Phase I, Multi-center, Open-label, Dose-escalation Study of Pasireotide LAR (PAS) in Patients With Advanced Neuroendocrine Tumors (NET)

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Background: Pasireotide, a novel somatostatin analog, has been previously investigated but the maximum tolerated dose (MTD) has not been determined in pts with advanced NET. We report results of a planned interim analysis of a phase I dose-escalation (DE) study to determine the MTD, characterize safety, tolerability, PK, and efficacy trends in pts with advanced NET.

Methods: Pts were enrolled in 2 phases: DE phase at a starting dose of 80mg PAS i.m. followed by a dose expansion (DX) phase. Associations between PK parameters and clinical outcomes were evaluated using regression analysis. Bradycardia is defined as heart rate < 40 bpm.

Results: As of July-2015, 29 pts (15, DE; 14, DX) were treated with 80 mg (13pts) and 120 mg (16pts) doses. No protocol defined dose-limiting toxicities were observed in the study; however in a post hoc analysis a higher incidence of bradycardia was seen with 120 mg (31.3%) vs 80 mg (0%). Treatment discontinuations (Table) were primarily due to disease progression (44.8%) or adverse events (AEs; 27.6%). In the PK analysis, probability of bradycardia showed a moderate increase with increasing PAS concentration that was not statistically significant [Odds ratio for every 1.5x increase (95% CI): daytime, 1.672 (0.381-7.338); nighttime, 2.024 (0.494-8.292)]. No significant association was observed between PAS concentrations and glucagon levels. Two partial radiographic responses (PRs) were observed, both in the 120mg dose. PAS concentrations correlated with % tumor shrinkage although the association was not statistically significant (P = 0.08). The most common AEs are listed in the Table 1.

Conclusion: MTD was defined at 120 mg for PAS in pts with advanced NET. Although objective radiographic responses are rarely observed with SSA, 2 PRs were observed among 16 pts in the 120mg cohort. Bradycardia appears to be a dose-limiting effect; however the mechanism and clinical significance are uncertain.

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Table 1:

	PAS 80 mg	PAS 120 mg
Treatment discontinuations	92.3%	75.0%
Most common AEs (all grade)		
Hyperglycemia	76.9%	81.3%
Fatigue	53.8%	50.0%
Nausea	53.8%	31.3%