Crinetics Pharmaceuticals

CORPORATE PRESENTATION

September 2021

SAFE HARBOR STATEMENT

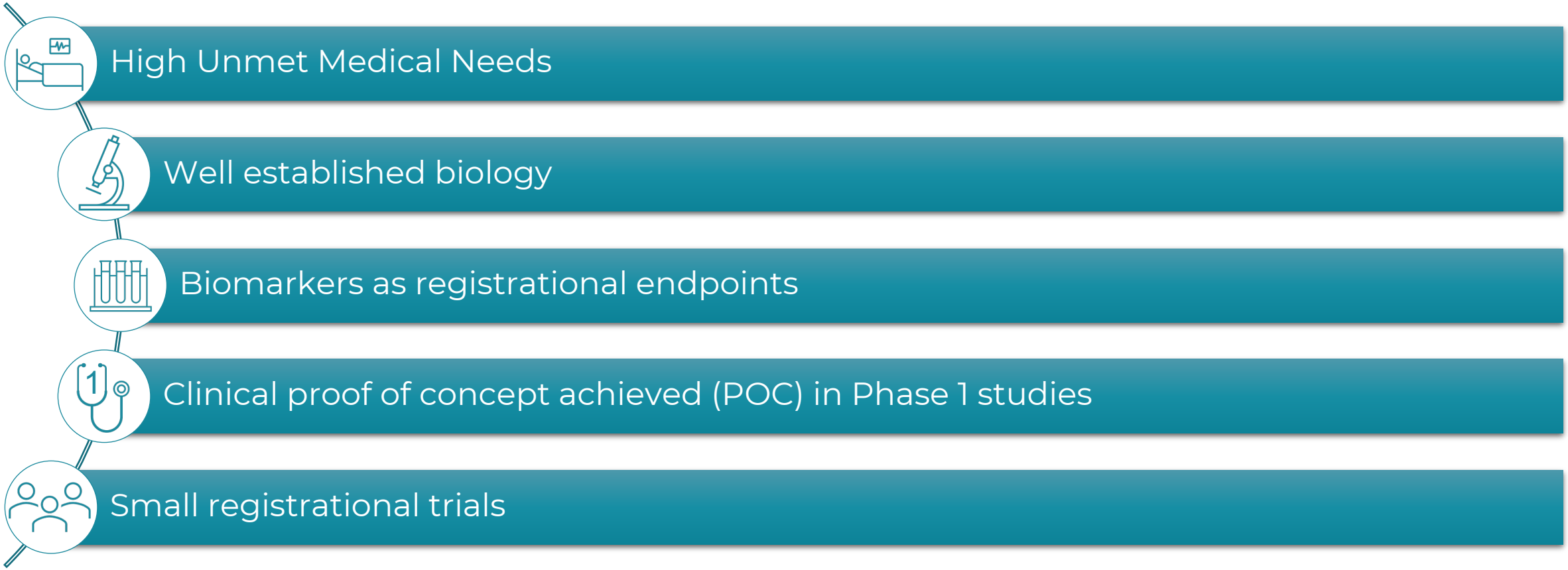
This presentation contains forward-looking statements. Crinetics cautions you that statements contained in this presentation regarding matters that are not historical facts are forward-looking statements. These statements are based on the company's current beliefs and expectations. Such forward-looking statements include, but are not limited to, statements regarding: the potential benefits of paltusotine for acromegaly patients and patients with carcinoid syndrome; ; the potential for the PATHFNDR program to support registration of paltusotine in the United States and Europe for all acromegaly patients who require pharmacotherapy; the expected timing of topline data from the PATHFNDR-1 trial; the potential to initiate a trial of paltusotine in patients with carcinoid syndrome due to NETs and the expected timing thereof; the potential benefits of CRN04894 in patients across multiple indications and the expected timing of the advancement of such program, including the potential to enroll a Phase 1 trial of CRN04894, report data therefrom, and the timing thereof; the potential benefits of CRN04777 in patients with congenital hyperinsulinism and the expected timing of the advancement of such program, including the potential to enroll a Phase 1 trial of CRN04777, report data therefrom, and the timing thereof; the potential benefits of PTH receptor antagonists for patients with primary hyperparathyroidism, HHM, secondary hyperparathyroidism due to chronic kidney disease and other diseases of excess PTH receptor activation; plans to initiate IND-enabling studies in 2022 for the PTH receptor antagonist program; the potential for any of our ongoing clinical trials to show safety or efficacy; and our plans to identify and create new drug candidates for additional diseases. In some cases, you can identify forward-looking statements by terms such as "may," "believe," "anticipate," "could," "should," "estimate," "expect," "intend," "plan," "project," "will," "forecast" and similar terms. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, without limitation: the risk that preliminary results of preclinical studies or clinical trials do not necessarily predict final results and that one or more of the clinical outcomes may materially change as patient enrollment continues, following more comprehensive reviews of the data, and as more patient data become available; potential delays in the commencement, enrollment and completion of clinical trials and the reporting of data therefrom; the FDA or other regulatory agencies may require one or more additional clinical trials of paltusotine or suggest changes to our planned Phase 3 clinical trials prior to and in support of the approval of a New Drug Application or applicable foreign regulatory approval; advancement of paltusotine into a a trial for carcinoid syndrome are dependent on and subject to the receipt of further feedback from the FDA; the COVID-19 pandemic may disrupt our business and that of the third parties on which we depend, including delaying or otherwise disrupting our clinical trials and preclinical studies, manufacturing and supply chain, or impairing employee productivity; our dependence on third parties in connection with product manufacturing, research and preclinical and clinical testing; the success of our clinical trials, nonclinical studies and preclinical studies for paltusotine, CRN04894, CRN04777, our PTH receptor antagonist program and our other product candidates; regulatory developments in the United States and foreign countries; unexpected adverse side effects or inadequate efficacy of our product candidates that may limit their development, regulatory approval and/or commercialization; our ability to obtain and maintain intellectual property protection for our product candidates; we may use our capital resources sooner than we expect; and other risks described under the heading "Risk Factors" in documents we file from time to time with the Securities and Exchange Commission. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. All forward-looking statements are qualified in their entirety by this cautionary statement, which is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and, except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

<u>Mission:</u> To build the leading endocrine company that consistently pioneers new therapeutics to help patients better control their disease and improve their daily lives

Strategy: Drugs Built from Scratch for Purpose

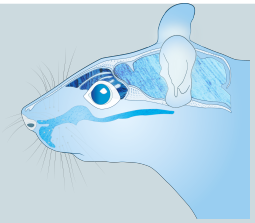
We aim to discover, develop and commercialize drugs for endocrine indications with:



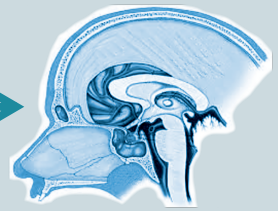
Endocrinology Development Strategy: Focus on Hormone Levels from Preclinical to Approval

Preclinical POC

ΔHormones,
PK, Safety



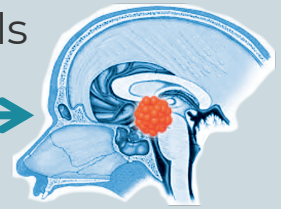
Phase 1 Healthy Volunteers



Phase 1 Healthy Volunteer Safety, POC

ΔHormones,
PK, Safety

Phase 2/3 Trials (Patients)



Phase 2/3 Safety, Disease Efficacy

ΔHormones, PROs,
PK, Safety

Pipeline Targets Multi-Billion $ Global Market Opportunity with Home Grown Pipeline

NCE patent portfolio provides protection into the 2040s

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
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		Adrenal Androgens/ Glucocorticoid Use	27K	6.7 – 10
CRN04777 (SST5 agonist)				
Congenital Hyperinsulinism		GIR/ Hypoglycemic Events	1.5 – 2K	0.64 – 1.3
Syndromic Hyperinsulinism		GIR/ Hypoglycemic Events	2K	Variable
PTH antagonist				
1° & 2° Hyperparathyroidism, HHM		Serum Calcium, (tbd for 2° HPT)	1° HPT: 480k 2° HPT: 13.2M HHM: 50-200k/yr	

Ongoing discovery efforts target future indications include nonfunctional pituitary adenomas, polycystic kidney disease and more.

PALTUSOTINE: AN INVESTIGATIONAL, POTENTIAL FIRST-IN-CLASS, ORAL NONPEPTIDE SST2 AGONIST

Acromegaly

Carcinoid syndrome

Nonfunctional neuroendocrine tumors

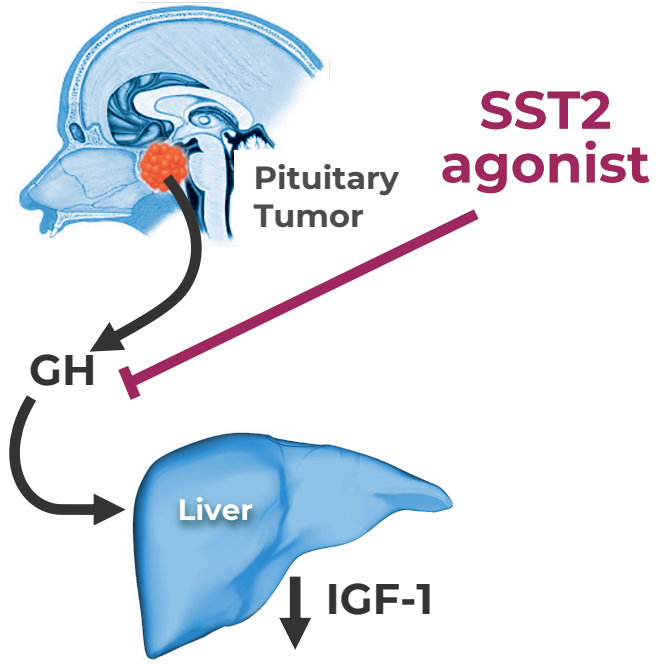
Acromegaly and NETS are Currently Treated with Injected SST2 Peptide Agonists

Acromegaly

- Caused by benign pituitary tumor that secretes excess growth hormone (GH)
- Excess GH causes excess secretion of insulin-like growth factor-1 (IGF-1)

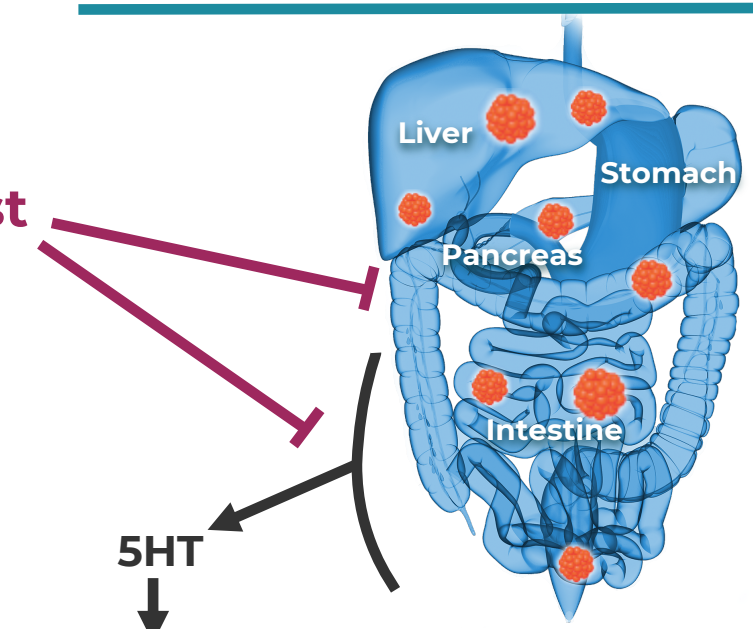
Results in:

1. Bone and cartilage overgrowth
2. Organ enlargement
3. Changes in glucose and lipid metabolism
4. Abnormal growth of hands and feet
5. Alteration of facial features



US Prevalence: **26,000**

Neuroendocrine Tumors (NETs)

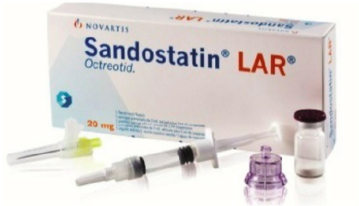


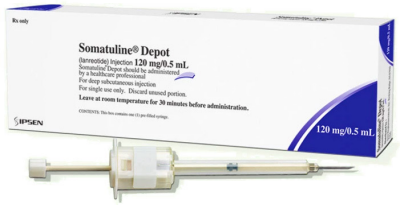
- NETs arise from aberrant enteroendocrine cells in GI, pancreas or lungs
- In ~19% of cases, tumors are associated with excess secretion of serotonin and other hormones resulting in carcinoid syndrome
- Majority of tumors are "nonfunctional" and not associated with secretory syndrome
- Patients with grade 1 and 2 NETs and distant metastases have a 5-year survival ranging from 30-70%

US Prevalence

Carcinoid Syndrome:	33,000
Nonfunctional tumors:	138,000
Total	**171,000**

~$3B Market Despite Limitations of Current Therapies



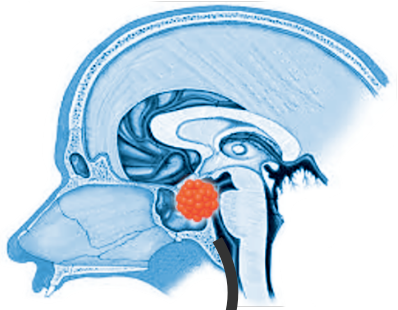


Sandostatin (octreotide)	Somatuline (lanreotide)	Somavert (pegvisomant)	MYCAPSSA (oral octreotide)
NOVARTIS $1.4B	IPSEN Innovation for patient care $1.4B	Pfizer $277M	CHIASMA $1M
Monthly intramuscular 5-mL vial; 1½" 19-gauge needle	Monthly deep subcutaneous .2-.5ml; 18-gauge needle	Daily injections 1 ml; 28 – 31-gauge needle not supplied	Twice daily oral capsule
Painful injections. Injection site reactions **Inconvenient monthly visits** to physician's office interrupts normal life **Limited efficacy,** as many patients experience return of symptoms near end of month	**Painful injections.** Injection site reactions **Inconvenient monthly visits** to physician's office interrupts normal life **Limited efficacy,** as many patients experience return of symptoms near end of month	**Inconvenient.** Daily dose kits require refrigeration. Patients often must buy a second refrigerator for storage, making travel difficult.	**Food effect.** Cannot be taken <1 hour before eating or <2 hours after eating[1] **Limited efficacy**, as 42% of pivotal study patients did not maintain IGF-1 biochemical response after switching to MYCAPSSA from injectables[1] **Multiple drug-drug interactions**[1] **Cold chain distribution**[1]
Approval date: 1988, 1998(LAR)	**Approval date:** 2007	**Approval date:** 2003	**Approval date:** 2020

