RESIST-TB:

Research Excellence to Stop TB Resistance

STATEMENT TO THE FDA **December 28, 2012**

We thank the Anti-Infective Drugs Advisory Committee for this opportunity to give a statement. RESIST-TB is a global organization of concerned patients, physicians, research scientists and stakeholders charged with promoting and conducting clinical research to cure and prevent drug-resistant tuberculosis. We are committed to addressing the substantial existing gaps in knowledge on—and facilitating access to—effective treatment for and prevention of drug-resistant tuberculosis.

The worldwide MDR-TB situation is becoming increasingly dire. The 2012 report from the WHO estimated that over 310,000 new cases of MDR-TB occurred in 2011. In some parts of the world (most notably in parts of Eastern Europe), MDR-TB constitutes more than 25 percent of new TB cases, and more than 50 percent of retreatment cases. Current treatments for MDR-TB are successful in roughly 60% of patients; success is even rarer among many important subgroups. Death occurs among as many as 20% of those in whom treatment is unsuccessful. Additional, acquired resistance, which requires longer and costlier treatment, is common among individuals who are not cured. Fewer than 5% of patients with MDR-TB are estimated to receive treatment of known quality each year, in part because of the difficulty in monitoring and delivery expensive and toxic regimens of long duration.

Based on the published evidence from the Phase II studies, we conclude that bedaquiline could contribute to significantly-improved interim and long-term outcomes. This is very encouraging news. Bedaquiline would be the first drug approved with a specific indication for MDR-TB and the first new TB drug class approved in over four decades. Approval of bedaquiline would signal to drug developers that there is regulatory support for improved anti-tuberculosis drugs and regimens. We hope that, after review of the additional information that has been provided to you, you concur with this assessment.

Fast-track approval of bedaqualine for the treatment of MDR-TB is an important first step in improving treatment options and outcomes. It will also allow for important clinical studies aimed at identifying optimal regimens of existing or other new drugs for the treatment of MDR-TB. These studies need to determine the best combinations of drugs and clarify the role of new drugs within the armamentarium for MDR-TB. Importantly, these studies need to be conducted in a range of populations showing various background resistance patterns, and should consider taking into account variables such as age, extent of disease, cavitation, and concomitant disease. The possible association of HIV with MDR-TB and XDR-TB indicates the importance of taking HIV infection into account when conducting such trials and considering the potential interactions between the various MDR-TB drugs and antiretrovirals. Numerous clinical trials are needed to assess the effectiveness of standardized or individualized MDR-TB regimens, as well as to evaluate the efficacy of new candidate drugs. The critical areas of investigation are the optimal duration and composition of the “intensive” phase, shortening treatment duration, decreasing the toxicity of drugs, drug-drug interactions, and reducing secondary spread of DR-TB.

The Steering Committee of RESIST-TB supports the approval of bedaquiline. We urge the FDA to negotiate with the sponsor to assure that the company performs and publishes PK studies of

bedaquiline in children, creates pediatric formulations of the drug, and further studies the interactions of bedaquiline with commonly-used antiretrovirals; in all these efforts, bedaquiline should be part of a multidrug regimen, delivered for sufficient duration to assure sustained cure. The FDA should also promote closer monitoring of long-term safety and tolerability and require studies that investigate the efficacy of bedaquiline in combination with other agents, in optimized background regimens. All these undertakings could be part of the follow-up program that accompanies “accelerated” approval.

FDA’s open and transparent evaluation of this application will be of great value to the global community as well as to the U.S., and will reflect positively on the regulatory process and the agency.