Crinetics Pharmaceuticals

# CRN04777: FIRST IN HUMAN SINGLE ASCENDING DOSE (SAD) PRELIMINARY RESULTS

September 15, 2021

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# Phase 1 Pharmacologic Proof-of-Concept for CRN04777 in Healthy Volunteers

| | |
|---|---|
| Safety Results | • Well-tolerated<br>• No Serious Adverse Events (SAEs)<br>• All Adverse Events (AEs) considered mild/moderate |
| Pharmacokinetics Results | • Orally bioavailable with dose proportional pharmacokinetics |
| Pharmacology Results | • Evidence of clinically meaningful suppression of insulin secretion<br>• Dose-dependent reduction in glucose-stimulated insulin secretion<br>• Dose-dependent reversal of sulfonylurea-induced insulin secretion (pharmacologic model of disease) |
| Next Steps | • Progress to Multiple Ascending Dose cohorts |

# Crinetics' Endocrine Development Strategy: Hormone Levels from Preclinical to Approval

**Preclinical POC**

Δ Glucose & Hormones, PK, Safety

**Phase 2/3 Safety, Disease Efficacy**

Δ Glucose & Hormones, PROs, PK, Safety



Phase 1 Healthy Volunteers

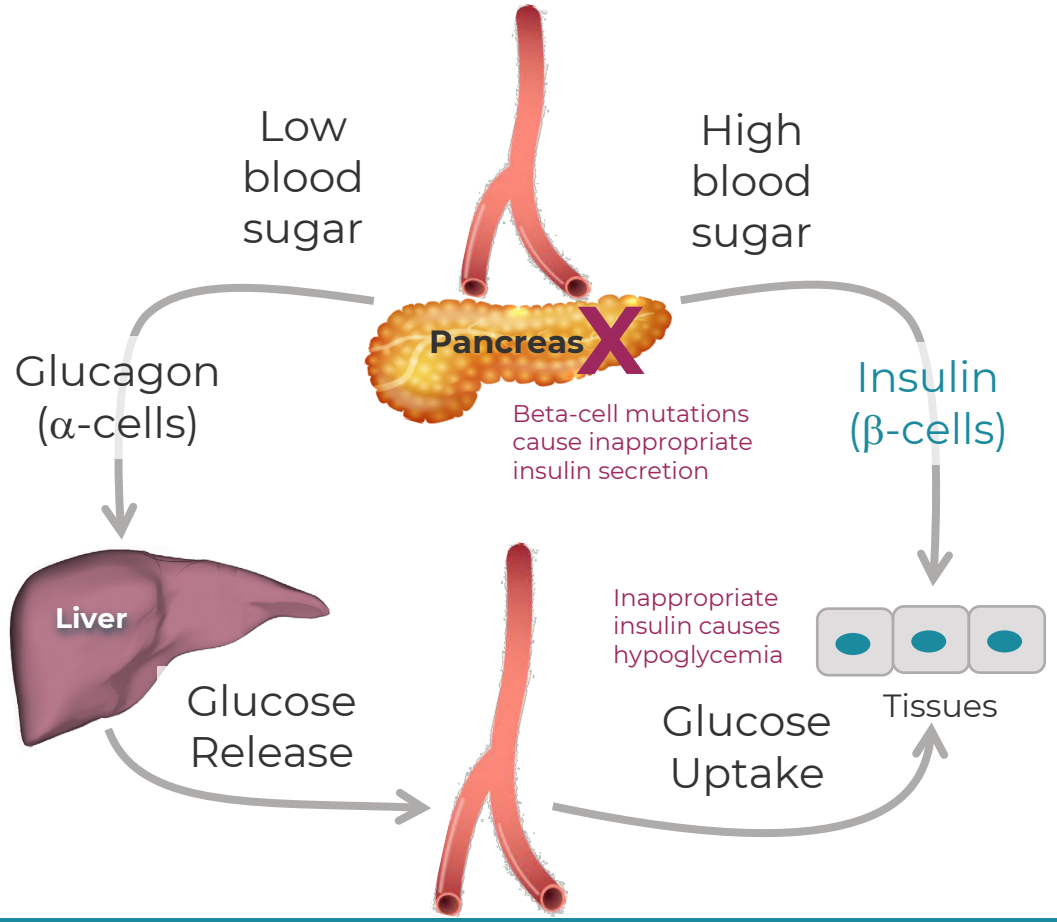
Phase 2/3 Trials (Patients)

