InspirMed Highlights Encouraging Data on ISPM21 and ISPM19 – Inhalable Liposome Formulations of Antiviral Drugs for COVID-19

SOUTH SAN FRANCISCO, CA and TAIPEI, Taiwan – May 23, 2021 – InspirMed Inc., a subsidiary of TLC (Nasdaq: TLC, TWO: 4152) that specializes in the development of proprietary inhalable liposome formulation programs, recently presented data on the potential advantages of inhalable liposome formulations of antiviral drugs at the 23rd International Society for Aerosols in Medicine (ISAM) Congress. Pharmacokinetic studies on inhalable liposomal GS-441524 (named ISPM21) and inhalable liposomal hydroxychloroquine (named ISPM19) showed significantly higher concentrations in the lungs than their conventional counterparts, giving ISPM21 and ISPM19 potential as prophylaxis and/or treatment for COVID-19.

GS-441524 is main plasma metabolite of the antiviral prodrug remdesivir, which is approved in the US for the treatment of COVID-19. GS-441524 holds several advantages over remdesivir, with better safety and efficacy profiles. Remdesivir shows poor stability in blood and is subject to high liver extraction/bioactivation, resulting in hepatotoxicity. SARS-CoV-2 enters cells via the ACE2 protein on cell surfaces and preferentially infects type I / type II (AT1/2) pneumocytes, but remdesivir is metabolized by alveolar macrophages rather than AT1/2, making it poorly suited for delivery of active drug to cells critical in the pathogenesis of COVID-19. Administration of remdesivir requires cyclodextrin, a complex excipient cleared by the kidneys and associated with nephrotoxicity. In comparison, GS-441524 demonstrated similar or superior potency to remdesivir in SARS-CoV-2-infected cells, is bioactivated by enzymes that are highly expressed in AT1/2 cells, and demonstrated an excellent safety profile against human liver and kidney cells in vitro, suggesting feasibility of higher dosing without hepatotoxicity or nephrotoxicity.

GS-441524's favorable chemical properties – low molecular weight, greater hydrophilicity, greater localization to AT1/2 cells and ability to cross the blood-brain-barrier – make it a promising candidate as a therapeutic or prophylactic agent for COVID-19. However, the low oral bioavailability of GS-441524 means an extremely high oral dose would be required to achieve therapeutic levels. By encapsulating GS-441524 in an inhalable liposome formulation to make ISPM21, there is no need for the complex excipient cyclodextrin, thus eliminating nephrotoxicity, and targeted delivery by the inhalation of liposomes enables increased availability and prolonged exposure of the active drug in the lungs.

"We are pleased to participate in development of antiviral treatments in the fight against the COVID-19 pandemic by applying our proprietary lipid-based drug delivery platform towards the development of novel direct-acting antivirals," commented Dr. Keelung Hong, Founder, Chairman and CEO of TLC. "Because our inhalable liposome technology directly targets the disease site, we hope that our emerging therapeutics can improve upon current COVID-19 treatments."

At the ISAM Congress, which is currently in session (May 22-26) at the Boise Conference Center in Boise, Idaho, USA as well as virtually, members of InspirMed presented findings from two separate pharmacokinetic studies in rats on ISPM21 and ISPM19, respectively, as well as from a ISPM19 lung deposition study.

Highlights from the poster presentation are as follows:

- Intratracheally administered ISPM21 had a long half-life of 22.8 hours, with significantly higher concentrations (>200-fold) in the lung and comparable systemic exposure in the plasma compared to an equal dose of intravenously administered GS-441524 solution.
- At just 1% of the proposed oral dose of hydroxychloroquine to treat COVID-19, intratracheally administered ISPM19 had a longer half-life (~2.5-fold) and higher exposure in the lung (~30-fold) than intravenously administered free hydroxychloroquine.
- ISPM19 nebulized into an aerosol exhibited a lung deposition rate (inhaled dose) of 26.67%.
- InspirMed's proprietary inhalable liposome formulation programs can deliver antiviral drugs directly into the lung with sustained drug levels, potentially providing efficacy at drastically lower doses while avoiding systemic side effects.

The poster presentation can be accessed under "Publications" in the Pressroom section of TLC's website at www.tlcbio.com.

About ISPM21

ISPM21 is a proprietary inhalable liposome formulation of GS-441524, the active ingredient that reaches the lungs following administration of remdesivir. Originally indicated for the treatment of hepatitis, remdesivir has shown efficacy in inhibiting viral replication of the SARS-CoV-2 virus that causes COVID-19 and is approved by the US Food & Drug Administration (FDA) for the treatment of COVID-19 requiring hospitalization. GS-441524's favorable chemical properties – low molecular weight, greater hydrophilicity, greater localization to AT1/2 cells and ability to cross the blood-brain-barrier – make it a promising candidate as a therapeutic or prophylactic agent for COVID-19. However, the low oral bioavailability of GS-441524 means an extremely high oral dose would be required to achieve therapeutic levels. By encapsulating GS-441524 in an inhalable liposome formulation (ISPM21), there is no need for the complex excipient cyclodextrin, thus potentially eliminating nephrotoxicity, and targeted delivery by inhalation of liposomes enables increased availability and prolonged exposure of the active drug in the lungs.

About ISPM19

ISPM19, formerly known as TLC19, is a proprietary inhalable liposome formulation of hydroxychloroquine. Hydroxychloroquine has shown potential in prophylaxis and/or treatment for COVID-19 in *in vitro* and preliminary clinical trial studies, but orally administered hydroxychloroquine cannot reach therapeutic levels due to its dose-limiting toxicities. ISPM19 utilizes ~1% of the highest oral hydroxychloroquine dose tested and delivers the drug directly to the airways and lungs, potentially avoiding systemic toxicities while providing a sustained effective concentration at the primary site of infection. ISPM19 is designed to be cost-effective, easily accessible and can be self-administered with a portable nebulizer. A Phase 1 randomized, vehicle-controlled, blinded study to assess the safety, tolerability, and pharmacokinetics of ascending doses of inhaled ISPM19 in healthy volunteer subjects is ongoing.

About InspirMed

InspirMed is a subsidiary of TLC specializing in the development of inhalable liposome formulation programs for severe acute and chronic pulmonary diseases. TLC (NASDAQ: TLC, TWO: 4152) is a clinical-stage, specialty pharmaceutical company dedicated to the research and development of novel nanomedicines that maximize the potential of its proprietary lipid-assembled drug delivery platform (LipAD™), including BioSeizer® sustained release technology and NanoX™ active drug loading technology, which are versatile in the choice of active pharmaceutical ingredients and scalable in manufacturing.

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