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Krish S. Krishnan, President, CEO and Chairman of Krystal Biotech Inc. discusses developing elegant off-the-shelf Topical Gene Therapy Approaches to Treat Debilitating Orphan Rare Skin Diseases

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CEOCFO: ***Mr. Krishnan, what is the idea behind Krystal Biotech, Inc?***
Mr. Krishnan: The idea behind Krystal was to find an elegant off-the-shelf topical gene therapy approach to fundamentally treat debilitating orphan rare skin diseases that presently do not have a treatment. Some of these diseases cause mortality in patients at a very young age. We also believe that our approach could help treat broad skin diseases and simple skin conditions that are more prevalent.

CEOCFO: ***Why are you looking at this problem? What led you to this particular situation?***
Mr. Krishnan: First, not many people are focused on finding treatments to rare skin diseases that affect so many children in the US and worldwide**.** We became aware of these diseases previously through our work and the more we got to know how severe the diseases were, the more we felt that the current approaches to treating them were difficult, cumbersome and impractical. That drove us to find a simple elegant way, using gene therapy, to treat these diseases.

CEOCFO: ***What have you found out?***
Mr. Krishnan: The first disease we are going after is called dystrophic epidermolysis bullosa, commonly known as butterfly syndrome. The signs and symptoms of this condition vary quite a lot among patients. It is a genetic condition that causes the skin to be very fragile and blister easily. Blisters form in response to minor injury, friction, rubbing and scratching. It is caused by a mutation in a single gene called COL7A1, which provides instruction for making a protein that assembles type VII collagen that, in normal people holds the epidermis and dermis together. For many of these patients there is also burning and pain. They have to be bandaged regularly and frequently. The disease causes a lot of aggravation, not just for the patient, but to their extended families. And because it is genetic, it starts at birth and manifests itself throughout the life of these patients. There are no fundamental ways to fix this disease, presently. Our idea was to find a way to deliver the gene that is missing or mutated in these patients in a simple effective manner, in order to provide them with the necessary protein and hopefully treat the underlying cause.

CEOCFO: ***Where are you right now in that development and research process?***
Mr. Krishnan: In May, we enrolled our first patient into the clinical studies that we are presently conducting at Stanford University. We recently announced that we have enrolled two patients in our Phase 1/2 study to date. We hope to announce the results of this clinical study by Q4 of 2018. Our expectation is to initiate a pivotal study in the 2H of 2019.

CEOCFO: ***As it is a rare disease how difficult is it to find patients? Is there a particular age that makes sense for a patient in the trial or does it matter at what point you might start the treatment?***
Mr. Krishnan: Yes. Because it is a rare disease and because many patients remain undiagnosed, it is difficult to enroll. However, knowledge and awareness of this disease has significantly increased in the last few years, because of the collective work that has gone into treating the disease. Also, the natural history database that exists that tracks these patients, their blisters and their conditions helps with enrollment.

CEOCFO: ***Is there any potential downside that you have seen so far or that you are on the lookout for?***
Mr. Krishnan: So far so good. However, we are keeping our fingers crossed and hope to see a similar profile in the clinic.

CEOCFO: ***What is the delivery method and process and time frame?***
Mr. Krishnan: The way we deliver the gene is to take a wild-type virus that has significant affinity to skin cells. We then modify the virus to get rid of its cytotoxic or bad properties while retaining the good properties that would enable us to infect these skin cells. Next we insert the gene that is missing or mutated into the virus's backbone. We then formulate the backbone containing the inserted gene into a topical gel that can be directly applied onto the wound. The modified virus helps carry the gene to the relevant cells that results in secretion of the required protein. It is the first time a company has thought about and is working on a painless, off-the-shelf topical approach to deliver a fundamental treatment to this disease without causing much pain or difficulty to the patient. As I mentioned earlier, we approach developing drugs with the patient in mind first. We wanted a simple, effective way to treat these patients that could be easily adopted.

"We approach developing drugs with the patient in mind first. We wanted a simple, effective way to treat these patients that could be easily adopted."- Krish S. Krishnan

CEOCFO: ***Are you applying it to one site or ten sites on the body?***
Mr. Krishnan: That is a good question. Because it is gene therapy our approach is incremental. We envision that when this drug is approved, a caregiver would start by treating say three wounds at a time. Over time as we learn about the safety of the drug there is a possibility that this number could increase. Safety first.

