Crinetics Pharmaceuticals

CRN04777: PHASE 1 MULTIPLE ASCENDING DOSE (MAD) PRELIMINARY RESULTS

March 30, 2022

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CRN04777 MAD Results Build on Pharmacologic Proof-of-Concept Data from SAD Study

Well-tolerated at doses from 30 mg to 120 mg administered once daily for 10 days

- No Serious Adverse Events (SAEs)
- All Adverse Events (AEs) considered mild/moderate

Further demonstrated pharmacologic POC by showing dose-dependent:

- Decreases in fasting insulin, leading to increases in fasting plasma glucose
- Reversal of sulfonylurea-induced insulin secretion in a pharmacologic model of disease

Favorable pharmacokinetics results support once daily dosing

- Showed oral bioavailability with ~40-hour half-life
- PK results and exposures consistent with expectations from SAD data

Next steps: Meet with regulators to discuss design of clinical program in patients

MAD: Multiple-ascending dose SAD: Single-ascending dose; POC: Proof-of-concept; PK: Pharmacokinetic

Crinetics' Endocrine Development Strategy

Preclinical POC

Δ Glucose & Hormones, PK, Safety

Phase 1 Healthy Volunteers

Phase 1 Healthy Volunteer Safety, Pharmacologic POC

Δ Glucose & Hormones, PK, Safety

Phase 2/3 Trials (Patients)

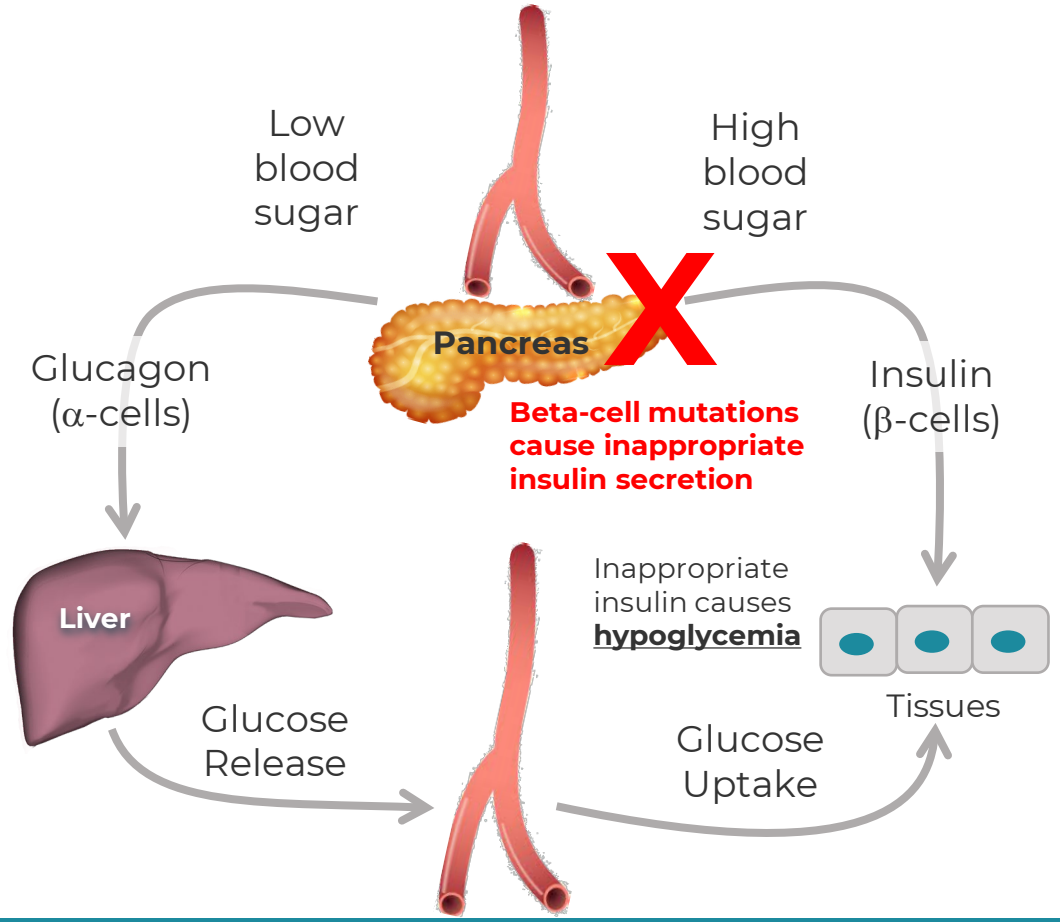
Phase 2/3 Safety, Disease Efficacy

Δ Glucose & Hormones, PROs, PK, Safety

POC: Proof-of-concept; PK: Pharmacokinetic; PRO: Patient reported outcome

Congenital Hyperinsulinism (HI) Results in Life Threatening Recurrent Hypoglycemia

Congenital HI patients secrete insulin even when blood sugar is low, causing hypoglycemia



Congenital HI is a devastating rare disease (U.S. prevalence = 1.5-2K)

- Untreated hypoglycemia can result in life-threatening acute complications and long-term neurodevelopment disorders
- 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

