July 2017 - ISSUE 14

WKMJ

World Korean Medical Journal

Cover Story
Inspirational Korean Healthcare Leader

Ki-Young Sohn, Chairman and Chief Executive Officer at Enzychem Lifesciences, Corp.

Biopharmaceutical Report

Eisai's Lenvima Should See FDA Approval in Hepatocellular Carcinoma (HCC)

Medical Device: Growing Cybersecurity Threat and Need for More Regulation

Strategic Shift of Dong-A ST Co. Ltd. in Drug Discovery

Entrepreneur Interview

Thomas Seoh, President and Chief Executive Officer at Kinexum

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Campers from "Aim High Academy," a reputable Korean-American summer camp located in Harrington Park, NJ, visited W Medical Strategy's office to learn about health-industry consulting. Michael, Alex, Mr. Shapiro, David, Lilly, Ian, Dr. Cho, Allyson, Alice, Rachelle

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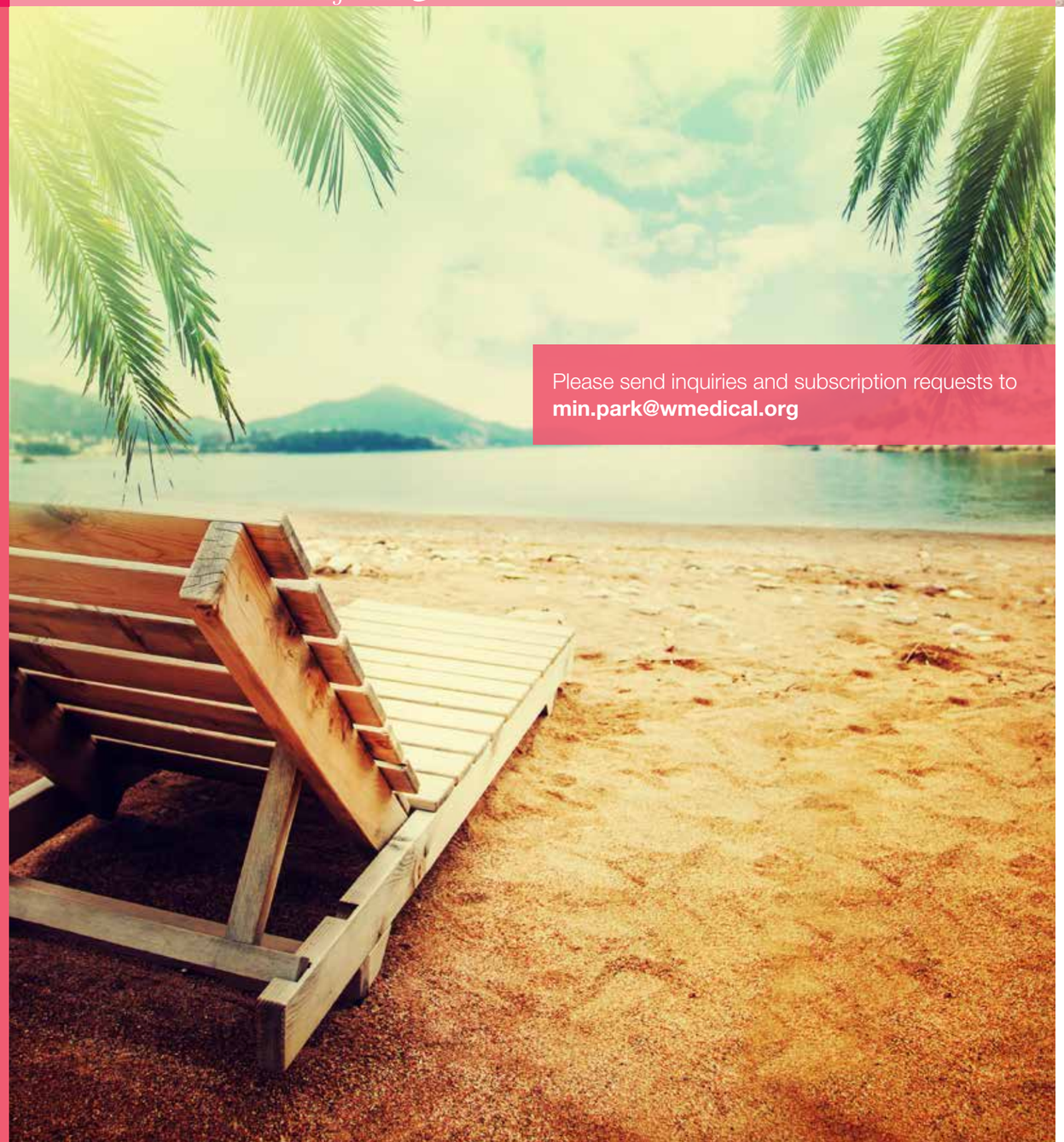

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TABLE OF CONTENTS

FROM THE PUBLISHER

The world, including the medical community, is seeing unprecedented instability. In the U.S., another attempt to repeal and replace the Affordable Care Act (A.C.A.), or Obamacare, is underway, which if successful, is expected to result in 24 million Americans losing their health insurance. In addition to domestic policy restraints, international relations has also become a challenge in the medical field. With added global tension subsequent to the unfortunate outcome of Otto Warmbier, an American university student who was convicted of theft in 2016 upon visiting North Korea, the efforts to improve the healthcare system worldwide is progressively becoming more difficult, especially since there is now a U.S. travel ban to North Korea.

Nonetheless, these setbacks do not impede the efforts towards advancement in the medical industry. In fact, innovation in the healthcare arena has forged greatly in recent years. I personally will be involved in a study that will compare my selection of a drug to that of IBM Watson, AI, an artificially intelligent operating system, which is only one of several processes that mark the beginning of computer analytics in medical decision making.

In this issue, we feature another Korean leader in healthcare innovation, Mr. Ki-Young Sohn, Chairman and CEO of Enzychem Lifesciences. Mr. Sohn as well as a number of other Korean entrepreneurs are representative of the burgeoning Korean Biopharma efforts. The Korean biopharmaceutical companies are relative newcomers in global terms, and their progress is gradual; yet, they are already seeing R&D come to fruition with new pharma products.

In addition, we feature CEO of Kinexum Thomas Seoh in the entrepreneur interview for this issue of WKMJ. Kinexum is a company that focuses on various aspects of drug development and approval, as it is an extensive, complex process to file for a drug or medical device. Citing the pharmaceutical field as an "old school industry" in need of new ideas and innovation, Mr. Seoh wishes to see a growth in the number of "start-ups," and encourages prospective new businesses to implement new methods of entrepreneurship.

Innovation is vital for a world that is undeniably changing at an accelerated pace. Who would have thought a relatively young car company like Tesla would overtake Ford in value in under ten years since its launching? Yet, this start-up mentality that Elon Musk possessed when pioneering Tesla is the attitude the healthcare industry needs to carry in coming years. Elon Musk has actually now entered the medical field with Neurolink, specializing within the brain computer interface sector, and hopefully, his spirit of innovation will not only improve the current state of healthcare, but also inspire others in younger generations to do the same. What we need is a revolution in the form of innovation.

David Y. Ko, MD
Publisher
President of WKMO
Keck School of Medicine of USC

FROM THE EDITOR-IN-CHIEF

Korean pharmaceutical and biotechnology companies are branching beyond the usual licensing-focused business model, and are now transitioning to more partnerships and joint ventures with U.S. and European pharmaceutical companies. This shift can prove to be a pivotal point in Korea's healthcare industry because if Korean biopharma companies discover global blockbuster drug candidates, monetizing them in the worldwide market through their own capabilities would allow them much greater participation in the overall industry revenue potential.

For the July edition of WKMJ's Cover Story, we feature a passionate achiever and inspiring leader in the Korean biopharmaceutical industry, Mr. Ki-Young Sohn, the chairman and CEO of Enzychem Lifesciences. Enzychem Lifesciences has been developing new drug candidates to address the unmet medical needs of immunocompromised patients. Furthermore, it launched major global initiatives and clinical programs to help facilitate licensing, strategic partnerships and investment opportunities for the self-developed global new drug candidate, EC-18. Mr. Sohn shared his vision with our readers, and conveyed his confidence that Enzychem is ready to take part in global biopharmaceutical innovation in order to fulfill the essential, yet unmet needs of patients.

In our Entrepreneur Interview, we meet Thomas Seoh, CEO of Kinexum. Having had extensive experience in law and business leadership, he defines a good leader as one who holds three mindsets; a focus on customer benefits as well as technical features, perseverance and belief tempered by evidence, and vision, tempered by management risk.

Moreover, this month's articles feature new trends and issues of the bio-health industry. In partnership with Biocentury and Biopharma Insight, we share significant and recent industry news with our readers.

Various writers and experts impart their knowledge and insights as co-authors in this edition of WKMJ. I sincerely hope that our readers will find these exciting selections of articles to be helpful and inspiring.

Enjoy the read!

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

WKMJ RECAP OF THE LAST ISSUE

Cover Story
Inspirational Korean Healthcare Leader Dr. Larry Kwak, Vice President of Translational Research and Developmental Therapeutics at City of Hope National Medical Center

Dr. Kwak is the Vice President and Cancer Center Associate Director of Translational Research and Developmental Therapeutics at City of Hope National Medical Center. He served as Head of the Vaccine Biology Section, Experimental Transplantation and Immunology Branch at the National Cancer Institute (NCI) for 12 years, and there, helped pioneer the bench-to-clinic development of a therapeutic cancer vaccine for B-cell malignancies, a positive landmark in cancer research. A committed physician, scientist, and mentor, his vision helped integrate basic discoveries from academic laboratories with translational clinical development to first-in-human clinical trials of novel “homegrown” therapeutics. To read more about Dr. Kwak, please read Issue 13 of WKMJ.

