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## A Phase I/II Study of TKM-080301, a RNAi Therapeutic Directed Against Polo-Like Kinase 1 (PLK1), in Patients with Gastrointestinal Neuroendocrine Tumors (GI-NET)

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**Background:** Polo-like kinase 1 (PLK1) regulates multiple critical aspects of cell progression, is highly expressed in many human tumors, and correlates negatively with patient outcome. TKM-080301 is a lipid nanoparticle formulation of a small interfering RNA (siRNA) directed against PLK1, a serine/threonine kinase that regulates multiple critical aspects of cell cycle progression and mitosis.

**Methods:** The previously reported dose escalation portion of this phase I/II open-label study supported a maximum tolerated dose (MTD) of 0.75 mg/kg/week. The study included an initial expansion cohort at the MTD in subjects with advanced solid tumors, and subsequent expansion cohorts in

subjects with adrenocortical carcinoma (ACC) and GI-NET. TKM-080301 was administered as a 30-minute IV infusion on Days 1, 8, and 15 of a 28-day cycle. Disease response according to RECIST 1.1 criteria was assessed following every two cycles of treatment.

**Results:** Fifteen previously treated subjects with GI-NET received TKM-080301; one subject was enrolled during the dose escalation phase and received two doses at 0.9 mg/kg and subsequently 0.6 mg/kg, one subject was enrolled during the initial expansion cohort at 0.75 mg/kg, the remaining 13 subjects were enrolled in the GI-NET expansion cohort at 0.75 mg/kg. In 13 GI-NET subjects who were evaluable, the best response observed was partial response (PR) for one subject (>60% reduction in tumor) and stable disease (SD) for 11 subjects (duration 1-52 weeks). Overall, 7/13 (54%) of subjects showed a best response of decrease in target tumor size (2.8% to 61%).
The most common adverse events were: chills, nausea, vomiting, pyrexia, hypertension, fatigue, and increased AST. Serious adverse events considered at least possibly related to TKM-080301 were observed for three subjects in total included myocardial infarction (2 subjects), atrial fibrillation, and pulmonary edema.

**Conclusion:** This first-in-human trial indicates TKM-080301 was generally well-tolerated by the majority of subjects. In addition, promising evidence of anti-tumor effect has been observed in GI-NET.