**Phase 1 Healthy Volunteer Safety, Pharmacologic POC**

Δ Glucose & Hormones, PK, Safety

# Congenital Hyperinsulinism (HI) Results in Life Threatening Recurrent Hypoglycemia

## Congenital HI patients secrete insulin even when blood sugar is low




## *Congenital HI is a devastating rare disease*

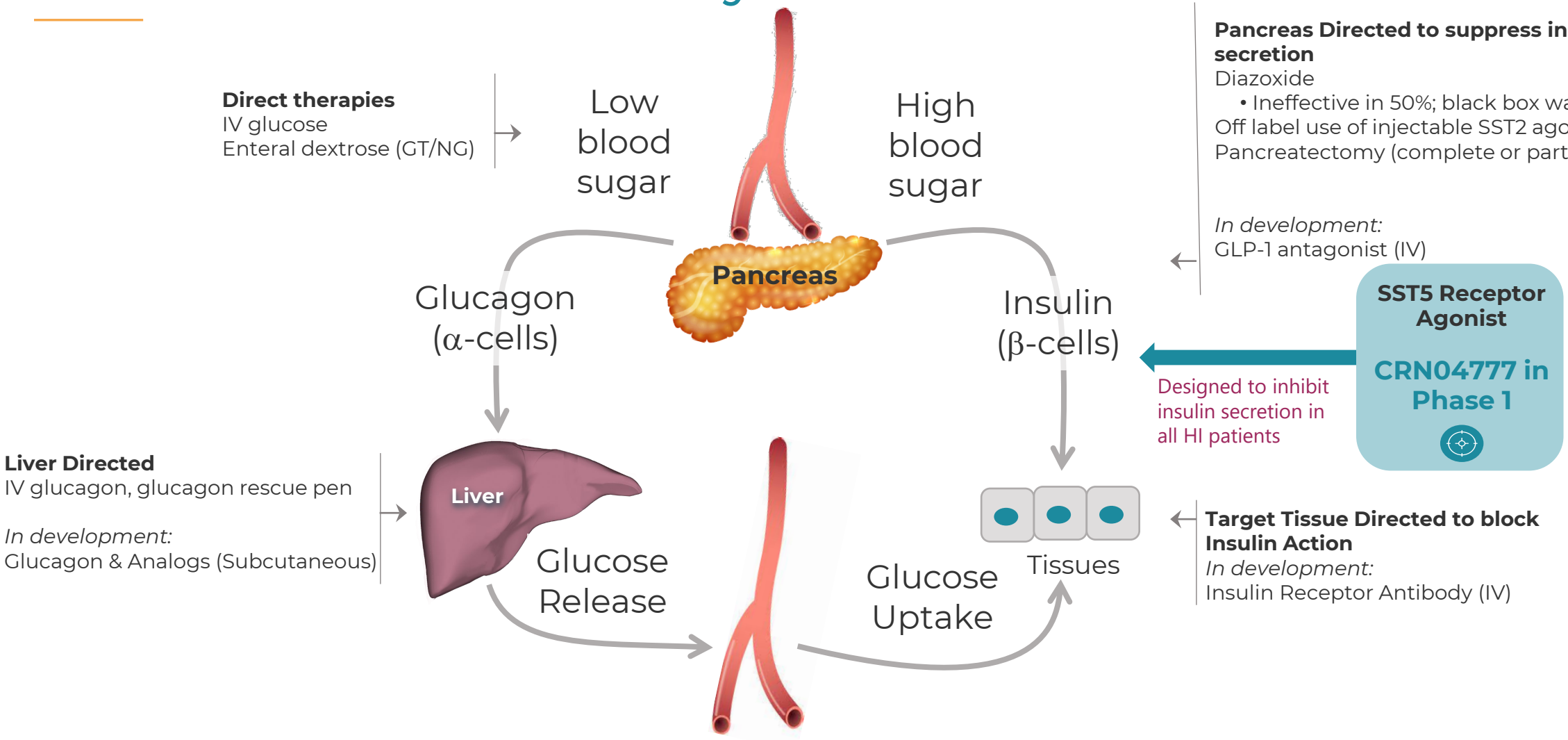
- Untreated hypoglycemia can result in neurodevelopment disorders and death
- Early identification and continuous intensive glucose management are critical
- Current treatment paradigms place high burden of care on families with all too frequent suboptimal outcomes
- Six Global Centers of Excellence named for treatment of patients with HI
- Robust global patient advocacy such as Congenital Hyperinsulinism International (www.congenitalhi.org)