Entrepreneur Interview
Mario Pennisi, Chief Executive Officer at Life Sciences Queensland

Mario Pennisi is the inaugural CEO of Life Scienes Queensland (LSQ) since its establishment in 2005. Mr. Pennisi holds over two decades’ worth of experience in the life science industry, particularly in managing commercial operations within the field. In fact, he has overseen LSQ’s growth to become Australia’s peak industry group for therapeutic product service providers. To learn more about the Australian industry-led organization and its vital roles in life science commercialization and research, please refer to Issue 13 of WKMJ.

Biopharmaceutical Report I
Legislation to Force Payer Cover of Abuse-Deterrent Opioids Faces Resistance

Proposed legislation across 23 US states to force payers to increase reimbursement of abuse-deterrent (AD) opioids will likely face significant resistance due to state cost implications, most experts said. Based on conversations with consultants, it is expected that only a few states will implement very strong legislation to force physicians to prescribe AD opioids.The extraordinary cost increase of AD opioids compared to cheap generic formulations is one of the major blocks to passage for most states. For more details, please refer to Issue 13 of WKMJ.

Biopharmaceutical Report II
Western CAR-Ts Face Chinese Development Hurdles Due to Regulatory Uncertainty

Western-origin chimeric antigen receptor T-cell (CAR-T) therapies being developed in China face an uncertain regulatory landscape at the national level, as well as disparities between hospitals’ practices at the local level, experts said. While regulation of cell therapies like CARTs may fall under Chinese Food and Drug Administration (CFDA) regulations, details of these regulations remain unclear. To read more, the full report can be found in Issue 13 of WKMJ.

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INSPIRATIONAL KOREAN HEALTHCARE LEADER

Ki-Young Sohn, Chairman and Chief Executive Officer at Enzychem Lifesciences, Corp.

COVER STORY

1. We recognize that Enzychem Lifesciences Corporation is one of the fastest growing biopharmaceutical companies in Korea, and we admire the efficient and proactive expansion. What are the major business philosophies and strategies of Enzychem Lifesciences? How would you distinguish Enzychem Lifesciences from other potential competitors throughout the globe?

- Dr. George Merck, who established Merck in the United States, founded the company with the principle that "Medicine is for patients, not for profits." Our company shares this very philosophy, and believes that it is our obligation to develop medicine for two reasons: to save lives, and to improve human well-being.
Enzychem Lifesciences develops new drugs to provide medication to all those who need it around the world. In doing so, our company strives to embody three traits: "creative," "unique," and "independent." To be creative means to discover new uses from old traditions and apply them with modern technology. Our company began developing a new medicine upon discovering a new compound called EC-18 from deer antler, which has been consumed for as long as 2,000 years by our Korean ancestors. To be unique means to develop and manufacture a new drug, using unprecedented methodologies. Enzychem has uniquely patented technologies to complete this process. Last but not least, to be independent means to build the company's capabilities in leading the process and utilizing its own resources. To this day, Enzychem is competent in fulfilling the operations of global new drug development and we will continue to successfully lead them until completion.

- There are many great biotech companies in the world that are constantly developing new medicine, and hold a stellar record of creating many blockbuster drugs. Our company does not intend to compete with them but rather, we seek synergistic collaboration through EC-18. EC-18 is an immunoregulatory substance which controls and modulates immunoproteins, such as cytokine and chemokine, movements of immunocytes, which are neutrophils and eosinophils, and inflammatory cells. Thus, there is a high probability that it will be used as a combination therapy with existing drugs, most of which function only as inhibitors or activators. Our new drug, which helps control the immune system, will mutually benefit both Enzychem and global biopharmaceutical companies through collaborative programs.

> **"As a life sciences corporation, Enzychem sustains the duty of constantly challenging ourselves to fight incurable diseases and work towards a world without illnesses"**

2. Enzychem Lifesciences has been developing new drug candidates to address the unmet medical needs. The development of EC-18, the world's first oral medicine to prevent and treat chemotherapy-induced neutropenia, has been strengthening Enzychem Lifesciences' global competitiveness. What does 'globalization' mean to Enzychem Lifesciences?

- We believe every company shares the ultimate goal of bettering society. As a life sciences corporation, Enzychem sustains the duty of constantly challenging ourselves to fight incurable diseases and work towards a world without illnesses, and for that reason, globalization is our priority.

Our company carries an ongoing effort in researching and developing new medicine in compliance with international standards and protocols. Furthermore, we are working closely with top experts in each field around the world in our efforts to achieve this goal.

ENZYCHEM LIFESCIENCES

3. As an entrepreneur, what would you say are the top three priority assets or skill sets needed to be successful in the global healthcare industry?

- As the CEO of Enzychem Lifesciences and an entrepreneur, I practice three things that can be the answer to this question: leadership, scholarship, and stewardship.

Leadership entails the ability to gather and usher various talents into a project with a clear objective. Successful entrepreneurs are able to do this by fostering teamwork, team efforts, and team spirit. Before seeking collaboration with companies outside ours, it's essential to maintain a harmony amongst the members of Enzychem. This way, both internal and external roles in the development of EC-18 can be interfaced and combined.

Scholarship involves continuous educational research, a necessary step in the development process. Scientific studies in a variety of areas, including medical science, pharmacy, biotechnology, biology, and chemistry, are vital in new medicine developments.

Stewardship is an invaluable entrepreneurial skill, especially in the development of a new, global drug. Projects like this require astronomical investments from outside parties, and therefore entrepreneurs hold the responsibilities of maintaining the value of assets, as well as being transparent to and sustaining trust with stockholders and investors.

Ki-Young Sohn at the 2017 Lotte World Tower International Sky Run

Chairman Sohn during an interview with WKMJ

One distinguishing quality of the healthcare industry is that changes and innovations require a great amount of time unlike other industry areas, such as fashion and IT, whom can produce new results on an annual basis. A single change in healthcare can take five to ten years, and requires endurance, patience, and the persevering spirit of a marathon runner. I completed the Chosun Ilbo Marathon Tournament in Korea for the last decade, and was inducted into the Hall of Fame. Doing so was a challenge, but was nonetheless possible with physical strength, pace adjustment, and the never-give-up mentality. The necessary capacities for running a marathon and developing new medicine is the same in the sense that milestone management, endurance, and patience are all imperative for success.

4. Chairman Sohn, you have been recognized as one of the most successful CEOs in Korea's pharmaceutical industry, according to Power Korea. As the chairman of Enzychem Lifesciences Corporation, what are some of the major performances and outcomes the company has accomplished under your leadership? What are the long-term goals and visions you hope to see the company achieve?

- Based on two decades of EC-18 substance and efficacy research by Professor Sang-Hee Kim, a hematological tumor specialist in Seoul Asan Medical Center, our company conducted six years of further research on the compound. As a result, our company is able to successfully mass produce EC-18. We've also completed construction of a GMP factory that will accommodate this entire process. Currently, we are conducting ongoing research on EC-18's immunoregulation mechanism of action from 2013, as well as clinical trials for two different indications both in Korea and United States.

As the leader of the company, I engage in every step of Enzychem's new drug development process and micro-manage details with great concentration. My belief is that the leader should not only provide far-sighted vision and goals, but also pay a great amount of attention to detail. Through such processes, Enzychem built an infrastructure and a set of comprehensive procedures for the global new drug development. Another strength of Enzychem is its multiple layers of networks and outside resources. We've established strong networks and resources that function as extended workforce to support our operations. Furthermore, we participate in many of government granted and supported programs, utilize the advice of outside experts and professionals, and collaborate with world class laboratories and scientists.

"It is our mission to develop the safest and most economical form of EC-18 to treat various immune disorders"

As I mentioned earlier, Enzychem's new drug candidate EC-18, with its immune regulating mechanism, will resolve existing medications' limits, minimize adverse events through combination therapy, and ultimately increase the value of already commercialized medicines. This will help reduce the development cost of big pharmaceutical companies and healthcare expenditures while also improving the efficacies of the treatment. It is our mission to develop the safest and most economical form of EC-18 to treat various immune disorders.


The photo of Chairman Sohn and Enzychem employees


Mr. Sohn with special advisor Dr. Waun Ki Hong and CMO Dr. Myung Hwan Kim

5. You serve as the Chairman of Enzychem Lifesciences. As one of the key opinion leaders in Korea's biopharmaceutical industry, what are some significant changes you have noticed in the particular work field? And what do you forecast will occur in global and Korean biopharmaceuticals within the next five years?

- In the recent decade, the Korean biopharma industry put its utmost efforts as well as significant investments into global new drug development. The Korean government designated the bio-health industry as the next growth engine of the nation. In an effort to enhance the competition of the industry, the government allocated many resources, established promotional policies and launched supporting programs. As a result, the Korean biopharma industry started to bear some fruit in recent years. These include mega-size global licensing deals, and a substantial growth in market capitalization for the Korean biopharma companies. I believe the global recognition of Korean biopharma as a fast growing industry will provide a beneficial environment for Enzychem's new drug development programs.

- The most significant trend of global biopharmaceuticals in the next five years will include the expansion of human immune and gene related technologies and therapies. Maintaining homeostasis and strengthening the immune system are essential in preserving human health. Thus, our immune regulating substance can be used in various ways for all of biopharma partners in the future.

WKMJ's Editor-in-Chief Dohyun Cho with Mr. Sohn

6. WKMJ has readers from more than 10 countries globally. Please share your final words with our readers.

- I'd like to pay tribute to WKMJ not only for introducing inspiring stories of eminent physicians who have contributed tremendously in the field of medicine, but also for investigating and introducing new stories related to the bio-health industry to promote attention to this industry. It is my great honor to be highlighted in WKMJ. I wish what I shared in this interview can provide interest to many readers and enhance their understanding and recognition of Korea and Enzychem Lifesciences as potential partners for future collaboration.

Ki-Young Sohn

Chairman and Chief Executive Officer at
Enzychem Lifesciences Corporation

Ki-Young Sohn is the CEO and Chairman of biopharmaceutical company, Enzychem Lifesciences Corporation, a number one leading corporation in the KONEX stock market of Korea. Enzychem's innovative new drug development program is backed by a 17-year history of API manufacturing. Prior to Enzychem, Mr. Sohn served as Chairman of Bridget Lifesciences Corporation, a professor at the International Management Institute of Federation of Korean Industries, and as Director of Samil Accounting Corporation, which is now known as PWC. Chairman Sohn holds a B.A. and an M.B.A. in Business Administration from Korea University.

