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Elevated Levels of 5-HIAA and CgA in Patients with Pancreatic Neuroendocrine Tumors (PanNETs): Analyses from the CLARINET Study

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BACKGROUND: While carcinoids frequently synthesize and secrete serotonin into the circulation and 5-HIAA is a common biomarker for carcinoids, 5-HIAA measurement in non-carcinoid PanNET patients (ie, no hormone-related symptoms or non-functional) is not routinely recommended. Underestimation of the incidence of serotonin-producing PanNETs may impact clinical outcomes when serotonin levels remain elevated. This analysis was conducted to characterize 5-HIAA and CgA levels in PanNET patients from the phase 3, placebo-controlled CLARINET study.

METHODS: Evaluable centrally-assessed data for urinary 5-HIAA and plasma CgA from CLARINET PanNET patients (baseline and every 12 weeks through Week 96) were analyzed. Biochemical response for urinary 5-HIAA and plasma CgA was defined as $\geq 50\%$ decrease from baseline. Upper limit of normal (ULN) was defined as 41.6 $\mu\text{mol/d}$ for 5-HIAA and 98.1 $\mu\text{g/L}$ for CgA. Changes in urinary 5-HIAA and plasma CgA levels were calculated using a non-parametric Wilcoxon 2-sample test.

RESULTS: 91/204 patients had PanNETs, and evaluable data for urinary 5-HIAA and plasma CgA were available in 79 and 88 patients, respectively. Elevated (>ULN) levels of urinary 5-HIAA were detected in 21/79 (27%) PanNET patients, and of these, biochemical response was achieved in 85% (11/13) of lanreotide-treated patients vs 63% (5/8) of placebo-treated patients at last available value (P=0.33). A total of 63/88 (72%) patients had elevated plasma CgA values, and biochemical response was achieved in 66% (19/29) of lanreotide-treated vs 18% (6/34) of placebo-treated patients (P=0.0002). Limited sample sizes may have precluded robust analysis for detection of statistically significant differences in biochemical response.

CONCLUSION: The percentage of patients with elevated urinary 5-HIAA was unexpected and may indicate a need for re-examination of PanNETs and serotonin secretion. The potential of 5-HIAA and CgA as biomarkers of response and follow-up in non-functioning PanNETs is alluring; however, further studies are necessary.