[1] MYCAPSSA Label

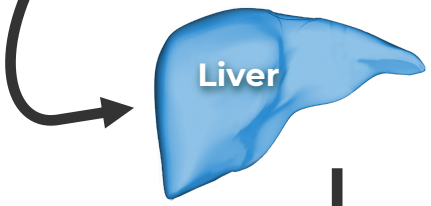
Endocrinology Invented Biomarkers! Pharmacologic POC in Phase 1 is Our Goal

Acromegaly



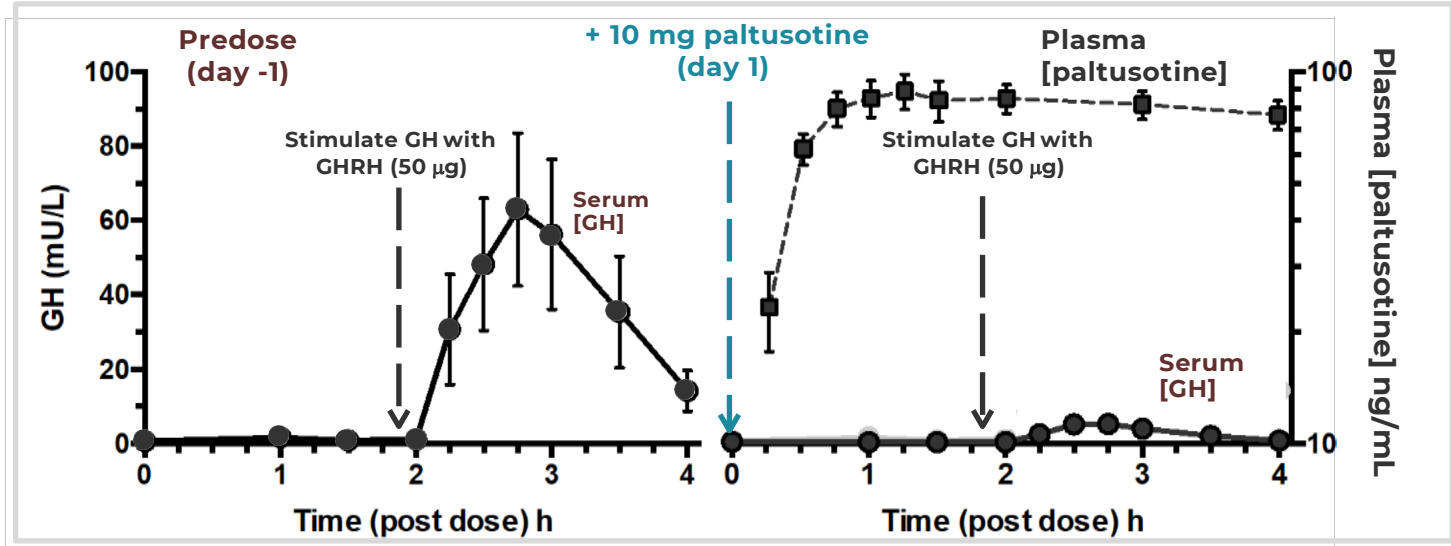
Paltusotine

GH

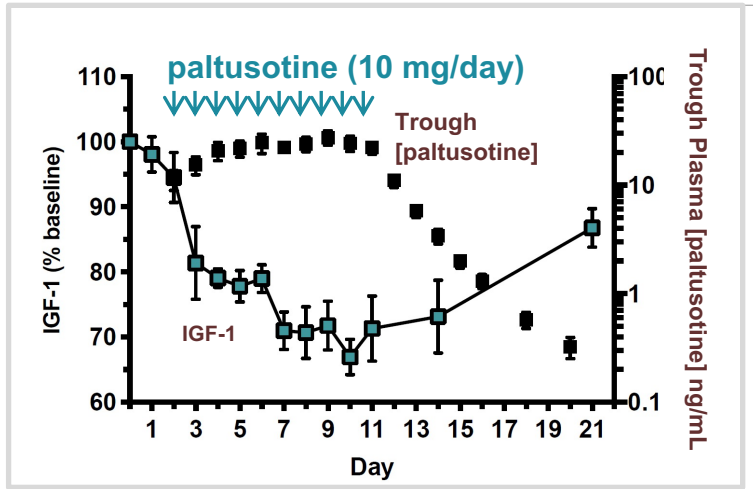


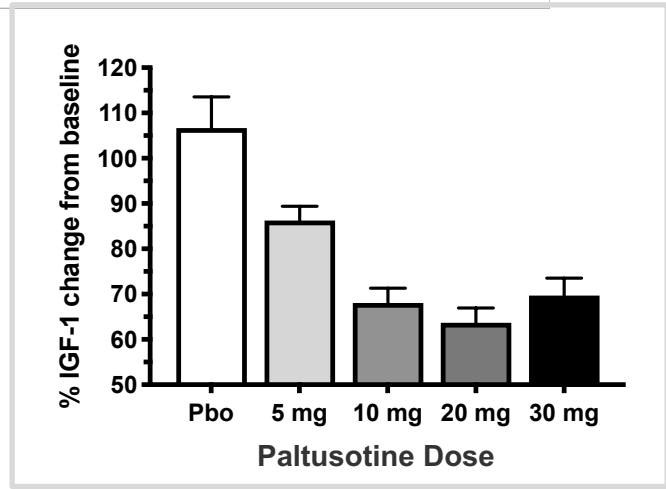
IGF-1
(1° Registration Endpoint)

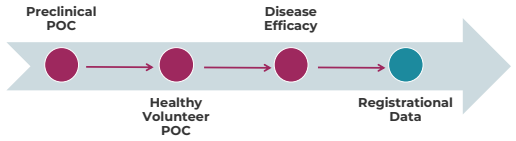
Phase 1 SAD Data: Suppression of GH



Phase 1 MAD Data: Suppression of IGF-1

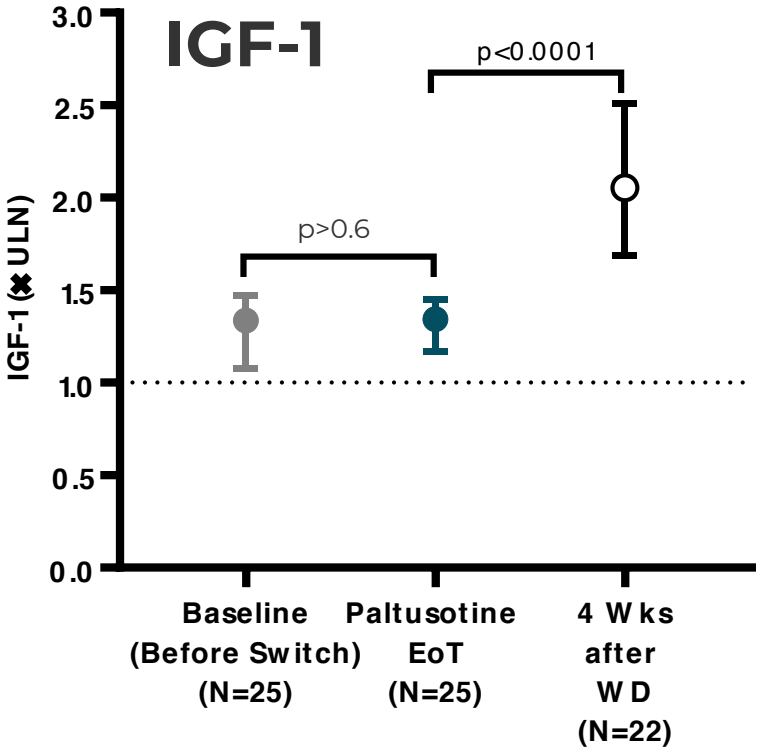


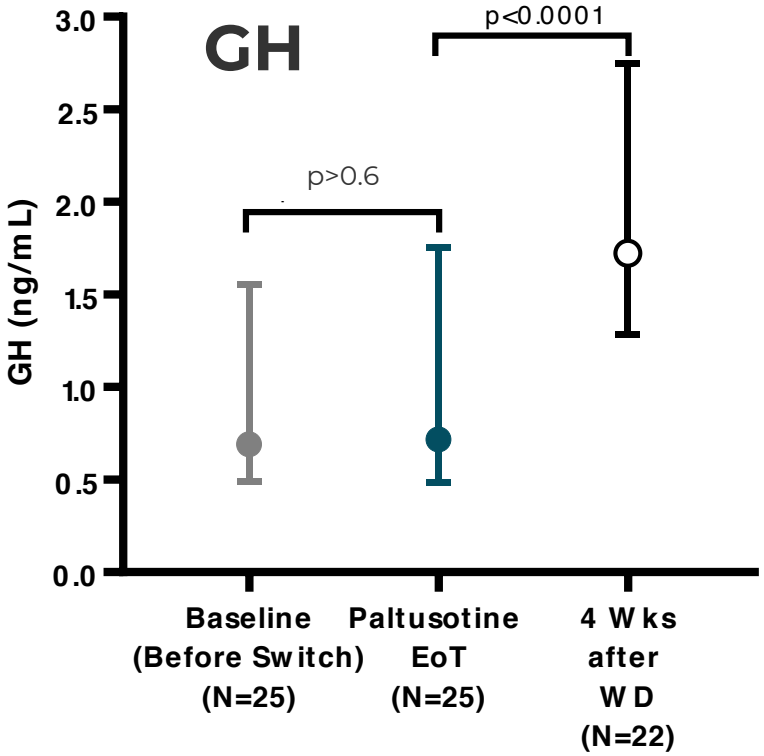




Phase 2 ACROBAT Edge Study Met Primary Endpoint

Hormone suppression maintained after switching from injected SOC to oral paltusotine





Data presented are median (Interquartile Range [IQR]: 25th percentile, 75th percentile) from the EDGE study's primary analysis population. EoT = End of Treatment defined as Week 13 (Visit 14) or last on treatment value carried forward (LOCF). Wks after WD is defined as Week 17 or result at least 22 days after last dose.
Note: p-values are based on non-parametric Wilcoxon Sign Rank test of whether the median change is different from zero.

Key Takeaways from ACROBAT Advance Open Label Extension Study as of August 31, 2021 Data Cut

1. Paltusotine maintained IGF-1 suppression for up to 51 weeks (comparable to injected SOC)
2. Paltusotine has been generally well tolerated
3. High rate of participation with 41 of 49 (84%) eligible patients enrolling as of August 31, 2021
4. High rate of patient retention

Data from ACROBAT Advance to be presented at the Society for Endocrinology BES Conference in Nov 2021

PATHFNDR Phase 3 Program: Designed to Support Potential for Broad First-Line Medical Therapy

PATHFNDR: Paltusotine Acromegaly Therapy Featuring a Non-Invasive Daily Regimen

Two double-blind, placebo-controlled studies planned to support broad labeling in the U.S. and Europe for use in all acromegaly patients who require pharmacotherapy

PATHFNDR-1: Switching from SOC

Evaluate safety and efficacy of paltusotine in acromegaly patients switching from injectable octreotide or lanreotide depots, who are currently *biochemically controlled*

(N=52, treatment duration 9 months, 1° endpoint % responders vs placebo)

PATHFNDR-2: Untreated Patients

Evaluate safety and efficacy of paltusotine in untreated acromegaly patients who are *biochemically uncontrolled*

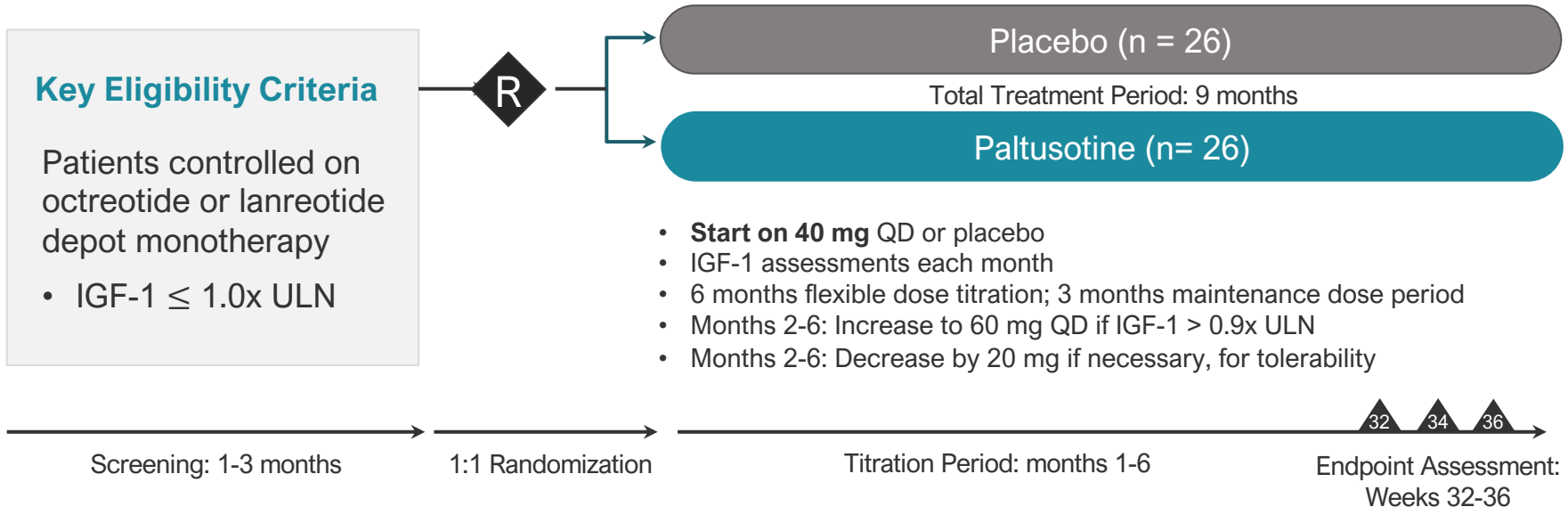
(N=76, treatment duration 6 months, 1° endpoint % responders vs placebo)

PATHFNDR-1: Enabling Switching from SOC

Key Eligibility Criteria

Patients controlled on octreotide or lanreotide depot monotherapy

- IGF-1 ≤ 1.0x ULN



Endpoints

Primary:

- Percent responders vs. placebo
  - Responders: mean IGF-1 ≤ 1.0x ULN at weeks 32, 34, 36

Secondary:

- Change from baseline IGF-1
- Proportion of patients with GH < 1 ng/mL at endpoint assessment out of those <1 ng/mL at screening
- Change from baseline in total Acromegaly Symptoms Diary (ASD) score

Statistical powering:

- Power > 90%

Rescue Criteria

Patient is rescued with an injectable and classified as a non-responder if following criteria are met at **60 mg dose**:

- Two consecutive IGF-1 ≥ 1.3x ULN

AND

- Exacerbation of acromegaly clinical signs/symptoms

Timelines

- Start Q2 2021
- Topline Data expected in 2023
- Trial to be followed by an OLE for eligible patients