Quotes from Enzychem's Medical Advisors

Waun Ki Hong, M.D., F.A.C.P., D.M.Sc.(Hon.)

Head, Division of Cancer Medicine,
The University of Texas MD Anderson Cancer Center

"I am a Special Advisor of Enzychem Lifesciences, whose Headquarter is located in Seoul, South Korea under the strong leadership of CEO and Chairman Sohn KY. The company has a new drug candidate, EC-18, a first-class PKC inhibitor which has been shown to effectively reduce the level of neutropenia in pancreatic cancer patients whom have been treated with systemic chemotherapy from clinical trials conducted in the Asan Hospital in Seoul. Based on this very intriguing finding, a prospective Phase II trial in breast cancer patients receiving AC regimen is underway at several institutions in Korea.
Enzychem Lifesciences is also interested in assessing the efficacy of EC-18 as a potential agent that will reduce the degree of mucositis in head and neck cancer patients who are receiving combined chemo and XRT. The therapeutic effect of EC-18 for chemotherapy-induced mucositis in Hamster model was very impressive. I believe the efficacy of EC-18 was demonstrated clinically and histologically by inducing epithelial differentiation in the animal model."

Stephen T. Sonis, D.M.D., D.M.Sc.

Professor, Oral Medicine and Diagnostic Sciences,
Harvard School of Dental Medicine

"Oral mucositis is a devastating complication of concomitant chemoradiation used for the treatment of cancers of the head and neck. More than two-thirds of patients being treated for tumors of the mouth, oropharynx, hypopharynx and nasopharynx develop mucositis-related ulcers which are so painful as to require a change in diet and significant analgesics. Severe mucositis also interferes with patients' ability to tolerate optimum cancer treatment, and results in hospitalizations, emergency room visits and increased costs of care. The pathogenesis of mucositis is similar to that of radiation-induced dermatitis and proctitis. Consequently an effective treatment for mucositis is likely to have similar efficacy for other indications. Mucositis represents a significant unmet clinical need. If EC-18 is effective, it would represent a valuable asset in the management of an important side effect of radiation therapy."

Myung Hwan Kim, M.D., Ph.D.

Director, Center for Pancreatobiliary Diseases, Asan Medical Center

"The study for EC-18 substance has been in research for over 15 years, and I, myself, have been in the research for over 10 years. In my perspective as a clinician, EC-18 can be a success as a global drug. EC-18, a substance produced by extracting the most important ingredients from the deer antler, is chemically synthesized and mass produced using unique techniques. This is the most ideal process in developing a new drug. For example, Aspirin, which was extracted from a substance found in the skin of the willow, was also chemically synthesized and mass produced for anti-pyretic and analgesic use. It is also used for anti-inflammatory uses and in treating heart disease, and recent studies have found that it has some anti-cancer effects as well. EC-18 is also underway in clinical trials for its efficacy in the treatment of neutropenia, and proved its effectiveness in reducing inflammation and assisting cancer treatment. These features suggest that EC-18 has the same potential as aspirin to become a globally successful drug."

G. Alexander Fleming, M.D.

Chief Technology Officer,
Enzychem Lifesciences Corporation

"I am greatly impressed with the tremendous vision and commitment of Chairman Sohn and the company that he leads. Though it is very important to start with a vision, Enzychem also benefits from a great story about its lead product EC-18 -how it was elegantly isolated from a natural material and later found to have multiple beneficial activities. EC-18 has a safety profile that is well supported by extensive animal testing and substantial human exposure. EC-18 has excellent prospects for a treatment that is safe, effective, and easy to take for people with a variety of conditions, ranging from sepsis to rheumatoid arthritis to asthma. We are systematically pursuing multiple therapeutic applications of EC-18. I am confident that this hard work and commitment will not only produce important clinical value, but will advance the scientific understanding of the immune system in health and disease. We expect to build on our science to create new compounds that extend the benefits of this platform."

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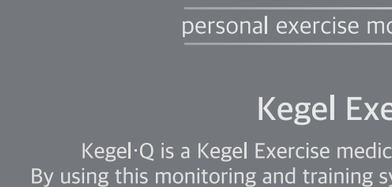

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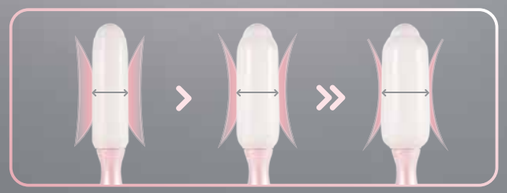

※ *Multicenter clinical trials are currently recruiting participants at reputable university hospitals in South Korea including Seoul National University Bundang Hospital and these trials are sponsored by Korea Health Industry Development Institute.*

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Thomas Seoh inauguration interview at Cosmos Club, Washington DC

Entrepreneur Interview

Thomas Seoh, J.D., President and Chief Executive Officer at Kinexum

1. Within a decade since its inception, Kinexum has earned recognition as a distinguished resource for research, development, and commercialization of life science products. What major philosophies and goals drive Kinexum to provide the excellence it does today?

Kinexum owes its character and success to founder and Executive Chairman G. Alexander ("Zan") Fleming, M.D., whom I sometimes half-jokingly refer to as a "rock star" in the life sciences regulatory world. Zan trained at Emory, Vanderbilt, and NIH, and was a senior reviewer at the US FDA, leading reviews of landmark approvals including the first statin, insulin analog and metformin.

From its original roots in regulatory and clinical development of small molecules for diabetes and other metabolic diseases, the firm has grown to assist over 300 companies to date from around the globe, respecting a range of therapeutic areas and modalities.

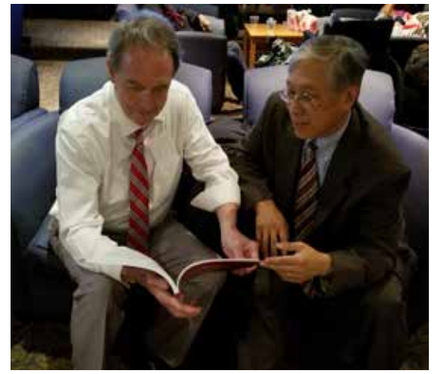
One of the things I bring to Kinexum is the clients' perspective. Having been on the operating side, I have lived the pressures on many CEOs of our emerging company clients, who have to juggle the expectations of investors and manage a limited cash runway. So at Kinexum, we prioritize the following four things:

First, taking extreme ownership by stepping in the shoes of our clients – we are more than just domain experts and advisors; we are constructively members of our clients' teams.

Second, striving for operational excellence, even if it's just 1% better per project.

Third, practicing the "human touch," treating clients, regulators, collaborators and others with whom we interact with respect, establishing ethos, then pathos, before pressing logos (after Aristotle/St. Thomas Aquinas/Stephen Covey).

Lastly, doing our part to advance translational science to accelerate useful products for patients.



Kinexum CEO Thomas Seoh with Kinexum Founder and Executive Chairman G. Alexander Fleming

2. Mr. Seoh, you've been appointed as the new CEO at Kinexum this past April. What about the organization drew you to become a prospective leader and key member in the company's business endeavors?

Zan and I actually met a decade and a half ago. We share a mutual mentor, Leigh Thompson, M.D., Ph.D., former Chief Scientific Officer of Eli Lilly, whom I came to know when Leigh joined the board of Guilford Pharmaceuticals, where I was working. Kinexum organized a couple conferences in Leigh's honor that I was privileged to attend.

We then went our separate ways until last fall, when I published a blog post on lean start-up methodologies in life science start-ups. Zan responded warmly. We started talking about my joining Kinexum to supplement its consulting services with my background in corporate strategy and corporate development, but our discussion broadened to building the Kinexum institution and brand. A few months later, I came on board as CEO.

What attracted me about Kinexum was the prospect of working with Zan and his band of experts, who typically have decades of experience in regulatory agencies, industry and/or academia, and share a mutual respect and collegiality for each others' expertise and skills, as well as a commitment to help accelerate medical products to patients. What was particularly intriguing was that the firm had grown primarily by word-of-mouth, so I am really curious what we can do with concerted new practice development.

Examples of projects I've been involved with in just these first months include preparing and filing an IND within an extremely compressed period of about 30 days for a Korean company that is bringing its small molecule clinical program to the U.S.; conducting the Human Factors testing for a medical device for which a European client wants to file a 510(k) clearance application; and helping Zan and his co-chair, Professor Larry Steinman of Stanford organize the World Congress on Metabesity that is to take place in London this October (www.metabesity2017.com), which will assemble world renowned scientists and their peers in policy and industry in a call to action for a "moonshot" program to develop common solutions to major non-communicable diseases of aging such as diabetes, neurodegenerative disease and cancer.

Mr. Seoh at a tennis tournament sponsored by the Institute of Corean-American Studies

Thomas Seoh, his wife, and their five children

3. You've had ample experience and previous titles in entrepreneurship, including your roles as President and CEO at Eqalix, Inc., President at NexGen Medical Systems, Inc., and CEO at Faust Pharmaceuticals S.A. prior to Kinexum. What would you say are the top three priority assets or skill sets necessary for success in the life science industry?

A simple answer might be money, a product that is safe, effective and clinically and commercially relevant, and people who know what they are doing. But I would offer three critical mindsets:

One, a focus on customer benefits, as well as technical features. The life science business involves making a business out of life sciences. Thus, while technology characterizes the business, the success or failure of the business depends on a clear demonstration of benefits for the customers (patients, payers, healthcare providers, etc.). Like any business, it doesn't matter how good the mousetrap is, customers have to reject alternatives to buy your mousetrap in sufficient volumes at a sufficient profit, or you've failed.

