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Expanding into Cell and Gene Therapies to Deliver Breakthrough Innovation

Wolfram Carius, Sheila Mikhail, Emile Nuwaysir

Ladies and Gentlemen,

It´s a great pleasure for me to introduce you to Bayer´s new activities in Cell & Gene Therapies, an emerging and exciting field that has the potential to revolutionize innovation in the Pharmaceuticals industry.

I am Wolfram Carius and I am the head of the newly established Cell & Gene Therapy Unit at Bayer´s Pharmaceuticals division. This unit steers our strategy in the area and orchestrates all activities along the value chain, providing an innovative ecosystem for all involved. Through this strategic platform, we further consolidate, strengthen our emerging leadership in this field, and we have taken a transformative step to deliver breakthrough innovation to patients.

But why investing in Cell and Gene Therapies? Cell and gene therapies offer for the first time the possibility to address the root cause of disease. It may provide options for conditions considered intractable or where the current standard of care is insufficient. Cell and gene therapies employ disease intervention mechanisms distinct from traditional treatments. Therefore, it may offer curative and regenerative treatments by for example replacing a faulty gene in the right tissue. Based on early evidence, we believe cell and gene therapies will dramatically alter the standard of care across multiple conditions to the benefit of the patients.

Bayer wants to be at the forefront of Cell and Gene Therapies. And to achieve this, we are strengthening our internal capabilities while pursuing external strategic collaborations as well as acquisitions and licensing. These investments are carefully curated and selected to establish a synergistic platform. Strategically, we are focusing on selected areas such as gene augmentation, gene editing, stem cell therapies and allogeneic cell therapies.

During the past months, we have made tremendous progress to set up our cell and gene therapy unit. The acquisition of AskBio last year created the basis for our gene augmentation program. AskBio now represents one of the most advanced and industry leading AAV vector gene augmentation platform. It already has demonstrated commercial applicability across different therapeutic areas. This acquisition also comprises integrated manufacturing capabilities and capacities including an established contract development and manufacturing organization called Viralgen which already generates revenues today.

Sheila, the CEO of AskBio, will tell you more about the great achievements they have already made.

With the acquisition of BlueRock in 2019, we built a leading position in cell therapies. BlueRock is a company focused on development of engineered cell therapies using an induced pluripotent stem cell platform. BlueRock´s lead program is in Parkinson’s disease for which Phase I clinical development was initiated just recently. Emile, the CEO of BlueRock will tell you more about this breakthrough.

We have not only made progress in setting up our gene augmentation and stem cell platforms, we also entered into a strategic collaboration for our allogeneic cell therapy platform with Atara Biotherapeutics end of last year for next generation, mesothelin-targeted CAR-T cell therapies for solid tumors. Atara is a pioneer in allogeneic - which means donor independent - T-cell immunotherapy. They apply industry-leading cell manufacturing processes and next-generation CAR-T technologies. This collaboration is a fundamental element of our strategy in the area of allogeneic cell therapies.

While gene editing is today the essential cross platform enabling technology for most gene and cell therapies, we further develop our CRISPR/Cas technologies with the ambition to be at the forefront of invivo gene editing.

But why don´t we let our partners at AskBio and BlueRock speak for themselves? With great pleasure, I´d like to introduce to you Sheila from AskBio and Emile from BlueRock.

Sheila will talk about her achievements at AskBio and Emile will speak about BlueRock´s approach for a potential treatment of Parkinson´s.

AskBio is a gene therapy company. We develop drugs for devastating disease. Often traditional methods of developing drugs have not yielded viable therapeutics for the diseases we are tackling. We represent over 350 professionals working in five different countries.

There are three different components to our business – first therapeutics, second contract manufacturing, and third IP monetization. Drs. Richard Jude Samulski and Kathy High lead our therapeutics' business. Dr. Samulski was the first to clone AAV for therapeutic purposes. He is largely known as the father of the field. Dr. Cathy High is the founder of Spark Therapeutics. There, she brought the first FDA-approved drug, using AAV, to the market. Our second business, the contract manufacturing business, is comprised of two different sub-components. First, we operate underneath the trade name Viralgen for the production of GMP virus for the industry. We use our Pro10 cell line which is the highest yielding cell line for that purpose. Our second segment is operated underneath the trade name Touchlight AAV. It produces an alternative to plasmid DNA for the beginnings starting materials of AAV virus manufacturing. Our alternative method is called doggie bone DNA. The third business is IP monetization. We do not use our IP in the development of our own drugs, we out licensed it to others and generate milestones and royalties. We have spun off several companies using our IP. First, we spun out Chatham Therapeutics for the development of hemophilia drugs using our IP. Chatham was sold to Baxter, now Takeda, in 2014. Second, we spun out Bamboo Therapeutics to use our IP for the development of a drug for Duchenne Muscular Dystrophy. Pfizer bought Bamboo in 2016. Every approved AAV therapeutic on the market today uses our technology. We generate milestones and royalties from the out-licensing activities.