ULN: Upper Limit of Normal; PBO: Placebo; OLE: Open label extension

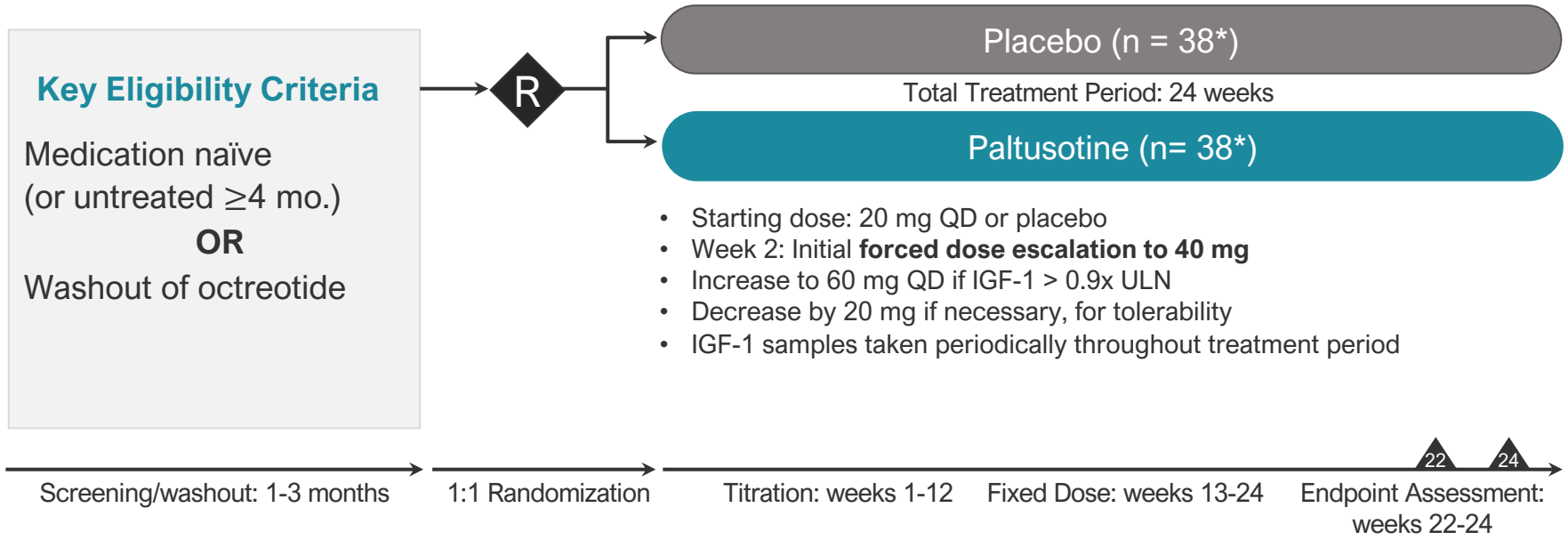
PATHFNDR-2: Enabling Use in Untreated Patients

Key Eligibility Criteria

Medication naïve
(or untreated ≥4 mo.)

OR

Washout of octreotide



Endpoints

Primary:

- Percent responders vs. placebo
  - Responders: mean IGF-1 ≤ 1.0x ULN during weeks 22-24

Key Secondary:

- Change from baseline IGF-1

Secondary:

- Proportion of patients with GH <1 ng/mL at endpoint assessment
- Change from baseline in total Acromegaly Symptoms Diary (ASD) score

Statistical powering:

- Power estimate = 90%

*Optional sample size re-estimation based on subgroup enrollment

Rescue Criteria

Based on assessments of:

- IGF-1 levels
- Clinical signs/symptoms

While on the 60mg dose

Timelines

- Start 2H 2021
- Topline Data expected in 2023
- Trial to be followed by an OLE for eligible patients

ULN: Upper Limit of Normal; PBO: Placebo; OLE: Open label extension

Anticipated Paltusotine Milestones

1. Initiate PATHFNDR-1: switching from SOC ✓
2. Initiate PATHFNDR-2: use in untreated patients
   (anticipated in 2H 2021)
3. Initiation of Phase 2 NETs trial in carcinoid syndrome
   (end of 2021)
4. Report topline data from PATHFNDR-1 & 2 trials
   (expected in 2023)

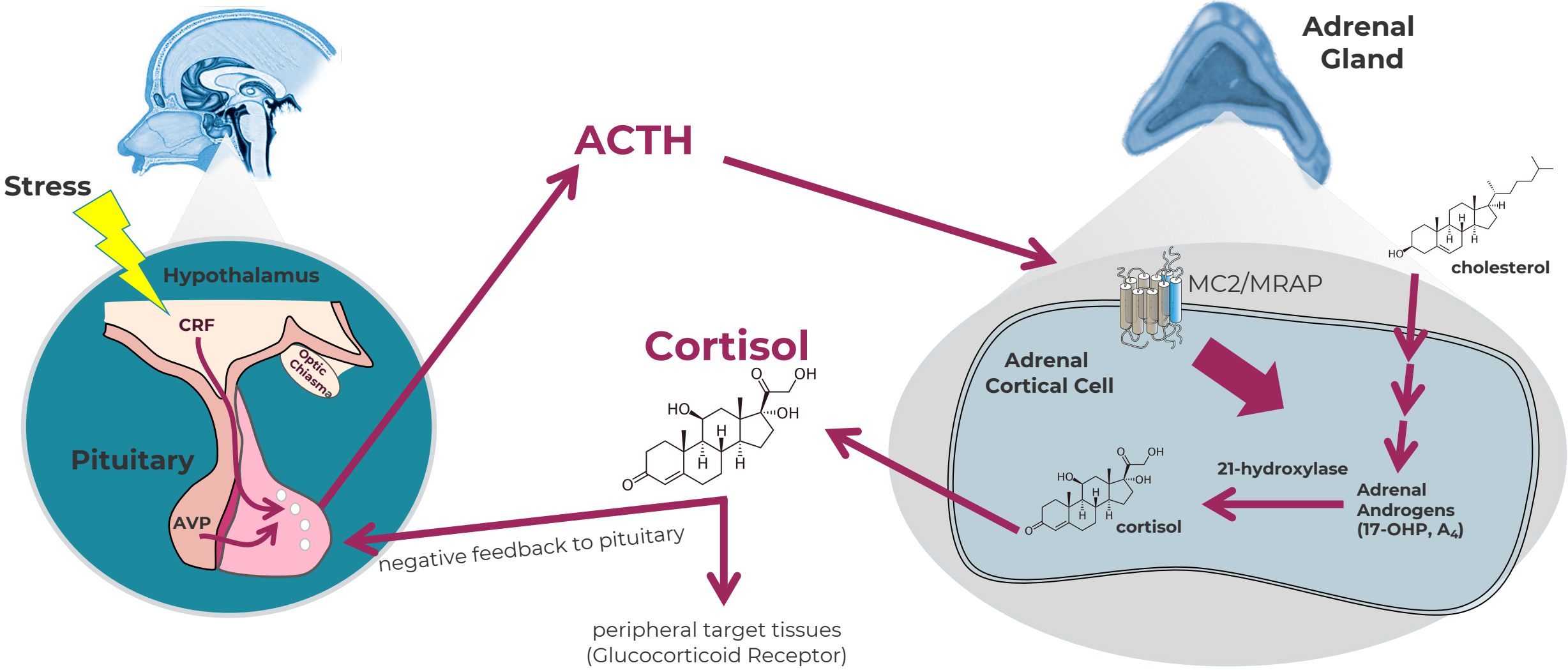
CRN04894: AN INVESTIGATIONAL, POTENTIAL FIRST-IN-CLASS, ORAL NONPEPTIDE ACTH ANTAGONIST

Congenital adrenal hyperplasia (CAH)

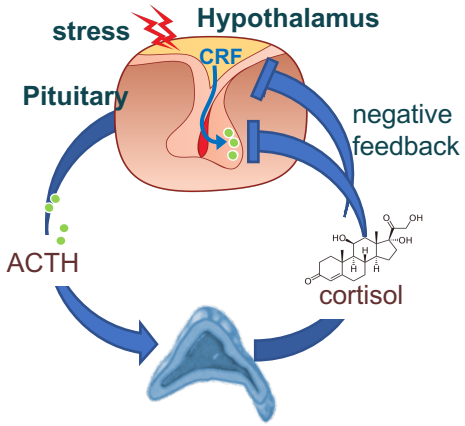
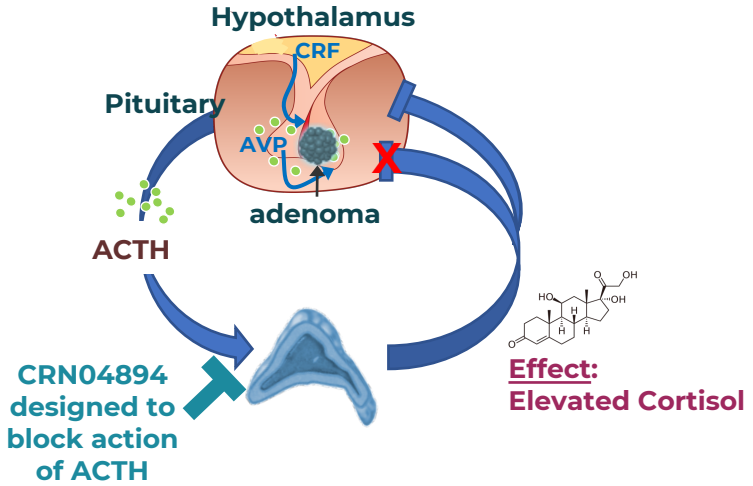
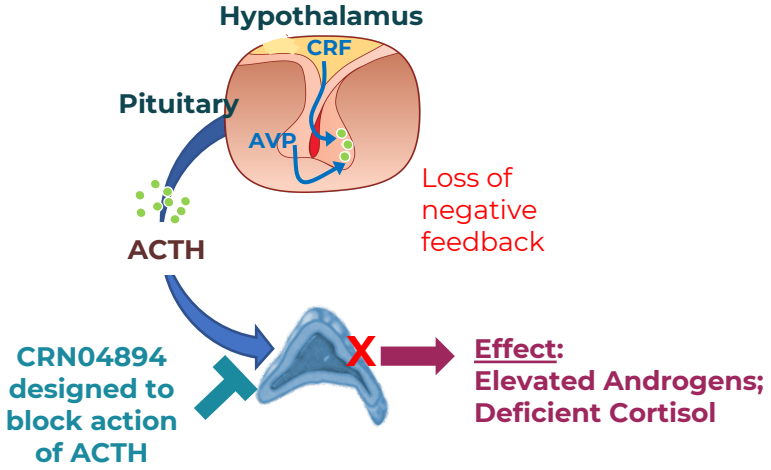
Cushing’s disease (CD)

Other conditions of ACTH excess

The Hypothalamic-Pituitary-Adrenal (HPA) Axis is the Body's Emergency Response System for Stress

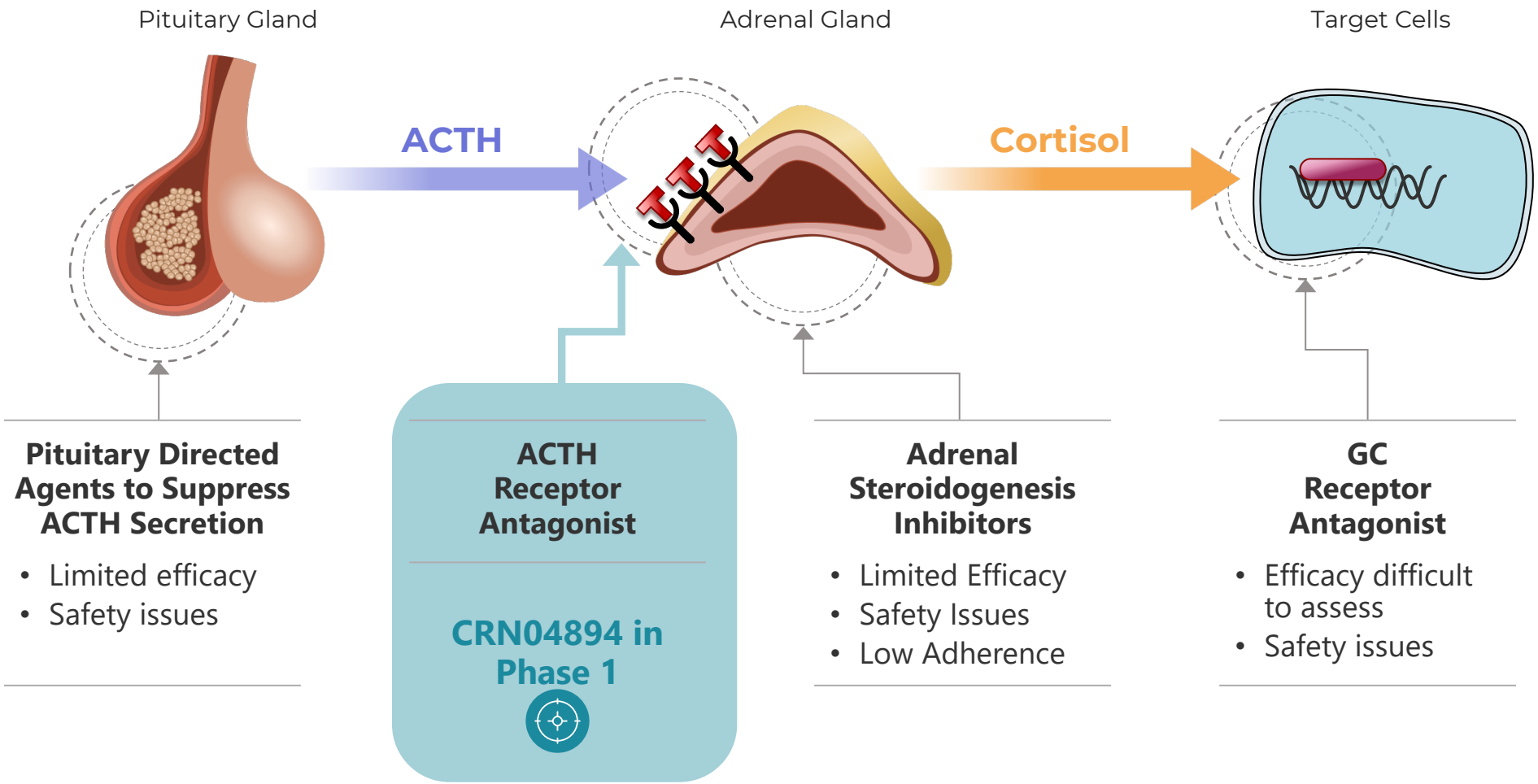


Hypothesis: An Oral, Selective ACTH Antagonist Will Have Utility in Treating Diseases of ACTH

Normal	Cushing's Disease (CD)	Congenital Adrenal Hyperplasia (CAH)
		