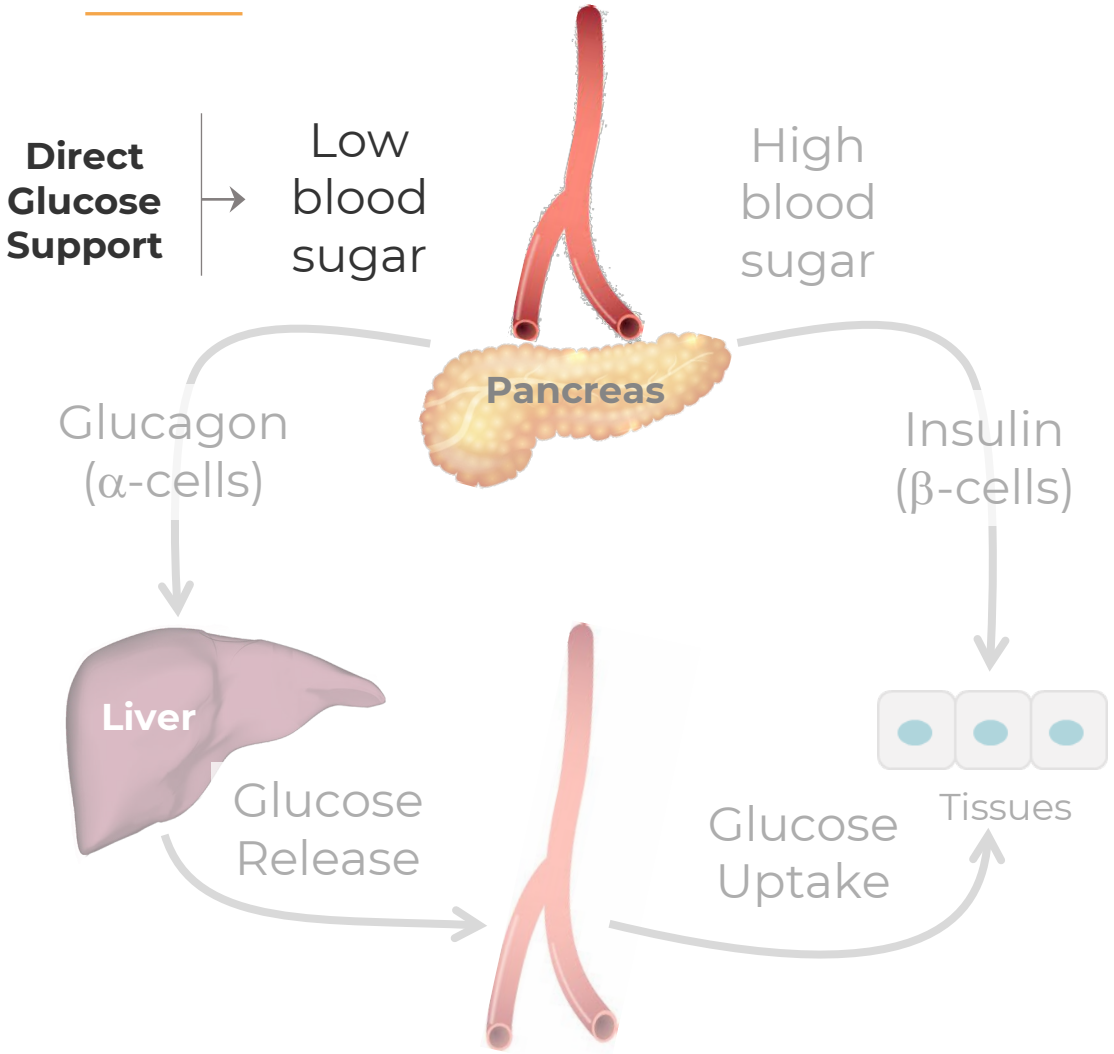
Patient & Parent Goals

- ✓ 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

Julieta is sweet because she has HI and she cares so deeply about everyone around her.

From Congenital Hyperinsulinism International's 2022 Rare Disease Day Awareness Campaign

Current Congenital HI Therapies have Limited Efficacy and Additional Shortcomings



Direct Glucose Support

In use:

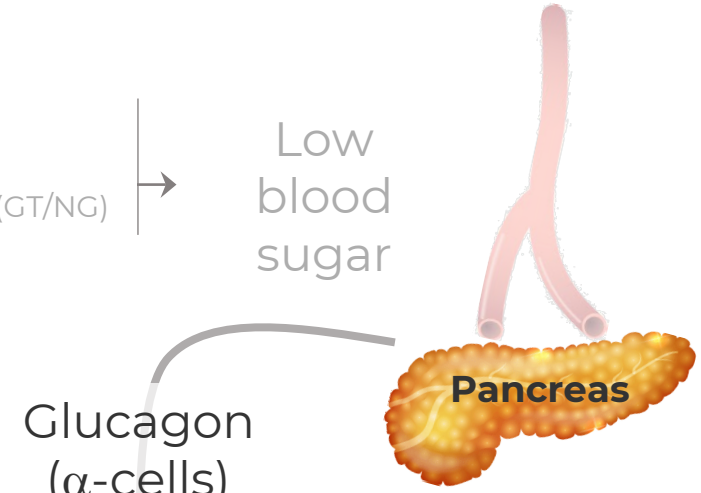
- Intravenous glucose sometimes requiring central venous administration
- Enteral dextrose delivered via a gastrostomy or nasogastric tube

Shortcomings include:

- Prolonged hospitalization
- Burdensome delivery route
- May contribute to feeding issues including eating aversion

Current Congenital HI Therapies have Limited Efficacy and Additional Shortcomings

Shortcomings related to safety, efficacy, & route of administration hamper congenital HI treatments



Direct therapies
IV glucose
Enteral dextrose (GT/NG)

Low blood sugar

High blood sugar

Glucagon (α-cells)

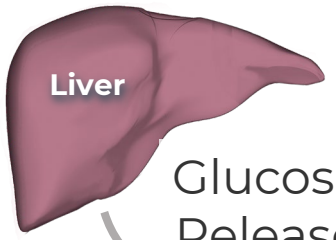
Insulin (β-cells)

Pancreas Directed to Suppress Insulin Secretion
In use:
Diazoxide
- Ineffective in ~50% of patients; black box warning

Injectable SST2 agonists (off-label)

Pancreatectomy (complete or partial)

In development:
Injected GLP-1 antagonist



Liver Directed
In use:
Continuous IV glucagon infusion (for prevention)
Injectable glucagon/analog boluses (for acute hypoglycemia)

In development:
Glucagon & Analog (continuous subcutaneous infusions)

