CRN04777 an Oral, Nonpeptide SST5-Selective Somatostatin Agonist Dose Dependently Suppresses Basal and Stimulated Insulin Secretion

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BACKGROUND

- Pathophysiology of congenital hyperinsulinism (HI)
  - Most common cause of hypoglycemia in neonates, infants and children
  - Mutations within the pancreatic beta-cell result in excess insulin secretion
  - Current treatments are limited, highly burdensome, and not effective in all patients
  - SST5 receptor activation inhibits insulin secretion downstream of known beta-cell mutations
  - CRN04777 acting at the SST5 receptor is the only oral therapy with the potential to suppress insulin secretion in patients with congenital HI regardless of the genetic cause

METHODS

- CRN04777 oral dosing in 80 healthy volunteers
  - Single ascending (0.5-120 mg; 6 active: 2 Pbo)
  - Multiple ascending (30-120 mg x10d; 6 active: 3 Pbo)
- Evaluate safety, tolerability, and pharmacokinetics
- Pharmacodynamic assessments
  - Intravenous glucose tolerance test (IVGTT)
  - Sulfonylurea (SU) challenge

SAFETY

Single and multiple doses up to 120mg are well tolerated with no discontinuations or modifications

INTRAVENOUS GLUCOSE TOLERANCE TEST

CRN04777 dose-dependently suppressed glucose stimulated insulin secretion

SULFONYLUREA CHALLENGE: PHARMACOLOGIC MODEL OF CONGENITAL HI

SST5 agonism by CRN04777 dose-dependently reversed sulfonylurea induced insulin secretion

CONCLUSION

Crinetics Pharmaceuticals has developed oral SST5 agonist that suppresses insulin secretion in basal and stimulated conditions. Given the mechanism of action, CRN04777 has the potential to be universally effective in all patients with congenital HI.