental Education, brushing up on industry best practice, finding out about the latest equipment, seeing what's happening in research and development, and attending workshops and special interest groups.

Conference Alerts

Global Conference on Addiction and Behavior Health (GAB)

August 22-24, 2019 | London, United Kingdom

Website: https://addiction-behavioral-conferences.magnusgroup.org/
Contact: addiction@magnusconferences.com

GAB 2019 is an international meeting ground focused on neuroscience contributions and it aims to advance the understanding of the action of drugs of abuse and addictive processes. The conference encourages research on the etiology, prevention, identification, and treatment of substance abuse; thus, providing a forum for the dissemination of information in the extensive field of addiction. GAB gives the participants direct access to the most significant and current research findings on the nature and management of alcoholism and alcohol-related disorders.

18th European Congress of Internal Medicine

August 29-31, 2019 | Lisbon, Portugal

Website: http://www.efim.org/ecim2019/
Contact: info@efim.org

The theme of the congress is "Innovation in Health Care: New Opportunities for Internal Medicine." The choice of this theme was motivated by their conviction that the demographic evolution, the super-specialization trends and the growth of the healthcare costs underscores the need for a medical specialty with the characteristics of Internal Medicine and makes emerge new challenges to the internists. ECIM 2019 will provide an excellent opportunity to consider changes that can be implemented, to share successful experiences and to discuss the latest knowledge in the clinical areas related to Internal Medicine, presented by the best experts, as well as a great setting for networking.

31st European Congress of Pathology

September 7-11, 2019 | Nice, France

Website: https://www.esp-congress.org/
Contact: ecp-amsterdam@cpo-hanser.de

Pathologists and scientists from all over the world are invited to join the 31st ECP and become updated on all aspects of diagnostic and molecular pathology. The theme for the ECP 2019 is direct and easy to memorize: "Pathology is Nice". Indeed, in September 2019 Nice will be the capital of European and International pathology where pathologists and their collaborators, molecular biologists, geneticists, bioinformaticians, and information technologists will meet to share advances in discipline that offers diagnostic, prognostic and predictive information essential for best patient care.

19th Annual Biotech in Europe Forum

September 25-26, 2019 | Basel, Switzerland

Website: https://www.sachsforum.com/bef19-about.html
Contact: SachsTeam@SachsForum.com

The 19th Annual Biotech in Europe Forum is recognized as the leading international stage for those interested in investing, partnering in the biotech, and life science industry. This highly transactional event draws together an exciting cross-section of early-stage/pre-IPO, late-stage, and public companies with leading investors, analysts, money managers, and pharma licensing executives. The Forum will provide a number of networking opportunities via online One-2-One meeting system which allows attendees to pre-book meetings with dedicated meeting facilities.

5th Annual Cell & Gene Therapy Congress 2019

October 29-30, 2019 | London, United Kingdom

Website: https://www.oxfordglobal.co.uk/celltherapy-congress/
Contact: info@oxfordglobal.co.uk

Over 350 delegates representing global pharmaceutical organizations, leading biotechnology companies, and internationally renowned academic institutions. Over 40+ presentations, case studies and panel discussions focused on Cell & Gene Therapy development and clinical research for oncology and rare disease, the commercialization of CAR T treatments, and Cell & Gene Therapy bioprocessing and manufacturing strategies. The congress is co-located with highly-anticipated 8th Annual Cell Culture & Bioprocessing Congress and 6th Annual Stem Cell & Regenerative medicine Congress.

Asia

HIMSS AsiaPac19

October 7-10, 2019 | Bangkok, Thailand

Website: https://www.himssasiapacconference.org/
Contact: dkoh@himss.org

HIMSS AsiaPac19, organized by HIMSS APAC and supported by the Ministry of Public Health Thailand, will be convened under the theme Empowering Value Creation. Pinpointing the value and impact of health information and technology is complex. Value is demonstrated in many ways and providers arrive at value differently. HIMSS AsiaPac19 will offer global best practice for you and your organization to plan for, implement and commit to creating quantifiable and sustainable value-based care for your patients and consumers.