Two, perseverance and belief, tempered by evidence. Drug and other medical product development is a highly regulated space, the things that have to go right are complex and interdependent, and it practically always takes longer and costs more than expected. To succeed, one has to be patient, persistent and resilient, so passion and belief are critical. At the same time, Nobel Laureate physicist Richard Feynman once said something like it's easy to fool ourselves, and science is the best way humans have come up with to help us not to fool ourselves. So I advise entrepreneurs to hold an unshakeable belief in the purpose of helping patients, but don't live or die by a specific technology or approach, which has to be assessed by the best available scientific evidence.

Three, risk management. Life science product development is basically buying a series of real options. A business case must justify staking an amount of money to buy a card to turn over, to use a poker analogy. Depending on the learnings, you buy another card, or cash in. Entrepreneurs should be extremely careful about 'going all in' based on one set of cards. Rather, buy meaningful incremental sets of cards and be ready to pivot based on the results.

4. Before pursuing entrepreneurship in pharmaceuticals, you formerly studied law and proceeded to become a corporate attorney. What compelled you to work within the medical industry?

I wish I could tell you that where I am today is the result of a decades-long strategic plan. But in fact, I kind of fell into life sciences, and before that, into law.

My initial intended major as a college freshman was cosmology, but I ended up studying philosophy and history and going to law school with the intention of becoming a jurisprude. I ended up practicing corporate law in New York and London, then going in-house as General Counsel at a couple companies, including a mid-size pharma in Orange County. There, I got exposed to the La Jolla biotech beach culture, read The Billion Dollar Molecule, landed a job at Guilford in Baltimore, and I was on my way.

5. WKMJ has readers from over 10 countries globally. Please share your final words or thoughts ur readers.

First, I am very honored to be included among the company of other entrepreneurial interviewees of your publication, and thank you for your interest.

We live in fascinating times, with the explosion of scientific knowledge and technologies that are revolutionizing human health. At the same time, I see fundamental innovations in business models, for instance the emergence of lean start-up methodology and de-complexification of many previously multipart activities, such as by Amazon, Uber and Airbnb.

This is particularly promising for your global readership, because I believe that there will be increasing 'democratization' of the life science product development process. Countries and companies around the globe have a 'third generation subway' opportunity to leapfrog current discovery, development, regulatory and commercialization models to better serve human health. W

Thomas Seoh on the summit of Mt. Kilimanjaro

Thomas Seoh, J.D.

President and Chief Executive Officer, Kinexum

Thomas Seoh, J.D. is the current President and CEO of Kinexum, a distinguished resource for research, development and commercialization of life science products. Mr. Seoh is a life sciences executive and entrepreneur with ample experience and functional expertise in corporate and business development and law. His previous titles in entrepreneurship include his roles as President and CEO at Eqalix, Inc., President at NexGen Medical Systems, Inc., and CEO at Faust Pharmaceuticals S.A. prior to his current occupation at Kinexum. With a fervor for start-up and emerging companies, Mr. Seoh has held senior and leadership positions in public and private biotech, pharmaceutical, medtech and other companies. In addition, he has been and continues to act as an invaluable advisor to academic teams on commercializing their research.

Biopharma Report

BIOPHARMACEUTICAL REPORT I

EISAI'S LENVIMA SHOULD SEE FDA APPROVAL IN HEPATOCELLULAR CARCINOMA (HCC)

BIOPHARMACEUTICAL REPORT II

MEDICAL DEVICE: GROWING CYBERSECURITY THREAT AND NEED FOR MORE REGULATION

BIOPHARMACEUTICAL REPORT III

STRATEGIC SHIFT OF DONG-A ST CO. LTD. IN DRUG DISCOVERY

BIOPHARMA REPORT I

Eisai's Lenvima Should See FDA Approval in Hepatocellular Carcinoma (HCC)

Eisai's (TYO:4523) Lenvima (lenvitanib) for first-line unresectable hepatocellular carcinoma (HCC) has a convincing FDA approval rationale based on positive Phase III results versus Bayer's (ETR:BAYN) Nexavar (sorafenib), a high efficacy bar, experts agreed. Although some experts raised reservations about the Phase III trial only showing Lenvima as non-inferior to Nexavar in an open-label trial, this shouldn't be an approval barrier, other experts noted.

Analyst reports have not commented on Lenvima's approval prospects. But experts noted their confidence in the data, highlighting the outperforming Nexavar which did not prevent Lenvima's non-inferiority. Lenvima's potent anti-angiogenic mechanism is ideal for HCC since its tumours are highly vascular and dependent on liver vessels to proliferate, further supporting approval justification, they added.

Although one analyst report states Lenvima's side effect profile is within the known scope, experts noted its hypertension rates are higher than Nexavar. This could potentially be a differentiating factor between the two drugs considering efficacy data puts them neck-andneck, some noted.

Based on data presented at this month's American Society of Clinical Oncology (ASCO) in Chicago, Eisai plans to submit regulatory applications for unresectable HCC to the FDA and other territories, a June 2017 media release shows. Data was collected from the randomised Phase III REFLECT trial, which compared Lenvima and Nexavar in 954 subjects (NCT01761266), ClinicalTrials.gov shows.

Some analysts predict Nexavar has potential to reach USD 1bn in all indications. Lenvima was FDA approved for the treatment thyroid cancer in February 2015 and advanced renal cell carcinoma in May 2016.

Eisai did not respond to a request for comment.

Healthy FDA approval prospects

All experts agreed Lenvima's Phase III results should secure FDA approval, particularly its primary endpoint of Overall Survival (OS) highlighting Lenvima as non-inferior to Nexavar. The median OS in the Lenvima group was 13.6 months compared to 12.3 months for Nexavar (p<0.00001) [Cheng, A. et. al. J Clin Oncol 35, 2017 (suppl; abstr 4001)].

> **"Nexavar's 12.6 months OS in the Lenvima trial is unusually high in contrast to other Phase III trials featuring Nexavar, which makes Lenvima's non-inferiority success encouraging for approval"**

Showing non-inferiority in first-line HCC is a high bar considering many drugs have failed in Phase III when pitted against Nexavar, said Dr Richard Finn, Phase III investigator and assistant professor of medicine, David Geffen School of Medicine, UCLA, and Dr Emmanuel Thomas, assistant professor, Sylvester Comprehensive Cancer Center, Schiff Center for Liver Diseases, Miami, Florida. Bristol-Myers Squibb's (NYSE:BMY) Phase III trial investigating brivanib (BMS-582664) versus Nexavar failed to demonstrate non-inferiority [Johnson, PJ et. al. J Clin Oncol. 2013 Oct 1;31(28):3517-24]. Pfizer's (NYSE:PFE) Phase III trial investigating Sutent (sunitinib) versus Nexavar was stopped for futility after first interim analysis [Cheng, A. et. al. J Clin Oncol. 2013 Nov 10;31(32):4067-7].

Finn noted Nexavar's 12.6 months OS in the Lenvima trial is unusually high in contrast to other Phase III trials featuring Nexavar, which makes Lenvima's non-inferiority success encouraging for approval. In the Phase III brivanib trial, Nexavar's OS was 9.9 months. A possible reason to Nexavar's high OS in the Lenvima trial is that investigators were very experienced with Nexavar and therefore subjects could have been treated earlier than real world patients leading to better outcomes, Finn said.

In the unlikely event Lenvima is not approved it could be due to the trial being a non-inferiority trial which is not very well established design in HCC, said Dr Jorg Trojan, head of gastrointestinal oncology, University Hospital Frankfurt, Goethe University, Frankfurt, Germany. It would have been ideal if the Phase III open-label trial was blinded as allowing investigators to know which drug the subject received may have reduced result subjectivity, added Dr Marcus Peck-Radosavljevic, associate professor of medicine, department of gastroenterology and hepatology, Medical University of Vienna, Austria.

But drug approvals based on non-inferiority studies are not unusual and the FDA are unlikely to consider it an approval roadblock, Peck and Finn said. Trojan added Phase III's head-tohead trial design is welcome as it spells out how Lenvima compares with Nexavar without having to compare two different trials.

Trojan said Lenvima's mechanism is also logical for HCC, further supporting its approval prospects. Peck said, like Nexavar, Lenvima is a tyrosine-kinase inhibitor (TKI) which seems to be ideal for patients who have failed chemotherapy.

But Lenvima theoretically should be more potent than Nexavar in HCC, since Lenvima has a more specific target, Trojan said. Lenvima is a potent anti-angiogenic drug, meaning it blocks blood

vessel growth in cancer, Trojan and Finn said. This is ideal for HCC because its tumours are highly vascular and dependent on liver vessels to spread, Trojan said. In contrast, Nexavar is dubbed as a “dirty TKI” as it targets many pathways, he explained.

Differentiated but reasonable toxicity profile

Trojan said Lenvima’s side effect profile also supports approval, with Finn noting there are no new Lenvima safety signals in the Phase III trial. The most common side effects were hypertension (42%), diarrhea (39%), weight loss (31%) and fatigue (30%), Phase III data shows. Hypertension seems to be more frequent with Lenvima, and it could be due to the drug’s anti-VEGF effect, Peck said. This shouldn’t be an approval barrier as it could be an indicator that the drug is reaching the right target, Peck added.

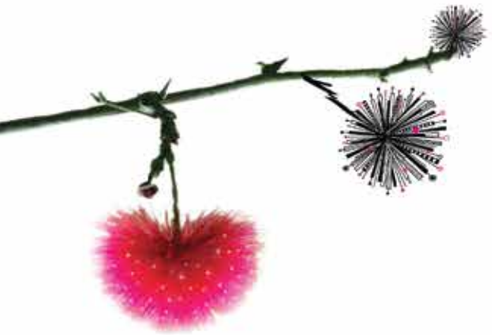
Trojan said this difference in side effects between Lenvima and Nexavar could be a critical differentiation point between the two drugs since Lenvima is only non-inferior. If Lenvima is approved, a likely real-world scenario would be patients who may be susceptible to hypertension would not be given Lenvima, Peck said. In patients who are sensitive to Nexavar’s side effects like diarrhea and hand-foot skin reaction could then be given Lenvima, Trojan said. Finn said there’s a lower frequency of skin reactions with Lenvima due to target profile nuances between the two drugs.