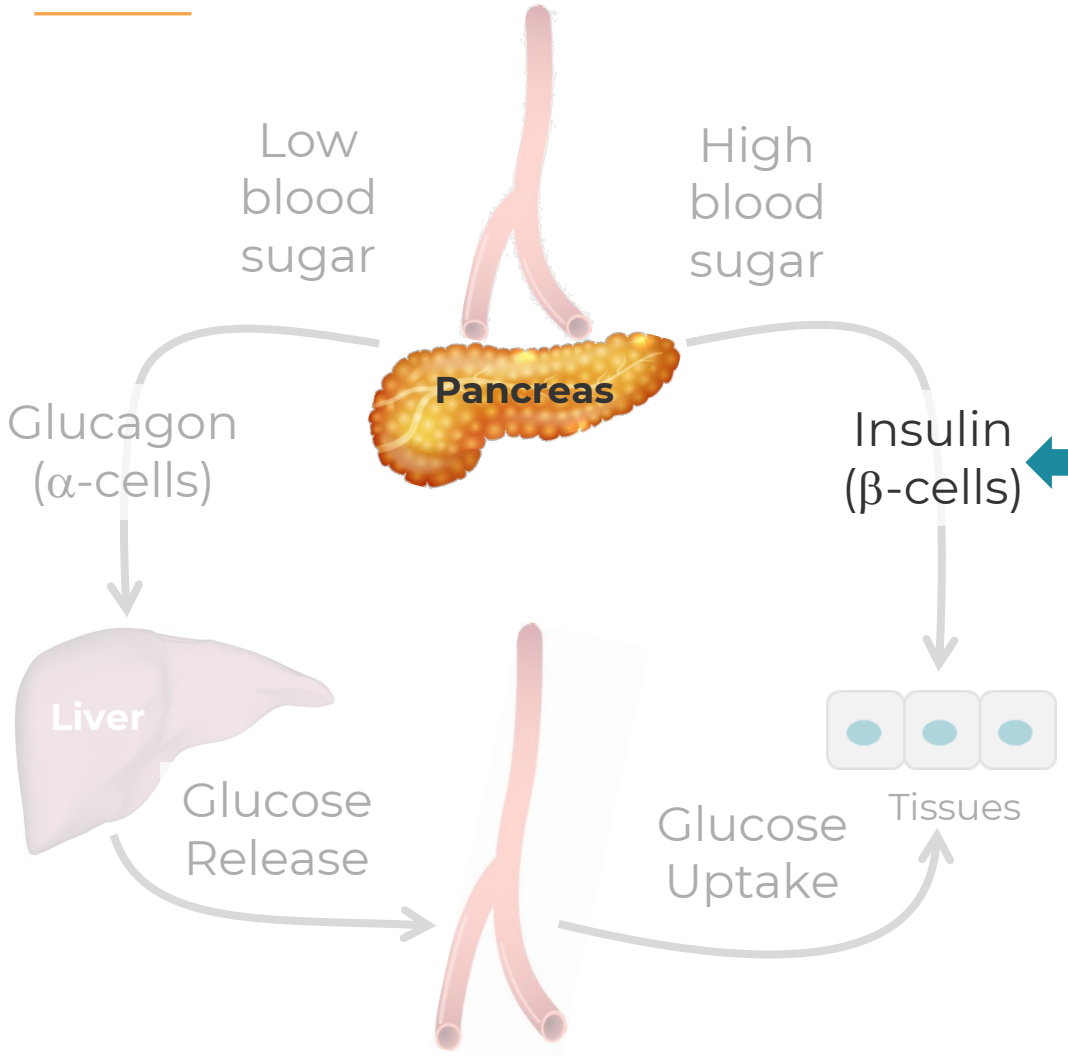
Glucose Release

Glucose Uptake

Tissues

Target Tissue Directed to Block Insulin Action
In development:
Insulin Receptor Antibody (IV)
- Requires biweekly IV administration

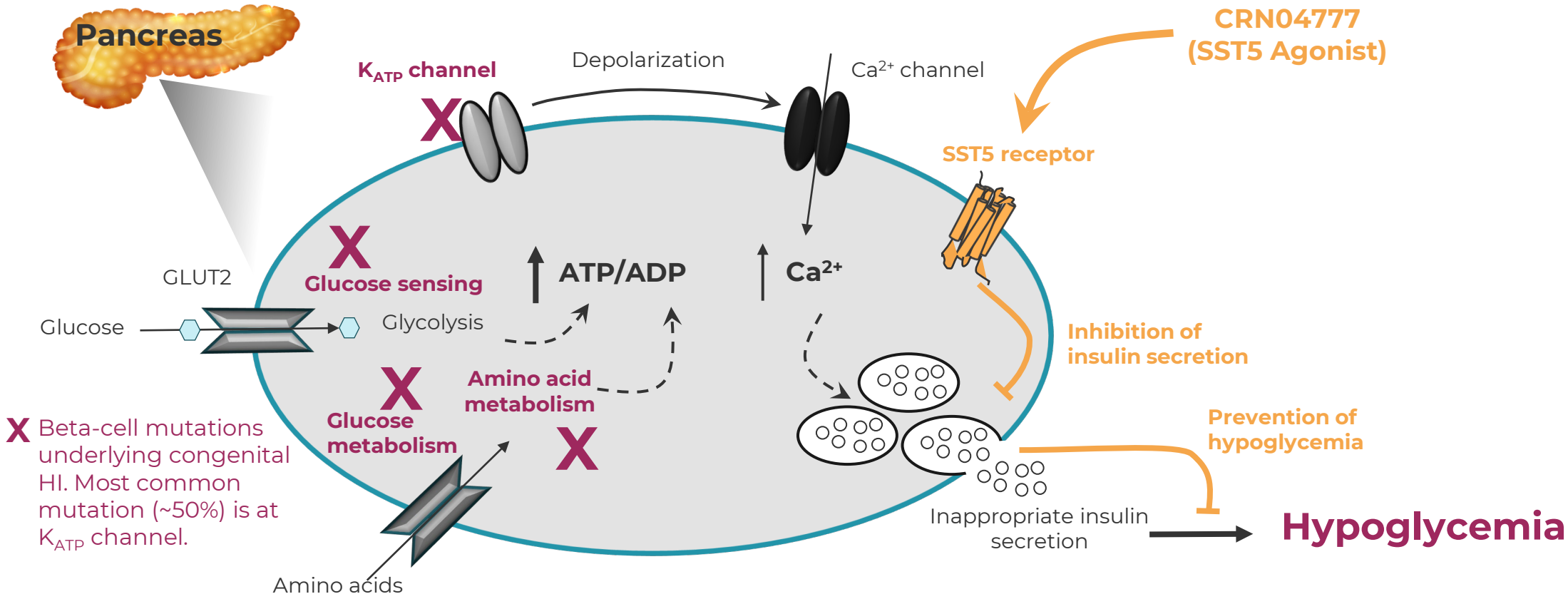
CRN04777: Oral SST5 Agonist with Potential to Overcome Shortcomings of Competing Therapies



