Congenital hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in neonates, infants, and children, and is caused by genetic mutations in the insulin secretion pathway in pancreatic beta-cells. Current medical and surgical treatments are often highly burdensome, only partially effective, and associated with significant morbidity. CRN04777 is a potent orally bioavailable SST5 agonist (EC50 = 0.41 nM) that is >1300 fold selective over other SST receptor subtypes. CRN04777 has been shown to suppress both glucose- and sulfonylurea (SU)-induced insulin secretion in rats. The latter is a model for the most common known monogenic form of human congenital HI.

We report initial results from a randomized, double-blinded, placebo-controlled single ascending dose study evaluating the safety, pharmacokinetics and pharmacodynamics of CRN04777 in 74 healthy volunteers. Endogenous insulin secretion was stimulated using intravenous glucose tolerance tests (IVGTT) or SU challenges in separate cohorts of volunteers. In the IVGTT cohorts, single doses of CRN04777 (0.5-120 mg) were administered after an overnight fast and 1 hour prior to an IV bolus of 300 mg/kg glucose, followed by serial measurements of blood glucose and insulin over 180 minutes. The SU-challenge cohorts received single doses of CRN04777 (30 and 60 mg) one hour after SU administration (5 mg of glibenclamide/glyburide), followed by measurement of the IV glucose infusion rate (GIR) over 8 hours under automated euglycemic clamp conditions (ClampArt®).

CRN04777 was orally absorbed (Tmax 1-3 hours) and demonstrated a dose dependent increase in systemic exposures with an apparent terminal elimination t1/2 of approximately 40 hours. Basal insulin secretion was reduced dose-dependently, with a 73% reduction following 120 mg of CRN04777. Likewise, glucose stimulated insulin secretion during the IVGTT (plasma insulin AUC) was reduced dose-dependently by approximately 50% with a parallel doubling of plasma glucose AUC following 120 mg of CRN04777. CRN04777 resulted in dose-dependent reversal of SU-induced insulin secretion, with 79% and 90% reductions in insulin AUC5-180min, respectively, at 30 and 60 mg doses. At the 60 mg dose of CRN04777, no exogenous glucose infusion was needed to prevent SU-induced hypoglycemia.

CRN04777 was well tolerated across the dose range evaluated. All adverse events (AEs) were considered mild or moderate and there were no serious AEs.
The data from this single-dose, proof-of-concept study show that the selective SST5 agonist CRN04777 is well tolerated after oral administration in healthy volunteers, is suitable for once daily dosing and suppresses insulin secretion under basal and stimulated conditions, including in a pharmacologic model of congenital HI. Multiple ascending dose evaluations in healthy volunteers are underway to support future studies in congenital HI patients.

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