ACTH Range = 5 – 60 pg/mL [1, 4, 5]	ACTH Range = 20-200 pg/mL [1]	ACTH Range = 150-500 pg/mL [2, 3]
Cause	ACTH-secreting pituitary tumor	Inability to produce cortisol leads to loss of negative feedback & excess ACTH
US Prevalence (global incidence per 100,000)	10k (2.5-3.8)	27k (6.7-10.0)
Symptoms	Central obesity and round face; Dorsal and supraclavicular fat pads; Hypertension; Stretch marks; Bone loss; Hyperglycemia; Psychiatric disturbances	Adrenal insufficiency; Infertility; Hirsutism; Short stature; Precocious puberty; Adrenal rest tumors

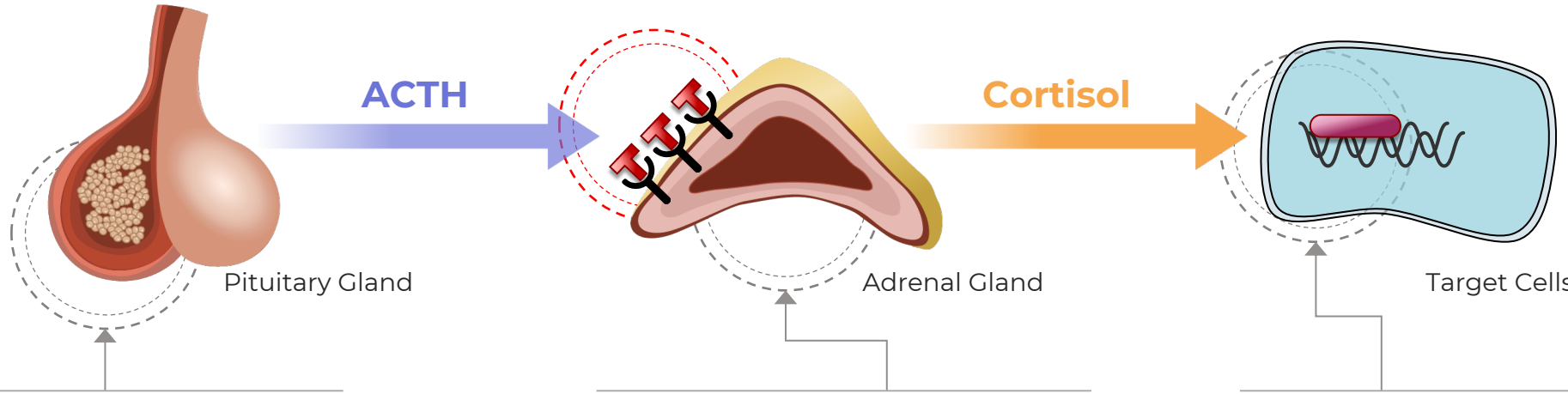
[1] Raff et al. Compr Physiol 2015, [2] Petersen Acta Pediatr Scand 1981, [3] NBIX ENDO Online 2020 presentation, [4] Oster et al., Endocrine Reviews 2017, [5] UpToDate Reference, [6] Oelkers et al, JCEM 1988, [6] Alia et. al Clinical Endocrinology 2006

CRN04894: First-in-Class ACTH Antagonist for ACTH Driven Diseases



There Are No ACTH Receptor Blocking Agents Available to Treat ACTH Driven Diseases

All currently approved agents and agents in development act upstream or downstream of ACTH



Pituitary Directed Agents to Suppress ACTH Secretion

Available: glucocorticoids, pasireotide, cabergoline
- Limited efficacy
- Safety issues

In Development: CRF antagonists

Adrenal Steroidogenesis Inhibitors

Available: ketoconazole, metyrapone/osilodrostat
- Limited Efficacy
- Safety Issues
- Low Adherence

In Development: levoketoconazole

Glucocorticoid Receptor Antagonist

Available: mifepristone
- Efficacy difficult to assess
- Safety issues

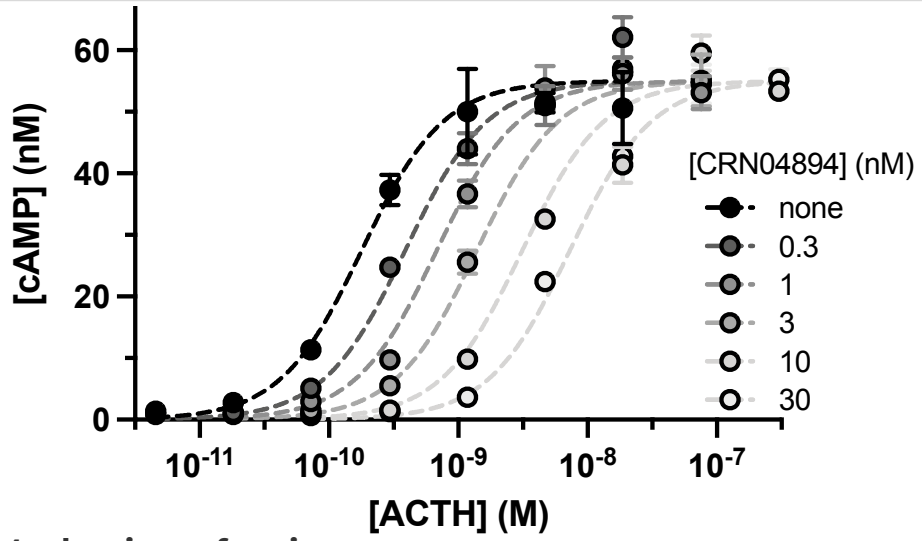
In Development: relacorilant

References: Felders et al. Lancet Diab Endo 7:300-12, 2019. Castinetti JCEM 99: 1623-1639, 2014. Castinetti JCEM 106: 2114-2123, 2021.

CRN04894 is the Only ACTH Antagonist in Clinical Development

CRN04894 was carefully crafted by Crinetics in-house discovery team

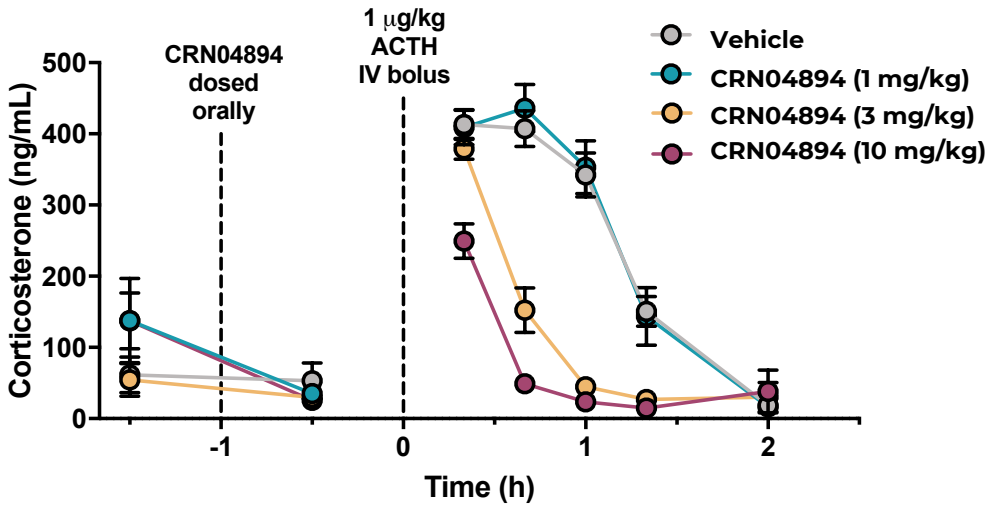
CRN04894 is a potent (K_b= 0.4 nM) competitive antagonist of ACTH signaling



Mechanism of action

- Designed to compete with ACTH for a common binding site in order to block the ACTH-induced signaling.
- Relative affinity and concentration of CRN04894 and ACTH potentially determine balance of occupancy (competitive antagonism).

Acute suppression of ACTH-induced corticosterone observed in rats



Experiment designed to mimic disease:

- CRN04894 orally administered
- Administer IV bolus of ACTH after 60 minutes
- Marked suppression of ACTH with increasing doses of CRN04894
- Analogous ACTH challenge in Phase 1 POC

CRN04894 SAD Study Design to Establish Pharmacologic Proof-of-Concept

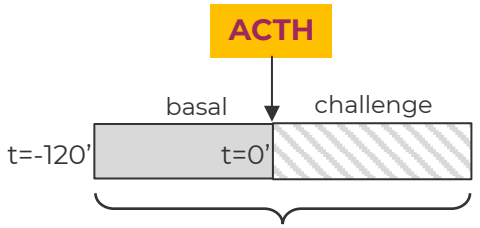
Follows Crinetics' core endocrine strategy of using hormonal biomarkers to drive development

Study Goals

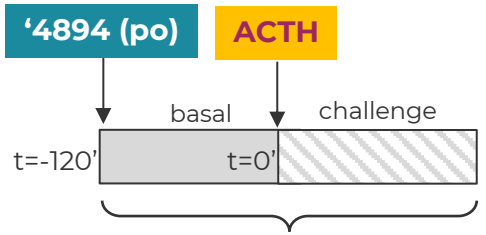
- Evaluate safety [10-80 mg]
- Evaluate pharmacokinetics: oral absorption, dose-proportional exposure, half-life [10-80 mg]
- Evaluate dose-response & PK/PD on basal cortisol [10-80 mg]
- Evaluate dose-response & PK/PD using supra-pathophysiologic ACTH challenge (250 mcg) [10-80 mg]
- Evaluate cortisol suppression with selected dose in response to disease-relevant ACTH challenge (1 mcg) [80 mg only]

ACTH Challenge Test

Baseline (Day -1)



Treated (Day 1)

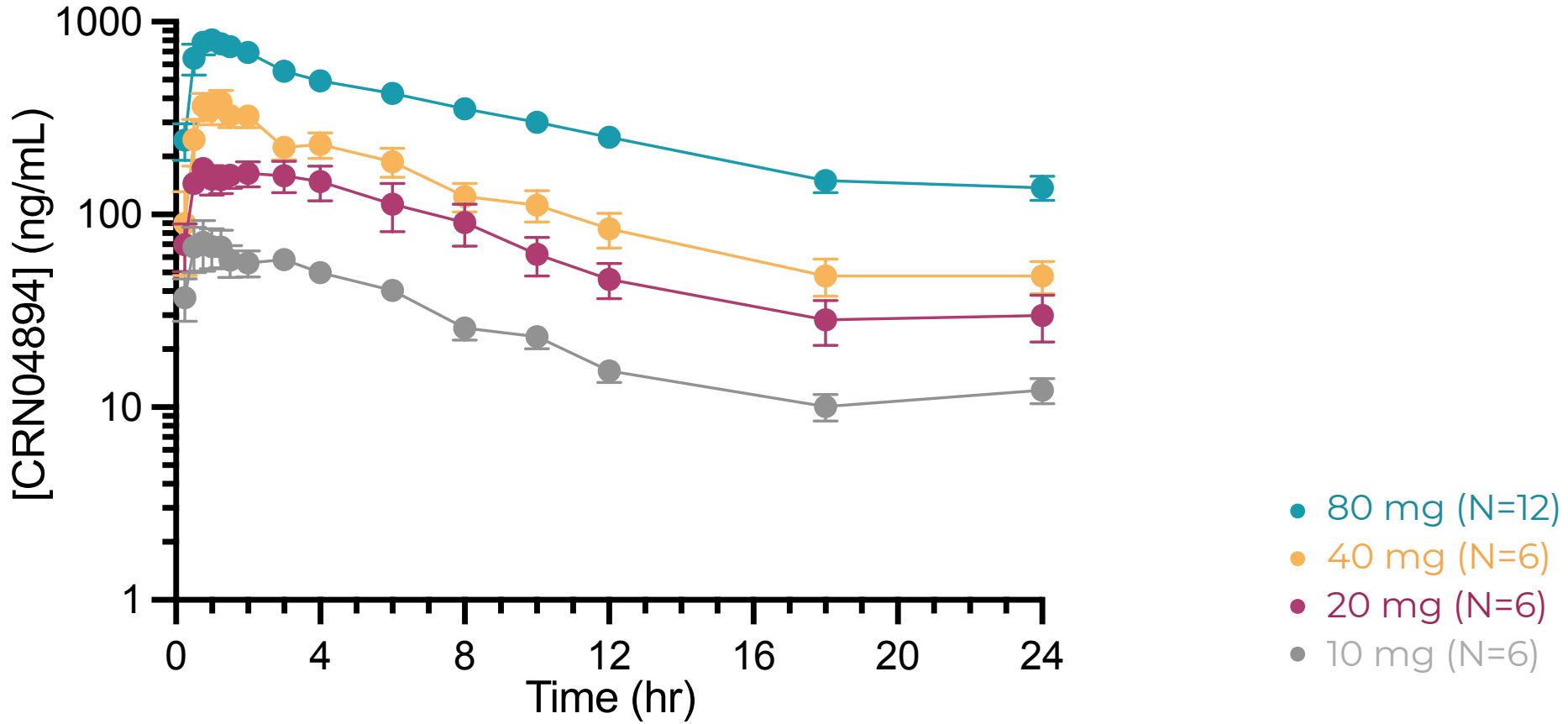


Healthy volunteers received single oral dose of CRN04894 (n=8, 6 active/2 Pbo in each cohort)

Proof of concept: dose dependent suppression of basal cortisol and ACTH-stimulated cortisol with CRN04894