# Unmet Medical Needs in Congenital HI are Very High

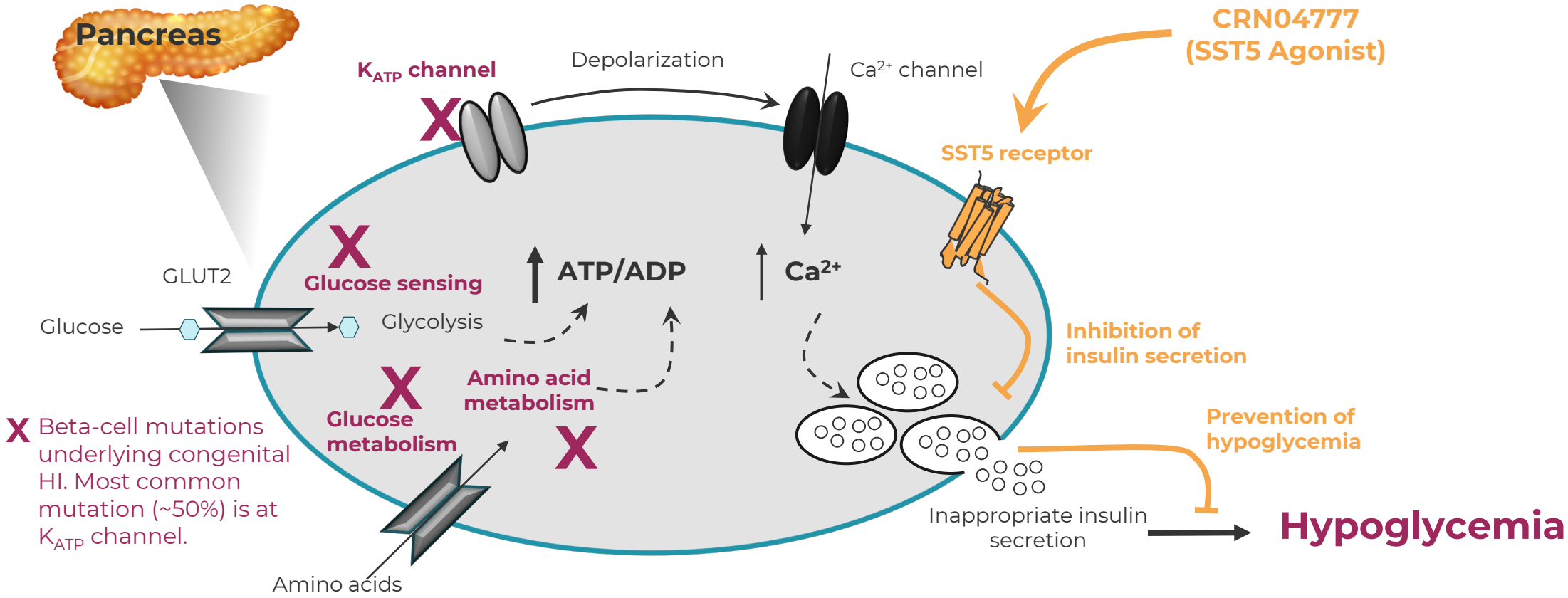
## Patient & Parent Goals

- ✓ Avoid hypoglycemia and its consequences including neurological damage
- ✓ Safely sleep through the night
- ✓ Avoid pancreatectomy
- ✓ Eliminate feeding tubes
- ✓ Reduce injections and glucose sticks
- ✓ Avoid side effects of diazoxide and other treatments
- ✓ Medical management until HI resolves with age
- ✓ Be a kid not a patient

# CRN04777: First-in-class Oral SST5 Agonist with Potential to be Broadly Effective in HI



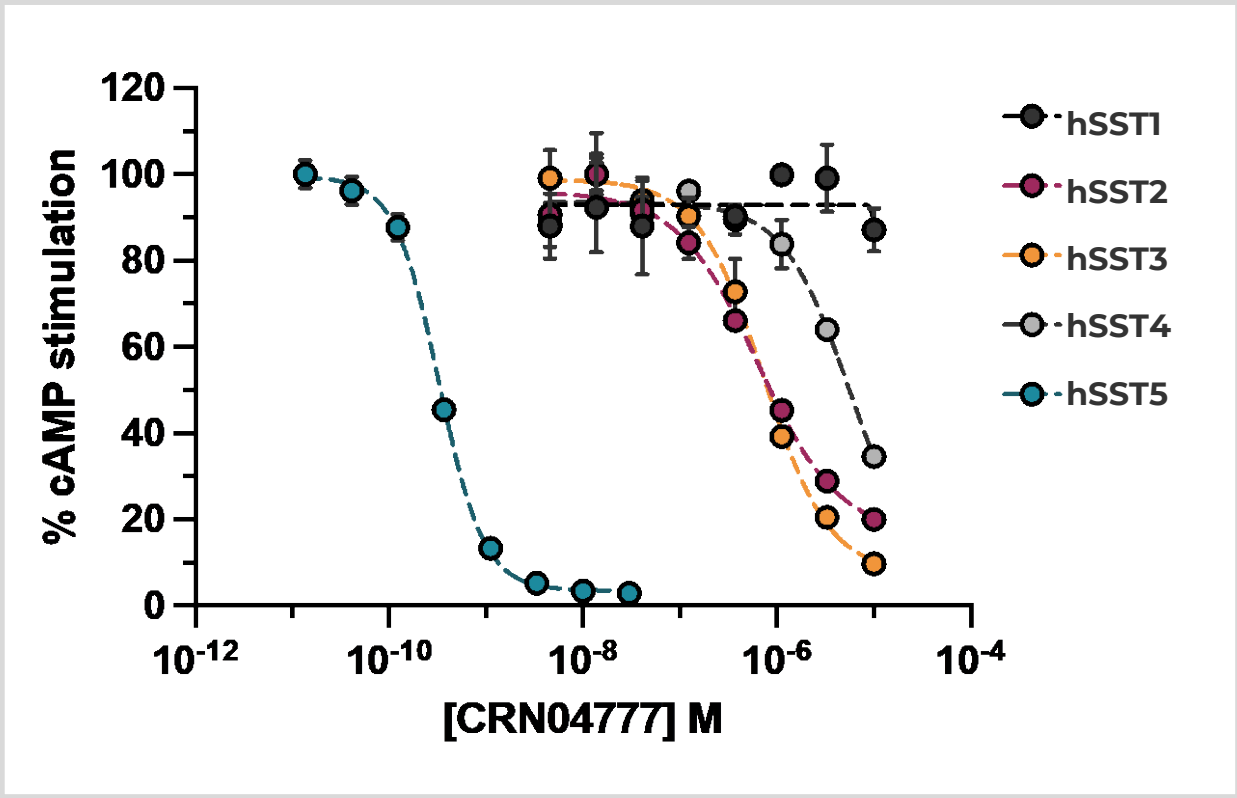
# Somatostatin Receptor SST5 Inhibits Insulin Secretion Downstream of all Known HI Causing Mutations



