Application of Ramucirumab Exposure-Response Modeling to Support Dose Selection for Post Marketing Studies in Patients with Gastric Cancer

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**Objectives:** Cyramza® (ramucirumab) as a single agent, or in combination with paclitaxel, is indicated globally for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma. The approved dose in patients with gastric cancer is 8 mg/kg every two weeks, which has shown to be safe and effective. This analysis was performed to assess the relationship between ramucirumab exposure and measures of efficacy in this patient population, and to evaluate alternative dosing regimens for post marketing commitment studies.

**Methods:** A total of 335 placebo and 321 ramucirumab treated patients from the Phase 3 RAINBOW study were included in the exposure-response analysis. Estimates of exposure (C_{min,ss}) for treated patients were generated using post hoc estimates from an established population pharmacokinetic model previously developed from a pooled analysis of 8 Phase 1/1b, 2, and 3 studies in a variety of cancer indications. Parametric time to event models for overall survival (OS) and progression-free survival (PFS) were subsequently developed, incorporating predicted exposure and patient factors found to be significant. A series of simulations were performed to evaluate the impact of higher dosing regimens on ramucirumab exposure and efficacy.

**Results:** A combined Weibull and Gompertz model was found to best describe the hazard for both OS and PFS. EC50 based on an 8 mg/kg dose in gastric patients was estimated to be approximately 50µg/mL. Increase in ramucirumab exposure was associated with improvement in efficacy in terms of both OS and PFS.

**Conclusions:** Higher doses of ramucirumab are predicted to produce greater C_{min,ss} that may be associated with longer survival. Alternative doses and dosing regimens in patients with advanced gastric cancer are currently being evaluated in ongoing clinical trials.