The 8th International Conference on Biomedical Engineering and Biotechnology (ICBEB 2019)

October 22-25, 2019 | Seoul, Republic of Korea

Website: http://www.icbeb.org/
Contact: icbeb@icbeb.org

The 8th International Conference on Biomedical Engineering and Biotechnology (ICBEB 2019), hosted by Institute of Bio-medical Engineering Research, Kyungpook National University and supported by Center for the Support of Medical Device Platform, Keimyung University. As an annual gathering, it provides an extensive platform for scientists, researchers and scholars to present their research results and newest findings in all fields of Biomedical Engineering and Biotechnology, discuss the practical challenges encountered recommend better solutions for human health.

China Healthcare Summit 2019: The Bridge to Innovation

November 18-20, 2019 | Shanghai, China

Website: https://www.BiocenturyChinaSummit.com
Contact: jberlin@biocentury.com

The BioCentury-BayHelix China Healthcare Summit: The Bridge to Innovation is a strategic, is a VIP-only event for busy biopharma and life sciences executives and investors to get a first-hand look at the innovation, business and policy transformations taking place in China. The conference is THE place to meet the right Chinese investors and partners in an intimate setting. The China Summit agenda is developed by an Organizing Committee that includes China industry KOLs and the BioCentury editorial team. Simultaneous translation is provided in all strategic sessions.

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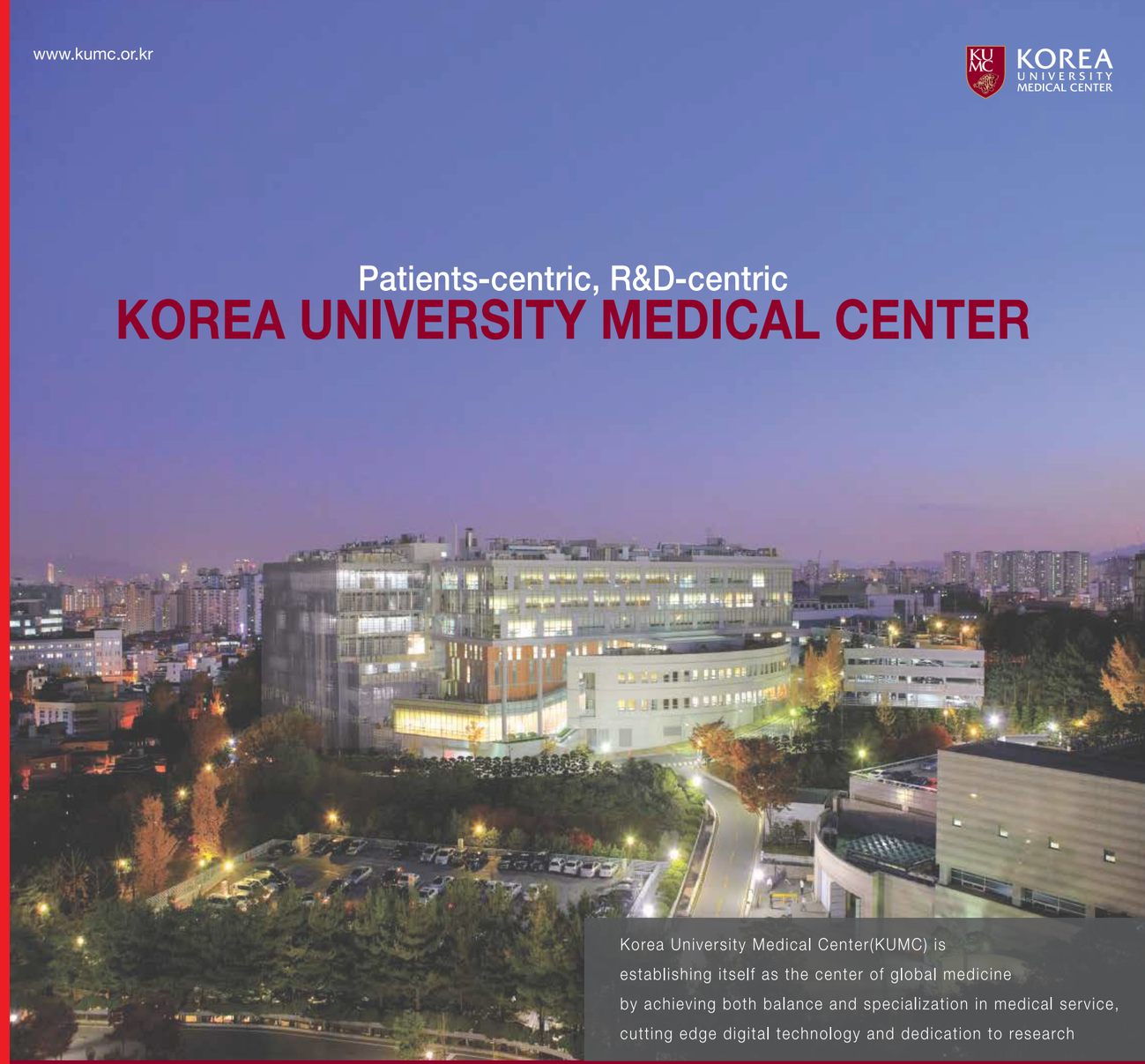

