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Chameleon Biosciences - Expanding AAV Gene Therapies with EVADER™

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CEOCFO: ***Ms. Winslow, what was the concept when you founded Chameleon Biosciences, Inc. in 2017?***
Ms. Winslow: When I founded Chameleon Biosciences about five years ago, I was working in the field of gene therapy on a program treating children suffering from a fatal genetic disease. These children did not live beyond two years. This patient population had an extreme unmet need, and we were working on a potentially lifesaving treatment for them.

However, at the time, I saw that the people working on gene therapy were not considering the immune aspects of their products. To put it simply, the immunologists and the gene therapy scientists were not sharing their knowledge with each other. I have a background in both fields as I had done graduate work in immunology and then I spent an entire career developing early-stage drugs for gene therapy. My response to the dilemma was, "We will do our best to make it work and try and save these children, but when you are developing a drug to potentially save the lives of infants, you have to start thinking about the immune response in the long run to ensure that these children live a long healthy life."

That is what got me started on Chameleon. I thought that we could better serve the patient population by bringing the two fields--immunology and gene therapy--together. I also thought that the melding of the two fields would lead to clinical success for the industry, as well as to financial success for investors. (Given the costs of gene therapy, investors have to be very financially successful in order to fund the types of drugs that we have to develop in order to treat these patients.)

CEOCFO: ***Where are you today? How has that played out for you so far?***
Ms. Winslow: It turns out that we were spot on in anticipating that the immune response to gene therapy drugs is very important; it is perhaps the most important obstacle that this field of Adeno-associated viruses (AAV) gene therapies faces today. Clinical trials have shown us that patients' immune system reactions strongly influence the safety profile of drugs that use the current technology, as well as how much drug can be administered and how many times. The human immune response to current therapies also prevents us from being able to treat all patients.

CEOCFO: ***How are you looking to move forward with the idea?***
Ms. Winslow: It was a pretty big idea at the time. Technically, we are not actually doing anything that had not been done before; just bringing together different components, if you will. We designed a drug that incorporated what we have

learned from different fields, such as the behavior of cancer cells that evade detection from immuno-oncology, and what we know about how vaccines activate our immune systems to fight off infectious diseases.

Our first big goal was to show that we could make this product, because it was something that was groundbreaking and paradigm-changing. Human nature is skeptical about paradigm-changing ideas. We knew that we had to work very hard to show that we could make our drug, and that we could scale the manufacturing to be able to get into clinical trials. We also needed to show that post clinical trials, we would be able to make enough of it to get market approval to start treating more patients.

In current gene therapy technology, manufacturing is the biggest risk in funding and growing our types of companies. Our investors have been steadfast and completely supportive in these efforts, and we are now in a position where we can make our product because its composition is very well understood and very well-documented. We now know that we can make enough of it, not just for clinical trials, but to take it to market, therefore, we have achieved the first set of goals that we had set for ourselves.

Our second goal was to show how well our technology platform worked; we had to show proof of concept. While we were developing the manufacturing approaches for our product, we tested it in different disease models. What we have found--every step of the way--is that our product works very well. We have basically cloaked our virus particle in a layer that effectively hides it from our patients' immune systems, so our patients' immune systems no longer see our product as something to be attacked. They see it as something that just belongs there.

"We are addressing a need, a gaping hole in the gene therapy market, by striving to treat all patients regardless of age or previous exposure to the AAV virus, and believe that our products may prove to be much safer than what is used currently. Once we have shown strong clinical results with EVADER gene therapies, we plan to apply this technology to treat more common diseases, not just to rare diseases." Genine Winslow

CEOCFO: ***Is this the EVADER™ Platform Technology that you are talking about?***
Ms. Winslow: Yes.

CEOCFO: ***Why does coating with this extra layer work? What is the science?***
Ms. Winslow: It is because, as I said, we start with a virus particle that has been gutted to act as a delivery vehicle, if you will. It shuttles the correct gene into our patient's cells and gets it to the right place in a patient's cells, to reverse the disease. We are starting with a virus, and even though it is a harmless virus, our patients' immune systems see it as in the category of all viruses, and it is something that needs to be gotten rid of. Therefore, our patients' immune systems see our drug like any other virus and attack it. This immune response is the underlying cause of some of the recent clinical setbacks in the field.

