Selective Somatostatin Subtype 5 (sst5) Agonists for the Treatment of Hyperinsulinism: Orally-Bioavailable Small Molecules Suppress Insulin and Rescue Glyburide-Induced Hypoglycemia.

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Congenital hyperinsulinism (CHI) results from excessive insulin secretion by pancreatic islet β-cells. The overall incidence in the US is estimated at 1/30,000 to 1/50,000 live births, but can be as much as 10-fold higher in communities with substantial consanguinity. If medical control of CHI is unsuccessful, pancreatectomy is standard, which can result in a lifetime of diabetes and difficult metabolic management. The neuropeptide somatostatin is an important modulator of hormonal signaling from the pancreas and activity at different somatostatin receptor (sst) subtypes dictates the inhibition of insulin and/or glucagon. Glucagon secretion from α-cells is inhibited through sst2 receptors and insulin secretion from β-cells is inhibited through sst2 and sst5. The injectable peptide drug octreotide, a potent agonist at sst2, and to a lesser extent sst5, is often deployed in an attempt to reduce insulin secretion in hyperinsulinemic patients. Octreotide's selectivity for sst2 leads to inhibition of glucagon secretion, thus potentially reducing its effectiveness and potentially compromising a key defense mechanism against hypoglycemia. This sst2 activity also inhibits GH and TSH secretion at the pituitary and may be implicated in the pathogenesis of necrotizing enterocolitis (NEC), a life-threatening development in neonates and infants. Because β-cell populations express sst5 in addition to sst2, we hypothesize that agonists targeting sst5 but lacking sst2 activity, will possess an optimal efficacy/safety profile for patients with CHI. Our discovery effort has yielded a potent and selective sst5 agonist, CRN02481 (in vitro human sst5 EC_{50}=0.37 nM, rat sst5 EC_{50}=0.36 nM). CRN02481 exhibits good exposure upon oral dosing in rat and dog pharmacokinetic experiments (F=32% and 55%, respectively). In rats, CRN02481 both acutely and chronically suppresses insulin secretion and normalizes blood glucose levels in a glyburide-induced hyperinsulinemic hypoglycemia model in male Sprague-Dawley rats.

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Hypothesis: An Oral Drug Selectively Targeting sst5 is the Optimal Strategy for Treating HI

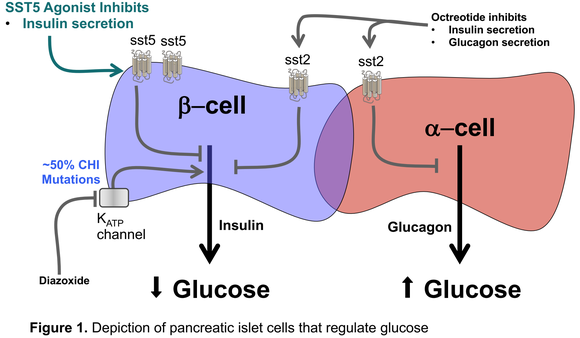

Figure 1. Depiction of pancreatic islet cells that regulate glucose

Discovery of Selective Nonpeptide sst5 Agonists

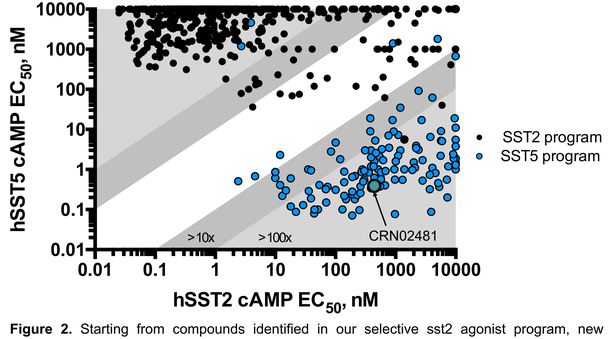

Figure 2. Starting from compounds identified in our selective sst2 agonist program, new compound series were developed and characterized by examining stimulated cAMP production inhibition by sst receptor activation. Simultaneous optimization for drug-like characteristics yielded CRN02481. In vitro, CHO-K1 cells stably expressing the desired receptor were plated with appropriate media and selection. On the assay day, media was discarded and cells were treated with NKH477 plus a dose-response of compound. Cells were incubated for 20 minutes at 37 C, lysed, and cAMP quantified.

