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Results from the Phase 1, Randomized, Open-Label, Cross-Over Study to Evaluate Pharmacokinetics of Three Escalating Doses of Oral Octreotide Capsules

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BACKGROUND

Oral octreotide capsules (OOC) are approved in the United Sates for long-term maintenance treatment in acromegaly patients who have previously responded to and tolerated injectable somatostatin analogs (SSAs, octreotide or lanreotide). Injectable SSAs are also approved and the standard of care in the treatment of carcinoid syndrome associated with neuroendocrine tumors (NET). Compared with acromegaly, patients with NET can require higher average doses of injectable SSAs to achieve adequate symptom control. Prior Phase 1 studies showed the comparability of 20 mg OOC to 0.1 mg Sandostatin SC. Here, single OOC doses up to 80 mg were assessed in healthy subjects for bioavailability, dose proportionality, safety and tolerability.

METHODS

Thirty subjects entered an open-label, six-sequence, 3 period cross-over Phase 1 study. Single doses of OOC (20 mg, 60 mg and 80 mg) were administered during the treatment phase. For each treatment period, subjects received a single dose of 1 of the 3 treatments on Days 1, 3 and 5. During each treatment period, serial blood samples for determination of octreotide plasma concentrations were collected pre-dose and through 24-hours following each dose. Approximately 7 days following completion of the last treatment period, subjects returned to undergo safety assessments.

RESULTS

There was a dose-related increase in the geometric mean (gMean) plasma concentrations of octreotide, the gMean values for C_{max}, and the AUCs after administration of 20 mg, 60 mg, and 80 mg. Power model exponents ranged from 0.73 (C_{max}) to 1.0 for $AUC_{0\text{-}inf}$. The 95% confidence intervals for the exponents for all 3 parameters included 1.0, suggesting dose proportionality. Eighteen subjects (18/30, 60%) experienced at least 1 treatment-related treatment-emergent adverse event (TEAE). The most common treatment-related TEAEs were diarrhea, abdominal pain, and nausea. All events were recovered/resolved. No TEAEs were assessed as severe in intensity and there were no serious adverse events.

CONCLUSIONS

This study demonstrates that doses of OOC up to 80 mg result in dose proportionality with a favorable safety profile, consistent with somatostatin analogs. The results showed that the exposure of 60 mg OOC twice daily should be comparable to 0.6 mg/day of Sandostatin SC (the highest recommended initial SC octreotide dose per US labeling). These results are consistent with a prior pharmacokinetics study undertaken with these higher doses (20 mg, 60 mg and 80 mg) and are comparable with data for injectable SSAs. The data supports dosing requirements for the planned Phase 3 study in patients with carcinoid syndrome associated with NET.

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