William H Lewis – Chairman & CEO, Insmed

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William H Lewis, chairman and CEO of serious and rare disease specialist Insmed, talks through the impact of recent product approvals in the US, preparations underway for international launches, the impact of COVID-19 on Insmed's operations, and the firm's highly promising clinical pipeline.

Will, 2020 has been an eventful year not only for the world but for Insmed as well. Could you take us through some of the highlights for you?

It is definitely a very exciting moment for Insmed. We have always been focused on helping patients with serious and rare diseases. We have experienced significant success with our lead program, ARIKAYCE®, which was approved in September 2018. ARIKAYCE® is a drug-device combination designed to treat refractory nontuberculous mycobacterial (NTM) lung disease caused by *Mycobacterium avium* complex (MAC). It utilizes our proprietary liposomal technology, PULMOVANCE, that is designed to deliver medicine directly to the site of infection. Following that approval, we have had a very successful commercial launch with great results on the market.

In parallel, two other clinical programs have also advanced successfully. The first is brensocatib, a DPP1 inhibitor being developed for the treatment of bronchiectasis and other inflammatory diseases, and the second is treprostinil palmitil, an inhaled prostanoid for the treatment of pulmonary arterial hypertension (PAH). Brensocatib, like ARIKAYCE, has received Breakthrough Therapy Designation from the US FDA. This sends an important signal that the FDA believes

brensocatib could generate a material and significant improvement to the care of patients with bronchiectasis and the fact that this disease is serious and life-threatening.

These three assets centre around the pulmonary space and we are very motivated that these milestones have occurred against the backdrop of the ongoing COVID-19 pandemic. In that way, while we may have to contend with many challenges outside of the company, there are many opportunities within Insmed.

Insmed's first commercial product, ARIKAYCE®, is the first and only therapy approved in the US for the treatment of refractory MAC lung disease. How has the commercial launch been?

The most important element of any drug is whether it has a meaningful impact on patient outcomes. If you get that right, everything else takes care of itself. ARIKAYCE® received both the Breakthrough Therapy designation and the Fast Track designation, which is testament to the value that the FDA sees in our product.

In parallel, we devoted an extraordinary amount of time and energy to education and stakeholder engagement. For instance, we created a first-class patient support group, the Arikares Support Program, to ensure that the patient experience on the drug is positive and successful. We also made sure we got the messaging to physicians right.

At the end of the day, we had a really effective drug for a clear unmet medical need. When these two elements are present, the commercial launch tends to proceed quite smoothly, and that has been our experience with ARIKAYCE®. Refractory MAC lung disease is caused by the presence of MAC bacteria in patients' lungs. Our drug eradicates that bacteria in an unprecedentedly effective manner and protects patients from reinfection for a period of time. This is a huge advance in this area and for that reason, the market access world has been very supportive of this drug. Testament to that, we have not experienced significant issues in terms of pricing and reimbursement.

How is Insmed preparing for the international launch of ARIKAYCE®?

We have filed NDAs in both Europe and Japan and we are very excited to bring this drug to these regions, as well as other parts of the world. This is the first ever approved drug for this indication

and we are confident that it will be a very meaningful addition to the standard of care currently available. If all goes well, we expect to receive approval in Europe by end-2020 and in Japan by mid-2021.

Much like our commercial strategy in the US, we have invested a significant amount of time and resources into education and stakeholder engagement in Europe and Japan. We have had a modest presence in Europe for the past five years so that reflects our long-term commitment to that geography. We have built a very active market access program and already, there are hundreds of patients across countries like France, Germany, Italy, the Netherlands and the UK with access to ARIKAYCE® through the respective compassionate use programs in these countries.

Just last week, ARIKAYCE® was added to the new international treatment guidelines for NTM lung disease, issued by the American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA). This is extremely remarkable considering that ARIKAYCE® has yet to be approved in Europe and it speaks to the highly positive perception of its value and potential impact within the region.

I have personally been fortunate enough to live and work in Europe for around five years so I do appreciate the complexities of entering the European markets. The EU is really a tapestry of countries and certainly, there are challenges in launching a product in so many different countries simultaneously. What works in Germany might not work in France, and what works in Berlin might not even work in Bavaria! We had considered all options including the establishment of direct operations, the development of partnerships, and the formation of distributorships, but at the end of the day, we decided it was important for us to be directly present in Europe because this is a disease that is not well-understood with no industry participation apart from Insmed. We wanted to be physically on the ground leading the charge so that we can educate stakeholders on this disease and improve the treatment paradigm for patients. We must keep the compass needle pointed at patients. While it may be the first launch for Insmed in Europe and Japan, we have highly experienced people on the ground in these markets. We are committed to heavily resourcing our international operations so that we can entrust these operations to the experts on the ground.

We have also already set up distributorships in some other international markets including Israel and South Korea, and we will be expanding our international reach steadily. At the end of the day, if you have an effective drug that addresses significant unmet medical needs in a very impactful manner, I think many of the commercial challenges that companies sometimes face during the regulatory processes simply do not come into play.

How has COVID-19 disrupted Insmed's operations and how has the company responded accordingly?

Certainly, COVID-19 is one of those black swan events that have forced everyone to revisit our normal paradigms of engagement. In particular, it has really opened the eyes of people to the devastating impact MAC lung disease has on the lives of patients. This is an infection that constantly threatens to recur, debilitates sufferers, and isolates patients socially. The COVID situation has served as a moment of education for people to understand and sympathize with patients of this disease. All the physicians we have spoken to during this period have emphasized the importance of respiratory health.

