Development and inhalation properties of Amikacin Liposome Inhalation Suspension (ALIS) for treatment of Mycobacterium avium complex (MAC) lung infections

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In some serious lung infections, including nontuberculous mycobacterial (NTM) lung infections, the bacteria can invade and multiply intracellularly within macrophages. The presence of an intracellular pathogen can make it more difficult for inhaled antibiotics to be effective if the drug is unable to access the intracellular compartment to an adequate extent. When non-liposomal amikacin is delivered via inhalation, the drug concentration in the lung falls significantly over the 24-hour period due to clearance and absorption from the lung [1]. The development of resistance may result when the drug concentrations fall below the pathogen's minimum inhibitory concentration (MIC).

In preclinical studies, an inhaled liposomal formulation of amikacin (ALIS) provided a sustained drug presence in the lung and attained higher drug concentrations within the macrophages over the same 24-hour period [1]. It is believed that macrophages, as part of their natural 'clearance' function, recognize and phagocytize foreign particulates like liposomes, resulting in high drug concentrations near the pathogens [2]. Therefore, the particle nature of the liposomes is key to the effect of ALIS. Furthermore, focused delivery of ALIS to the lung minimized systemic exposure to other organs.

In order to develop an inhaled liposomal product like ALIS, many technical hurdles had to be overcome [2]. Compared to other inhalation products like steroids and bronchodilators, inhaled antibiotics require much higher drug doses. The challenge is thus how to design a liposome composition that maximizes the amount of encapsulated drug and minimizes the amount of lipid excipients. Additionally, liposomes experience high shear forces and increased exposure to the air-liquid interface during nebulization with the potential to lose a portion of encapsulated drug [2]. Thus, a liposomal composition must be selected to achieve the proper balance of free and encapsulated drug after nebulization. A further requirement is to minimize the nebulization time. This can be accomplished by increasing the liposomal drug concentration in a reduced volume of fluid. However, there may be a tradeoff if the higher suspension concentrations result in slower rates of nebulization. Finally, the aerosol droplet size distribution should be within the respirable range.

This presentation describes the development of ALIS. High encapsulation of amikacin in the liposomal formulation of ALIS is achieved by a 2-stream ethanol infusion method; essentially a stream of the lipid in ethanol solution is rapidly combined with a stream of drug in aqueous medium promoting vesicle formation with high encapsulation efficiency. The process conditions were optimized resulting in a liposomal formulation with an average liposome size of ~300 nm containing ~70 mg/ml amikacin with a lipid to drug weight ratio of ~0.7.

During early development, all commercially available mesh-based ultrasonic nebulizers were tested with ALIS and only the PARI eFlow nebulizer met the target drug delivery rate. Insmed in partnership with PARI optimized the device further resulting in the proprietary LAMIRA™ nebulizer (PARI Pharma GmbH). One dose of ~8.4 mL ALIS (70 mg/mL, 590 mg dose) can be nebulized in approximately 14-20 minutes. The aerosol properties have been characterized using an Anderson Cascade Impactor (ACI) demonstrating that the aerosol droplet size is in the respirable range and the percent of associated amikacin after nebulization, liposome size and the lipid to drug ratio are consistent across the different size aerosol droplets collected on stages 1 to 5 of the ACI.

The ALIS/LAMIRA drug/device combination product received U.S. Food and Drug Administration (FDA) accelerated approval on September 28th, 2018 under a New Drug Application. ALIS is not approved in the European Union.

References:

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2. Cipolla, D., Gonda, I., Chan, H.-K., 2013. Liposomal formulations for inhalation. *Therapeutic Delivery*. 4, 1047-1072