PK Results: CRN04894 Showed Oral Bioavailability With Dose-Proportional Exposure

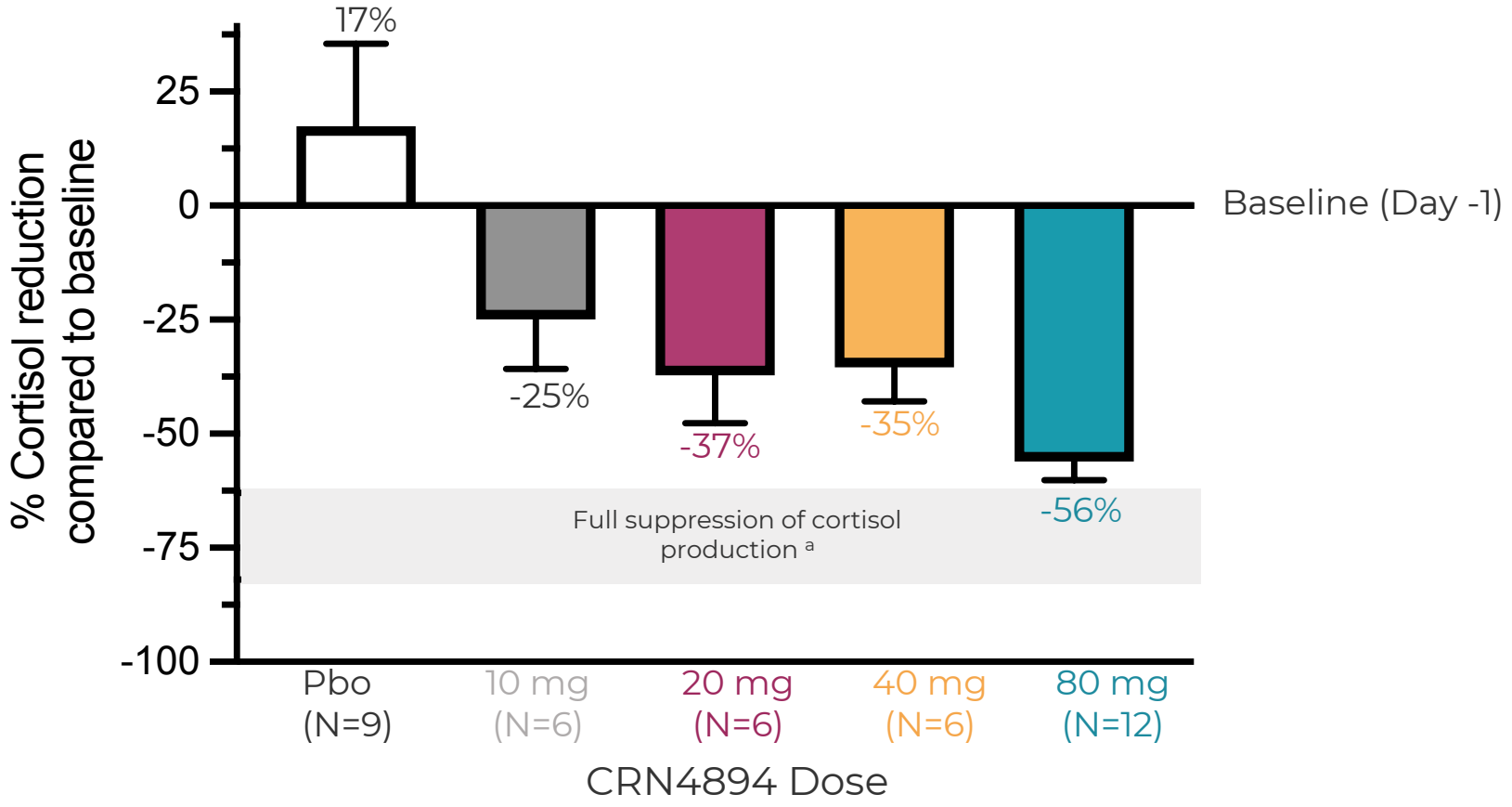
Half-life ~24 hour and t_{max} ~1 hour



Data shown are mean±SEM

CRN04894 Rapidly Reduced Basal Cortisol Output from Adrenal Glands

Acute reduction of basal cortisol (56% @ 80 mg) 2 hours after administration of CRN04894

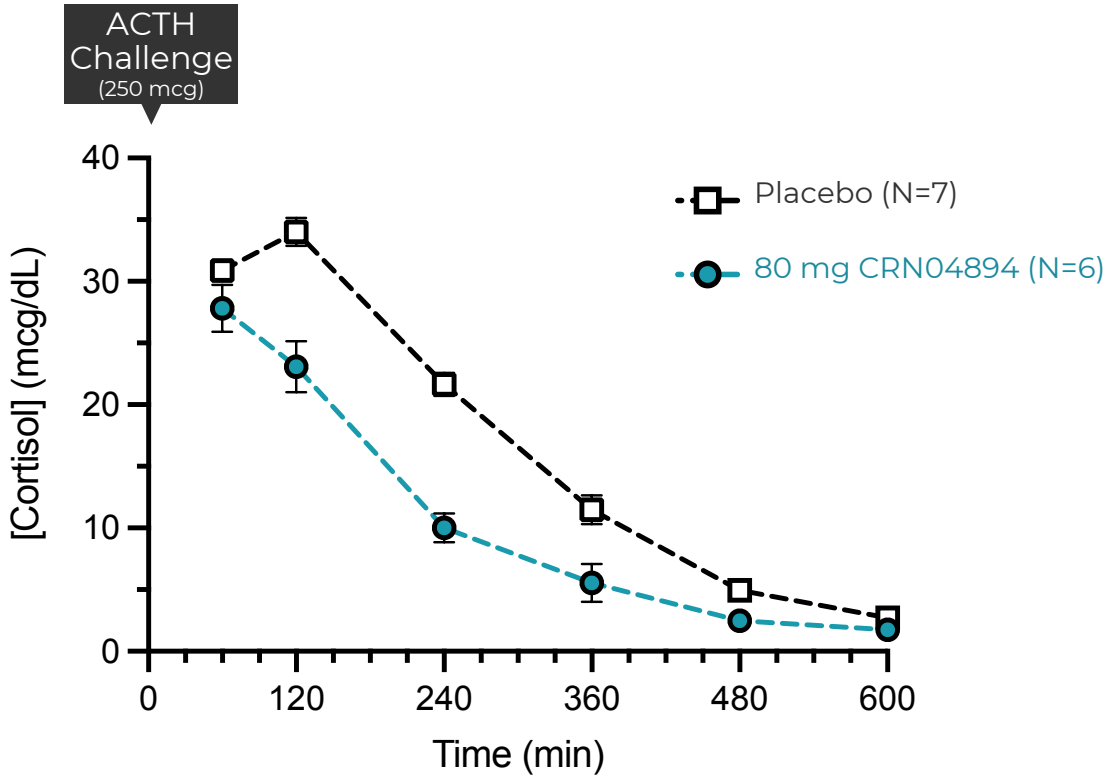


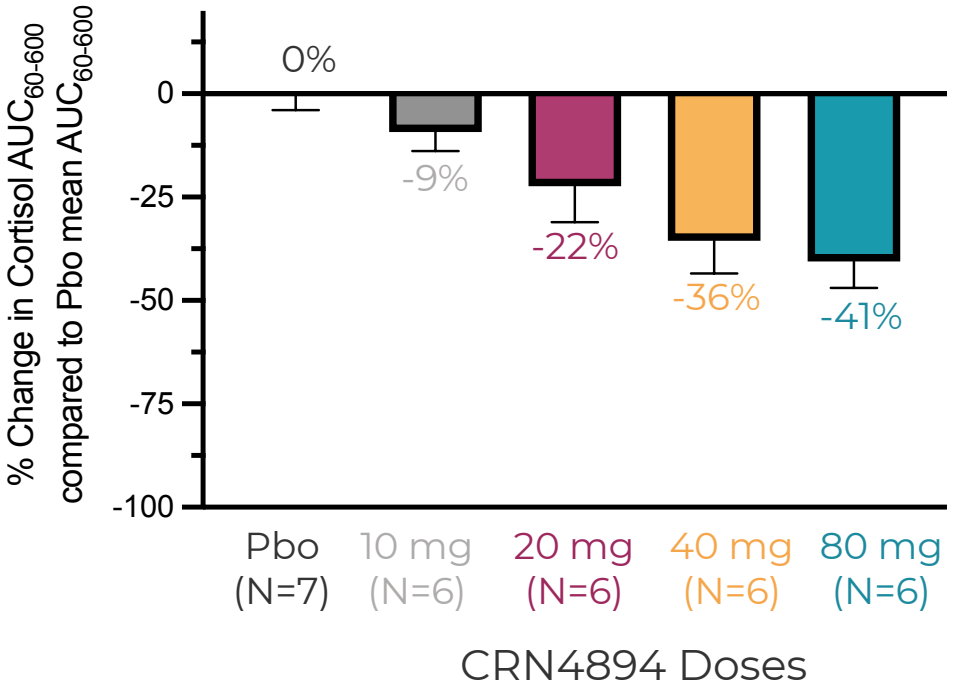
Data shown are mean±SEM

[a] Full suppression of cortisol production assumes no more cortisol is produced at time of CRN04894 dose and cortisol half-life is 66 ±18 min from McKay LI, Cidlowski JA. Pharmacokinetics of Corticosteroids. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON); 2003

Dose-Dependent Suppression of Cortisol Observed Following Supra-Pathophysiologic ACTH Challenge (250 mcg)

CRN04894 resulted in strong cortisol suppression (41% @ 80 mg) despite anticipated ACTH exposure orders of magnitude higher than disease states

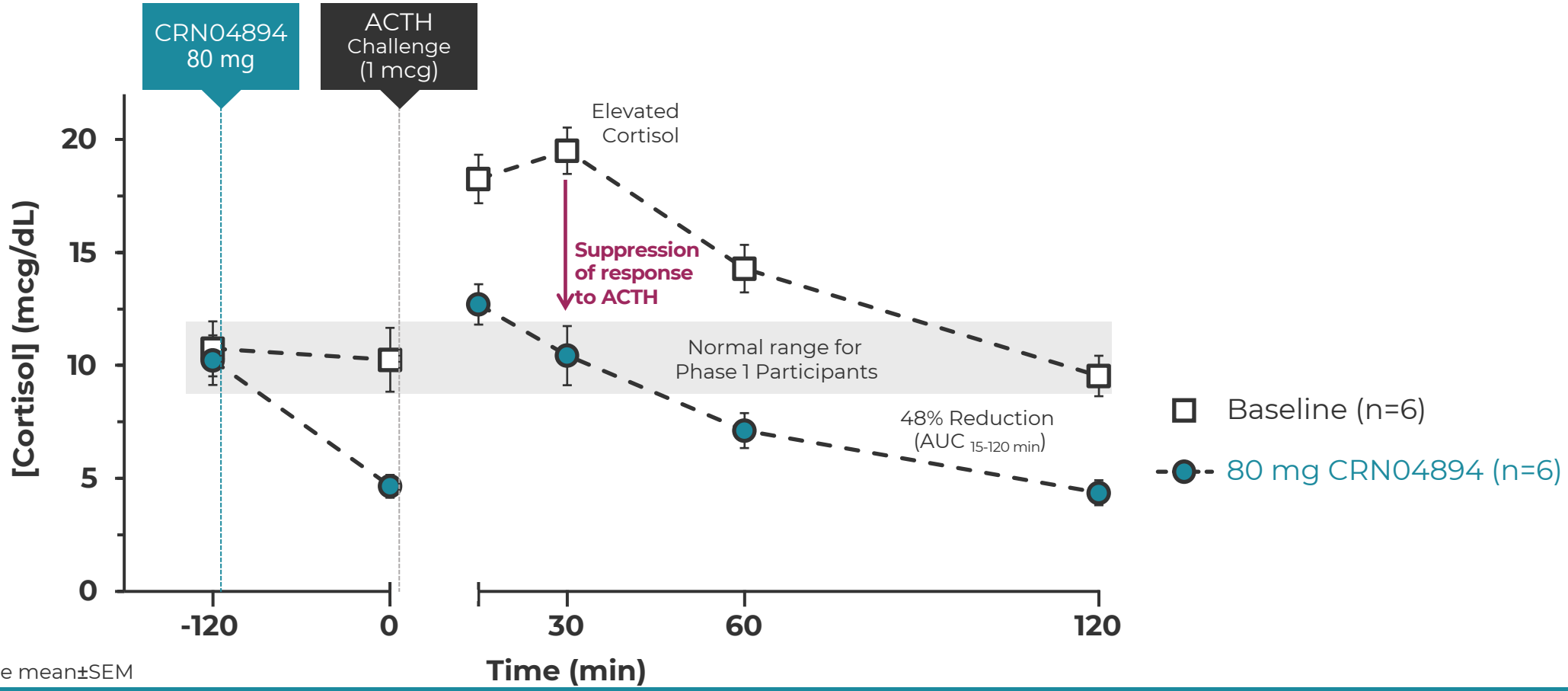




Data shown are mean±SEM

Clinically Meaningful Cortisol Suppression Observed in Response to Disease-relevant ACTH Challenge (1 mcg)

CRN04894 maintains normal cortisol levels for these subjects in face of disease-relevant ACTH (1 mcg) challenge



Data shown are mean±SEM

Conclusions from CRN04894 SAD Results

Objectives

- Safety and tolerability
- Drug-like Pharmacokinetics
- PK/PD for suppression of ACTH-induced adrenal activity

Generally safe and well tolerated at single doses from 10 to 80 mg

Achieved targeted pharmacokinetic profile

- **Rapidly absorbed after oral administration (tmax ~1 hr)**
- **Dose proportional exposure from 10 to 80 mg**
- **Favorable half-life of ~24 hours**

Demonstrated pharmacologic proof-of-concept for ACTH antagonism

- **Strong suppression of basal cortisol (56%)**
- **Dose-dependent, strong cortisol suppression (41%) following supra-pathophysiologic ACTH (250 mcg) challenge**
- **Maintains normal cortisol levels for the Phase 1 participants in face of disease-relevant ACTH (1 mcg) challenge**

Recent and Anticipated CRN04894 Milestones

1. Open US IND ✓
   (complete)
2. Initiate Phase 1 FIH healthy volunteer POC study ✓
3. Report Phase 1 SAD data ✓
   (reported August 2021)
4. Report Phase 1 MAD data
   (expected 1Q 2022)

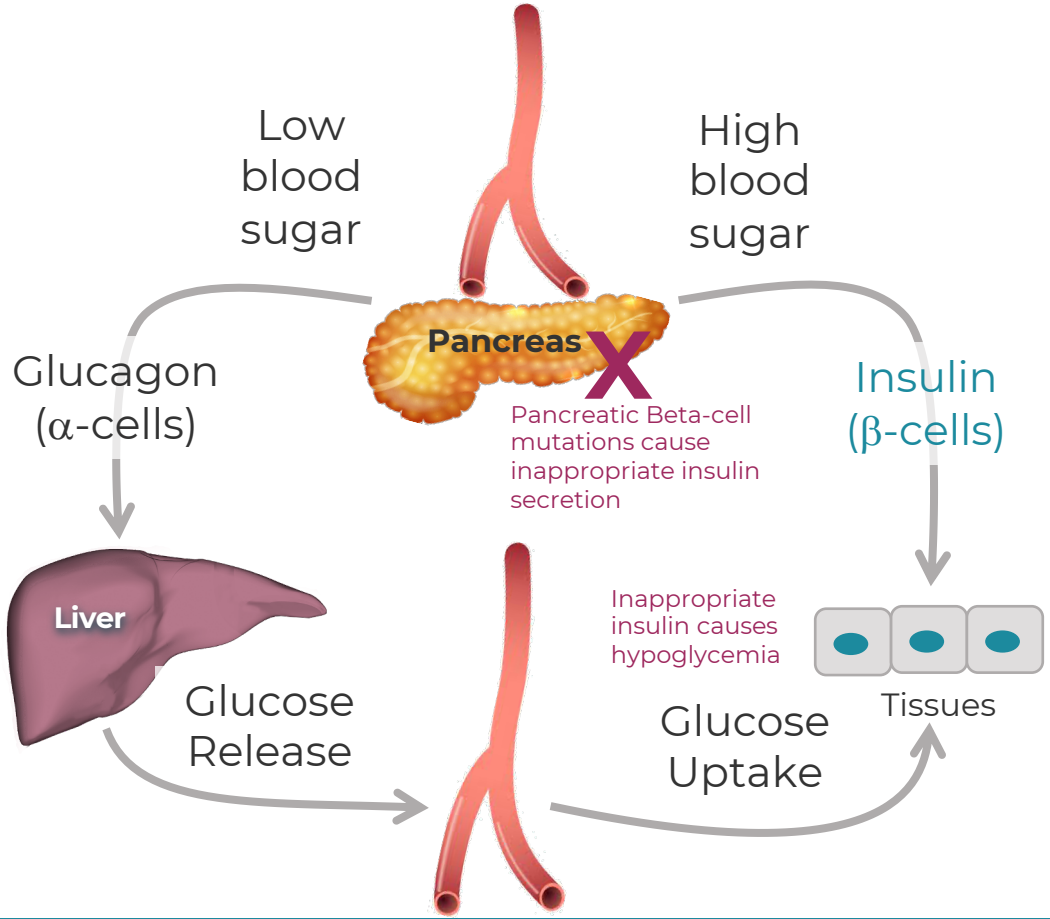
CRN04777: AN INVESTIGATIONAL, POTENTIAL FIRST-IN-CLASS, ORAL NONPEPTIDE SST5 AGONIST