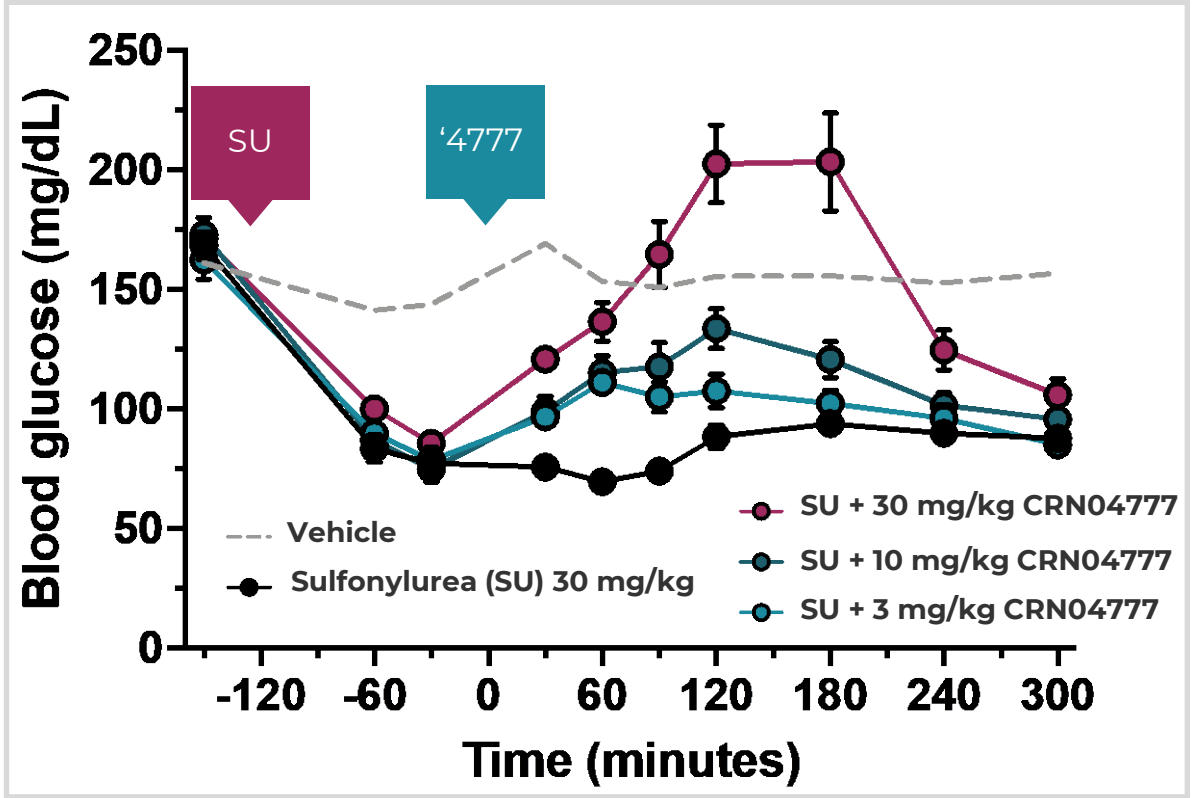

Syndromic hyperinsulinisms (e.g. those associated with Beckwith-Wiedemann syndrome, Sotos syndrome, Kabuki syndrome, and Turner syndrome) may also respond to SST5 agonism

# CRN04777 is the Only Oral SST5 Agonist in Clinical Development

CRN04777 is a potent ($EC_{50}$=0.4 nM) and selective SST5 agonist




CRN04777 suppressed sulfonylurea (SU)-induced insulin secretion and reversed hypoglycemia in rats



# CRN04777 SAD Study Design to Evaluate Pharmacologic Proof-of-Concept

Follows Crinetics' core endocrine strategy of using hormonal biomarkers to drive development

## Study Goals

- Evaluate safety [0.5-120 mg]
- Evaluate pharmacokinetics: oral absorption, dose-proportional exposure, half-life [0.5-120 mg]
- Evaluate dose response and PK/PD on pre- and post-stimulated glucose and insulin in an IVGTT [0.5-120 mg]
- Evaluate dose response and PK/PD on reduction/reversal of sulfonylurea-induced insulin secretion (pharmacologic model of disease) [30-60 mg]

