Population Pharmacokinetics of AZD-5847 in Adults with Tuberculosis

Abdullah Alsultan1,2, Jennifer J. Furin3, Jeannine Du Bois4, Elana van Brakel5, Phalkun Chheng3, Amour Venter3, Bonnie Thiel3, Sara A. Debanne6, W. Henry Boom3, Andreas H. Diacon4,5, and John L. Johnson3, Charles A. Peloquin2

1King Saud University College of Pharmacy, 2University of Florida College of Pharmacy, 3Tuberculosis Research Unit, Case Western Reserve University, 4TASK Applied Science, 5MRC Centre for Tuberculosis Research, 6Department of Epidemiology and Biostatistics, Case Western Reserve University

Objective: AZD-5847 is an oxazolidinone derivative being developed for the treatment of tuberculosis (TB). A phase II trial to evaluate its pharmacokinetics and early bactericidal activity in adults with pulmonary TB was recently completed. We developed a population pharmacokinetic (PK) model for AZD-5847 using data from patients in this phase 2 study.

Methods: The study included 60 adults with newly-diagnosed, drug-susceptible TB. Patients were randomized to four treatment arms - 500 mg once daily, 500 mg twice daily, 800 mg twice daily or 1200 mg once daily. PK sampling occurred on day 1 and 14. Blood samples were collected at 0, 1, 2, 3, 4, 5, 6, 8, 12, 13, 15, 16, 17, 18, 20 and 24 hours.

Results: A total of 1723 samples were used for the analysis. A two compartment model with linear elimination and Tlag for absorption adequately described the data. AZD-5847 showed non-linear absorption likely due to saturable absorption. Bioavailability started to decrease at the 800 mg daily dose and was 67% at the 1200 mg dose. Typical values (relative standard error %) for Tlag, Ka, Cl, V1, Q and V2 were 0.27 hours (18%), 0.38 hour⁻¹(9%), 7.96 L/hour (3%), 43.3 L (7%), 8.9 L/hour (13%) and 31.9 L (9%). The coefficient of variation (relative standard error %) for Tlag, Ka, Cl, V1, Q and V2 were 68.6% (22%), 21.6% (19%), 22% (10%), 14.9% (36%), 47.1% (28%), 55.6% (13%). The figure below shows the typical PK profile for AZD-5847 at steady state.

Conclusion: AZD-5847 shows biphasic elimination. Absorption of AZD-5847 is nonlinear and administering doses above 800 mg might not be beneficial.