There have been concerns Lenvima could lead to severe bleeding events but this has so far not surfaced, Trojan said. Lenvima has been linked to bleeding events in thyroid cancer and bleeding events can happen with HCC as demonstrated when Roche’s (VTX:ROG) Avastin (bevacizumab) -- a drug which similarly targets VEGF -- was investigated for the indication, Trojan added. W

Reynald Castaneda

Reporter, London

Reynald Castaneda, prior to moving to London, was a journalist for healthcare newspaper New Zealand Doctor, covering primary care health politics and medical research. He has a BSc in Biological Sciences from the University of Auckland and a postgraduate diploma in journalism from AUT University. Prior to venturing into journalism, Reynald worked as a laboratory technician for Massey University’s Institute of Molecular Biosciences.



Happy smile and hope after pain

Cancer-free D.K. Lee

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

D.K. Lee attending
beauty classes while chemotherapy treatment

BIOPHARMA REPORT II

Medical Device: Growing Cybersecurity Threat and Need for More Regulation

Despite an expected increase in the frequency in cybersecurity threats in the near future that will affect networked medical devices, experts debated whether existing US and European guidelines are adequate to ensure device manufacturers are up to date with the highest security.

Some called for more stringent regulation, and others argued overly specific rules are impractical against a constantly changing threat. They added any attempts to tighten regulation will face industry opposition and political apathy.

Experts said medical devices vulnerable to accidental threats from software coding errors to criminal hacking include implantable devices, diagnostic and monitoring equipment and medical device data systems (MDDS). If exploited, vulnerabilities can compromise patient care and have almost certainly already caused patient deaths, said Mike Ahmadi, global director of critical systems security, Synopsys.

Any devices connected to a hospital network can be compromised, such as devices exposed to removable media containing malware, said Rob Suarez, head of Product Security at medical device firm BD. Infusion pumps or cardiac monitors which rely on a radio connection to transfer data can also be susceptible, said Tara Swaminatha, partner, Data Privacy & Cybersecurity, at law firm Squire Patton Boggs, Washington, DC. Hackers could not only read patient data coming from these devices, but also alter the output of a pacemaker or infusion pump, they said.

Implantable devices such as pacemakers have been proved vulnerable to attacks in academic situations, noted Swaminatha (Halperin et al, 'Pacemakers and implantable cardiac defibrillators: Software radio attacks and zero-power defences,' Proceedings of the 29th Annual IEEE Symposium on Security and Privacy, May 2008). Fabien Roy, senior associate, Life Science, at law firm Hogan Lovells, Brussels, Belgium, confirmed one of his clients is addressing an unspecified vulnerability it has discovered in its implantable medical device.

Ahmadi said the extent of harm from medical device cybersecurity failures is hard to pinpoint, in part because hackers could erase unsecured device logs, which would make it hard to tell whether, for instance, a pacemaker had failed because of an attack rather than a mechanical issue, he said. Victoria Hordern, senior associate, Data Privacy, Hogan Lovells, London, UK, agreed there will be more hacking of medical devices in future, however, she believed targeted attacks on specific device users will be several years away.

Industry debates guidelines

Medical device cybersecurity is largely covered by FDA guidance, not regulation, experts agreed: guidance on premarket device submissions published in October 2014, and postmarketing device guidance issued in December 2016. The guidance includes some specific recommendations, such as premarket appropriate controls for device user identification and postmarket patch management, said Suarez.

"Some called for more stringent regulation, and others argued overly specific rules are impractical against a constantly changing threat"

However, Ahmadi said more prescriptive regulation is "extremely necessary" for better patient safety, since self-policing under FDA guidance has failed: Synopsys surveyed 6,000 medical device manufacturing staff and found 49% admitted to not following this guidance. The survey also found 67% of experts believe an attack on a medical device built by their organisation is likely to occur in the next year, he noted.

As a result, Ahmadi suggested US regulation should be introduced with more specific cybersecurity requirements for 510(k) approvals, verifiable via third-party certification, with manufacturers required to provide a report showing rigorous testing for vulnerabilities. Such a regulation could end, for example, numerous devices running on known flawed operating systems such as Windows XP, he said.

However, other experts disagreed with this call to tighten regulation and said current guidance is adequate, and more regulation would be counterproductive.

As evidence that the FDA is able to use current rules to enforce safety, one expert noted the FDA's 12 April warning letter to Abbott Laboratories (NYSE:ABT), giving the company 15 days to address a fault which left Abbott's Fortify, Unify, and Assura defibrillators potentially vulnerable to access by hackers who could drain the devices' batteries.

Swaminatha and Suarez agreed more specific US regulatory prescriptions are unnecessary, noting the range of possibilities for medical device attacks is so broad, it is not possible to detail all possible precautions in the regulation. To craft regulation would be "dangerously slow," said Suarez, since hacking methods move so fast that the regulations will never be up to date. Instead, manufacturers need to voluntarily and proactively update their risk management continuously, Suarez said.

In addition to the aforementioned guidelines, FDA can enforce safety via regulations which state unsafe devices should not be released, although they may not mention cybersecurity specifically, said Swaminatha. For instance, although there is no affirmative obligation for devices to require a password of a particular strength, if a weak password caused pacemakers to be attacked, FDA will certainly hold the manufacturer responsible, she said.

Hordern and Roy noted a similar regulatory situation in the EU: the April 2017 European Medical Device Regulations largely do not delve into prescriptive cybersecurity requirements at the level of patches and operating systems, instead requiring compliance with "the generally acknowledged state of the art" safety protections (Annex 1, Chapter 1). Manufacturers may choose to follow more detailed advice from ENISA, the European Union Agency for Network and Information Security, said Hordern.

Hordern and Roy said requiring compliance with state of the art safety precautions, without designating what these are in the regulation, is optimal because safety standards are constantly changing, so it would be counterproductive to specifically detail this. In the future, Hordern said, using block chain to encrypt data may be considered state of the art, but it is too early in the development of this technology, which prevents retroactive data alteration, to make it a requirement now.

WannaCry prompts regulation debate

Ahmadi said another necessary change is in response to ransomware attacks on internetfacing Electronic Health Records (EHRs) and medical device data systems (MDDS), such as the May WannaCry attack which hit part of the UK's National Health Service, enabled by a failure to install a Microsoft patch.

MDDS were once regulated by the FDA as Class III medical devices but were downgraded in 2011 and deregulated in 2015, meaning they do not fall under FDA's purview, Ahmadi said. The rising frequency of global ransomware attacks on hospitals – with 14 recorded in 2016, rising to 45,000 so far in 2017 – means MDDS must return to FDA purview, said Ahmadi.

However, Suarez disagreed, saying the industry's response to WannaCry shows a positive trend in medical device cybersecurity, with BD preparing a public advisory with recommendations to customers within 24 hours. The US Department of Homeland Security's Industrial Control Systems Cyber Emergency Response Team also responded quickly with guidance, he said.

Experts on both sides of the debate said passing stricter requirements will be difficult. Software and device companies will naturally oppose stricter regulation that delays speed to market, said Ahmadi, and Roy added there is little appetite among legislators to fill in the gaps where the law is not explicit about cybersecurity methods. Ahmadi said it may be that only a catastrophic event which is so devastating it requires an industry-wide change in behaviour will prompt regulatory change.

Fiona Barry
Reporter, London

Fiona previously worked in France as a journalist at William Reed Business Media, covering global manufacturing, regulatory and outsourcing news for the biopharmaceutical industry. She has also reported on global food and beverage companies. Fiona holds an M.A. in English and a B.A. in English and Philosophy from Bristol University. She speaks English and French

STRATEGY

Strategic Shift of Dong-A ST Co. Ltd. in Drug Discovery

BY EMILY CUKIER-MEISNER, SENIOR WRITER

Dong-A ST Co. Ltd. has spent the last four years building an R&D organization and using its chemistry chops to begin developing first-in-class drug candidates against genetically validated targets. A December cancer immunotherapy deal with AbbVie Inc. is the first payoff from the work.

AbbVie agreed to pay Dong-A $40 million up front and up to $485 million in milestones for exclusive worldwide rights outside of South Korea to preclinical inhibitors of c-Mer proto-oncogene tyrosine kinase (MERTK), a class of molecules AbbVie also was working on.

The program came out of a strategic shift intended to expand Dong-A beyond its established business, which has included selling imported drugs, generics, botanicals, biosimilars and branded small molecules that are not first in class.

SVP and Head of Global Business Chae Lee said the decision to expand to R&D on novel targets was made about five years ago as the company considered how to globalize. One of the first steps was hiring SVP and Head of Research Taeyoung Yoon. Yoon was previously a senior research investigator at Novartis AG's Novartis Institutes for BioMedical Research (NIBR) for eight years.

He began with a drug discovery team of about 20 scientists.

Yoon chose not to start with *de novo* target discovery, but with genetically validated targets that hadn't been well-studied due to lack of tool compounds. Going forward, he plans to focus on discoveries in South Korea.

"We would like to take an active role in helping to translate such good science into something that's druggable, then introducing it to the Western and global markets," said Lee.

Once it chooses a target, Dong-A makes tool compounds to test therapeutic hypotheses successively at the level of proteins, cells and animals.

According to Yoon, validating MERTK's role in cancer has been tricky because it is difficult to create an inhibitor that is sufficiently selective.

"WE WOULD LIKE TO TAKE AN ACTIVE ROLE IN HELPING TO TRANSLATE SUCH GOOD SCIENCE INTO SOMETHING THAT'S DRUGGABLE."

CHAE LEE, DONG-A

MERTK is a member of the TAM (TYRO3-AXL-MERTK) receptor family of transmembrane proteins. It sits upstream of BRAF, and is primarily expressed in subtypes of myeloid cells including some macrophages and dendritic cells.

Yoon said MERTK induces immunosuppression when nearby cells undergo apoptosis — a natural form of cell death that in normal circumstances should not trigger the immune system. But when tumor cells die via apoptosis, MERTK may contribute to the immunosuppressive tumor microenvironment.