## Pharmacodynamic Assessments

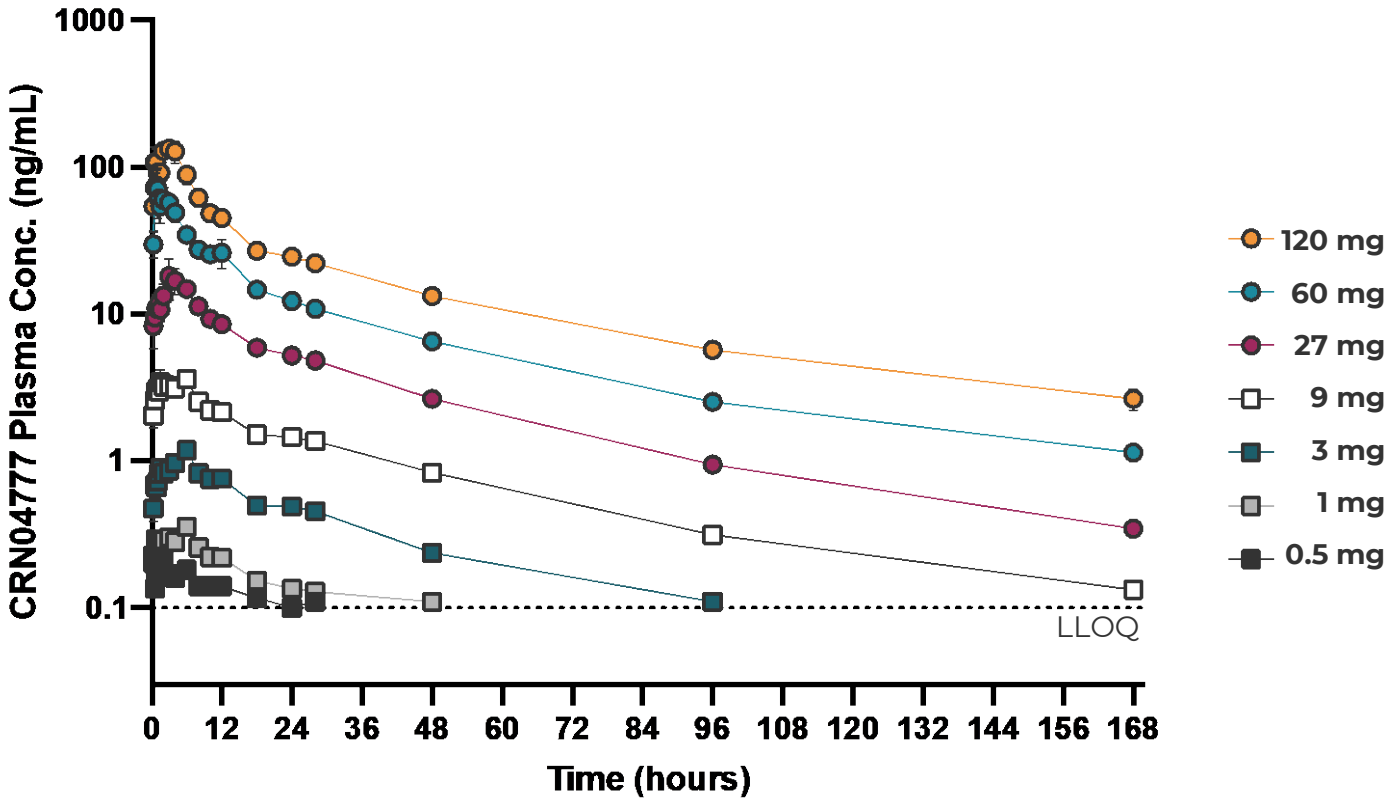
1. Intravenous Glucose Tolerance Test (IVGTT)
2. Sulfonylurea (SU) Challenge

## Proof-of-Concept

- Dose dependent suppression of glucose- or sulfonylurea-induced insulin secretion with CRN04777

# PK Results: CRN04777 Showed Oral Bioavailability with Dose-Proportional Exposure

## Half-life ~40 hours and $t_{max}$ ~1-2 hours at efficacious doses




Data shown are mean±SEM; LLOQ = lower limit of quantitation
All doses n=6; except n=12 for 60 mg which was evaluated in both IVGTT and sulfonylurea challenge
*When 120 mg was administered within 30 minutes of a standard adult high fat breakfast, a significant reduction in exposure was observed. Evaluation of pediatric relevant meals pending.

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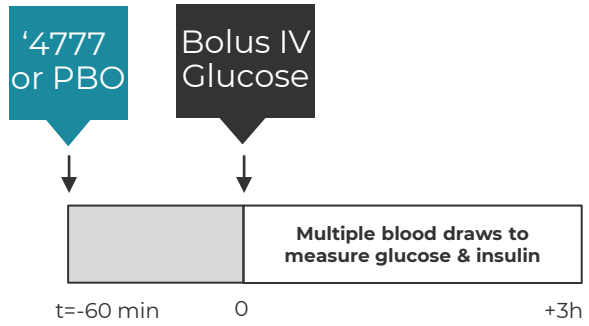
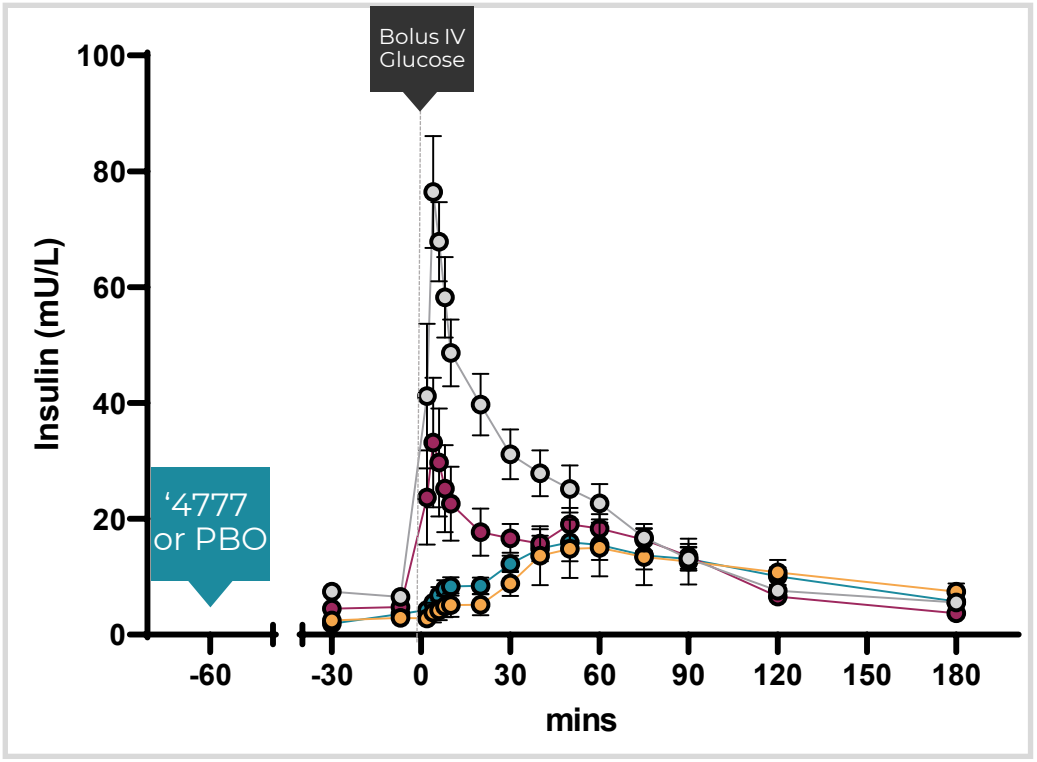
### 1. Intravenous Glucose Tolerance Test (IVGTT)



