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Bayesian Adaptive Study Design for Efficient Dose Finding for an Octreotide Implant in Patients with Carcinoid Syndrome (CS)

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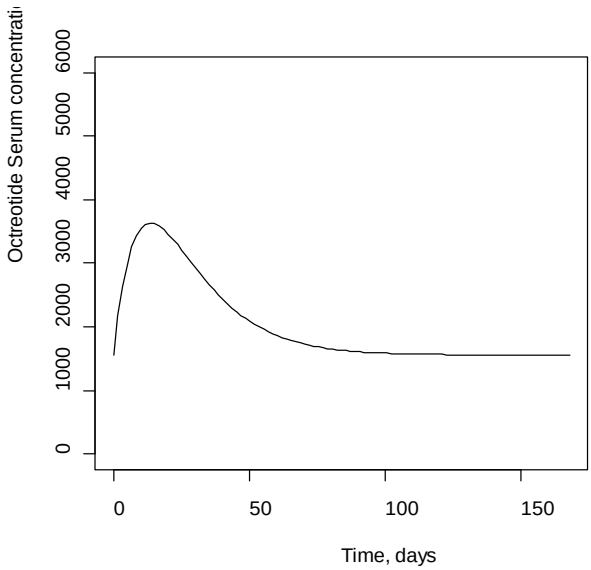
Background: Endo is developing a diffusion-controlled reservoir drug delivery system (implant) designed to deliver octreotide continuously for at least 6 months following subcutaneous implantation. The safety and tolerability of the octreotide implant has been studied in patients with acromegaly. This is the first study to evaluate the implant in patients with CS. Bayesian adaptive design was incorporated into this study to allow efficient dose escalation and minimizing exposure of patients to sub-optimal doses.

Methodology: A PK model was built using published data from octreotide and data from implant studies in acromegalics. The model incorporated the observation that clearance of octreotide appears to be higher in the acromegalic than in the CS population and allowed the prediction of C_{max} and C_{trough} (day 168) based on all accumulated data. The rules for dose escalation were based on the precisions of the estimated C_{max} and C_{trough}, the acceptable C_{max}, the desired C_{trough} as well as safety and tolerability considerations. The study includes two cohorts of up to 10 patients each, with the first cohort to receive a single 117 mg octreotide implant and the second to receive 2 implants. Each cohort will be followed for 6 to 9 months, but dose escalation will be based on at least 5 patients in cohort 1 observed for at least 56 days.

Results: Seven patients in cohort 1 contributed PK data to day 14, 5 had data to day 56, and 3 had data to day 112. The model was updated (shown on the following page) using the available PK data, and satisfied both the predefined precision and concentration limits.



Conclusion: Based on these results, recruitment of the second cohort has been initiated. Using this type of approach may allow accurate assessment of pharmacokinetic profiles with fewer patients per cohort.