CRN04777 in Phase 1

We believe CRN04777 is the only investigational oral product candidate in clinical development that is designed for *ALL* hyperinsulinism patients

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 MAD Study Designed to Build on SAD Pharmacologic Proof-of-Concept Data

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

MAD Study Goals

- Evaluate safety and tolerability with repeat dosing
- Evaluate PK at steady state
- Evaluate basal PD with repeat dosing
- Evaluate PD after a sulfonylurea challenge (pharmacologic model of disease)
- Inform dose selection for patient studies

Pharmacodynamic Assessments

1. Fasting plasma glucose and insulin
2. Sulfonylurea (SU) challenge

Proof-of-Concept

- Dose dependent suppression of SU-induced insulin secretion with CRN04777

MAD: Multiple-ascending dose SAD: Single-ascending dose; Proof-of-concept; PK: Pharmacokinetics; PD: Pharmacodynamics

CRN04777 was Well Tolerated with No Dose Discontinuations due to Adverse Events

All causality treatment emergent adverse events

Most Frequent TEAEs	Placebo (SAD+MAD) (N=29) n (%)	‘4777 (SAD+MAD) (N=78) n (%)
Nausea	0 (0)	15 (19.2)
Vomiting	0 (0)	7 (9.0)
Diarrhoea	0 (0)	5 (6.4)
Headache	0 (0)	5 (6.4)
Chills	0 (0)	3 (3.8)
Hypoglycaemia*	0 (0)	3 (3.8)
Abdominal pain	0 (0)	2 (2.6)
Nasopharyngitis	0 (0)	2 (2.6)
Phlebitis	4 (13.8)	1 (1.3)
Skin Irritation	2 (6.9)	1 (1.3)

*Post glucose clamp and not treatment related

- As expected, GI side effects (mild to moderate nausea, vomiting, diarrhea) were the most common treatment-related adverse events
  - Time course for these dose-dependent GI events shortly followed treatment initiation and resolved without the need to discontinue study drug
- No study drug discontinuations due to Adverse Events
- No Serious Adverse Events
- No safety signals seen with vital signs, laboratory testing, ECGs

TEAE: Treatment emergent adverse event; GI: Gastrointestinal; SRL: Somatostatin receptor ligand; ECG: Electrocardiogram

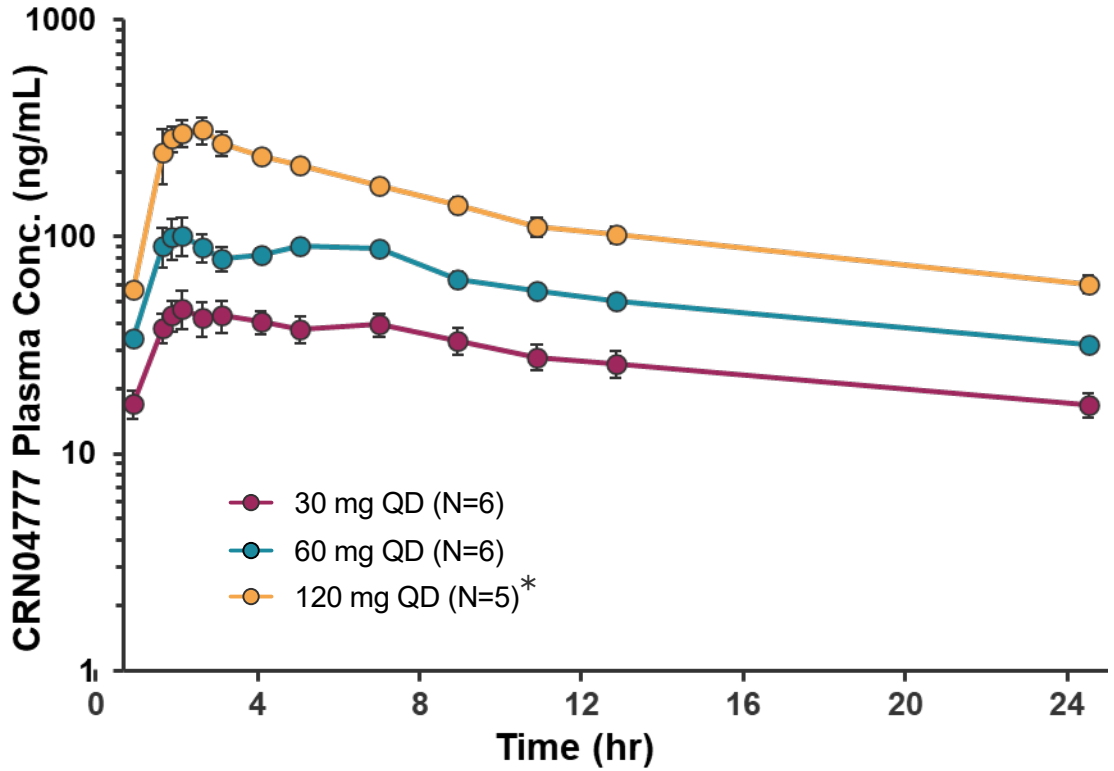
MAD PK Results and Exposures were Consistent with Expectations from SAD Data at the Same Doses

Favorable PK results support once daily dosing

Steady State PK

- Oral bioavailability
- Favorable half-life of ~40 hours
- Rapidly absorbed with a t_{max} of ~1-3 hours

Concentration-Time Profile at Steady State (Day 9)

