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In the Czech Republic, all HIV-positive patients can be immediately treated after diagnosis, which is key to stopping the epidemic.

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Pavel Brezina, who led the establishment of Gilead's affiliate in the Czech Republic and Slovakia seven years ago, shares the amazing journey of bringing the company's life-saving treatments for HIV infection and chronic hepatitis C (CHC) to patients and presents the way the affiliate collaborates with authorities and associations to put an end to both epidemics. Pavel also recounts the preparations he and his team have made to introduce CAR-T therapy to Czech patients and discusses the coming changes in market access for orphan drugs.

Pavel, you led the establishment of Gilead's affiliate in the Czech Republic and Slovakia seven years ago. What have been the main milestones you have achieved since then?

I would like to mention first that the history of Gilead is intricately tied to the Czech Republic as tenofovir was discovered by Prof. Antonín Holý at the Institute of Organic Chemistry and Biochemistry in Prague. Unfortunately, we did not have the opportunity to meet him in person as he died in July 2012, six months before the opening of the affiliate. His discovery significantly

impacted the lives of millions of people living with HIV around the world, and I think his achievements have not received the appreciation they deserve. Even though his discovery is more than 20 years old, and is now off-patent, it has not been surpassed since. In this case, his invention is still considered the backbone of HIV therapy and key medicine in the treatment of hepatitis B (HBV) infection for most patients around the world.

We started the affiliate at the beginning of 2013 with a small team of four people. Our mission was to bring the entire portfolio of innovative products from Gilead's labs to Czech patients. We have been quite successful: we started with three products and subsequently we have launched 12 new innovative products with full reimbursement over the last seven years. Our ranks have also grown, and we are now a team of 20 associates. Although our organization is much leaner than our competitors' in the country, we are comparable in terms of revenue. I am extremely proud of my team and what we have been able to achieve together.

Our HIV portfolio has of course been a major driver of our growth, along with the increasing importance of the treatment of chronic hepatitis C (CHC). In CHC, there was a huge unmet medical need. The introduction of new antivirals in this area has significantly improved the quality of care, effectively leading patients to a cure. Sooner or later, we will hopefully achieve complete elimination of the infection around the globe. While in the treatment of CHC there is a clear chance to cure, HIV and HBV infections remain uncurable diseases. Therapy regimens can only stop the replication of the virus so that the viral load becomes undetectable in the blood but cannot eliminate the virus completely. Gilead remains committed to antivirals though efforts to develop a cure for HIV and HBV.

While antivirals are in the DNA of the company and remain a key focus, we are now diversifying in other therapeutic areas such as haemato-oncology with a product for chronic lymphocytic leukemia and a breakthrough CAR-T therapy for diffuse large B-cell lymphoma. While we are moving into new areas, Gilead's core mission remains the same: finding solutions to life-threatening diseases, as opposed to chronic civilization diseases.

According to Politico, new HIV cases in the Czech Republic have increased by 128 percent in the past eight years, making the Czech Republic the fifth country with the highest rise in the number of new HIV cases. What solutions is Gilead bringing to combat the epidemic?

This quite significant growth over the last eight years is mainly because the Czech Republic started from a very low base. Despite the increase in new cases, the Czech Republic still belongs to countries with lower prevalence. This being said, it is a growing epidemic, with around 250 newly diagnosed patients per year. Something must be done to stop it. Besides treatment, we support several educational activities, prevention programs and screening campaigns organized by patient associations and other NGOs by providing educational materials and financial support for testing. We must make sure that people know the risks and minimize them, but also have the right support to avoid infection, for instance by distributing free condoms, or providing drug users with free sterile syringes.

I would especially like to mention the Fast-Track Cities initiative, led by the International Association of Providers of AIDS Care (IAPAC), and supported by Gilead, among other partners. This initiative is a global partnership between cities and municipalities around the world. The network has grown to include more than 300 cities and municipalities that are committed to attaining the UNAIDS 90-90-90 targets by 2020. I am happy to say that Prague recently joined the Fast-Track Cities network. On December 5, 2019, the mayor of Prague, Mr. Zdeněk Hřib, signed a declaration, together with representatives from IAPAC, pledging to support education and prevention activities. As an example, the city of Prague will donate ambulance cars to a local patient association which will use them for screening activities in front of night clubs. To support and complement this Prague's commitment, Gilead will support the patient association partnering the initiative with funds for the testing kits.