Congenital hyperinsulinism (HI)

Syndromic hyperinsulinism

Congenital Hyperinsulinism Results in Life Threatening Recurrent Hypoglycemia

Congenital HI patients secrete insulin even when blood sugar is low



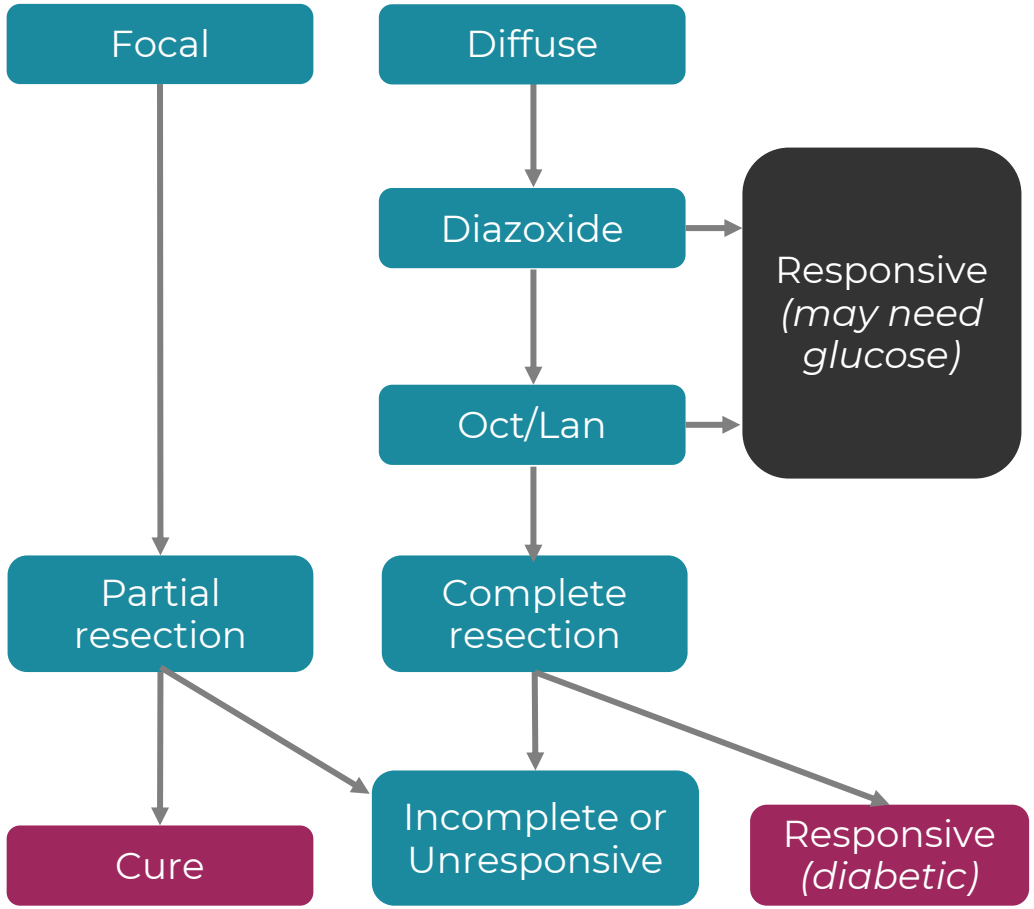
Congenital HI is a devastating rare disease

- 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)

Serious Unmet Medical Needs in Congenital HI

Intensive 24h-glucose management (monitoring, feeding, glucose tube)

Current Standard of Care for Congenital HI

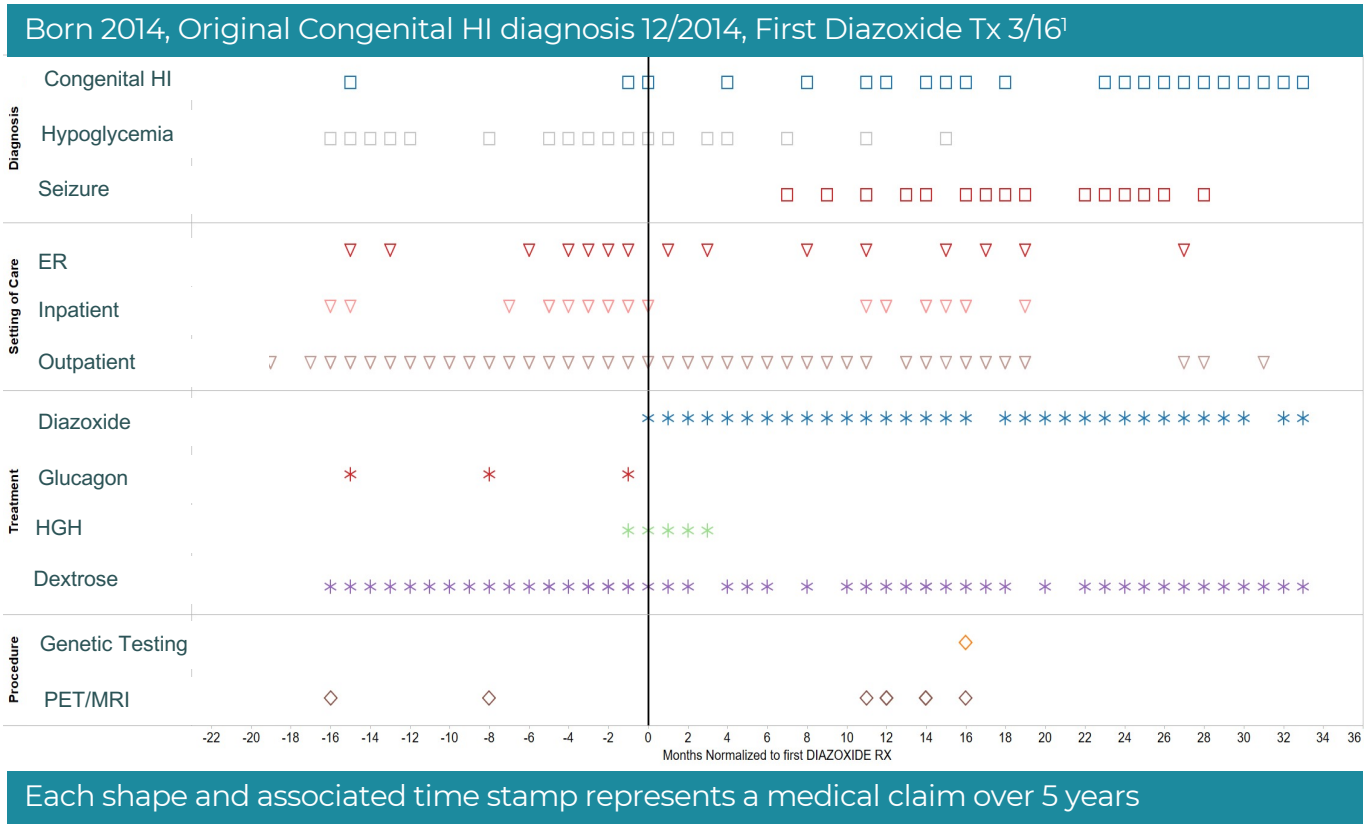


Patient & Parent Goals

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

Congenital HI Patient Care is a High Burden on Healthcare Systems

Healthcare utilization by a baby girl with Congenital HI



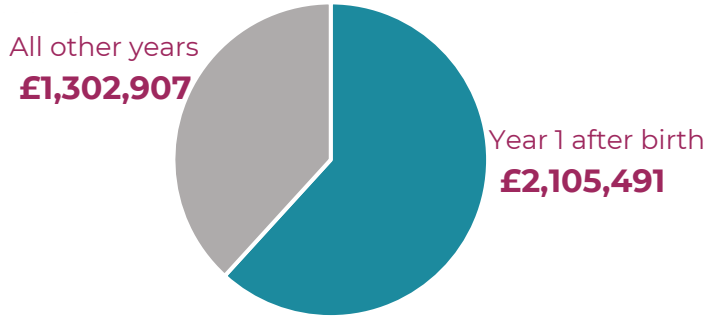
Current Challenges

- Variable time to diagnosis
- Constant dextrose infusion to maintain normal blood sugar levels
- Surgical removal of all or part of the pancreas – *Or*
- No surgical options
- Ineffective diazoxide treatment with multiple untoward effects

As a result:

- Hypoglycemic crises warranting repeat need for emergency services (can include seizure, loss of consciousness and death)
- Frequent and multi-day inpatient hospital stays
- Long-term consequences including neurodevelopmental impairment

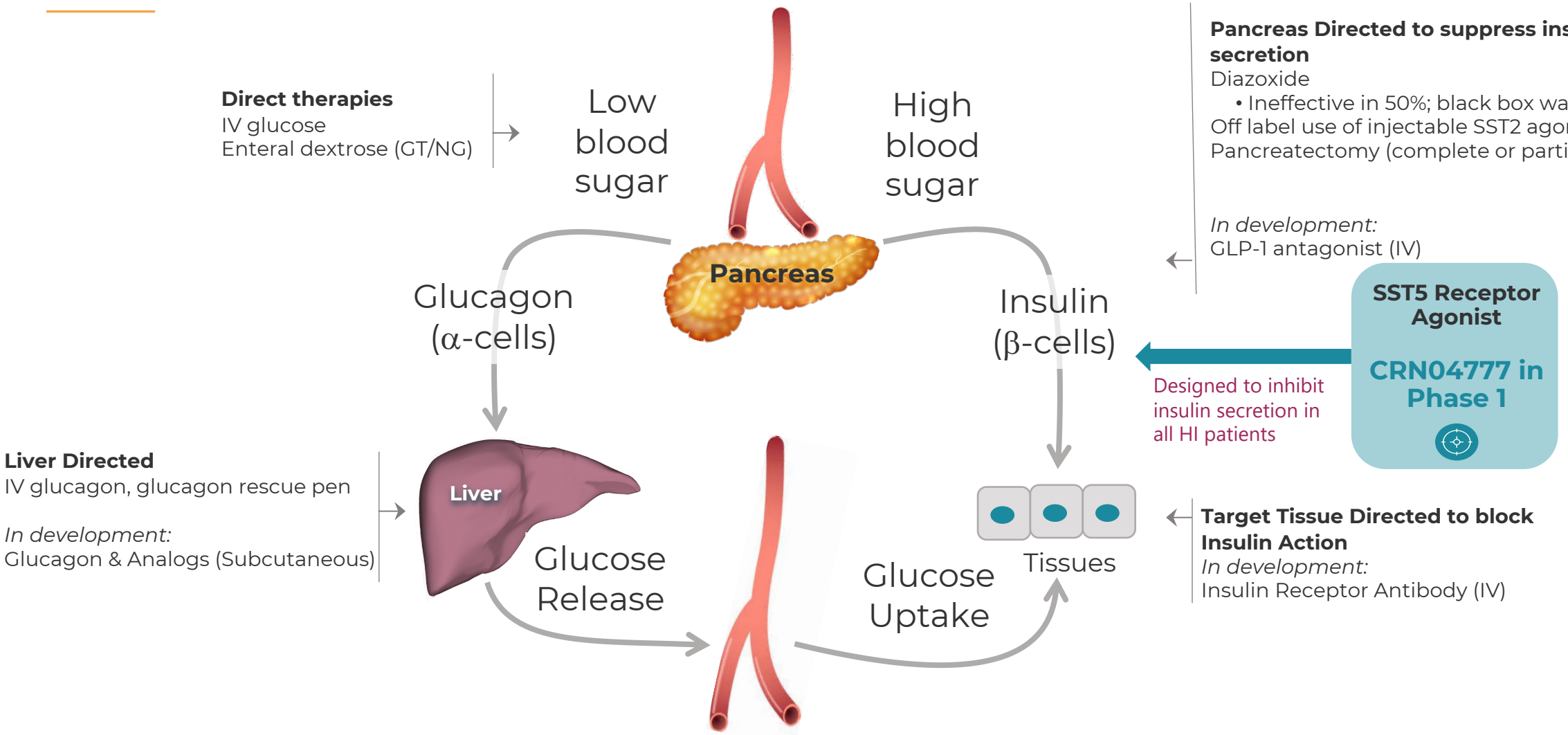
Cost of Illness Estimate from the UK[2], £ 3,408,398 ($4,630,939): first 11 years of life