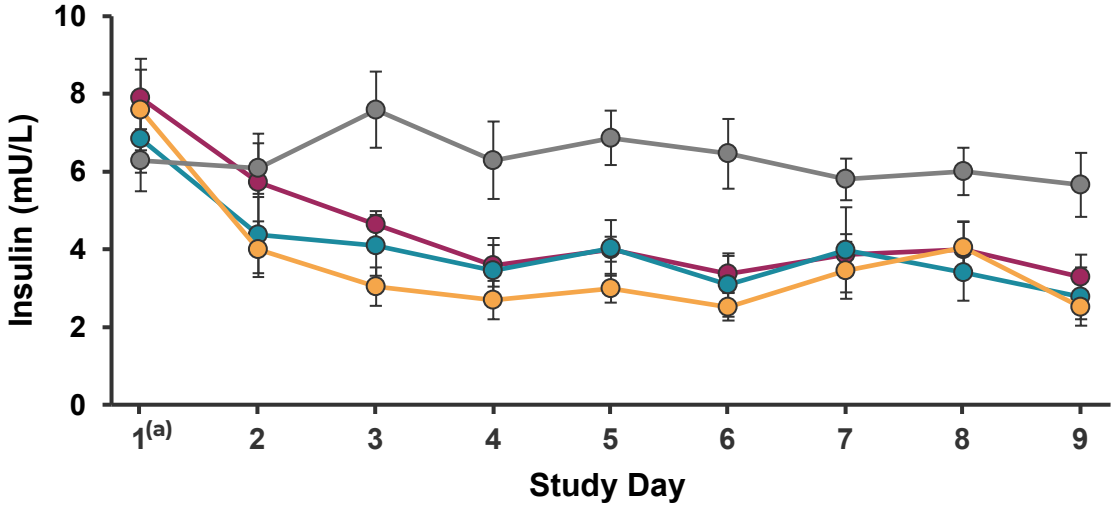


Data represent mean ± SEM; MAD: Multiple-ascending dose; PK: Pharmacokinetic; SAD: Single-ascending dose; QD: Once daily
* n=1 subject withdrew consent (not treatment related)

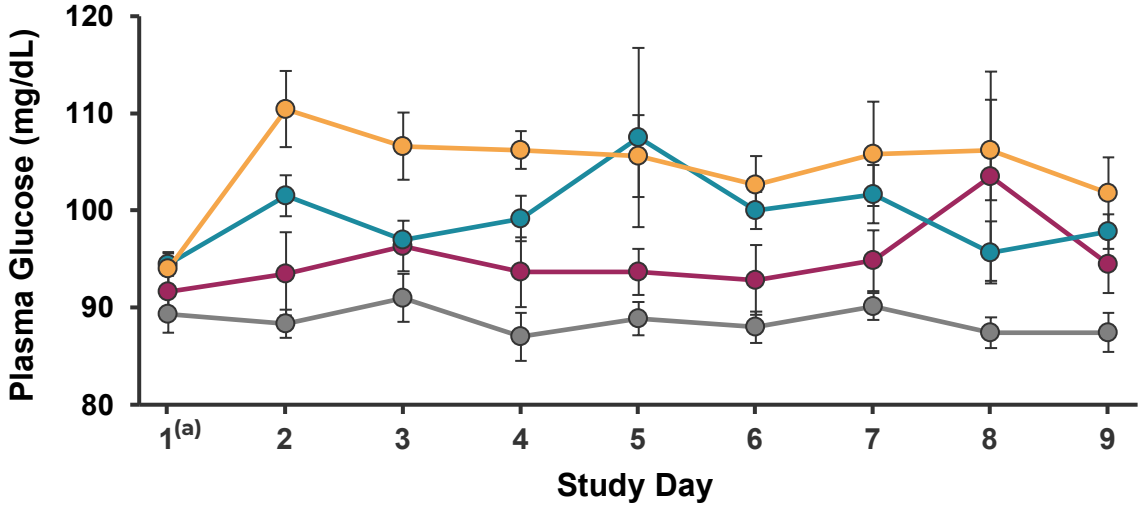
Dose-Dependent Decrease in Fasting Insulin Led to Increases in Plasma Glucose

CRN04777 drove rapid and sustained changes in insulin and glucose levels in healthy volunteers

Fasting Insulin Levels



Plasma Glucose Levels



PBO (N=6) 30 mg QD (N=6) 60 mg QD (N=6) 120 mg QD (N=5)(b)

(a) Day 1 measurement occurs prior to the first dose of CRN04777. Measurements on Days 2-9 occurred after ≥ 10 hours overnight fasting and prior to CRN04777 daily dosing. Measurement on Day 10 was after sulfonylurea dose, hence excluded.
(b) n=1 subject withdrew consent (not treatment related)

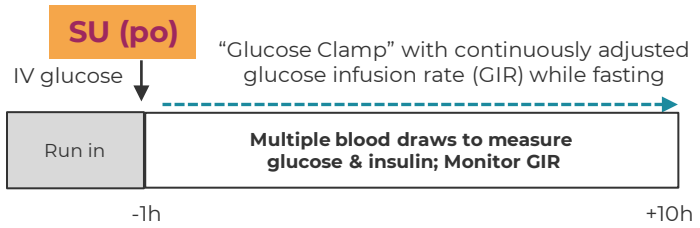
Data represent mean ± SEM; PBO: Placebo; QD: Once daily

CRN04777 MAD Study Designed to Build on SAD Pharmacologic Proof-of-Concept Data

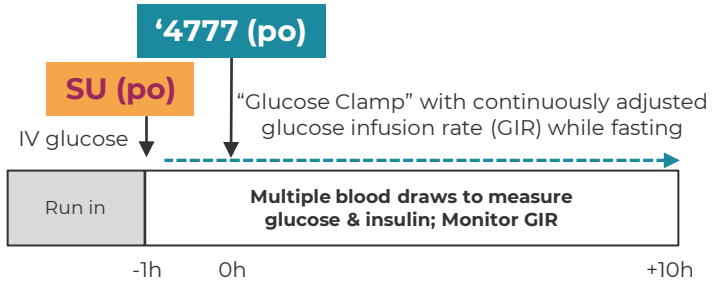
Follows Crinetics' core endocrine strategy of using hormonal biomarkers to drive development