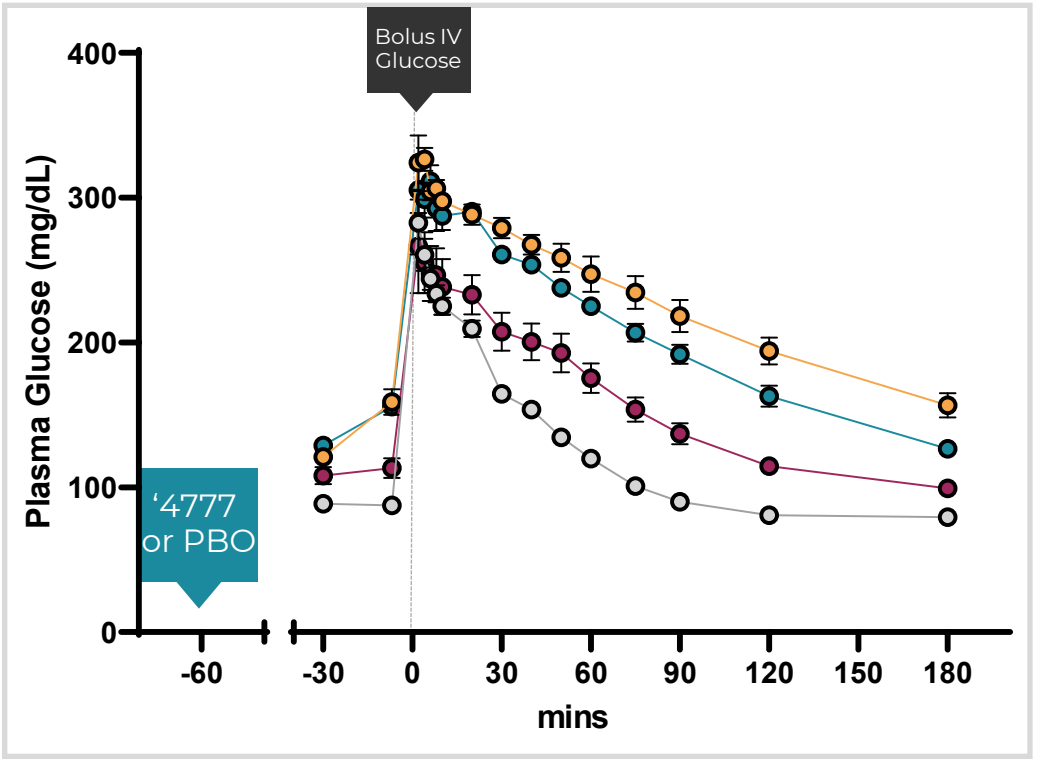

Healthy volunteers received single oral dose of CRN04777
(n = 8, 6 active/ 2 placebo in each cohort)

# CRN04777 Dose-Dependently Suppressed Glucose Stimulated Insulin Secretion

CRN04777 dose-dependently reduced insulin secretion stimulated by bolus IV glucose (IVGTT)...




...and reduced insulin secretion reduces glucose uptake by tissues resulting in prolonged elevation of plasma glucose




Data shown are mean±SEM
N=6 CRN04777 treated per dose; N=14 placebo
IVGTT=intravenous glucose tolerance test; PBO=placebo