MERTK is overexpressed or hyperactivated in multiple cancer types including prostate cancer, brain cancer and leukemia.

To improve selectivity of its inhibitors, Yoon said Dong-A added bulky groups to its molecules outside of a flat portion needed to fit within the MERTK active site. Yoon said the group created a selective inhibitor in three years with a 10-person project team.

In a poster presented in November 2015 at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Yoon and colleagues reported the design of a lead compound, XL1547, with an IC50 of 1 nM that was over 300 times more selective for MERTK than AXL. A follow-on compound, SA3686, was over 10 times more potent than XL1547 in inhibiting MERTK and was suitable for oral dosing.

SA3686 was efficacious in a tumor allograft model of subcutaneously implanted Ba/F3(CD8:MERTK) cells. Yoon declined to say which animal was tested or how efficacy was measured.

Yoon said AbbVie reached out to Dong-A to discuss the poster, which led to partnering discussions.

"Dong-A has identified potent and selective MERTK inhibitors and brings medicinal and structural chemistry expertise to the collaboration," said AbbVie VP of Oncology Discovery Steve Davidsen in an email to BioCentury.

Yoon added that selectivity is particularly important because unlike many other tyrosine kinase inhibitors used in oncology, MERTK inhibitors act mainly in healthy cells — which raises the bar for safety.

"When you want to inhibit a host target, you want to be very selective," he said.

ENGINE FOR GROWTH

Yoon is now expanding Dong-A's drug discovery group to more than 100 scientists and is drawing on his experience at NIBR to create a culture of science and lower barriers to knowledge sharing.

Previously, Dong-A's chemists, biologists and ADME specialists were siloed across project-based teams that had little reason to communicate with each other, which gave the specialists few chances to share on-the-job learning.

Yoon said tackling novel targets requires a deeper understanding of the science that uses "all of the connected wisdom available," so he is grouping the discovery researchers according to function — putting all the chemists, biologists and ADME specialists into their own teams.

The new researchers will come from internal teams that had previously been working on follow-on products in metabolic and infectious diseases.

He also hopes to build Dong-A's clinical experience with first-in-class programs through partnerships that will eventually let it keep programs in-house longer.

As with the AbbVie deal, Yoon said Dong-A hopes to find partners that have studied the same target so that both parties can contribute knowledge, which could increase the odds a project will succeed.

Lee said in addition to offering a competitive bid and a compatible culture, AbbVie's in-house experience with MERTK gave the pharma realistic expectations about how much information would be available about the compounds' biologic activity at their early development stage.

The partners will collaborate to select a clinical candidate and perform GLP toxicity studies. They intend to test combinations of MERTK inhibitors with AbbVie's immuno-oncology programs to treat solid tumors. AbbVie is responsible for clinical development.

Lee declined to give a timeline for the project.

Dong-A did say it expects the first compounds from its target validation projects to reach the market in the mid-2020s. Yoon said he hopes that in two or three years, two-thirds of the company's pipeline will be first-in-class molecules.

COMPANIES AND INSTITUTIONS MENTIONED

AbbVie Inc. (NYSE:ABBV), Chicago, Ill.

Dong-A ST Co. Ltd. (KSE:170900), Seoul, South Korea

Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland

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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

The Healthcare Analytics Summit 2017
September 12 – 14, 2017 | Salt Lake City, Nevada, USA

Website: https://hasummit.com
Contact: has17@healthcatalyst.com

Designed around the theme of "Changing the Digital Trajectory of Healthcare," the Healthcare Analytics Summit '17 will present a strategic long-term vision of the massively growing importance of data in healthcare and the emphasize the importance of accelerating the pace of clinical, operational, and financial outcomes. Representatives from data-driven healthcare organizations will be in attendance to showcase their latest innovations. How data and analytics become a central function for healthcare organizations both big and small will be a main topic for discussion at the panels and breakout sessions.

SHSMD Connections 2017 Annual Conference
September 24 – 27, 2017 | Orlando, Florida, USA

Website: http://www.shsmd.org/conference/17
Contact: shsmd@aha.org

The Society for Healthcare Strategy and Market Development of the American Hospital Association is holding its annual conference to advance excellence in healthcare strategy. This four-day, intensive, face-to-face event is designed to equip healthcare strategy professionals with the necessary information and resources to face these challenges head-on and implement ideas and solutions that deliver measurable results. Open and beneficial to all healthcare marketing, public relations and communications, and strategic planning professionals, the SHSMD Connections Annual Conference will learn the latest on topics such as analytics and improving the customer experience.

Health 2.0 11th Annual Fall Conference
October 1 – 4, 2017 | Santa Clara, California, USA

Website: https://events.bizzabo.com/fall2017
Contact: tarek@health2con.com

Health 2.0 is an upcoming conference that will explore the Latest Health Technologies and Network with Decision Makers. It sees more than 2,000 executives gather at their event on average, and they expect to see more than 150 live product demos at the 2017 Fall Conference, giving attendees a first glance at companies developing new cutting-edge technologies across healthcare and wellness, ranging from chronic diagnosis and geo-analytics to financial management. Health 2.0's past speakers include representatives from the U.S. Dept. Of Health and Human Services (DHHS) and 23andme. Ranging from the next new innovation or to network with the most influential health care providers, to start-ups, the Annual Health 2.0 Fall Conference is the place to be each year.

TEDMED 2017
November 1 – 3, 2017 | Palm Springs, California, USA

Website: http://www.tedmed.com/event/stageprogram
Contact: press@tedmed.com

TEDMED is bringing in startups for their 2017 conference in Palm Springs, CA to assist in the development of life and other sciences, public health, and other core facets of the healthcare industry. The theme is centered upon how advances in the field entails incremental progress, yet unbounded vision. In short, people create a healthier world by working in that fertile zone between the limited (knowledge, resources, time) and the limitless (imagination, creativity, curiosity).The event will focus on that productive tension between "what is" and "what if," the inspiration that continues to drive us further into what's possible. Together, we are limitless. Encompassing a total of 7 separate sessions, speakers vary but can be found on their website.

59th ASH Annual Meeting & Exposition
December 9 – 12, 2017 | Atlanta, Georgia, USA

Website: http://www.hematology.org/Annual-Meeting/
Contact: (202) 776-0544

Termed as the world's most comprehensive hematology event of the year, the 59th ASH Annual Meeting and Exposition will provide an invaluable educational experience and the opportunity to review thousands of scientific abstracts highlighting updates in the hottest topics in hematology. With a primary focus on both malignant and non-malignant hematology, attendees will be engaged with a global community of more than 25,000 hematology professionals from every subspecialty. Furthermore, all participants will be given the opportunity and environment to network with top minds in the field.

MedTech Impact
December 14 – 15, 2017 | Las Vegas, Nevada, USA

Website: https://www.medtechimpact.com/
Contact: info@medtechimpact.com

The MedTech Impact Expo and Conference is designed to bring together technology manufacturers and developers, investors, entrepreneurs, hospital administrators, and medical providers to discuss the emergence of new medical technology. Attendees will explore the latest developments in equipment and what their impact might be in the future. You can expect to get insight into new software and technology that assists with diagnosis and automatically keeps track of patients as they progress to improved health. Keynote speakers will include Pablos Holman, Robin Farmanfarmaian, and David Rhew, M.D., Chief Medical Officer and Head of Healthcare and Fitness at Samsung Electronics America.

Europe

9th International AIDS Society Conference on HIV Science 2017
July 23 – 26, 2017 | Paris, France

Website: https://www.ias2017.org/
Contact: registration@ias2017.org

IAS 2017 is the largest open scientific conference on HIV and AIDS related issues – bringing together a broad cross-section of more than 6,000 professionals from around the world to meet and examine the latest scientific developments in HIV-related research with a focus on moving science into practice and policy. This biennial gathering aims to highlight major advancements in understanding the intricate network of viral-host interactions, in better characterizing and targeting the HIV reservoir, and ways to tackle persistent HIV, as well as the interaction and synergies with other fields, such as cancer research and immune-based therapies. The conference also provides a platform to showcase new science on preventive and therapeutic vaccinations, and on improved tools and strategies for pre-exposure prophylaxis (PrEP), as well as new insights into the novel areas of personalized medicine and biomarkers.

European Society of Cardiology (ESC) Congress 2017
August 26 – 30, 2017 | Barcelona, Spain

Website: https://www.escardio.org/Congresses-&-Events/ESC-Congress
Contact: info@esc-2017.org

ESC Congress 2017 is to be the world's largest cardiovascular congress with over 500 experts sessions and more than 10 800 abstracts submitted contributing to the advancement of cardiovascular medicine worldwide. Taking place in Barcelona, Spain from August 26th to 30th later this year, the conference will include presentations of recently completed, unpublished, important findings from major clinical trials, as well as recently completed Late Breaking Trials as well as Clinical Trial Updates obtained from long-term follow-up in previously presented and pertinent analyses of large-scale registries.

Europe

European Society for Medical Oncology (ESMO) 2017 Congress

September 8 – 12, 2017 | Madrid, Spain

Website: http://www.esmo.org/Conferences/ESMO-2017-Congress

Contact: esmo@esmo.org

The annual ESMO Congress is the most prestigious and influential oncology platform in Europe and is the ideal place to learn about the latest science, network with colleagues and keep pace with today's rapid developments in cancer research. ESMO 2017 is accessible to certified healthcare professionals, associated press, industry representatives and other stakeholders in the science, management and prevention of oncology diseases. Registered participants will have access to all official sessions, industry sponsored symposia and exhibition. Delegates' professional profiles will be stated on their congress badges, enabling exhibitors to interact with them accordingly.

The 17th Annual Biotech in Europe Forum

September 26 – 27, 2017 | Basel, Switzerland

Website: http://www.sachsforum.com/17bef-about.html

Contact: silvia@sachsforum.com

The forum is recognised as the leading international stage for those interested in investing and 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. Supported and designed by leading figures within Europe's pharmaceutical and biotech industry, this event will once again be covered by our regular media partners. We expect over 650 delegates and over 100 presenting companies.The Forum will provide a number of networking opportunities via our online one-to-one meeting system which allows you to pre-book meetings with all the attendees with dedicated meeting facilities. We expect more than 1500 meetings to take place throughout the 2 days.