Sulfonylurea (SU) Challenge

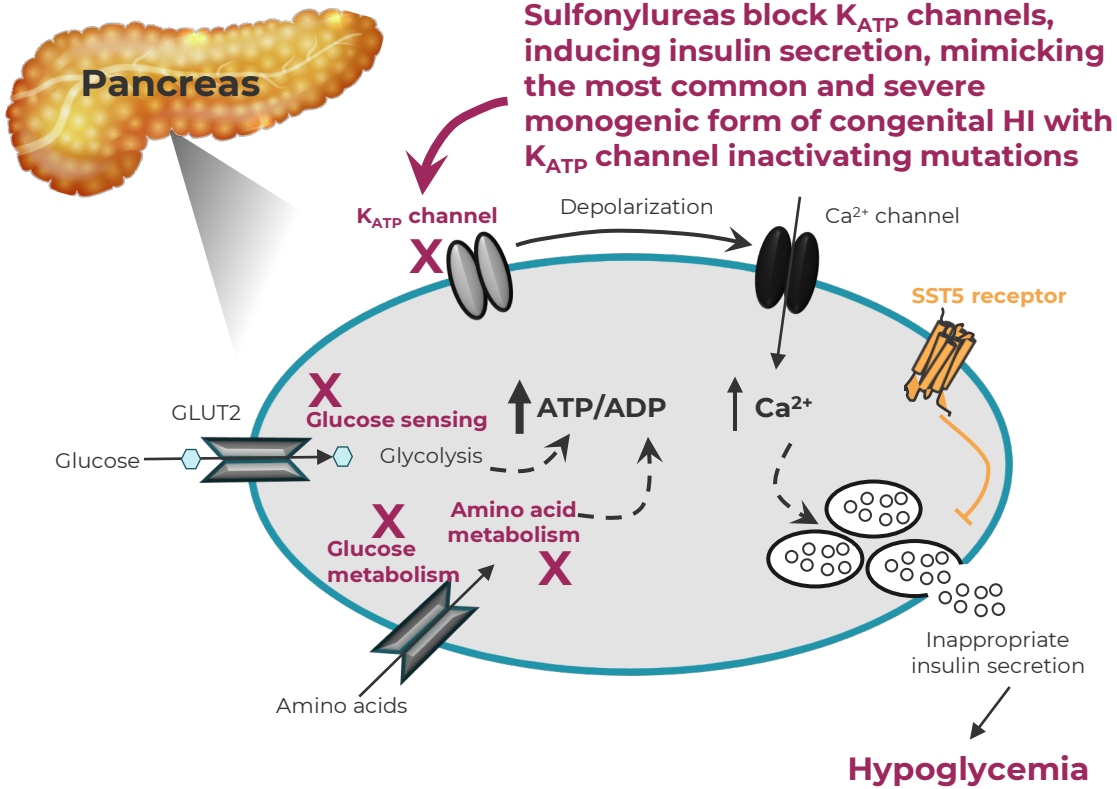
Baseline (Day -2)



Treated (Day 10)



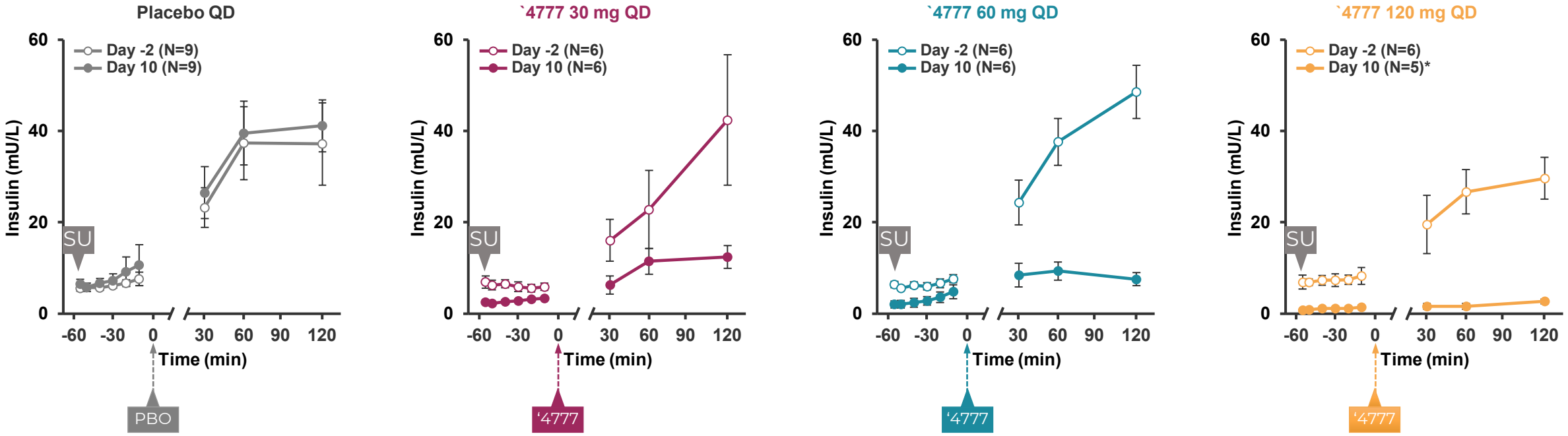
Healthy volunteers receive repeated oral doses of CRN04777 for 10 days and a sulfonylurea challenge on Day 10 (n = 9/cohort)



MAD: Multiple-ascending dose SAD: Single-ascending dose; po: By mouth

CRN04777 Reversed SU-Induced Insulin Secretion in a Pharmacologic Model of Congenital HI