CEOCFO: ***What else are you working on?***
Mr. Krishnan: There are, sadly, numerous monogenic skin diseases. We recently issued a press release for one that was just designated as an orphan indication. It is our second product, and is for the treatment of lamellar ichthyosis (LI). The exact technical term is transglutaminase-1 (TGM-1) deficient autosomal recessive congenital ichthyosis ("ARCI"). It is also a monogenic skin condition. It is one where the skin gets significantly dehydrated and scaly and there is also a debilitating visual component to this disease. There are a few centers in this country that know how to maintain and provide the right kind of care to a patient. We are focusing on a few of these monogenic indications for now before we think about using this approach for some broader skin diseases.

CEOCFO: ***When the FDA is reviewing, as you have done this before, do they look a little bit differently at the second or third items you might present or does each one have to stand one hundred percent alone?***
Mr. Krishnan:. We look at every one of these products as a standalone produce with its own set of safety and efficacy requirements. There is a possible learning curve effect based on the fact that the fundamental difference in products is the missing gene that is inserted and so any concerns about the safety of the backbone gets somewhat established in the first indication. So hopefully, it gets easier and faster as we move along.

CEOCFO: ***What is the feeling of people in the medical community who are aware of what you are doing? What is the interest from the investment community?***
Mr. Krishnan:
Because there are no treatments presently and given the severe nature of this disease, I believe that anyone working toward developing a treatment for epidermolysis bullosa should be applauded, without exception. That is because it is a good cause and a difficult disease to treat. The idea of simply applying a gel like product to a wound to treat this disease has received a lot of positive feedback because of the ease of application and the potential for the patients to be treated locally where they live. However, it is important to realize that we are in the early stages of finding a treatment for this disease. I would characterize the researchers and the opinion leaders of the community as being excited but cautiously optimistic about our approach. In terms of the investment community, we have received some really good feedback, because of the nature of the modified virus that we are using. This modified virus, unlike some other gene therapies, does not integrate into your DNA. The concern among integrating approaches is that once your DNA is modified, the

modification is permanent and the long-term consequences of an integrating virus is unknown at the moment. In our case, albeit a gene therapy, the virus serves to simply deliver the gene and then get eliminated with cell replication and dilution. We have also modified the virus to be non-replicating. That has caught the attention of some really good investors in a space where some of our competitors working in this space have a more cumbersome and individualized approach to treating this disease. Ours is viewed as an off the shelf topical treatment and that has gotten some traction in the investment community. However, I think the real test for us is to validate our results to date in the clinic and that put us in a great place to treat many of these diseases.

CEOCFO: ***Are you funded for your next steps? What is your position like today?***
Mr. Krishnan: We are good financially at the moment. We currently believe that we have enough money to take us through the next twelve months at least. We are pretty conservative in our consumption of cash.

CEOCFO: ***What surprised you so far as you have been working on this?***
Mr. Krishnan: First, we tried many different approaches before we settled on this viral based approach. The feedback we got from a couple of opinion leaders, who conducted our animal studies, was positive. That was exciting news because no one previously had tied a modification of this virus and its ability to treat skin diseases. The patients are hopeful and excited given the simplistic nature of their disease. Therefore, the hopefulness of patients, the robust animal data we have to date and the support from the overall EB community have been some of the biggest surprises!

CEOCFO: ***Why does Krystal Biotech standout?***
Mr. Krishnan: Should this approach work, one could envision so many areas in skin that could be beneficial to patients. You could imagine us using this approach to go after debilitating large skin conditions, like atopic dermatitis and psoriasis. It is a huge market. Although there are treatments available in those markets there is really not one good treatment as I understand it. However, the approach can also someday be used to go after simpler skin conditions. The whole area of nasolabial folds or wrinkles is based on not having enough of a protein, like collagen one or a collagen three and should be a broad market area for us to tackle. By no means, am I equating a simple skin condition to debilitating skin orphan disease but simply discussing the broad applicability of our platform. Also, there may be other diseases, like diseases of the central nervous system (CNS) diseases or ocular diseases where this approach could be beneficial. But simply put, we stand out because of our smart and dedicated employees who spend so much of their time working diligently on such a great cause.