# CRN04777 SAD Study Designed to Evaluate Pharmacologic Proof-of-Concept

## Follows Crinetics' core endocrine strategy of using hormonal biomarkers to drive development

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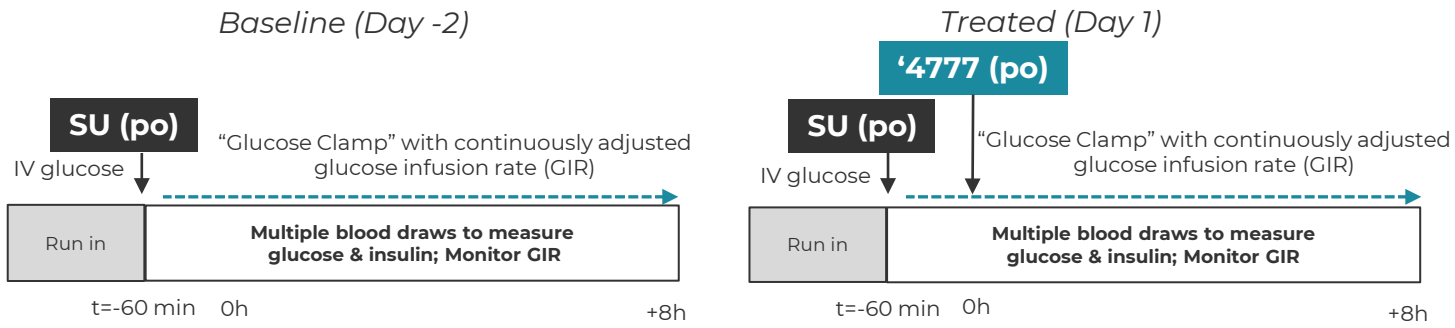
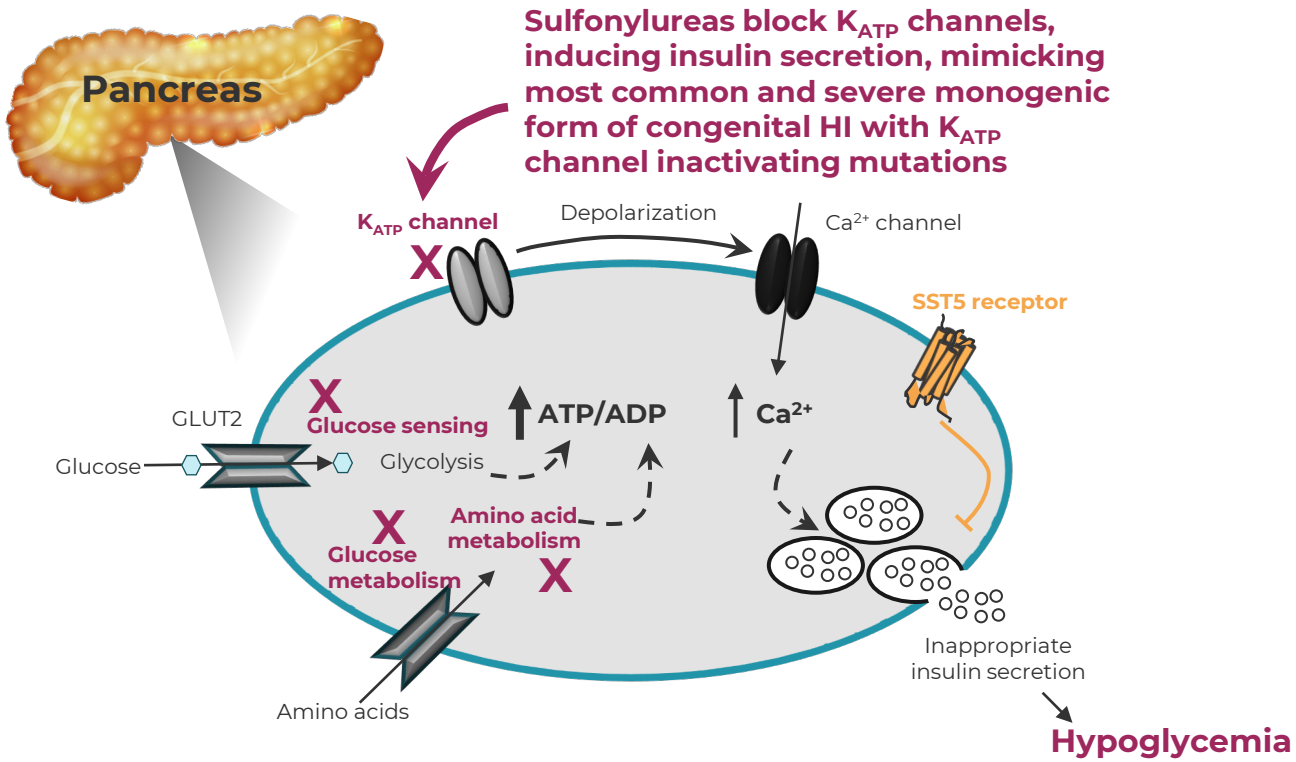
### 2. Sulfonylurea (SU) Challenge




Healthy volunteers received single oral dose of CRN04777
(n = 9, 6 active / 3 placebo in each cohort)

# Sulfonylurea Challenge Provided Disease Relevant Proof-of-Concept

## The administration of sulfonylurea is a pharmacologic model of congenital HI



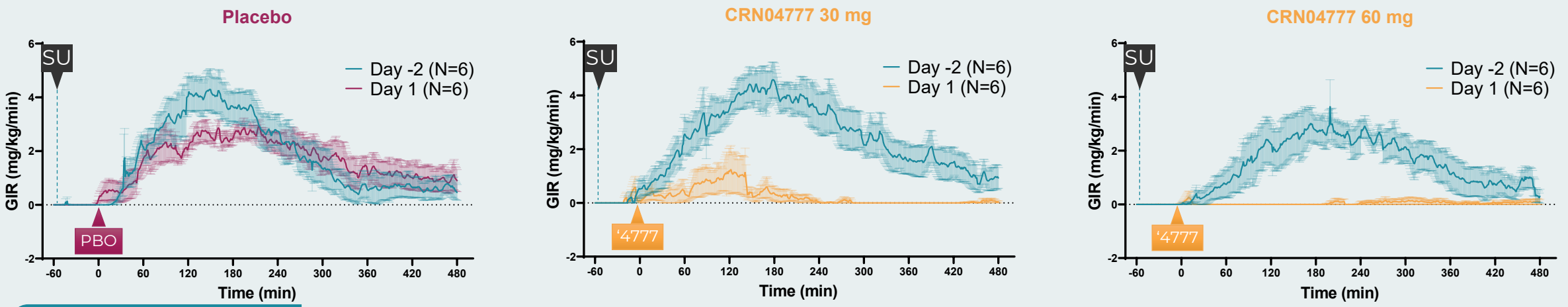

### Sulfonylurea Challenge

- Sulfonylurea induces endogenous insulin secretion
- Automated delivery of supplemental IV glucose maintains blood glucose in the normal range (glucose clamp)
- Glucose infusion rate (GIR) increases in proportion to insulin secretion