Our product adds a lipid membrane around each virus particle that effectively "cloaks" the virus so the patient's immune system does not try to attack it and get rid of it. In addition, we attach checkpoint immune-signaling molecules to the membrane--very well understood from the immune oncology field as a way that some cancer cells avoid detection--and we incorporate these into the extra layer surrounding a gene therapy virus particle to improve the "disguise" even more.

CEOCFO: ***Are there particular conditions or diseases where your drug is most effective? How have you decided what to test first? I am guessing that there are many different conditions that need attention.***
Ms. Winslow: Yes, there are many different genetic diseases currently being addressed with gene therapy, and hundreds more that have not yet been worked on. In terms of what to work on first, we chose a disease that was one of the first to be treated with gene therapy about 10 years ago now, at the University College of London: hemophilia B.

Most people have heard of hemophilia. Hemophilia is a disorder where patients have a defect in a gene that is necessary for clotting blood. Normally, if most of us get a cut or an injury, our blood clots and stops the bleeding. People with hemophilia B are missing a key molecule needed to form blood clots and they bleed uncontrollably.

The reason that we chose hemophilia B as the first program is because we have the most clinical information about it, so we know how gene therapies work in humans for treating this disease. That gives us more information to start with, and to design our first clinical trial with safety as the highest priority. Remember I said our drug has a virus particle at the center? We will be using the same virus particle, the inner component of our product, that has already been used in clinical trials in humans. We know it works to reverse symptoms of the disease, and we know it is safe at lower doses in humans.

In addition, we plan to treat patients who have no other choices, meaning that we will treat hemophilia B patients who can't be treated with the current gene therapy approaches, and treat them using our EVADER technology. We will maintain that strategy as much as possible going forward as we expand our pipeline.

In the future, we will pursue strategic alliances and partnerships to help us to test our platform to treat other types of genetic diseases as soon as possible. As the platform grows more over the long-term, and we understand how it works in humans, ensure that it is safe and effective as a result of clinical trials, we can then expand our platform for non-rare genetic diseases. For example, there may be a long-term application to treat cancer or heart failure with our technology. We could also use it to treat certain autoimmune diseases, or transplant rejection or graft versus host diseases.

We have a very clear, focused strategy to get into the clinic, to demonstrate that our platform produces products that are safe and effective. Then beyond that, there is almost unlimited growth potential to utilize the platform, to treat patients and also to grow the company and get returns for our investors.

CEOCFO: ***How often would someone need to take the drug? Would it be on an ongoing basis? Does it depend on what condition or is that yet to be determined?***
Ms. Winslow: That is a very, very good question, because the current AAV technology can only be given once in the lifetime of a patient. It was referred to as a "one-and-done" model, which defined a whole set of parameters around the types of diseases you can treat, the types of people you can treat, and the types of clinical trials you have to design.

We are finding that one-and-done does not do it in many situations. Some patients will have been previously exposed to the native version of the virus that we use. With the "one-and-done" technology these patients cannot be treated. Additionally, genetic diseases affecting growing tissues in children cannot be treated because they would require more than one dose to maintain disease correction.

We want to be able to treat every patient, and we are changing that one-and-done paradigm. We are going from a very high-risk model of drug development and drug administration to a model that is closer to more traditional drugs, where we can do dose escalation trials. We can get a clearer idea of PK/PD [pharmacokinetics/pharmacodynamics] because we can administer more than one dose to a patient. We are planning a minimum of two doses for treating hemophilia B patients. We have an option to give additional doses if individual patients require more drugs to more fully correct for the disease. We also can administer additional doses a few years later if a patient requires it to more fully correct for the disease. The total number of doses will be different when treating different diseases and different tissues. Our first clinical trial, right now, is planned to be a two-dose minimum. Beyond that, we will administer subsequent doses as needed.

One difference between the way our drugs work and the way traditional pharmaceuticals work is when you talk about dose escalation with traditional pharmaceuticals, you literally start out low in a clinical trial and give higher and higher doses, to show that it is safe. We administer a low, safe dose, and then cumulatively add to that, with subsequent low safe doses. Therefore, we end up with a cumulative therapeutic effect, with a two-dose minimum, and then we will be monitoring it.

