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August 21, 2018

Sumathi Nambiar, MD, MPH
Director, Division of Anti-Infective Products
U.S. Food & Drug Administration
10903 New Hampshire Avenue, Bldg. W022, Rm. 6236
Silver Spring, MD 20993

Dear Dr. Nambiar,

We write collectively as an interested and highly vested group of experts and advocates in pulmonary nontuberculous mycobacterial disease (PNTM) in support of an FDA decision to grant accelerated approval of amikacin liposome inhalation suspension (ALIS). Our group includes patient advocates as well as scientists and clinicians with expertise in PNTM disease, comorbidities, microbiology, treatment, patient care, and natural history, as well as the performance and interpretation of clinical trials for PNTM.

The Antimicrobial Drugs Advisory Committee (AMDAC) meeting convened on August 7, 2018 included briefing documents and extensive discussion regarding the value of the selected primary endpoint in Study 212, conversion to negative sputum for three consecutive months, as well as the secondary endpoints of the study.

It is remarkable that a new treatment option with a more acceptable safety profile may soon be available to patients with pulmonary MAC infections which have not responded well to the standard multidrug regimen. For decades, amikacin and many other antibiotics have been used to treat PNTM, often despite their poor safety profiles, without the benefit of double-blind, placebo-controlled trials studies to demonstrate that these drugs do, in fact, act *in vivo* to treat this disease.

Conversion of sputum to culture negative is the stated goal in the ATS/IDSA Statement developed to address the diagnosis and treatment of nontuberculous mycobacterial infection. These guidelines were developed by a group of 16 experts who collectively have more than 550 years of experience in this field. They selected the microbiologic goal understanding that the patient likely will not feel better until the infection is treated, and therapy halted as a result of successful treatment. Given the expertise that has gone into determining this as a desired outcome of treatment, it seems prudent to acknowledge that the authors of these guidelines have the most experience in making this determination.

Insmed's clinical trial demonstrated two key findings: 1) amikacin has efficacy in the treatment on NTM; and 2) the inhaled liposomal formulation has a better safety profile. To compare it to standard inhaled or IV amikacin in a clinical trial, knowing that standard amikacin has a poor safety profile and adverse impact on patient health, would present significant ethical issues.

Culture conversion is a holy grail of therapeutic development for NTM, and to achieve it in a clinical trial setting hails a breakthrough clinicians, researchers, and patients have long awaited. It is solid evidence, gathered in a scientifically sound manner, that a drug used in one of the standard regimens to treat PNTM disease is effective.

ALIS is now the first drug to have undergone a clinical trial on PNTM disease with the ultimate goal of FDA approval for the indication of treating the disease. There are two dozen or more anti-infective products that may be used in the treatment of PNTM, but all are off-label. There are no comparative studies between different therapies because there are no approved therapies to compare it to, making the microbiologic endpoint a logical goal.

Because PNTM requires a multi-drug regimen for an extended period of time, secondary endpoints are difficult to determine at this point as well. Many of these drugs have harsh side effects which, like the disease itself, often make the patients feel unwell. Cancer patients are not expected to feel well while on chemotherapy; it is unreasonable to expect PNTM patients to feel well while they are on treatment for their disease. Any quality of life measures or other clinical endpoints such as a six-minute walk test (6MWT) would likely need to be measured outside the timeframe of the clinical trial for truly accurate comparative data.

The many challenges presented in designing the clinical trials for ALIS highlight the complexity of them. Every new study, however, yields more data which gives us more insight into this problem and will eventually point to answers to these and other issues which we have been asking about for so long.

Insmed, as a pioneer in this field, has met these challenges and has soundly demonstrated that their product is an effective treatment for pulmonary *M. avium* complex infections. We urge the FDA to approve this therapy as the first safe and effective treatment for refractory MAC infections, in the hope that this and many other therapies will become available to help reduce the burden of pulmonary NTM disease.

Sincerely,

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