In terms of treatment, the great thing is that all of Gilead's therapies are available and reimbursed, and for that, we are extremely grateful towards health authorities and health insurance funds. Thanks to them, there is unrestricted access to these therapies in the Czech Republic. In contrast, there are still countries in Europe where access to innovative HIV treatments is restricted, and patients cannot receive the same quality of care. In the Czech Republic, all HIV-positive patients can be immediately treated after diagnosis, which is key to stopping the epidemic. When patients are properly treated, their viral load usually becomes undetectable. As a result, they do not represent a risk to others anymore. Moreover, their average life expectancy is almost identical to the general population. So making sure that everyone knows about their HIV-positive status and gets properly treated is crucial.

While proper diagnosis and treatment are important, as Korab Zuka, Vice President of Public Affairs for Gilead, noted in a Forbes article, "it takes more than medicine to

impact diseases like HIV” because “stigma is still a major factor in why individuals do not get tested or seek medical care.” How is Gilead working with local associations, communities and health authorities to address this stigma?

We feel that the stigma is still significant, which is very problematic. Many people still perceive HIV-positive patients as a risky population and are afraid of being near them or shake their hands. This, of course, stems from a lack of information and education. These people do not understand that it is impossible to get infected by simply shaking hands with a HIV-positive patient, whether the patient is being properly treated or not. Moreover, they ignore the fact that if patients are properly treated, even their blood does not represent any to risk to others. The only way to get rid of stigma is through educational activities, especially aimed at the younger generation. For instance, one patient association, which we support, runs online and face-to-face seminars at schools where they inform students about HIV.

At the same time, it is also the case that, since many people now know that there are effective therapies available, they might be less worried and behave in riskier ways compared to ten or fifteen years ago, unaware of the fact that these therapies do not cure the infection. This is an area where we as a company, but also governmental authorities, must make sure that people are properly educated and behave responsibly, while at the same time do not discriminate against people living with HIV.

According to a 2016 study by the Faculty of Military Medicine at the Czech Army’s University of Defense in Hradec Králové, the prevalence of hepatitis C in the Czech Republic is far higher than previously estimated, suggesting that more than 80,000 people in the country may have a chronic form of the disease without even being aware of it. How are you making sure these people are properly diagnosed and treated in this area?

In the Czech Republic, we regrettably do not have enough epidemiological data to say exactly how many people are living with CHC. Older studies suggest a prevalence of 0.2 percent, or around 20,000 people, while a new study, such as the one you mentioned, indicates up to 80,000 cases. We still need more precise epidemiological data. Nevertheless, it is clear there are thousands of people infected with the hepatitis C virus (HCV). In the past, around 1,000 new cases were diagnosed every year. In 2019, the number of new diagnosis increased to 1,700, a considerable improvement compared to previous years, which was probably a result of public awareness

campaigns. However, there still exists a huge gap in comparison to the estimated number of infected people. We believe that our educational activities, which we combine with HIV awareness activities, also played a key role in the improvement of the diagnosis rate. For instance, we recently launched a campaign focusing on high-risk populations. The message is: “Don’t be afraid of getting tested, if you are infected with HCV, you can get cured, and in the case of HIV, you can receive effective treatment and live normal lives”.

In addition, we are currently working on a national elimination plan together with authorities and scientific associations. The plan should address many elements which are currently lacking. First, there should be proper education, in collaboration with the Ministry of Education. Second, the Ministry of Health should establish clear guidelines for each subgroup of potential patients. For instance, pregnant women get tested for HIV, HBV, and syphilis at the 14^{th} week of pregnancy, but not for HCV. It is an obvious gap, especially when the positive diagnosis rate of HCV is much higher than in the case of HBV infection. There are less than 100 new HBV cases per year, compared to 1,700 new HCV cases per year. In case of pregnant women, the lack of HCV testing generates a risk not only for the mother but also for her child and healthcare professionals during birth. It is a typical example illustrating the need for clear rules to be established together with scientific associations. Moreover, payers must, of course, be willing to reimburse the tests so that an increasing number of people can get properly tested. Many European countries have already such plans in place and the Czech Republic should close this gap.