To some extent, we are planning to do individualized medicine for AAV-based gene therapies. We plan to give patients those two initial doses, then measure the clinical response and see if it is enough. If they need more, we could administer more doses.

CEOCFO: ***When you are talking to the medical community, as well as the investment community, do they understand? Is there something you say where the light bulb goes off? How do you address both of these communities, so they recognize the importance of what you are doing at Chameleon?***

Ms. Winslow: That is a good question, too, because of course, the medical community and the investor community have a shared mutual end goal, but how you get there is where they differ. The medical community wants to help patients to be as safe as possible. They want the very best drug that they can possibly get. We need the investment community in order to develop drugs, but they also have to see returns on their investments. We marry the conversation we have with those two by emphasizing that first of all, it is a new paradigm and a new way to treat gene therapy patients.

We have got a lot of data. Data speaks volumes. We can show in our animal models for example, that we can safely administer two doses with less of an immune response than the standard technology ends up resulting in now. It is a combination of showing that we can overcome the limitations that we have seen in the clinics with the first-generation gene therapy technology, and showing that we already know how to manufacture it, and that our products are even more effective and potentially safer than the existing gene therapy products.

CEOCFO: ***Would it be harder to get people for trials as some of these diseases are not very prevalent, or is the fact that people have fewer options make it more likely someone would go into a trial? What do you see there?***
Ms. Winslow: Trial participation was another reason we chose hemophilia B for our lead program. In our first clinical trial, we are planning to treat patients with higher levels of pre-existing neutralizing antibodies. These are patients who could not get into current clinical trials, because they had previously been exposed to the native version of the virus. We plan to treat these patients while existing gene therapies can't; that is how we anticipate, even with these very rare diseases, having access to patients for our clinical trials.

CEOCFO: ***How do you deal with some of the frustration personally, in knowing you have such a good idea that can help so many people, and yet, it takes quite a while to get to the point where it can actually be used?***
Ms. Winslow: One thing I have learned, as a CEO and in starting Chameleon, is that you cannot ever give up. You have to persevere no matter what. I think of a parent I met. This was way back before I started Chameleon. His child was suffering from a fatal genetic disease, he was part of a patient advocacy group, and I was giving him a tour of our lab. He explained to me how, when he heard his son's diagnosis, his world went black. Those were literally his words. His world went black.

Yes, it takes longer than I like. Yes, it is hard. I may get knocked down a lot by various parties along the way, but if I think about that parent and those children, I can pick myself up when I need to.

CEOCFO: ***Why should I pay attention to Chameleon Biosciences? Also, what might someone miss that really needs to be understood?***
Ms. Winslow: What we are doing is unlike anything that anyone else is doing. We have very strong IP [intellectual property]. We have freedom to operate, and we have a platform with massive potential growth. We are addressing a need, a gaping hole in the gene therapy market, by striving to treat all patients regardless of age or previous exposure to the AAV virus, and believe that our products may prove to be much safer than what is used currently. Once we have shown strong clinical results with EVADER gene therapies, we plan to apply this technology to treat more common diseases, not just to rare diseases.

I think that the potential is not always completely apparent at first. The more data we get, the more I see that we should be able to safely redose patients. We reduce immune response indicators in our models. Those models also show that our efficacy is much better than the current technologies, even than our closest competitor. It is a game changer.

Initially, there was more resistance to it than there is now. I think that what I am trying to convey to investors is very new. It has been significantly de-risked, because while the particle itself is new, the way we are making it, the way it works, is based on commercially viable precedents. You combine that with a strong strategy to de-risk the first clinical trials, and a solid plan for the development of our pipeline, and we are more likely to succeed.

We are developing our own products, gene therapy drugs using EVADER technology, to generate proof of concept in clinical trials, and realize the largest value inflection point in drug development. At the same time, we cannot treat every

disease. Therefore, we will strategically license or partner with large pharmaceutical companies to accelerate development of gene therapies to treat additional diseases as we grow the company to help fund internal efforts.

CEOCFO: ***You have all of the bases covered. A really good overall plan, taking into account the business as well as the medical aspects at Chameleon Biosciences. I do not hear this often, so kudos to you.***
Ms. Winslow: Thank you very much!