Gene therapy attempts to fix disease at the root cause. If you have a genetic defect, that means, that you have a gene that is not properly functioning. What gene therapy does is it puts a good gene into the body to do the work that the defective one could not do. You may ask how do we do this? Well, all of us are familiar with Covid and we now know that viruses are very good at infecting cells. What we do is we take a nonpathogenic virus called adeno associated virus, AAV, and we take out the wild type DNA of the virus. This leaves a protein shell. Into that protein shell we can put a normal gene. We can use the shell then to infect our cells of interest. Typically, we can deliver it with an IV injection. Once it gets into the body, it goes to the cell where it uses the cell's machinery to pump

out the protein of interest. We have the potential to do that with just a one-time treatment and the effects are expected to be sustain, potentially life long.

There are several benefits to the AAV system over other factor systems. First, it produces high yield, so that means it is relatively easy to manufacture. Second, it has a very mild immune response, meaning that it doesn't really create much immunogenicity when we deliver the therapeutics. Third, we can target a wide variety of cell types and that gives us the ability to develop drugs for a multiple of different diseases. Fourth, it has a very good safety record. It's been in the clinic many times and has established a safety. And fifth, it can be used for gene editing purposes as well as gene augmentation.

We have created a large toolbox of novel AAV technologies. This toolbox enables us to create an infinite number of AAV therapeutics. Our toolbox consists of technologies that are the best-in-class capsids and promoters. Capsids are the delivery system that gets our AAV therapeutics to the target cells. We have the ability to target specific cells, de-target other cells and minimize the effects of pre-existing neutralizing antibodies. With respect to the promotors, our promotors increase the potency of our AAV therapeutics and avoid off target expression consequences. We also have promotors that can turn on and off trans gene expression and can rheostat up or down the amount of therapeutic that is given.

We have one of the best-in-class manufacturing processes to support the development of our AAV therapeutics, using our novel technologies. The Pro10 system is the foundation for our manufacturing processes. It is a HEK 293 cell suspension system, it has one of the highest yields in the industry for a produced serum cell line. We are also fully backward integrated into plasmid production, but we don't make traditional plasmid DNA. Instead we innovated and created a newer type of production called doggie bone DNA. Doggie bone DNA has several advantages relative to plasmid DNA. First, it has a much faster cycle time, second, its costs are much lower, and third, it has the potential to have a safer product because we avoid E.coli and fermentation processes. There are over 800 patents that support our novel toolbox.

And as you can see from our pipeline chart, we are developing AAV therapeutics for both rare, monogenic diseases as well as pathway diseases. We are currently in the clinic for Pompe, congestive heart failure, Parkinson's, and multiple systems atrophy. Within the next 12-18 months, we will also be in the clinic for Limb-Girdle 2i, MMA, and Huntington's disease. We have several other projects in earlier stages of development, including for Angelman's disease.

Forth, we needed to combine our technology with the best-in-class medicinal chemist. Bayer has the best compound library. They also have word-class medicinal chemist. We know that with the use of small molecules we can increase the potency of our AAV delivery systems. We can also use small molecules to turn on and off trans gene expression. We want to stay focus on what we do best – AAV drug development. Therefore, it was essential that we partner with a Big Pharma that has extensive distribution channels. We will use Bayer's distribution channels to distribute our products on a global basis to all patients who need them.

I now like to turn it over to Emile Nuwaysir.

Thank you, Sheila.

Our mission at BlueRock is to develop authentic cellular medicines to reverse devastating diseases. And we have chosen that mission because there are hundreds of millions of people worldwide today that suffer from degenerative conditions for which medicine really has no answer. As an example, there are 34 million heart failure patients who suffer today, 8 million people who suffer from Parkinson's disease. And for those 42 million people, the best that we can do with medicines today is manage their symptoms and hope to slow their decline. Why is that? Why is it that these diseases are so difficult to treat? It's because these diseases and many others like them have a terrible common root. And that root is the degeneration of the tissue and the loss of the healthy cell. And once that cell is lost, these incredible powerful medicines that we think of today, drugs, devices, surgeries, don't work well. When the tissue is degenerated, these medicines don't work well. We need a new answer, something that addresses the degeneration itself that has the potential to reverse the disease and at BlueRock we think we have that answer.