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LATEST HEALTHCARE INDUSTRY NEWS

May - Aug 2019

1. Measles Outbreak Now at 880 Cases, With Fastest Growth Still in New York

There have now been 880 measles cases reported in this year's outbreak, already the largest since 1994, federal health officials said on May 20. An additional 41 cases were reported last week, according to the Centers for Disease Control and Prevention. Of those, 30 were in New York State, which is having the country's most intense outbreak, largely in Orthodox Jewish communities. Measles transmission tends to fade when warm summer weather arrives, other experts said. It is not clear whether that is because children are no longer gathered close together in school, because families spend less time indoors or because virus-laden droplets — like those containing influenza virus — stay airborne longer in cold, dry air than in warm, humid air.
https://www.nytimes.com/2019/05/20/health/measles-outbreak-washington-new-york.html

2. To Fight Deadly Candida Auris, New York State Proposes New Tactics

New York State health officials are considering rigorous new requirements for hospitals and nursing homes to prevent the spread of a deadly drug-resistant fungus called Candida auris. The requirements could include mandatory pre-admission screening of patients believed to be at-risk and placing in isolation those patients who are infected, or even those just carrying the fungus on their skin. Dr. Howard Zucker, the state health commissioner, and a fungal expert from the federal Centers for Disease Control and Prevention met on May 17 in Manhattan with nearly 60 hospital officials from across the state to discuss the proposed guidelines.
https://www.nytimes.com/2019/05/23/health/candida-auris-hospitals-ny.html

3. US Crackdown on Foreign Biotech Investment Makes Us Poorer, Not Safer

A new US law intended primarily to curb Chinese investment is threatening the US biotechnology industry and the jobs and health benefits it brings. After passing Congress 400 to 2, the updated version of this little-known law, administered by a government committee called CFIUS, immediately triggered layoffs and reduced international fund flows into biotech companies. Because of its overly broad implementation and lack of an appeal mechanism, CFIUS is not only drastically reducing Chinese investment into US biotech. It is also threatening our country's drug discovery engine.
https://www.forbes.com/sites/stevedickman/2019/05/24/us-crackdown-on-foreign-biotech-investment-makes-us-poorer-not-safer/#2ec1abe65581