Insulin Levels Following Sulfonylurea (SU) Challenge

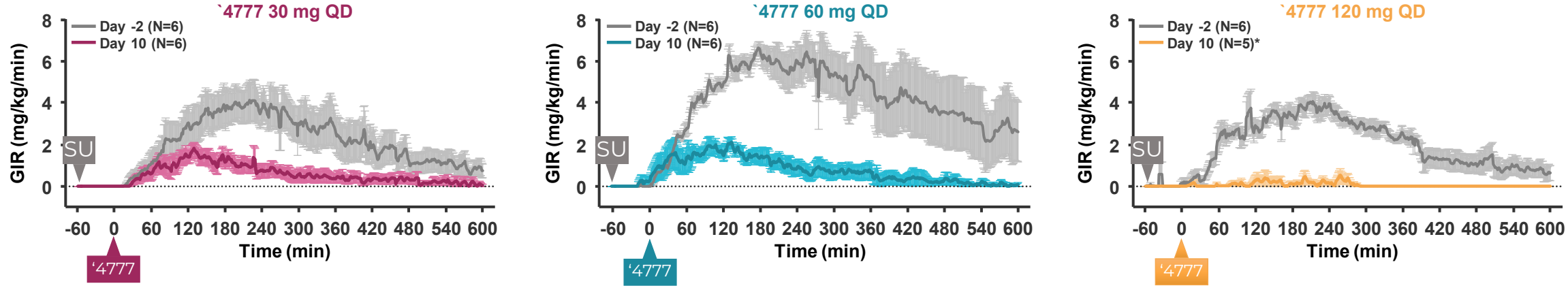


Data represent mean ± SEM; PBO: Placebo; QD: Once daily
* n=1 subject withdrew consent (not treatment related)

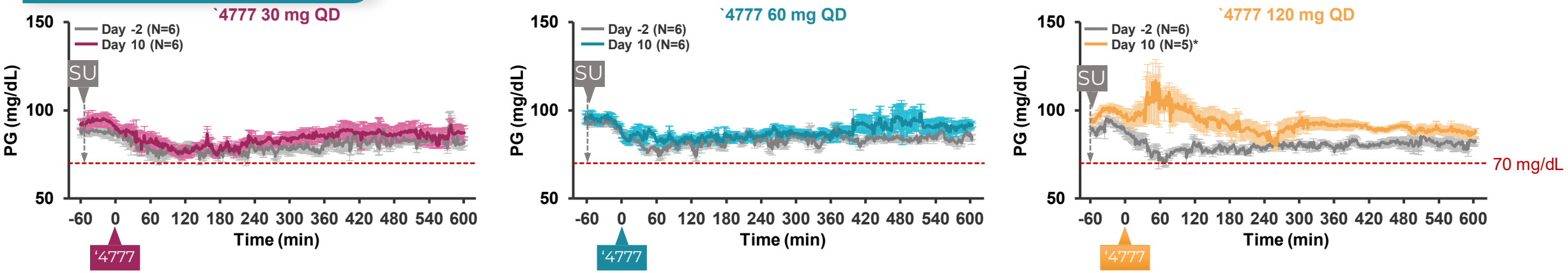
CRN04777 Reversed SU-Induced Hyperinsulinism in a Pharmacologic Model of Congenital HI

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

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



Plasma Glucose (PG)

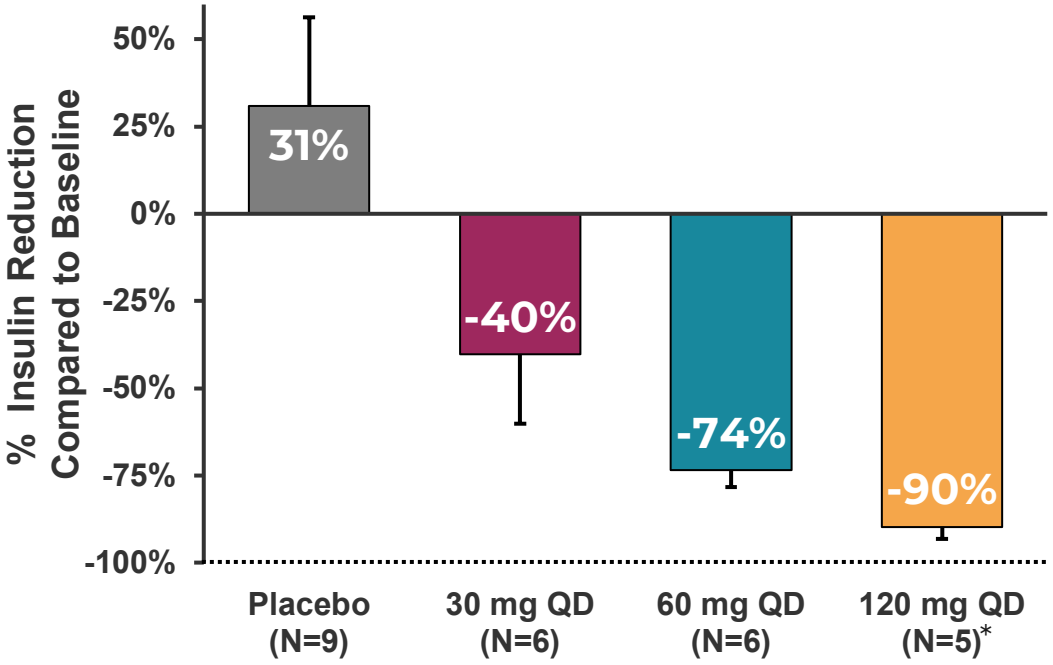


Solid line in each figure represents the mean value; shaded area: SEM
* n=1 subject withdrew consent (not treatment related)