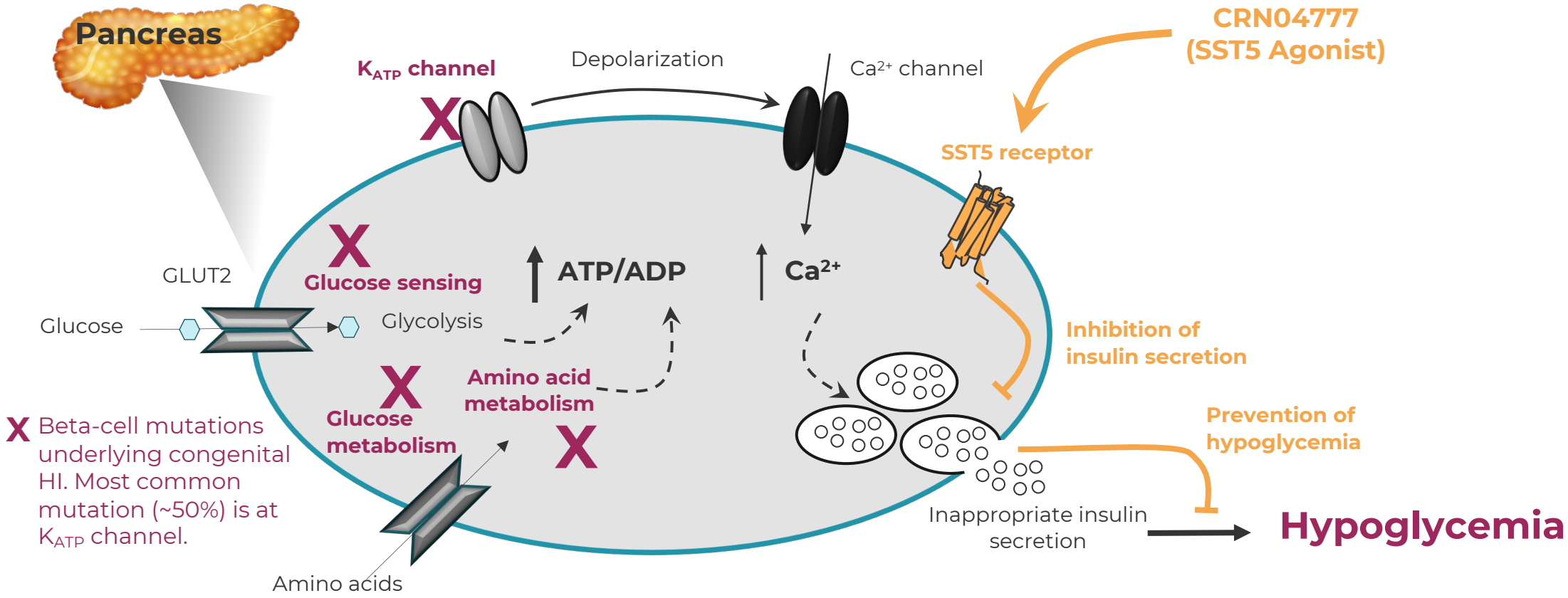
Patients unresponsive to first-line drug therapy (diazoxide) represented the greatest driver of costs

1. Claims data on file, 2013-2018 2. Eljamel, S et al The burden of congenital hyperinsulinism in the United Kingdom: a cost of illness study 2018

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

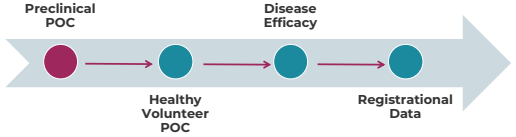


SST5 Inhibits Insulin Secretion Downstream of all Known HI Causing Mutations

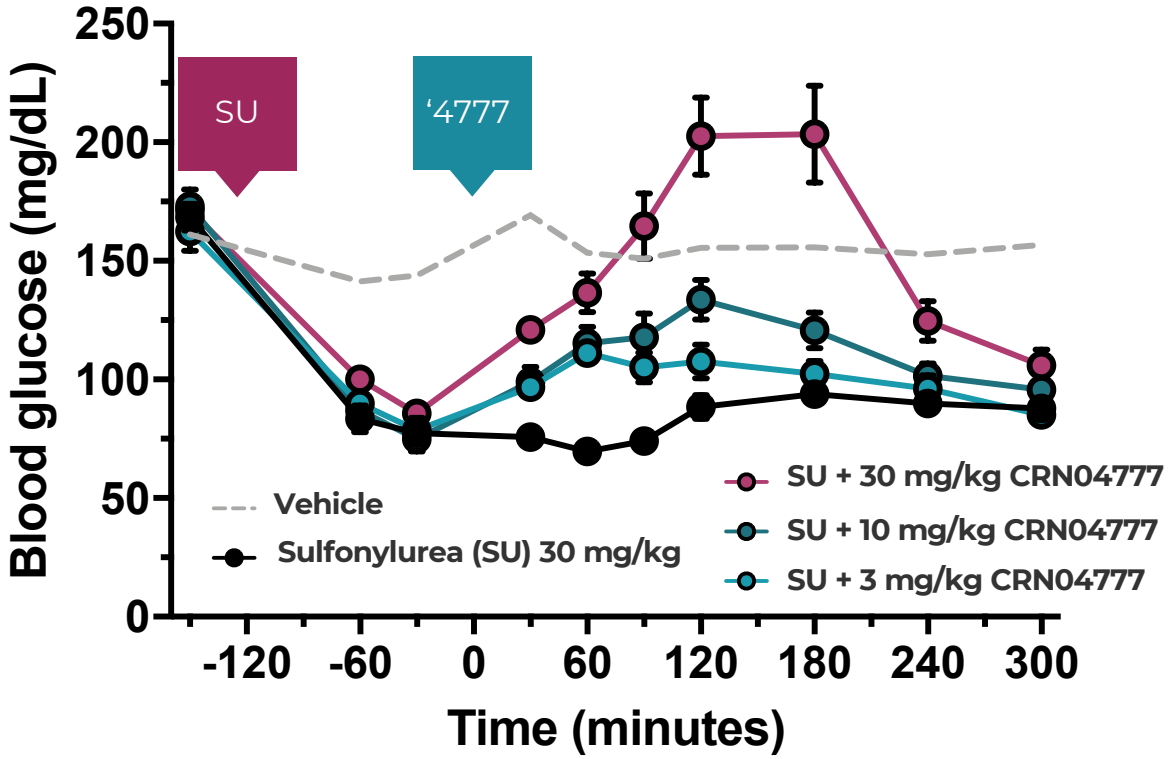


Syndromic hyperinsulinisms (e.g. those associated with Beckwith-Wiedemann syndrome, Sotos syndrome, Kabuki syndrome, and Turner syndrome) may also respond to SST5 agonism

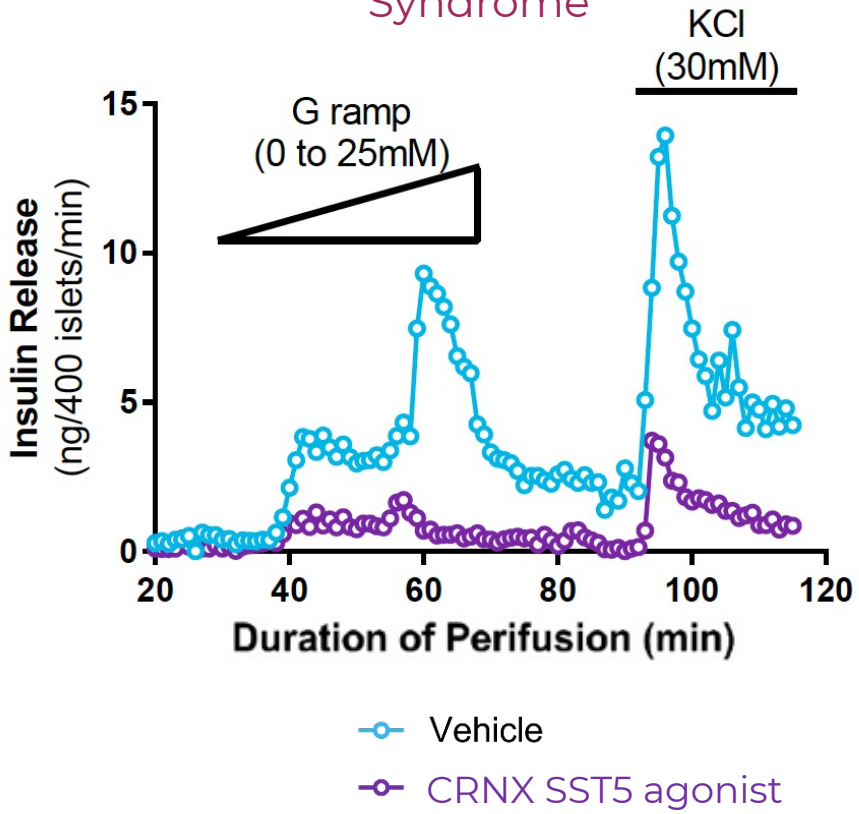
Proof of Mechanism Achieved in Animal Models and Patient Islets



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



CRNX SST5 agonist suppressed insulin from islets isolated from patient with Beckwith-Wiedemann Syndrome



Islet data was obtained using another Crinetics SST5 agonist candidate before CRN04777 had been selected for development

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

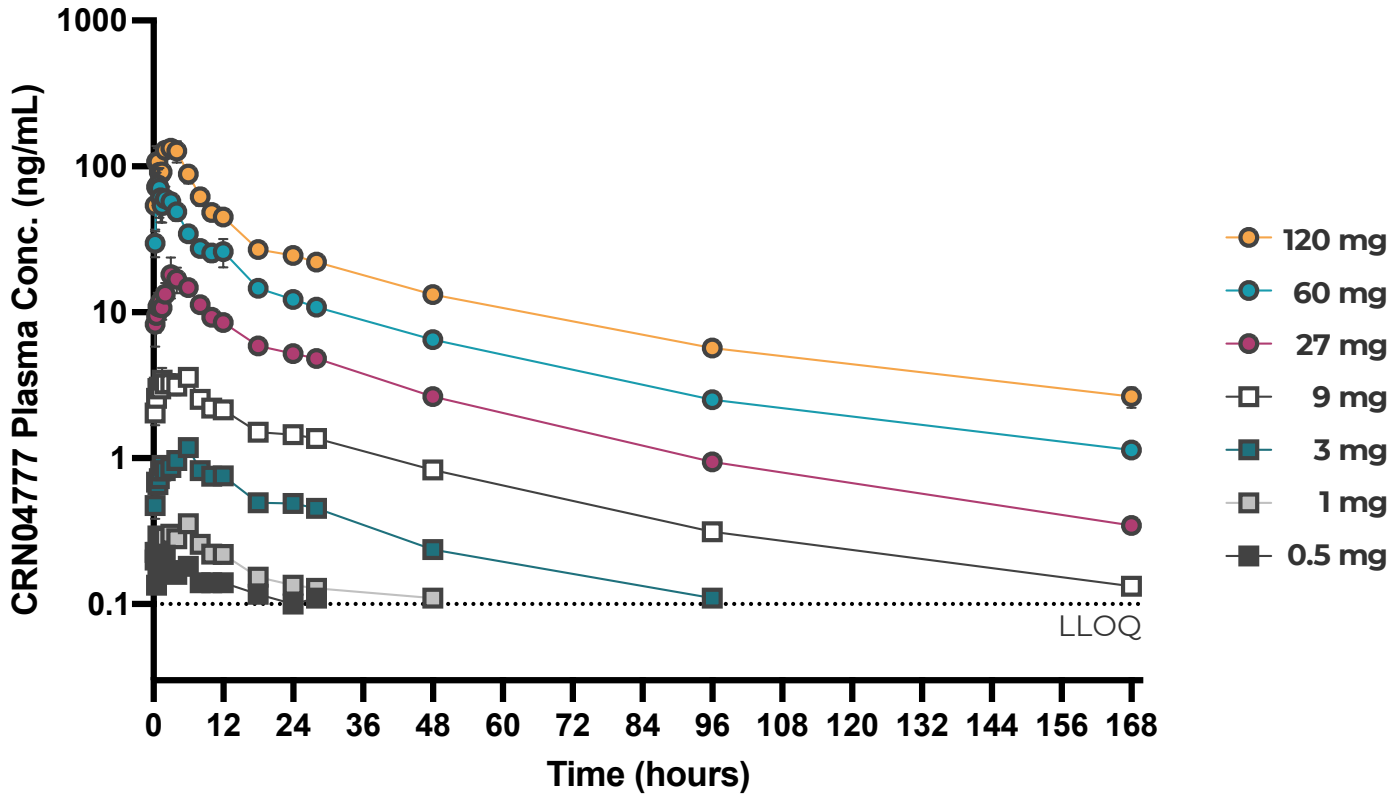
1. Intravenous Glucose Tolerance Test (IVGTT)
2. Sulfonylurea (SU) Challenge

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.

CRN04777 SAD Study Designed 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]**
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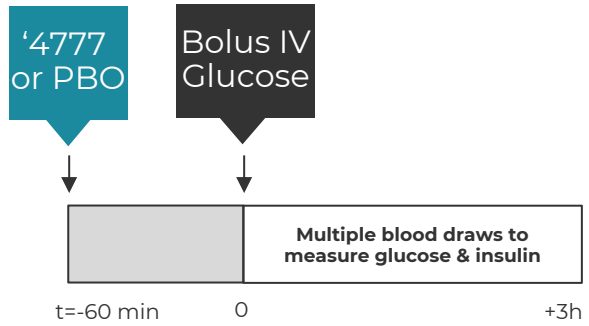
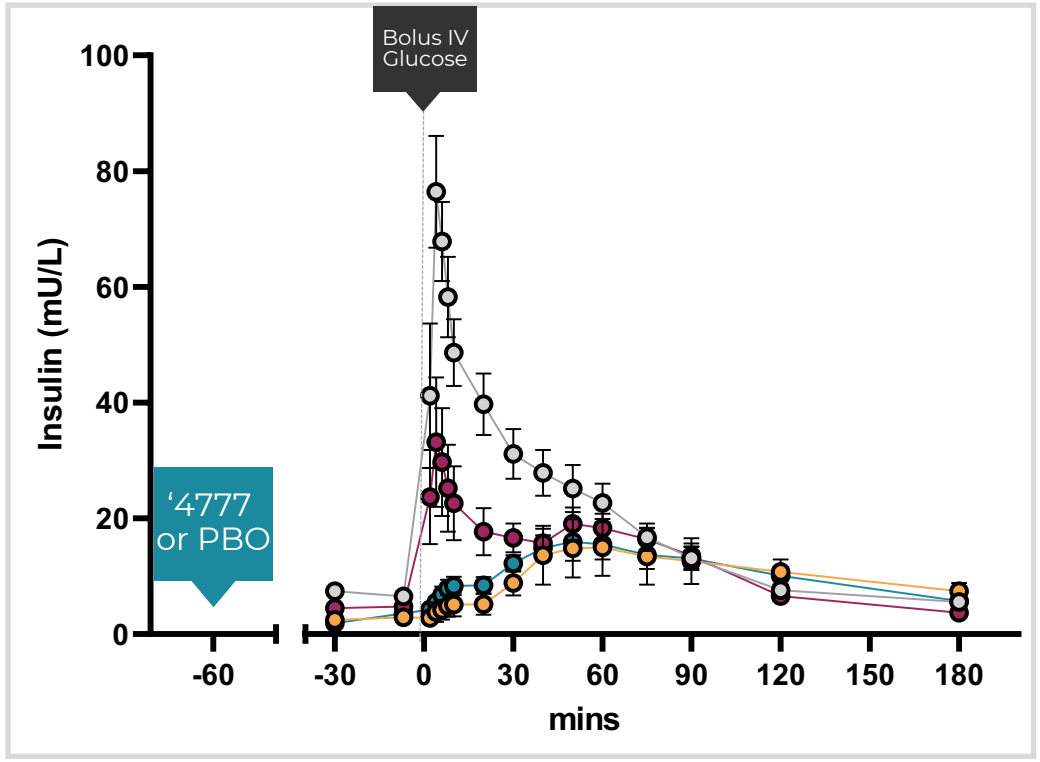
1. Intravenous Glucose Tolerance Test (IVGTT)