4. Warning of 'Pig Zero': One Drugmarker's Push to Sell More Antibiotic

Facing a surge in drug-resistant infections, the World Health Organization issued a plea to farmers two years ago: "Stop using antibiotics in healthy animals." But at last year's big swine industry trade show, the World Pork Expo in Des Moines, one of the largest manufacturers of drugs for livestock was pushing the opposite message. "Don't wait for Pig Zero," warned a poster featuring a giant picture of a pig peeking through an enormous blue zero, at a booth run by the drugmaker Elanco. The company's Pig Zero brochures encouraged farmers to give antibiotics to every pig in their herds rather than waiting to treat a disease outbreak caused by an unknown Patient Zero.
https://www.nytimes.com/2019/06/07/health/drug-companies-antibiotics-resistance.html

5. Gilead Taps Nurix's Protein Degradation Tech in $45M Cancer Pact

Gilead Sciences is enlisting Nurix and its drug development technology to create new cancer medicines that break down disease-causing proteins. The Big Pharma is handing over $45 million upfront in a deal that could reach $2.3 billion in value if all milestones are met and royalties realized. Nurix's drug discovery platform focuses on manipulating the ubiquitin system, which breaks down damaged or unneeded proteins. Gilead will have the option to license programs against up to five targets from the deal, and Nurix could choose to co-develop up to two of those programs in the U.S. In the latter case, the pair will split development costs, profits and losses down the middle.
https://www.fiercebiotech.com/biotech/gilead-taps-nurix-s-protein-degradation-tech-45m-cancer-pact

6. Sanofi to Ax 466 Jobs, Step up Focus on Cancer, Gene Therapy R&D

Sanofi is to cut 466 jobs in France and Germany as part of the reorganization of its R&D group. The job losses are part of a pivot away from cardiovascular diseases and toward immune-oncology drugs and gene therapies. In recent years, Sanofi has sought to revitalize its R&D group, making changes intended to lessen its reliance on external partners and hiring ex-Roche executive John Reed to lead the operation. The changes have seen Sanofi prioritize programs in oncology, immunology, rare diseases and vaccines and jettison several R&D projects that no longer fit with its focus.
https://www.fiercebiotech.com/biotech/sanofi-to-ax-466-jobs-step-up-focus-cancer-gene-therapy-r-d

7. Dassault Systems Eyes Life Science Boost with $5.7B Medidata Buy

Clinical trial specialist Medidata Solutions is being bought out by France's Dassault Systemes in a $5.7 billion deal designed to help the tech firm diversify deeper into the biopharma services world. The cash deal sees the New York-based company subsumed into Dassault, which has specialized in design software but now wants in on the lucrative CRO and clinical trial space that has seen a bunch of high-end deals and buyouts in recent years. Medidata, which had sales of $636 million last year, has been making its own deals over the years, including pacts with biotechs such as Forty Seven.
https://www.fiercebiotech.com/cro/dassault-systemes-eyes-life-science-boost-5-8b-medidata-buy

8. FDA Proposes Tighter Opioid Rules That Would Make New Drugs Less Addictive

The Food and Drug Administration is proposing to tighten the rules for opioid manufacturers by requiring new drugs to be less addictive. Acting FDA Commissioner Ned Sharpless withdrew the agency's previous guidance June 20, laying out a tougher new regulatory framework for evaluating applications for new opioids coming to the U.S. market. Under the proposal, drugmakers would have to say whether their drug has "any characteristics that would mitigate the risks of overdose, abuse or the development of addiction." The FDA is taking public comments on its proposal through Aug. 20 and has scheduled a public meeting Sept. 17 to discuss it.

https://www.cnbc.com/2019/06/20/fda-proposes-tighter-opioid-rules-that-would-make-new-drugs-less-addictive.html

9. Trump Issues Executive Order Increasing Transparency in Hospital Prices, Doctor Fees

President Donald Trump on June 24 issued an executive order designed to pressure insurers, doctors and other health-care providers to disclose more information about their prices. High health costs have become a rare bipartisan issue with lawmakers on both sides of the aisle demanding changes. Trump has made lowering prices one of the key issues of his administration as health care remains a top issue for voters in the 2020 elections. Earlier this year, the Trump administration announced it would require pharmaceutical companies to disclose the price of their prescription medicines in television commercials starting in July, sparking a lawsuit from Amgen, Merck and Eli Lilly.