CRN02481 Pharmacokinetic Profile in Dog and Rat

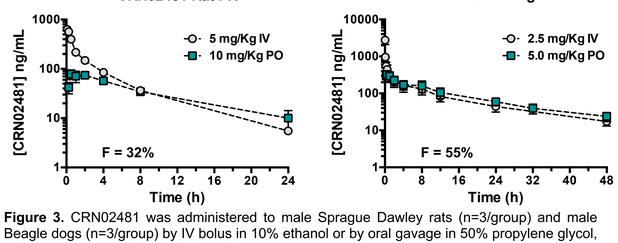

Figure 3. CRN02481 was administered to male Sprague Dawley rats (n=3/group) and male Beagle dogs (n=3/group) by IV bolus in 10% ethanol or by oral gavage in 50% propylene glycol, 10% Vitamin E TPGS, 40% 0.01N HCl.

CRN02481 dose dependently reverses glyburide-induced hypoglycemia in rat

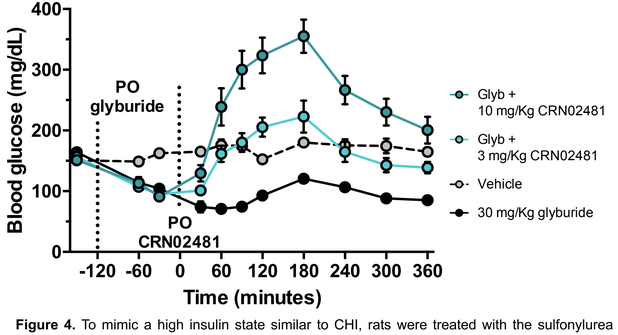

Figure 4. To mimic a high insulin state similar to CHI, rats were treated with the sulfonylurea glyburide. Glyburide inhibits K_{ATP} channels in pancreatic β-cells leading to insulin release. Glyburide or vehicle was orally administered to non-fasted male Sprague Dawley rats 2 hours prior to administration of CRN02481 (n=8/group).

CRN02481 increases blood glucose, decreases insulin, and has no effect on glucagon in rat

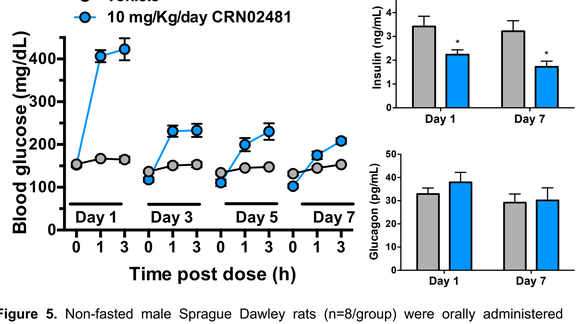

Figure 5. Non-fasted male Sprague Dawley rats (n=8/group) were orally administered vehicle or 10 mg/Kg/day CRN02481 daily for 7 days.

Hyperinsulinemic State

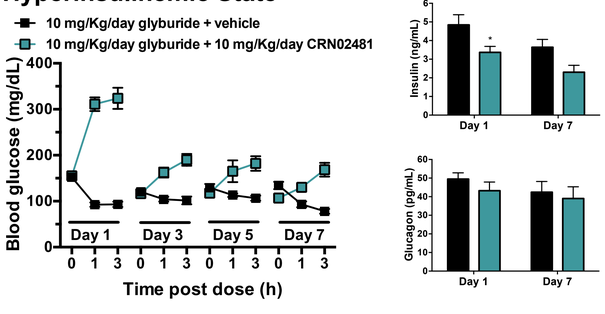

Figure 6. Male Sprague Dawley rats (n=8/group) were orally administered 30 mg/Kg glyburide or glyburide + 10 mg/Kg CRN02481 daily for 7 days.

Conclusions

CRN02481 is a novel sst5-selective agonist being developed for the treatment of congenital hyperinsulinemia:

- **Potent agonist at sst5 and selective over other sst receptor subtypes**
- **Exhibits good PK in both the rat and the dog**
- **Increases basal blood glucose and rescues hypoglycemia induced by treatment with glyburide**
- **Suppresses insulin while having no effect on glucagon**
- **Preclinical safety and toxicology studies are underway to determine if CRN02481 is suitable for human clinical trials.**

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