We are developing a novel approach we call *cell+gene* which allows us to manufacture authentic human cells and to replace them in the body. And by replacing them, we can restore the function that is missing and reverse the degenerative condition and reverse the disease. We call this authentic cell replacement. But because these cells are manufactured, we can engineer them for enhanced efficacy and safety and to carry payload into the tissue. And this payload we believe could be very powerful to treat rare and chronic disorders and we call that engineered authentic cells. We are focused today on three therapeutic areas, cardiology, neurology and immunology and I will explain our lead program and some of our earlier programs in a moment. This is all based on foundational science, the subject to the 2012 Nobel price called an induced pluripotent stem cell.

What we do is we take a normal blood draw from a consenting adult and in a one-time process convert the blood cells in that sample to a pluripotent stem cell, an induced pluripotent stem cell. And that cell has two very powerful properties that make it the ideal basis for a medicine that is it will double every day if you put it under industrial control, it can double every day. It also has the potential to turn into any cell type in the human body. And when you combine those two things under industrial control, you have a very powerful manufacturing platform. You can also combine this with CRISPR/CAS genome engineering, the subject of the 2020 Nobel price and this allows you to engineer the cells so that they carry enhanced function, efficacy and safety, for example engineering for shelf so that they are not rejected by the patient. Or engineering to carry additional functions we call payload. An example of this would be the mid-brain dopaminergic neuron that we are developing to treat Parkinson's disease or a microglia cell which is your brain's primary immune cell and engineering that so that it can carry enzymes and payload into the brain. Those are two examples, real-life examples of things we are developing at BlueRock.

We have applied this platform to a very broad number of potential indications, you can see this listed on the slide here, in neurology, immunology and cardiology. In neurology, we have four programs, in oligodendrocytes which are supporting cells of the brain for demyelinating disorders, the dopaminergic neurons I will tell you about in a moment to treat Parkinson's disease, microglia that could broadly be used to treat neurodegenerative conditions and enteric neurons to treat Hirschsprung's disease.

Specifically, our lead program is Parkinson's. You may know Parkinson's is the second most common neurogenerative disorder worldwide. Today, it affects almost 8 million people. It is a

crushing and debilitating disorder that's progressive and today, it is irreversible. And it leads to a loss of motor control so that simple things like swallowing become impossible. If you have seen it up close, you want to do something about it.

Our founder Lorenz Studer in 2010 and 2011 published seminal research papers where he showed how to turn a pluripotent stem cell into that authentic mid-brain dopaminergic neuron that is lost first in Parkinson's. In the middle of your brain to help the adult has several hundred thousands of tiny number of these cells, about the size of a half a grain of rice in your mid-brain, and that controls your motor function, the connection between thought and action. He demonstrated how you could turn a pluripotent stem cell into this exquisite and rare cell and he showed for the first time that it had all the functions that were needed and when he put it into an animal model, it reversed the symptoms of Parkinson's in that animal model.

We have done similar studies, we industrialized the manufacture of that cell, done the careful safety and efficacy studies, prepared and filed with the FDA and we are entering the clinical trial to test that cell in Parkinson's patients.

That trial will initiate this quarter, it will be an open label trial where the goal is safety and tolerability, but it is in Parkinson's patients where we hope to see some therapeutic benefit. There are 10 subjects, patients that are between 5 and 15 years of diagnosis in Parkinson's who do respond to L-dopa but are inadequately managed and inadequate relief from that drug. We expect over the next 1-2 years to see the safety and hopefully the efficacy from that study as we enroll patients.

I am very happy and pleased to tell you the story today and be part of BlueRock. We are incredibly excited about what we are doing and to be part of Bayer. And with that, I turn it back to Wolfram Carius.

I hope that you share our excitement about the future we see for our engagement in cell and gene therapies.

As Sheila and Emile outlined, our approach in building this unit is somewhat different from most of our competitors.

Our operating model for cell and gene therapies leaves partners operate autonomously and fully accountable to develop and progress their portfolio and technology.

In fact, this should enable our partners to realize the benefits that can come from being part of a larger organization to get the best of both worlds. In our view, this is essential for preserving their entrepreneurial culture and positions Bayer as a partner of choice.

And this effort is already bearing fruit.

Our development portfolio of cell and gene therapies comprises already six clinical assets.

Leading programs include Pompe disease, Parkinson's disease, hemophilia A, and congestive heart failure. With over fifteen preclinical assets in the cell and gene therapy field as of today, the pipeline is expected to grow steadily year by year, too.

We have made bold steps to expand into cell and gene therapy. And we are convinced that this technology will revolutionize the way we may treat or even cure diseases that are not addressable today.

Bayer has laid the foundation to be a leader in this critical endeavor.

Thank you.

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