Moving on to immuno-oncology, in 2018, the EMA granted marketing authorization to CAR-T therapies. Can you explain what it is and when Czech patients will have access to this breakthrough therapy?

It is indeed a breakthrough. Without this therapy, patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) have a median overall survival of only five to six months. However, CAR-T has shown to be able to achieve remission of the tumor and median overall survival of up to three years for approximately half of the patients.

CAR-T is a technology that requires harvesting the patient’s T cells, a type of lymphocyte which plays a central role in the immune response. A gene for a special receptor called chimeric antigen receptor (CAR) is then added to the T cells in the laboratory. These changed T cells, called CAR-T cells, are grown in large numbers in the laboratory and given to the patient by infusion. I am extremely happy to say that this therapy will be available to Czech patients soon. In fact, the first

Czech patient received the therapy on Monday, December 2nd, completely for free at the University Hospital in Brno. In September, a memorandum was signed between VZP, the largest health insurance fund in the Czech Republic, and the Czech Society of Hematology, granting funding to this therapy for the next twelve months. Thanks to payers, this therapy will be available to Czech patients immediately and the Czech Republic will be the first country in Central Europe to reimburse the therapy!

Introducing breakthrough cell and gene therapies like CAR-T not only requires funding, but also the right medical knowledge, infrastructure, and supply chain by building a direct link between hospitals and pharmaceutical companies. Are these elements in place in the Czech Republic?

Yes, each center in Czech Republic which can provide CAR-T therapies to patients must go through a certification procedure comprising several aspects like training of staff on many operating procedures, check on technical equipment and available hospital infrastructure, legal agreements, etc. All this is done with the single aim to assure highest quality standards which are critical for best possible treatment outcomes for the patients.

Although Czech patients will be among the first in Europe to be able to receive this treatment, there is currently no regular pathway for breakthrough cell and gene therapies to gain access to reimbursement. How are you advocating for the creation of such a pathway?

There is currently a gap in legislation, as these orphan treatments and advance therapy medicines are not addressed by the law. As a result, companies do not know how to submit an application for regular reimbursement. The law is designed for standard drugs requiring the applicant to prove cost-efficiency, which is not possible in cases of such costly and innovative therapies.

We are happy that Ministry of Health is currently preparing an amendment to the Act on Public Health Insurance to address orphan drugs. They plan to introduce so-called soft criteria and create an advisory committee composed not only of payers and representatives of the Ministry but also scientific associations and patient groups. All these stakeholders will be assessing these orphan drugs against soft criteria, which should in my opinion take into consideration the impact on the quality of life of patients and their families, as well as indirect socioeconomic outcomes on

disability costs, tax income, and other factors which are not taken into account for regular drugs. In fact, I wish these factors would be taken into consideration for regular prescription drugs as well. Right now, the healthcare budget and social budget are managed separately. Nevertheless, treating a patient in serious conditions with an innovative therapy, although more expensive than the standard of care, can reduce disability costs and increase tax income when the patient is able to return to work. All these factors should be accounted for in the calculation of budgets so that society can decide if investing in an innovative therapy pays off not only from a healthcare perspective but also socially and economically. I am optimistic that in the future the health and social budgets will be managed in sync.

What does the future hold for Gilead in the Czech Republic in the next three to five years?

Healthcare is going through a paradigm shift. Besides orphan drugs, we can imagine that in the near future there will be cell and gene therapies for civilization diseases. Authorities and payers will have to adapt to this new world by adopting a forward-looking approach and the industry by implementing innovative risk-sharing agreements and pay-for-performance schemes.

I hope that we will remain successful in bringing breakthrough treatments to Czech patients and that Czech authorities will continue being increasingly willing to enable access to innovative therapies. As Gilead is diversifying into new therapeutic areas beyond antivirals, we will continue growing and we hope to bring even more innovations against life-threatening diseases in the coming years.

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