Asia

International Forum on Quality and Safety in Healthcare: Asia

August 24 – 26, 2017 | Kuala Lumpur, Malaysia

Website: http://internationalforum.bmj.com/kuala-lumpur/

Contact: events@bmj.com

"Aim. Act. Achieve." Following the designated theme for this year's international forum on quality and safety in healthcare, the programme looks to aim high with the goals of quality improvement, to act together across professions and with service users, and to achieve real success in improving care worldwide. BMJ and IHI, working closely with strategic partners in the region, will bring together healthcare leaders and practitioners. The conference showcases the best international and regional thinking and offers an opportunity for international networking.

XXIII World Congress of Neurology (WCN 2017)

September 16 – 21, 2017 | Kyoto, Japan

Website: http://www.2017.wcn-neurology.com/

Contact: +41.3.15.28.04.32 Ext. 63

Cohosted by the Japanese Society of Neurology and Asian and Oceanian Association of Neurology, WCN will bring together leading scientists, public health experts, policy-makers to translate recent momentous scientific advances into action that will address means to end the epidemic, within the current context of significant global economic challenges.With this year's theme as "Defining the Future of Neurology," attendees can participate in very active discussions and cutting- edge lectures by the world's top scientists and neurologists including three Nobel laureates as well as hear all the advances of scientific and clinical neurology. Topics entail gene therapy and stem/ iPS cell medicine as well as Brain Machine Interface, information technology and robotics in care and rehabilitation. Neurology related to environmental and disaster medicine will also attract many neurologists particularly in rapidly developing countries.

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1. With Obamacare, More Breast Cancers Diagnosed at Earlier Stages

More breast cancers have been found at earlier — and potentially more treatable — stages since the implementation of the Affordable Care Act. The study in Cancer Epidemiology found that after Obamacare, the percentage of cancers diagnosed at the earliest stage increased by 3.2 percent for white women, 4.0 percent for blacks and 4.1 percent for Latinas. "The same woman who pre-A.C.A. would have been diagnosed at Stage 2 was diagnosed at Stage 1 after A.C.A.," said the lead author, Abigail Silva. "The A.C.A. had the potential to improve public health, and there's more and more evidence coming out each day to show that it is doing that."
https://nyti.ms/2ueCcvU

2. 'Pharma Bro' Martin Shkreli Goes On Trial On Securities Fraud Charges

Martin Shkreli is known for a number of things. Jacking up the cost of a life-saving drug for AIDS patients by 5,000 percent. Grinning his way through a House hearing as he pleaded the Fifth. Badgering a journalist on Twitter until his account was suspended. Today, jury selection begins in federal court as 34-year-old Shkreli goes on trial for something else entirely: securities fraud charges. Prosecutors say he was swindling investors in his hedge fund well before he became "the most hated man in America." If Shkreli is dreading his day in court, he isn't showing it. "I'm excited," he told the AP last week. "I can't wait." The boy genius-turned-"pharma bro" told The New Yorker he doesn't expect to serve time.
http://www.npr.org/sections/thetwo-way/2017/06/26/534411641/pharma-bro-martin-shkreli-goes-on-trial-on-securities-fraud-charges

3. Senate Health Care Bill Includes Deep Cuts to Medicaid

Senate Republicans, who for seven years have promised a repeal of the Affordable Care Act, took a major step on Thursday toward that goal, unveiling a bill to make deep cuts in Medicaid and end the law's mandate that most Americans have health insurance."We are extremely disappointed by the Senate bill released today," the medical school association wrote. "Despite promises to the contrary, it will leave millions of people without health coverage, and others with only bare-bones plans that will be insufficient to properly address their needs."
https://nyti.ms/2tT8Ti9

4. U.S. Health Sector Hits Record High on Senate Bill, Biotech Rally

U.S. healthcare stocks posted sharp gains with hospitals and insurers climbing after Senate Republicans released a draft bill to replace Obamacare, while a recent surge in biotechnology shares showed no signs of slowing. Shares of hospitals and health insurers, the main focus of investors during Republican efforts to dismantle the Affordable Care Act, known as Obamacare, were higher after the release of the proposed legislation in the Republican-controlled Senate.Hospitals, in particular, have benefited from Obamacare's coverage expansion. HCA Healthcare Inc rose 3 percent, while Tenet Healthcare Corp surged 7 percent.
https://www.reuters.com/article/us-usa-healthcare-stocks-idUSKBN19C2V2

5. Novartis Drug Becomes First to Prevent Heart Attacks and Strokes by Targeting Inflammation

Novartis, the Swiss drug giant, announced that a drug that targets inflammation prevented heart attacks and strokes in a 10,000 patient trial of people with established heart disease. It could be a scientific breakthrough, and a commercial one, too. A lot will depend on full results that will be presented at a medical meeting later this year, and on price. The drug, Ilaris, costs $200,000 a year now, and a price cut could be necessary. More than 7 million patients in Europe and the U.S. could be eligible for the drug. Assuming a $15,000 price, like the PCSK9s, would yield a $60 billion market opportunity.
https://www.forbes.com/sites/matthewherper/2017/06/22/novartis-drug-becomes-first-to-prevent-heart-attacks-and-strokes-by-targeting-inflammation

6. Hospitals Handling Growing Debt Loads—For Now

Storm clouds notwithstanding, hospital companies are borrowing as if they'll be able to handle whatever's ahead. Some of the dollar amounts are eye-popping. Nashville-based HCA is preparing to sell $1.5 billion of senior secured notes with an interest rate of 5.5% that will be used to retire higher-cost debt and pay for the $725 million announced acquisition of three hospitals in Houston from rival Tenet Healthcare Corp. Community Health Systems in March raised $2.2 billion through the sale of senior secured notes and another $900 million in May. The Franklin, Tenn.-based hospital giant, which is selling hospitals to try to reduce $15 billion in total debt, used much of the proceeds to retire debt maturing in 2018 by pushing its new borrowings further into the future.
http://www.modernhealthcare.com/article/20170622/MAGAZINE/170629974/hospitals-handling-growing-debt-loads-x2014-for-now

7. GSK Wins $235 Million From Teva in Coreg Patent Trial

A U.S. jury has ordered Teva Pharmaceutical Industries Ltd to pay GlaxoSmithKline Plc more than $235 million (£185 million) for infringing a patent covering its blood pressure drug Coreg, court documents showed. A federal jury in Wilmington, Delaware on Tuesday found that Teva willfully infringed the patent in connection with its sales of a generic version of the drug with a label indicating it could be used for treating chronic heart failure. GSK in a statement said that it was pleased with the trial's outcome. Teva said it was disappointed. "We still intend to present our equitable defences to the court at a separate hearing which could eliminate the liability determination or significantly reduce the assessed damages," Teva said in a statement. "We are also considering an appeal."
https://nyti.ms/2tuA0TG

8. EU court: Vaccines can be blamed for illness without scientific evidence

The Court of Justice of the European Union ruled that courts may consider vaccines to be the cause of an illness, even in the absence of scientific evidence confirming a link. The EU's highest court said that if the development of a disease is timely to the person's receiving a vaccine, if the person was previously health with a lack of history of the disease in their family and if a significant number of disease cases are reported among people receiving a certain vaccine, this may serve as enough proof. The EU court is authorizing national courts to make such judgments about causality themselves, based on evidence they are presented with, without reliance on expert opinion, said Professor Tony Fox from the pharmaceutical medicine group at King's College London.

http://www.cnn.com/2017/06/21/health/vaccines-illness-european-court-bn/index.html

9. FDA Wants To Stop Pharma From 'Gaming' Generic Drug System

The U.S. Food and Drug Administration moved to prevent pharmaceutical companies from "gaming" the system to block or delay entry of generic rivals. FDA Commissioner Scott Gottlieb said in a blog post that the agency plans to hold a public meeting on July 18 to identify ways pharmaceutical companies are using FDA rules to place obstacles in the way of generic competition.The move comes as President Donald Trump and lawmakers in Congress search for ways to lower the cost of prescription drugs.The FDA does not include price considerations when deciding whether to approve a new drug, but Gottlieb said the agency can facilitate increased competition by approving lower-cost generics. That means removing some of the obstacles placed by branded companies in the way of generic manufacturers.

http://www.nbcnews.com/health/health-news/fda-wants-stop-pharma-gaming-generic-drug-system-n775151

10. Pamplona Capital to Take Parexel Private for $4.5 Billion

U.S. pharmaceutical research services provider Parexel International Corp said on Tuesday it would be taken private by Pamplona Capital Management LLP in a $4.5 billion deal. Pamplona will pay $88.10 per share in cash for Parexel, representing a 5 percent premium to the stock's Monday close. Parexel's shares were trading at $87.67 before the bell, just shy of the offer price. Pamplona had been scouring the market in the last year, seeking to acquire a contract research organization. It made an unsuccessful bid earlier this year for Pharmaceutical Product Development LLC (PPD), a U.S. clinical trials firm valued at more than $9 billion.

https://www.nytimes.com/reuters/2017/06/20/business/20reuters-parexel-intl-m-a-pamplona.html?mtrref=undefined

11. He Broke Ground in Stem-Cell Research. Now He's Running for Congress.

Stem-cell researcher Hans Keirstead, 50, announced last week that he will try to unseat California's Rep. Dana Rohrabacher (R). Keirstead, a Democrat with a PhD in neuroscience from the University of British Columbia, was a professor at the University of California at Irvine before launching and selling several biotech companies. Keirstead emerged from academic and entrepreneurial fields. He pioneered a technique to purify stem cells — "You can't go putting toenails into the spinal cord," he said — and applied this method to spinal-cord injuries and diseases such as cancer and amyotrophic lateral sclerosis, or ALS. "I'm delighted that Dana Rohrabacher loves science. That's fabulous. But I'm also very convinced that he doesn't understand science. There's a real big difference. If you love science, that's one thing. If you don't understand it, you can't effect change, and you make wrong decisions," remarked Keirstead.