On a practical level as a company, through our close relationships with pulmonologists, infectious diseases specialists and other healthcare practitioners, we were able to anticipate potential issues and act quickly. For instance, we grounded our US salesforce early because we were concerned about the risk of their infecting patients and caregivers as well as about the health of our own employees. At the same time, we are continuing to work closely with healthcare practitioners through remote engagement and other means to ensure that patients continue to receive the support they need during these challenging times.

Clinical operations have been challenging, especially in the area of respiratory diseases. We are looking to implement new solutions like remote access technology so that patients can be evaluated at home, reducing the risk of potential exposure. Nevertheless, our clinical timelines have thus far not been impeded by COVID-19.

In terms of supply chain, we are also in a good position. One of the lessons we have taken from the experiences – good and bad – of other pharma companies is the importance of supply chain security. I believe that once we have a drug approved, we have an intense obligation to ensure its uninterrupted supply for the patients that need it. Thus, we resource our supply chain heavily even before we receive approval. This means building inventory and incorporating redundancies to be prepared for any eventualities. We currently have three manufacturing facilities producing ARIKAYCE®: in Canada, the US and England. Our facility in England is actually our largest and most advanced facility, and we are currently in the process of securing approval for it, after which it would be ready to supply global needs.

Generally speaking, management in the era of COVID-19 is and will remain a challenge for all leaders. We will have to rethink the way we do business while ensuring that patients continue to

receive the support they need. Here, the learning and adoption curves are being pushed upon people and there remains a lot of uncertainty about how the world might look in six months.

At the same time, there is an interesting dynamic because the crisis also offers a sort of blank slate to reflect on new innovations for the industry. As an example, we recently surveyed a number of physicians on their needs during this period of time. We assumed that they would be so inundated with work that they would prefer some space from our therapeutic specialists and medical sales reps. In reality, a much higher percentage than before said they would like more frequent interactions with our medical sales reps in order to obtain specialized knowledge in the field of pulmonary medicine. It is precisely due to the pandemic that physicians need more knowledge and support from the industry.

In addition to ARIKAYCE®, Insmed's portfolio contains a number of other exciting assets, including brensocatib. What can we expect from your clinical programs moving forward?

Firstly, we are looking to expand ARIKAYCE® to all NTM indications with a post-approval confirmatory study in a front-line setting. We will commence this this year and we hope that ARIKAYCE® will become the new standard of care for the treatment of MAC lung disease.

Brensocatib is a DPP-1 inhibitor that breaks up the inflammatory cascade occurring within the lungs as a result of non-cystic fibrosis bronchiectasis (NCFBE). This is globally prevalent and currently has no approved treatment specifically for this indication in the US, Europe or Japan. Based on our most recent Phase II data, we believe brensocatib could have a game-changing impact on this disease state. We will start our Phase III program before the end of this year. We will be increasing our dialogue with the FDA moving forward and we believe that brensocatib is now a favourable candidate for the Priority Review designation.

At the same time, Professor James Chalmers at the University of Dundee in Scotland has also initiated a study to explore the potential of brensocatib for the treatment of COVID-19 patients. By end-2020 or mid-2021, we should know if brensocatib would have a role to play in the treatment of COVID-19 and we are hopeful. It feels good to be active in the fight against COVID-19.

Our third asset is treprostinil palmitil, a novel treatment candidate for PAH that has produced very positive results in animal models. It is currently set to enter Phase I trials and by the end of this summer, we will have enough preclinical data to compare against that of the existing PAH products

on the market. So far, the disease modification that we have seen in animal models is quite striking. We believe this asset has the potential to represent an important advance in the current standard of care for PAH.

You have emphasized Insmed's commitment to keeping the compass pointed at patients. How do you understand and promote this concept of patient-centricity within the company?

From my perspective, I believe that once we do the right thing for patients, the rest of the business takes care of itself. This means not only ensuring that patients receive access to our drugs but that their experiences with our drugs are as successful as possible. From that first principle, we need to foster good disease awareness, understanding, and support. This means talking and listening to patients. We hold town hall meetings every couple of weeks and we have invited patients as well as representatives from patient advocacy groups to share with our employees their experiences with the diseases they have. We need to stay close to the patient experience.

I always say to my team, imagine that, God forbid, someone in your family has a disease like MAC lung disease or PAH. The drugs we develop need to clear the standards you would personally set in order to feel confident delivering them to your own family member.

Being headquartered in New Jersey, USA can be a double-edged sword because on one hand, you have access to one of the most thriving and dynamic life sciences ecosystems in the world, and on the other hand, you have to compete with so many Big Pharma and biotech companies in terms of talent. How does Insmed navigate this challenge?

This is an evolving and ongoing challenge for us because the profile of Insmed has changed so dramatically over the years. When I joined in 2012, we had fewer than 40 employees but now we number nearly 500 with operations in the US, Europe and Japan. The kind of talent we look for has changed. At the same time, it goes back to the question of patient-centricity. We ask all our candidates what they are passionate about. We look for patient-centricity as one of the core drivers.

We also invite candidates to visit Insmed so that they can experience and understand our culture better. We have a very hands-off, autonomous culture. We want people to bring their talents here and use them in a self-directed manner for the best of the organization and in the service of

patients. We want our employees to take responsibility for their work. For instance, we do not have fixed vacation days. Our employees can take vacation days at their discretion with the support of their managers. During this COVID-19 period, I have told my staff that their first priority is to their families and their home situation because that is the only way for people to bring their best selves to work. I think these are little aspects that ripple through our corporate culture and ultimately attract the best talents to come work with us. Each and every time that happens, I consider Insmed very lucky to have these talented people within our organization.

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