



Data on Investigational Drug TMC207 for Treatment of MDR-Tuberculosis, Published in New England Journal of Medicine

Clinical Activity Of TMC207 shows ATP-Synthase is a Viable Target for treatment of TB

[Mechelen Belgium, June 3, 2009] -Interim results from an ongoing phase 2, randomized, placebo-controlled trial of the investigational drug TMC207 for the treatment of multidrug-resistant tuberculosis (MDR-TB) were published in the New England Journal of Medicine today. TMC207 is being developed by Tibotec BVBA. The data show that the addition of TMC207 for eight weeks to a 5-drug background regimen, in patients with multidrug-resistant tuberculosis (MDR-TB), resulted in a significant increase in the proportion of patients achieving a negative sputum culture and a shorter time to sputum culture conversion compared with the background regimen alone.

"The results of this study are highly encouraging news for the treatment of tuberculosis," said Peter Donald M.D., Professor Emeritus, Stellenbosch University in Capetown, South Africa. "Not only is this an agent with a radically different means of action, but it shows potential to shorten the treatment of tuberculosis in the foreseeable future, something the tuberculosis community has been hoping for years."

Treatment of TB is protracted and burdensome. MDR-TB is currently responsible for an estimated 490,000 incident cases of TB and 110,000 fatalities worldwide each year¹. MDR-TB requires extended treatment for at least 18 months with second-line drugs that are less effective and associated with more side effects than first line regimens². This underscores the need for effective drugs with the potential to shorten and improve MDR-TB treatment outcomes.

TMC207 is being investigated as part of a combination therapy for the treatment of MDR-TB. The results reported are from the first stage of a two-stage Phase II randomized placebo-controlled trial. Forty-seven hospitalized patients with newly diagnosed multidrug-resistant pulmonary TB were randomized to receive TMC207 (400 mg daily for 2 weeks, followed by 200 mg three-times weekly for 6 weeks) (n=23) or placebo (n=24) in combination with a standardized 5-drug background second-line antituberculosis regimen. Six subjects (3 in each treatment group), discontinued the study prematurely. This first stage was conducted in South Africa, where the prevalence of MDR-TB is particularly high.

The results of bacterial culture of sputum showed more patients were TB culture-negative at 8 weeks in the TMC207 group, 47.6% versus 8.7% in the placebo group. In addition TMC207 reduced the time to culture conversion. The probability of becoming culture negative on any given day within the 8-week treatment period was 11.8 times higher in the TMC207 group, versus in the background regimen alone hazards ratio (95% CI): 11.8 (2.26, 61.3); p=0.003 by Cox regression analysis. Mean sputum colony-forming units (CFU) count declined more rapidly in the TMC207 than in the placebo group. Most adverse events were mild to moderate and only nausea occurred more frequently with TMC207 than with placebo (26% vs. 4 %). One subject in each treatment group experienced a serious adverse event, neither of which was considered to be related to the study medication. The data obtained validate ATP synthase as a viable target for the treatment of TB.

"The nearly half a million estimated new cases of MDR-TB annually highlights the urgent need for a paradigm shift in the way this disease is being tackled," said Roger Pomerantz, President, Tibotec Research & Development. "The development of TMC207 is a tribute to the dedication of our scientists, to innovation and to the commitment of our company to accelerating the development of new drug regimens for tuberculosis."

TMC207 is a diarylquinoline that offers a novel mechanism of action by specifically inhibiting mycobacterial ATP-synthase³, responsible for the cell's energy production. In vitro, TMC207 potently inhibits both drug-sensitive and drug-resistant *M. tuberculosis* isolates and is bactericidal against both actively replicating tubercle bacilli and non-replicating bacilli⁴. The safety and efficacy of TMC207 are being further evaluated in ongoing and future trials.

The second stage of the study, which will evaluate efficacy following 24 weeks of treatment, is currently ongoing with active recruitment in South Africa, Peru, Latvia and Russia. Results from the second stage of the study are expected to be available in 2010.

About Tibotec

Tibotec BVBA, based in Mechelen, Belgium, is a pharmaceutical research and development company, with offices in Yardley, PA and Co Cork, Ireland. Tibotec is dedicated to the discovery and development of innovative HIV/AIDS drugs and anti-infectives for diseases of high unmet medical need.

Tibotec BVBA is a subsidiary of Johnson & Johnson

1 World Health Organization. Global tuberculosis control: surveillance, planning, financing. Geneva, WHO, 2007

2 Matteelli A, Migliori GB, Cirillo D, Centis R, Girard E, Raviglioni M. Multidrug-resistant and extensively drug-resistant Mycobacterium tuberculosis: epidemiology and control. Expert Rev Anti Infect Ther 2007; 5: 857-71

3 Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science 2005; 307: 223-7

4 Koul A, Vranckx L, Dendouga N, et al. Diarylquinolines are bactericidal for dormant mycobacteria as a result of disturbed homeostasis. J Biol Chem 2008; volume 283, number 37, pages: 25273-80

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