https://www.washingtonpost.com/news/speaking-of-science/wp/2017/06/20/he-broke-ground-in-stem-cell-research-now-hes-running-for-congress/

12. Bristol-Myers Selling Ireland Plant to South Korean Company with Large Aspirations

Bristol-Myers Squibb, which is shifting its focus toward biologics manufacturing, will unload an API plant in Ireland to a South Korean company that has aspirations of becoming a big deal in contract manufacturing. The U.S. drugmaker said today that it will sell its plant in Swords to SK Biotek, a unit of South Korea's third largest conglomerate, SK Holdings. SK has been a BMS ingredient supplier for a decade. SK Biotek, the first South Korean company to set up shop in Ireland, will use the BMS plant as a base for its burgeoning contract development and manufacturing business. "This transaction is an important step to achieve our goal of becoming a leading global CDMO," SK Biotek CEO Junku Park said in a statement.

http://www.fiercepharma.com/manufacturing/bristol-myers-selling-ireland-plant-to-south-korean-company-will-large-aspirations

13. Drug Deaths in America Are Rising Faster Than Ever

Drug overdose deaths in 2016 most likely exceeded 59,000, the largest annual jump ever recorded in the United States, according to preliminary data compiled by *The New York Times*. Drug overdoses are now the leading cause of death among Americans under 50. Although the data is preliminary, the Times's best estimate is that deaths rose 19 percent over the 52,404 recorded in 2015. And all evidence suggests the problem has continued to worsen in 2017. Early data from 2017 suggests that drug overdose deaths will continue to rise this year. "It's the only aspect of American health", said Dr. Tom Frieden, the former director of the C.D.C., "that is getting significantly worse."

https://nyti.ms/2rI5lBB

14. Pfizer Drug Delays Lung Cancer Growth Longer than Astra's Iressa: Study

A targeted drug being developed by Pfizer Inc. held advanced lung cancer in check longer than AstraZeneca's Iressa in newly diagnosed patients, but with a higher rate of side effects, according to data presented on Monday. About 60 percent of patients receiving the Pfizer drug in the study had the dose lowered due to side effects. Liver enzyme abnormalities were the most common serious side effect observed in the Iressa patients. Despite the higher rate of side effects, "the activity seen in this study should allow for consideration of this effective therapy in this patient population," Dr. Tony Mok from Chinese University of Hong Kong, who led the study, said in a statement.

http://www.reuters.com/article/us-health-cancer-pfizer-idUSKBN18W1HD

15. Many COPD Patients Struggle To Pay For Each Breath

An estimated 1 in 9 Medicare beneficiaries are diagnosed with chronic obstructive pulmonary disease, or COPD. And, in 2014, COPD was the third-leading cause of death in the country, according to the U.S. Centers for Disease Control and Prevention. Inhalers like Spiriva and Advair account for billions in Medicare spending each year. Across the country, doctors who treat COPD say costs are a common problem for patients. Dr. David Mannino at the University of Kentucky College of Public Health says some patients cut pills in half or take a prescription once a day instead of twice, just to save money. Spiriva's list price has jumped 31 percent the past five years to $368 for a 30-day supply, according to drugmaker Boehringer Ingelheim. And Breo Ellipta's price has risen 20 percent since 2013 to $321.74 a month, according to drugmaker GlaxoSmithKline.

http://www.npr.org/sections/health-shots/2017/06/02/529759280/many-copd-patients-struggle-to-pay-for-each-breath

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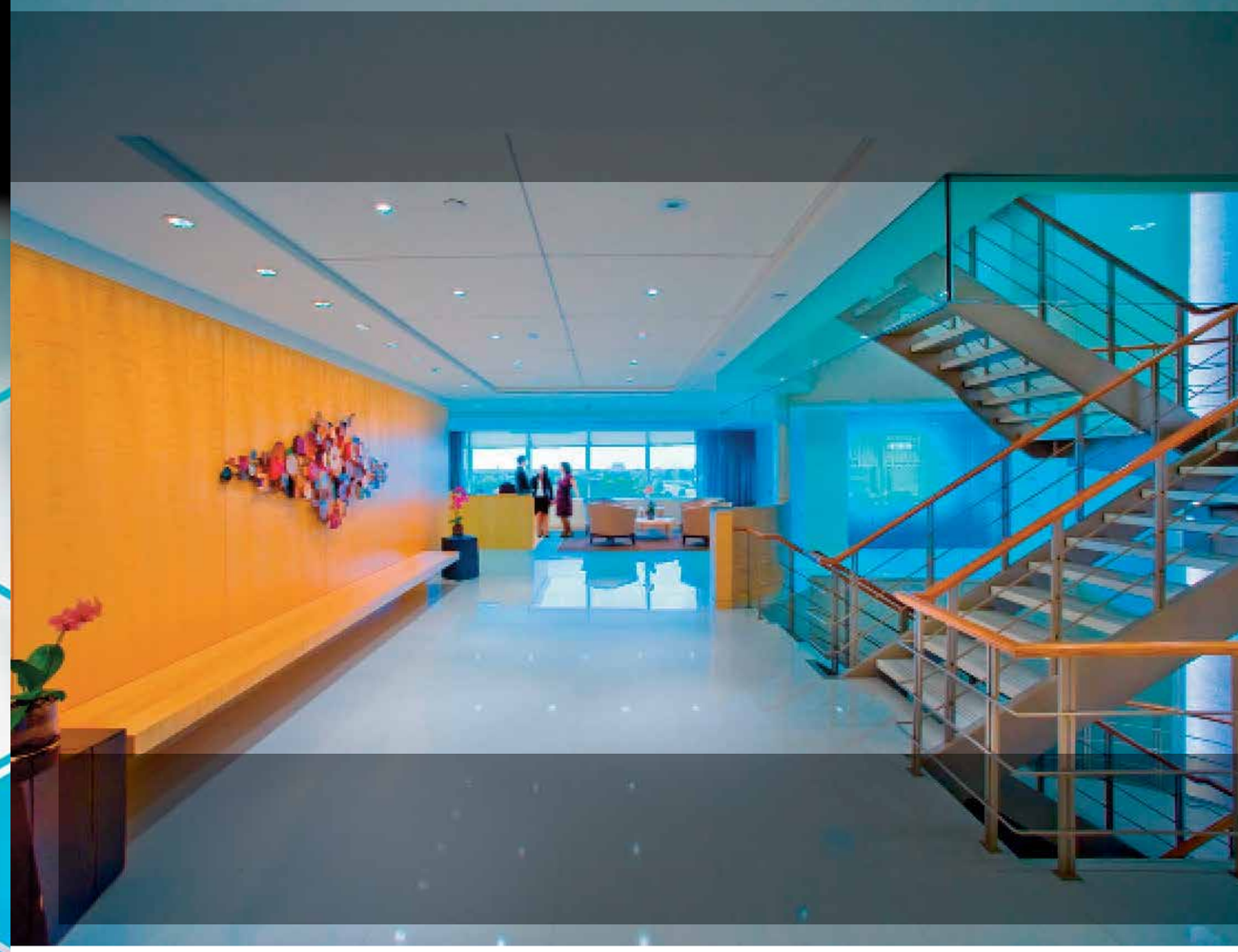

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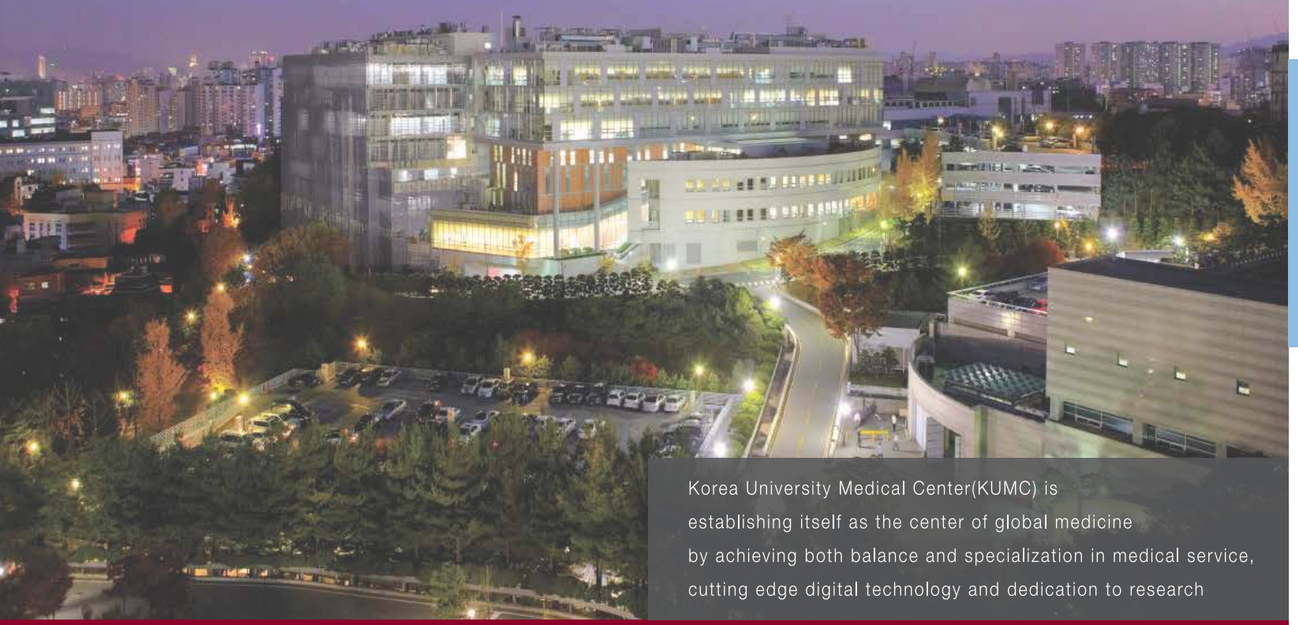

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