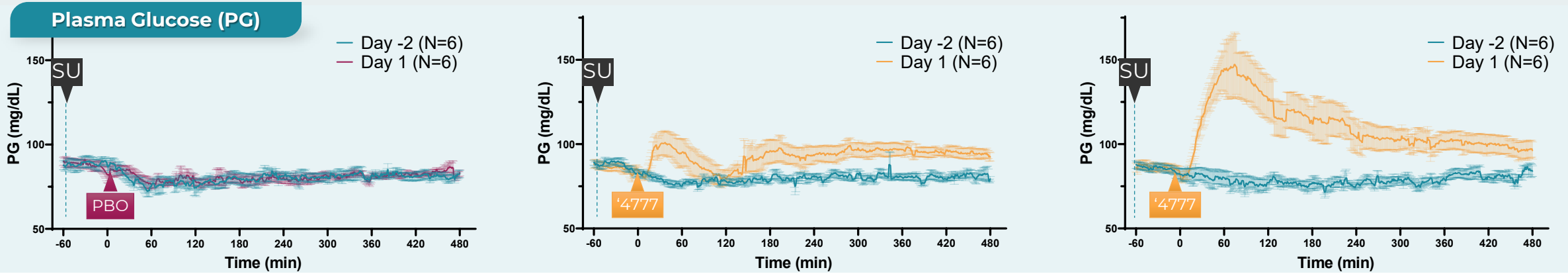
# CRN04777 Reversed Sulfonylurea-Induced Hyperinsulinism in a Pharmacologic Model of Congenital HI

## CRN04777 eliminated the need for IV glucose support by inhibiting insulin secretion

**Glucose Infusion Rate (GIR) – Increases in Proportion to Insulin Secretion**




**Plasma Glucose (PG)**




More detailed data (insulin, C-peptide) to be presented at future medical conferences

Solid line: mean value; shaded area: SEM

# Conclusions from CRN04777 SAD Results

**Objectives**

- Safety and tolerability
- Drug-like pharmacokinetics
- PK/PD for suppression of insulin secretion

**Safe and well tolerated at single doses from 0.5-120 mg**

**Achieved targeted pharmacokinetic profile**
- **Rapidly absorbed after oral administration ($t_{max}$ ~1-2 hrs)**
- **Favorable half-life of ~40 hours observed**
- **Dose-proportional exposure from 0.5-120 mg**

**Demonstrated pharmacologic proof-of-concept for SST5 agonism**
- **Dose-dependent reduction in glucose-induced insulin secretion achieved in an intravenous glucose tolerance test**
- **Dose-dependent reversal of sulfonylurea-induced insulin secretion achieved in a pharmacologic model of hyperinsulinism**

# Pipeline With Three Candidates Beyond Pharmacologic Proof-of-Concept

| PROGRAM | Development Stage | Registrational Endpoint | Prevalence | |
|---|---|---|---|---|
| | Preclin / Phase 1 / Phase 2 / Phase 3 | | US Total | Global Range per 100,000 |
| **Paltusotine (SST2 agonist)** | Pharmacologic POC | | | |
| Acromegaly | | IGF-1 Levels | 26K | 2.8 – 13.0 |
| Carcinoid Syndrome | | Diarrhea & Flushing | 33K | 3.7 – 9.7 |
| Nonfunctional NETs | | Anti-tumor activity | 138K | 17 – 46 |
| **CRN04894 (ACTH antagonist)** | | | | |
| Cushing's Disease | | Cortisol Levels | 10K | 2.5 – 3.8 |
| Congenital Adrenal Hyperplasia (CAH) | | Adrenal Androgens/ Glucocorticoid use | 27K | 6.7 – 10.0 |
| **CRN04777 (SST5 agonist)** | | | | |
| Congenital Hyperinsulinism | | Glucose Levels/ Hypoglycemic Events | 1.5-2K | 0.64 – 1.3 |
| Syndromic Hyperinsulinism | | Glucose Levels/ Hypoglycemic Events | 2K | Variable |

*We continue to invest in ongoing discovery of new molecules targeting new indications with our in-house discovery team who are actively pursuing multiple programs in parallel. Indications include hyperparathyroidism, nonfunctional pituitary adenomas, polycystic kidney disease and more.*

# Achieved 2021 Goal of Three Programs with Clinical Proof-of-Concept

| | 1H21 | 2H21 | 1H22 | 2H22 |
|---|---|---|---|---|
| **Paltusotine**<br>SST2 Agonist for Acromegaly & NETs<br>**POC Achieved** | Initiate PATHFNDR-1 ✓ | Initiate PATHFNDR-2 | PATHFNDR-1 and PATHFNDR-2 Ongoing | |
| | | Initiate P2 NETs Trial in Carcinoid Syndrome | Carcinoid Syndrome Phase 2 Ongoing | |
| **CRN04894**<br>ACTH Antagonist for Cushing's Disease & CAH<br>**POC Achieved** | Initiate Phase 1 ✓ | Phase 1 POC SAD Data ✓ | Phase 1 MAD Data(Q1) | Initiate Phase 2 in Patients |
| **CRN04777**<br>SST5 Agonist for Congenital HI<br>**POC Achieved** | Initiate Phase 1 ✓ | Phase 1 POC SAD Data ✓ | Phase 1 MAD Data(Q1) | Initiate Phase 2 in Congenital HI Patients |

Executed development strategy with three NCEs: paltusotine, '4894, and '4777