https://www.cnbc.com/2019/06/24/trump-to-issue-executive-order-increasing-transparency-in-health-prices.html

10. WHO Study Finds 'Strong Evidence' HPV Vaccine Can Prevent Cervical Cancer

International researchers say there's "strong evidence" the HPV vaccine prevents cervical cancer and should be expanded to boys and adults, according to a World Health Organization study published Wednesday in The Lancet. HPV, or human papillomavirus, is the most common sexually transmitted disease in the U.S., according to the Centers for Disease Control and Prevention. Researchers analyzed data from 14 high-income countries, covering more than 60 million people over eight years. They found cases of HPV infections, two types of HPV that cause most cervical cancers, anogenital warts and precancerous cervical lesions — possible precursors to cervical cancer — all declined since the vaccine was introduced.

https://www.cnbc.com/2019/06/26/who-study-shows-strong-evidence-hpv-vaccine-can-prevent-cervical-cancer.html

11. Apple Continues Expanding into Health Care by Selling a Consumer-focused Diabetes Monitor in Stores

Some Apple retail locations now sell a glucose monitor that integrates with the iPhone to give people with diabetes a way to track their blood sugar through Apple's Health app. One Drop is an aesthetically designed blood glucose monitor with an associated iPhone app that integrates with Apple's Health app, as well as a separate Apple Watch app. It's the only diabetes product that Apple is currently selling in its physical stores, although it previously carried One Drop online and carried a Sanofi monitor in 2012. The introduction of One Drop is a prime example of how Apple is breaking into the health space by selling consumer-oriented products and integrating the data from them in its Health app, making the iPhone and Apple Watch hubs for people's personal health.

https://www.cnbc.com/2019/06/27/apple-store-to-sell-one-drop-monitor-its-first-diabetes-product.html

12. Google's Next Battleground as It Gets into Health Care Will Be Privacy, Lawsuit Shows

A new lawsuit against Google and the University of Chicago Medical Center alleges that researchers did not strip out date stamps or doctor's notes buried within hundreds of thousands of patient medical records, and that this information could be used to identify a patient. A new lawsuit alleges that the companies did not take the proper steps to protect patient health information. The lawsuit specifically calls out Google's massive data collection as a reason it could use seemingly harmless information to identify patients — a sign of deep mistrust, and a problem for Google's ambitions in the space.

https://www.cnbc.com/2019/06/28/google-u-chicago-hipaa-lawsuit-shows-next-battleground-privacy.html

13. Digital Health Company Livongo Files for an IPO

In a much anticipated move, Livongo which uses a combination of devices, AI-driven data and specialized coaches to help people manage chronic conditions, filed today to go public. Livongo is part of a crop of companies operating at the intersection of healthcare and technology going public this year. Digital health companies have raised billions in venture funding but produced zero IPOs since 2016, falling short of the excitement they've generated and raising questions about their growth potential. Livongo's revenues grew 122% to $68.4 million from 2017 to 2018, and in the first quarter of this year they increased 157% to $32 million compared to the same period last year, but losses have widened as well.

https://www.forbes.com/sites/zinamoukheiber/2019/06/28/digital-health-company-livongo-files-for-an-ipo/#34be3c3734a6

14. Researchers Say They're Closer to Finding Cure for HIV After Using CRISPR Technology to Eliminate Disease in Live Mice for the First Time

Researchers say they're one step closer to finding a potential cure for HIV after successfully eliminating the virus in living mice for the first time. Using a combination of CRISPR gene-editing technology and a therapeutic treatment called LASER ART, scientists at Temple University and the University of Nebraska Medical Center said they erased HIV DNA from the genomes of animals in what they call an unprecedented study that was published July 2 in the journal Nature Communications. The CRISPR-LASER ART method is now being tested in primates.