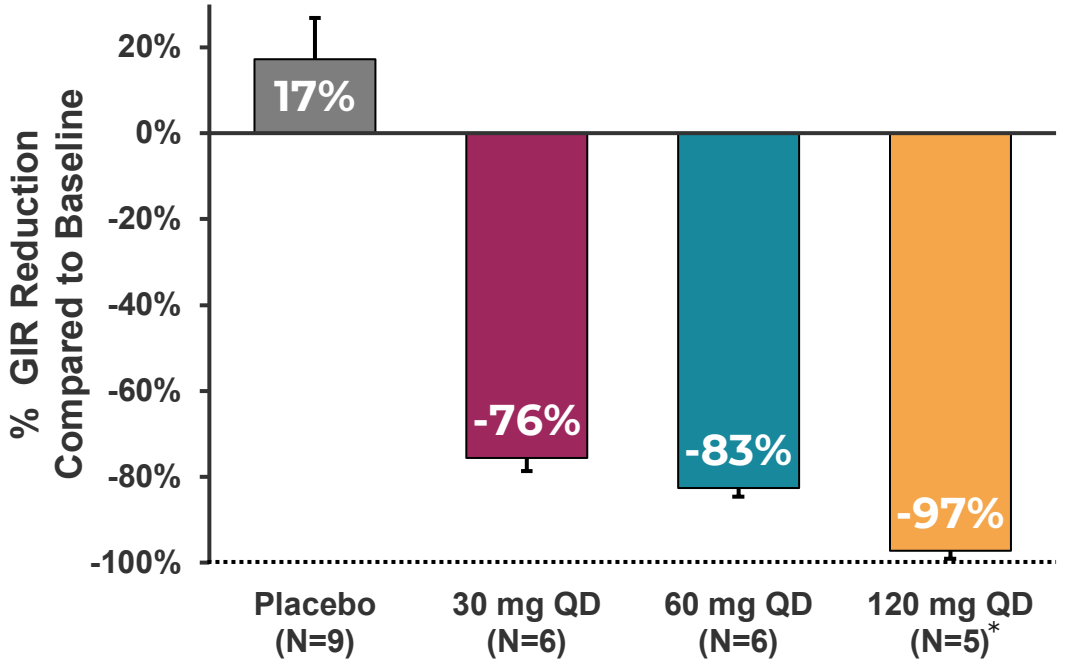
Dose-Dependent Reduction in IV Glucose Support Needed to Maintain Normal Blood Glucose Levels

CRN04777 inhibited SU-induced insulin secretion & eliminated the need for IV glucose support

Change in Insulin ($AUC_{-55-120min}$)



Change in Glucose Infusion Rate (AUC_{0-10h})



Data shown are mean ± SEM, reduction of each subject's AUC on Day 10 vs. baseline (Day -2); SU: sulfonylurea; GIR: glucose infusion rate QD: once daily; AUC: area under the curve; * n=1 subject withdrew consent (not treatment related)

SU Challenge / Glucose Clamp Study Designed to Mirror the Congenital HI Patient Experience

Crinetics' goal is to obviate the need for IV dextrose and/or feeding tubes

Mirroring Patient Experience

- Sulfonylurea recapitulates the effects of the most common genetic mutations in congenital HI patients by stimulating excess insulin secretion
- Without CRN04777, direct glucose support was needed to maintain glucose in the normal range, ***modeling the experience of patients*** who are dependent on glucose infusions (IV or enteral)

From Congenital Hyperinsulinism International's 2022 Feeding Tube Awareness Campaign

SU: sulfonylurea

Conclusions from CRN04777 Phase 1 Program

Objectives:

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

CRN04777 was well tolerated in the Phase 1 program

Favorable pharmacokinetics results support once-daily dosing

- **Rapidly absorbed after oral administration (t_{max} ~1-3 hrs.)**
- **Half-life of ~40 hours**

Demonstrated pharmacologic proof-of-concept for SST5 agonism

- **Dose dependent reduction in fasting insulin observed, which led to increases in fasting plasma glucose**
- **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**

Next Steps: Advancing Towards Program in Congenital HI Patients

1. Discuss program data package with global regulators
2. Initiate program in congenital HI patients (anticipated in 2H22)
3. Continued engagement with international congenital HI patient advocacy groups and Centers of Excellence

Pipeline Targets Multi-Billion $ Total Addressable Market with Internally Discovered Drug Candidates

NCE patent portfolio expected to provide protection into the 2040s

PROGRAM	Development Stage (Potential Registrational Endpoints)				Prevalence	
	Preclin	Phase 1	Phase 2	Phase 3	US Total	Global Range per 100,000
Paltusotine (SST2 agonist)		Pharmacologic POC				
Acromegaly		IGF-1 normalization			26K	2.8 - 13
Carcinoid Syndrome		Diarrhea & Flushing			33K	3.7 – 9.7
Nonfunctional NETs		Anti-tumor activity			138K	17 – 46
CRN04777 (SST5 agonist)						
Congenital Hyperinsulinism		Hypoglycemia/GIR			1.5 – 2K	0.64 – 1.3
Syndromic Hyperinsulinism		Hypoglycemia/GIR			2K	Variable
CRN04894 (ACTH antagonist)						
Congenital Adrenal Hyperplasia		A4, 17OHP, GC use			27K	6.7 – 10
Cushing's Disease		Cortisol			10K	2.5 – 3.8
PTH antagonist					1° HPT: 480k 2° HPT: 13.2M HHM: 50-200k/yr.	
Hyperparathyroidism, HHM		Ca^{++}				

Radionetics Oncology

Spin-out company advancing nonpeptide precision radiotherapeutics targeting oncology indications.

NETs: Neuroendocrine tumors; GIR: Glucose infusion rate; GC: Glucocorticoid; A4: Androstenedione; 17OHP: 17-hydroxyprogesterone; HHM: Humoral hypercalcemia of malignancy

2021 Accomplishments and Anticipated 2022 Milestones

2021 Accomplishments	2022 Accomplishments & Anticipated Milestones
✓ Initiated Ph 3 PATHFNDR program of paltusotine in acromegaly	✓ Strategic partnership for paltusotine in Japan
✓ Phase 1 POC data for CRN04894	✓ CRN04777 MAD data in 1Q22
✓ Phase 1 POC data for CRN04777	CRN04894 MAD data in 2Q22
✓ Launched Radionetics Oncology spinout	CRN04777 patient study initiation in 2H22
✓ Strengthened balance sheet and extended cash runway into 2024	CRN04894 patient study initiation in 2H22
✓ Identified potential development candidate PTHR1 antagonists for hyperparathyroidism and HHM	Initiate IND enabling studies for PTHR1 antagonist

POC: Proof-of-concept; HHM: Humoral hypercalcemia of malignancy; MAD: Multiple-ascending dose