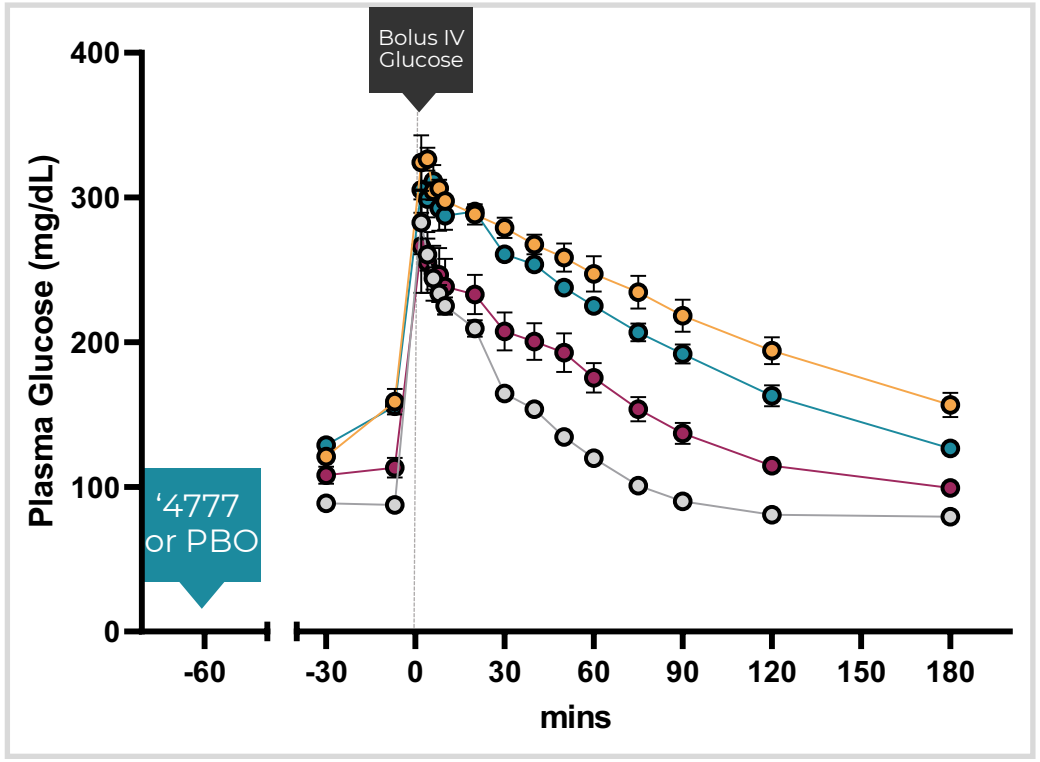
Healthy volunteers received single oral dose of CRN04777
(n = 8, 6 active/ 2 placebo in each cohort)

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

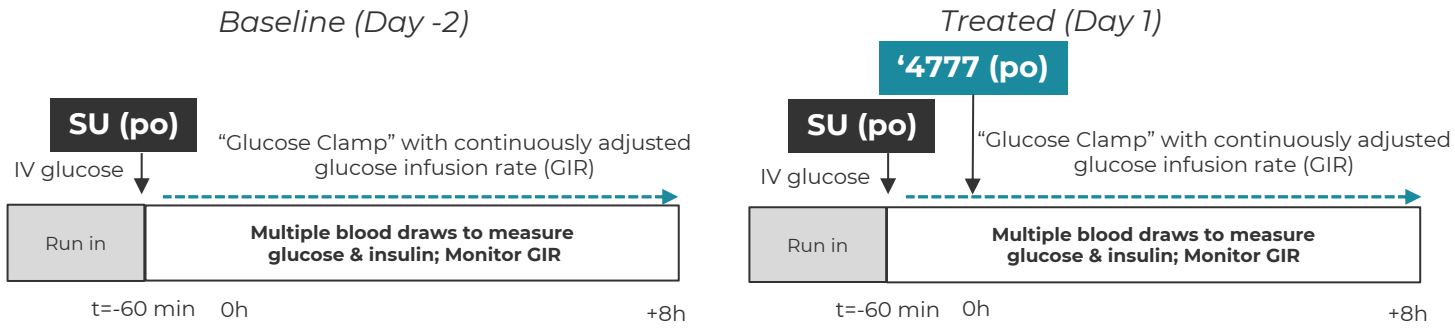
CRN04777 SAD Study Designed to Evaluate Pharmacologic Proof-of-Concept

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

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]**

2. Sulfonylurea (SU) Challenge

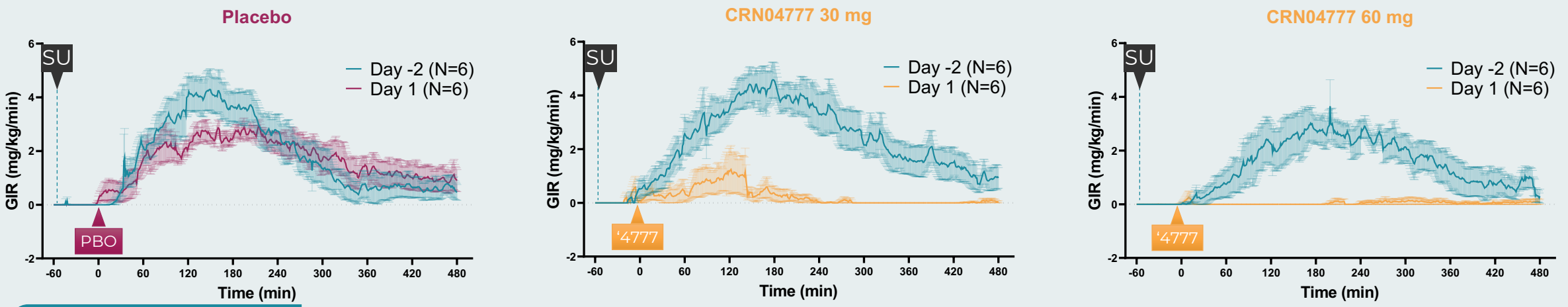


Healthy volunteers received single oral dose of CRN04777
(n = 9, 6 active / 3 placebo in each cohort)

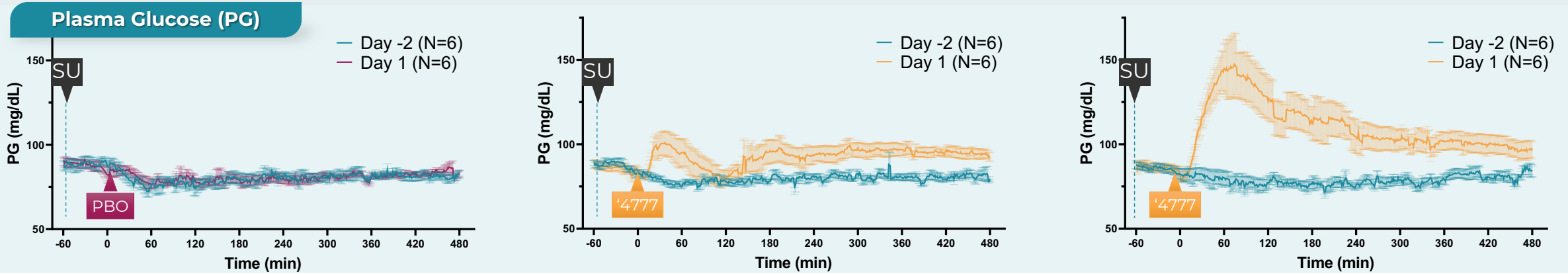
CRN04777 Reversed Sulfonylurea-Induced Hyperinsulinism in a Pharmacologic Model of Congenital HI

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**

Recent and Anticipated CRN04777 Milestones

1. US Rare Pediatric Disease and EU Orphan Drug Designations ✓
   (received; CRNX may be eligible for priority review voucher in the US)
2. Initiate Phase 1 FIH healthy volunteer POC study ✓
3. Report Phase 1 SAD data ✓
   (reported September 2021)
4. Report Phase 1 MAD data
   (expected 1Q 2022)

UP NEXT: PARATHYROID RECEPTOR TYPE-1 (PTHR1) ANTAGONIST FOR HYPERPARATHYROIDISM

Primary hyperparathyroidism (1° HPT)

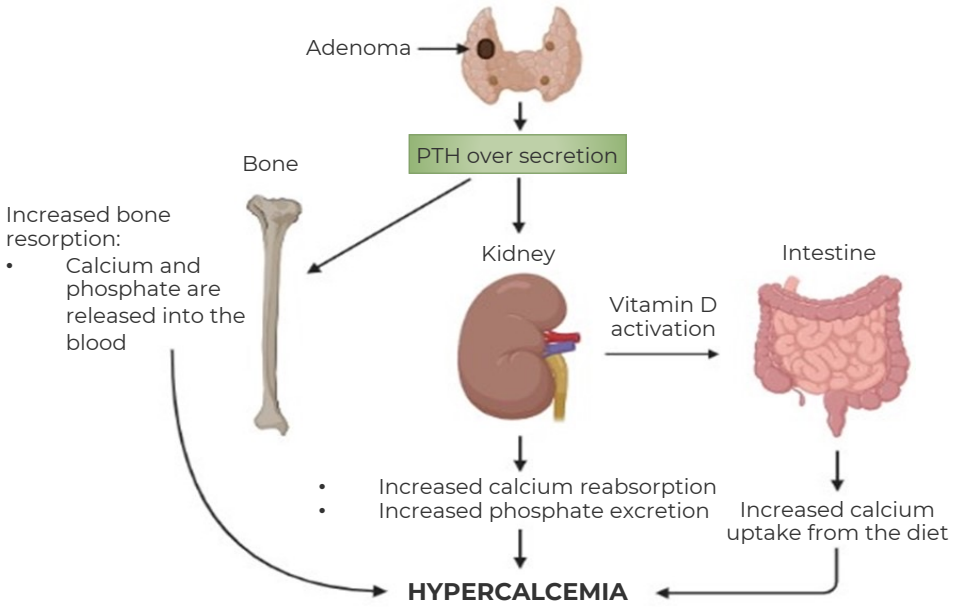
Humoral hypercalcemia of malignancy (HHM)

Secondary hyperparathyroidism due to chronic kidney disease (2° HPT)

Hyperparathyroidism is a High Unmet Need for Endocrinologists, Nephrologists and Oncologists

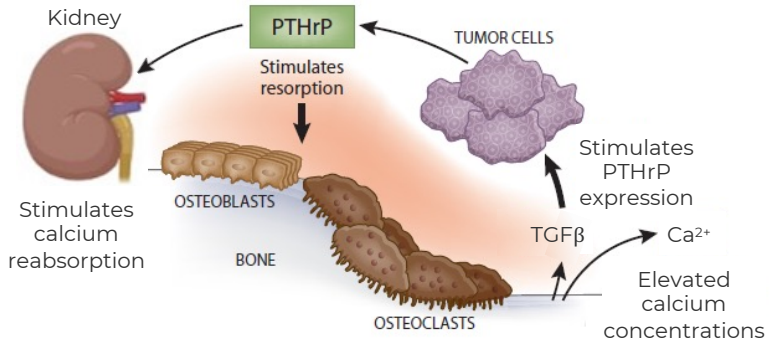
Endocrinology: It's not just for endocrinologists!

Primary Hyperparathyroidism (1°HPT)



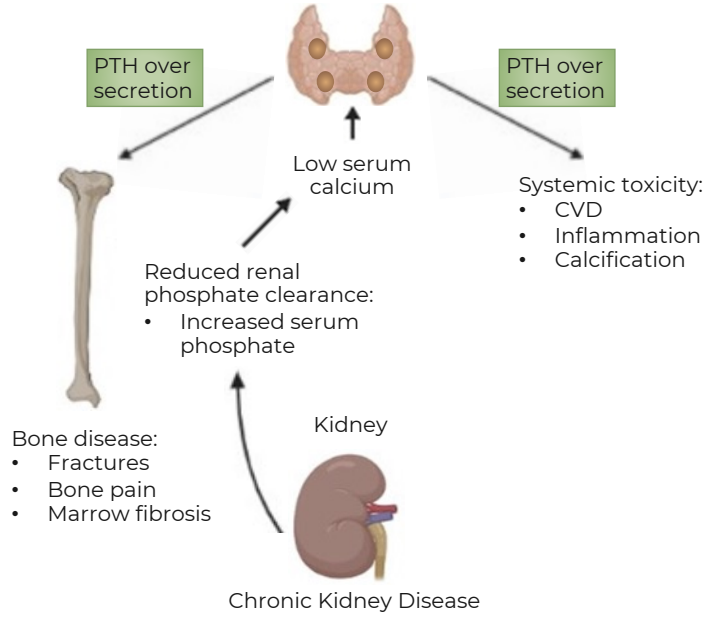
~480K prevalence (U.S.)
100K new cases/year (U.S.)

Humoral Hypercalcemia of Malignancy (HMM)



50-200K new cases/year (U.S.)

Secondary Hyperparathyroidism (2°HPT)



13.2M prevalence (U.S)

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

	1H21	2H21	1H22	2H22
Paltusotine SST2 Agonist for Acromegaly & NETs **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 ACTH Antagonist for Cushing's Disease & CAH **POC Achieved**	Initiate Phase 1	Phase 1 POC SAD Data	Phase 1 MAD Data(Q1)	Initiate Phase 2 in Patients
CRN04777 SST5 Agonist for Congenital HI **POC Achieved**	Initiate Phase 1 ✓	Phase 1 POC SAD Data ✓	Phase 1 MAD Data(Q1)	Initiate Phase 2 in Congenital HI Patients
PTHR1 Antagonist for Hyperparathyroidism & HHM			Initiate IND enabling studies	

APPENDICES

Key Patent Families Anchor a Robust IP Portfolio

Patent Family Subject Matter	Patent Status	Priority Date	Estimated Expiration
Paltusotine Portfolio			
Composition of Matter	**Granted in**: US, AU, IN **Pending in**: foreign jurisdictions representing >96% of pharmaceutical markets	July 2016	July 2037
HCl Salt and its Polymorph Form	**Granted in:** U.S. **Pending in**: foreign jurisdictions representing >96% of pharmaceutical markets	January 2018	January 2039
New Formulation	**Pending in:** PCT, U.S., TW, AR, VE	September 2020	September 2041
Acromegaly Treatment Methods	**Pending in:** U.S	May 2021	May 2042
CRN04894 Portfolio			
Composition of Matter	**Granted in:** U.S. **Pending in:** foreign jurisdictions representing >96% of pharmaceutical markets	June 2018	June 2039
Treatment Methods	**Pending in:** U.S	March 2021	March 2042
CRN04777 Portfolio			
Composition of Matter	**Pending in:** PCT, U.S., TW, AR, VE	Aug 2019	Aug 2040
Polymorph Form	**Pending in:** U.S	February 2021	February 2042
Treatment Methods	**Pending in:** U.S	February 2021	February 2042

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