https://www.cnbc.com/2019/07/02/researchers-used-crispr-technology-to-cure-hiv-in-living-mice.html

15. Ebola Outbreak in Congo Is Declared a Global Health Emergency

The year-old Ebola epidemic in the Democratic Republic of Congo is now considered a global health emergency, the World Health Organization said on July 17, in a formal declaration that many public health experts called long overdue. the panel was persuaded by several factors that have made combating the epidemic more urgent in recent weeks: The disease reached Goma, a city of nearly two million people; the outbreak has raged for a year; the virus has flared again in spots where it had once been contained; and the epidemic hot zone has geographically expanded in northeastern Congo near Rwanda and into Uganda.

https://www.nytimes.com/2019/07/17/health/ebola-outbreak.html

16. Drug Overdose Deaths Drop in U.S. for First Time Since 1990

Three decades of ever-escalating deaths from drug overdoses in the United States may have come to an end, according to preliminary government data made public July 17. Total drug overdose deaths in America declined by around 5 percent last year, the first drop since 1990. The decline was due almost entirely to a dip in deaths from prescription opioid painkillers, the medicines that set off the epidemic of addiction that has lasted nearly two decades. Fatal overdoses involving other drugs, particularly fentanyl and methamphetamine, continued to rise. The overall reduction, reported by the Centers for Disease Control and Prevention, suggests some possible relief from an epidemic so severe that it has reduced life expectancy.

https://www.nytimes.com/interactive/2019/07/17/upshot/drug-overdose-deaths-fall.html

17. How Drug Companies Are Using Your DNA to Make New Medicine

Genetic test-kit company 23andMe Inc. has for years used saliva to tell millions of consumers how closely related they are to Neanderthals or whether they are likely to develop diseases like diabetes or Alzheimer's. Now, it's fulfilling a bigger ambition: drug development. For 23andMe, using genetic data for drug research "was always part of the vision," according to Emily Drabant Conley, head of business development. Since its founding in 2006, the company has amassed a huge collection of data from the millions of people who have submitted spit samples—and up to $199 each—in return for insights on their genes.

https://www.wsj.com/articles/23andme-glaxo-mine-dna-data-in-hunt-for-new-drugs-11563879881

18. Lyndra Bags $13M Gates Grant for Long-Acting Contraceptive Pill

Lyndra Therapeutics, the MIT spinout, picked up $13 million grant from the Bill Melinda Gates Foundation to work on a contraceptive pill that only needs to be taken once a month. One of the things that the Gates Foundation's Family Planning program aims at is bringing contraceptive information, services and supplies to women in low- and middle-income countries. Lyndra plans to use the funds to create a pill that delivers a continuous dose of the hormones such as estrogen and progestin with a focus on proving the pill can stay in body for a whole month.

https://www.fiercebiotech.com/biotech/lyndra-therapeutics-bags-13m-gates-grant-to-develop-once-monthly-contraceptive-pill

19. 3D Tissue Printer Prellis Biologics Raises $8.7M to Build Replacement Arteries, Vascular Blanks for Cell Cultures

Prellis Biologics, a San Francisco-based 3D tissue printing startup, has gathered $8.7 million in new funding alongside positive news from the first transplantation of its vascular tissue scaffolds into animals. The company's series A round brought its total capital funding to $10.5 million, which was led by Khosla Ventures with additional backing from its previous seed round investors, True Ventures and SOSV's Indie Bio accelerator. Prellis uses laser and holographic printing techniques that build 3D hydrogel structures for R&D or transplantation. Several promising study results, including the animal studies showed the spontaneous growth of additional blood vessels into the transplanted structure over an eight-week period, including branched vasculature which was about five times larger than a typical capillary, to connect the graft with the animals' circulatory system. The first 3D printed human organ transplantation of replacing arteries is planned for later this year.

https://www.fiercebiotech.com/medtech/3d-tissue-printer-prellis-biologics-raises-8-7m-to-build-replacement-arteries-vascular

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