Crinetics Pharmaceuticals

CORPORATE PRESENTATION

Leerink Global Healthcare Conference, February 24, 2021

SAFE HARBOR STATEMENT

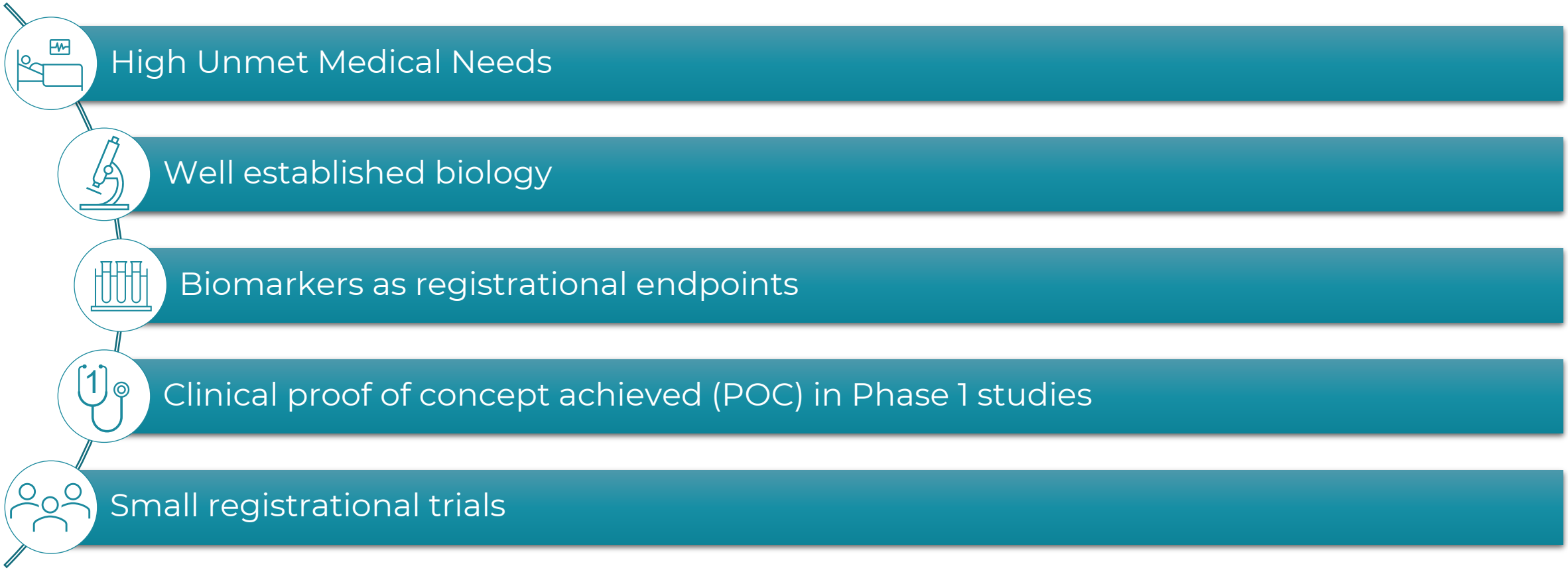
This presentation contains forward-looking statements. All statements other than statements of historical facts contained in this presentation are forward-looking statements, including statements regarding: the potential benefits of paltusotine for acromegaly patients and patients with carcinoid syndrome; the potential to initiate a pivotal Phase 3 trial of paltusotine in acromegaly and the expected timing thereof; our plans to meet with the FDA in the first quarter of 2021; the benefits of our improved tablet formulation of paltusotine; 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 initiate 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 initiate a Phase 1 trial of CRN04777, report data therefrom, and the timing thereof; 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, including hyperparathyroidism, nonfunctional pituitary adenomas and polycystic kidney disease, among other indications. 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 interim results of a clinical trial 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; advancement of paltusotine into a Phase 3 trial in acromegaly or 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 and nonclinical studies for paltusotine, CRN04894, CRN04777, 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:



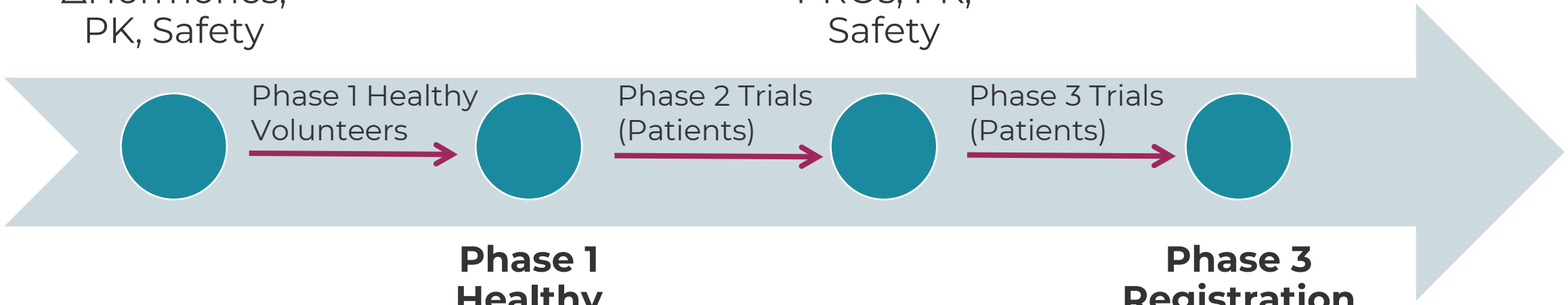
Endocrinology: Early Derisking and Value Creation

Preclinical POC

ΔHormones,
PK, Safety

Phase 2 Disease Efficacy

ΔHormones,
PROs, PK,
Safety



Phase 1 Healthy Volunteer POC

ΔHormones,
PK, Safety

Phase 3 Registration Data

ΔHormones,
PROs, Safety

Pipeline Targets Indications with Unmet Need

Well established endocrinology has the potential to allow for the use of biomarkers as registration endpoints

PROGRAM	Development Stage				Registrational Endpoint	Prevalence	
	Preclin	Phase 1	Phase 2	Phase 3		US Total	Global Range per 100,000
Paltusotine (SST2 agonist)							
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 (CHI)					Glucose Levels	2-4K	0.64 – 1.3
US TOTAL						**~236K**	

All candidates are NCEs discovered in-house

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

Acromegaly

Carcinoid syndrome

Nonfunctional neuroendocrine tumors

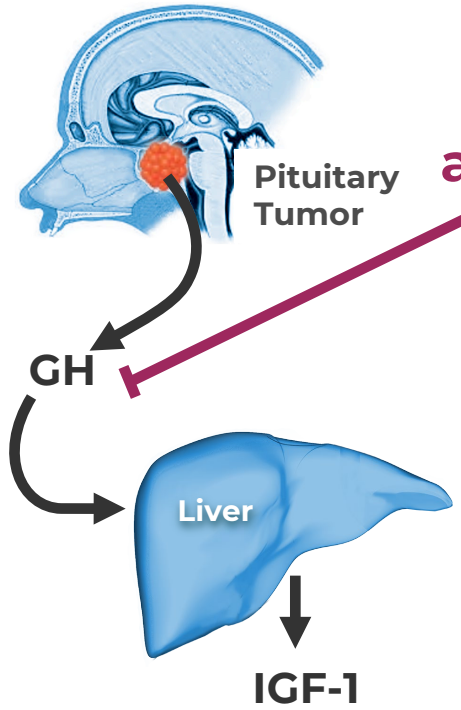
Acromegaly and NETS are Currently Treated with Injected SST2 Peptide Agonists

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)

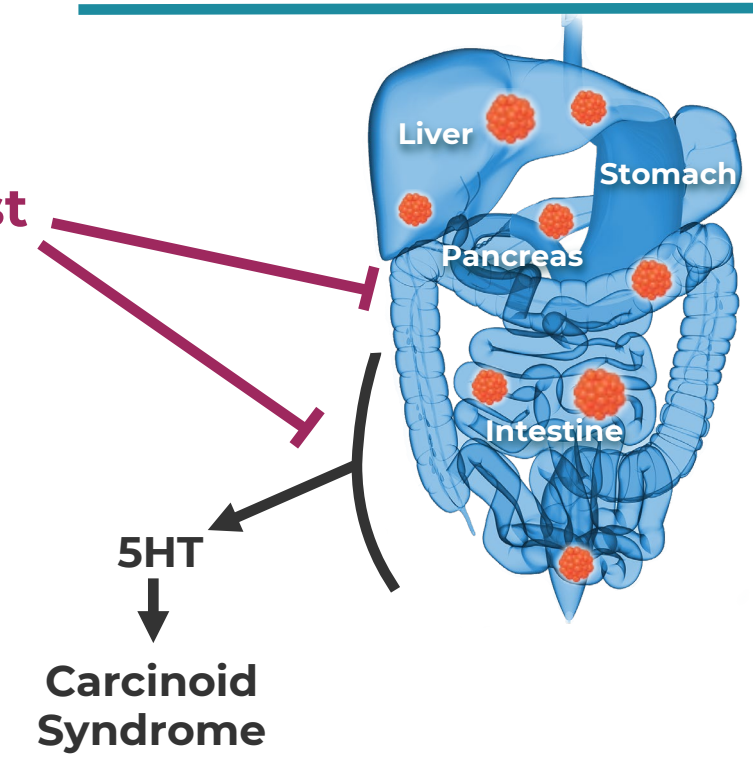
Results in:

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)

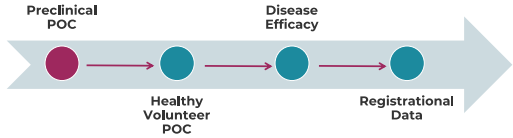


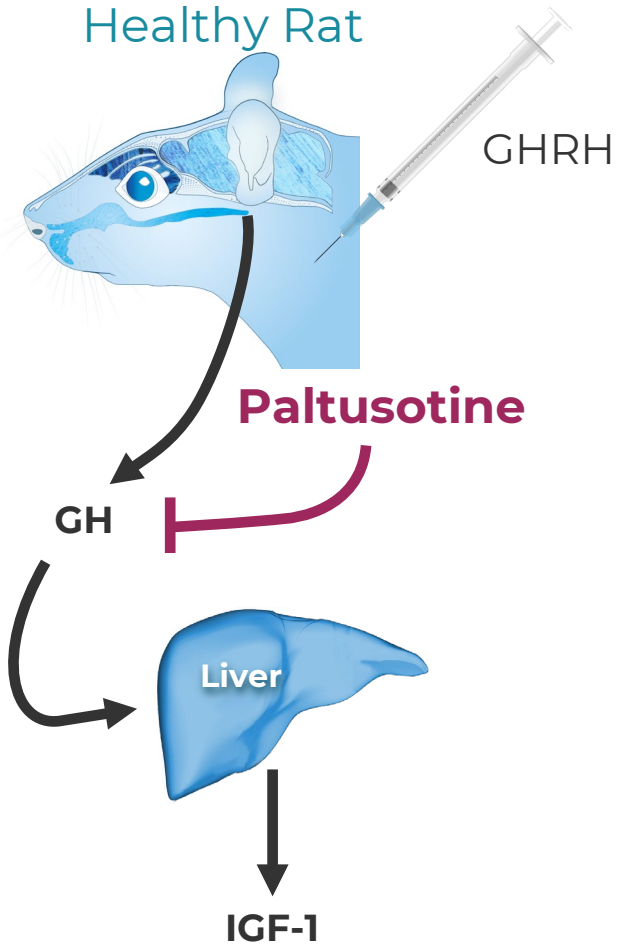
- NETs arise from aberrant enteroendocrine cells in GI, pancreas or lungs
- In ~19% of cases, tumors are associated with excess secretion of serotonin and other hormones resulting in carcinoid syndrome
- Majority of tumors are "nonfunctional" and not associated with secretory syndrome
- Patients with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

US Prevalence

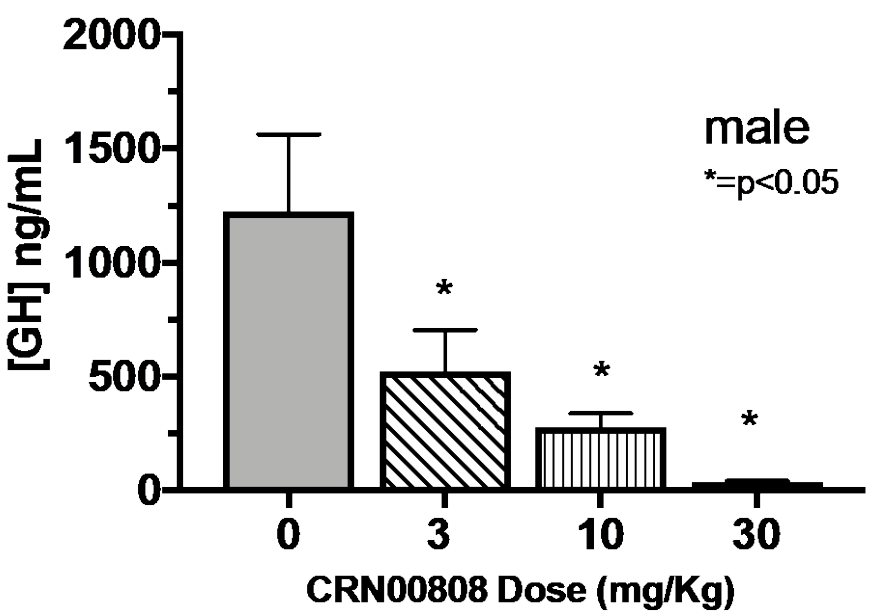
Carcinoid Syndrome:	33,000
Nonfunctional tumors:	138,000
Total	**171,000**

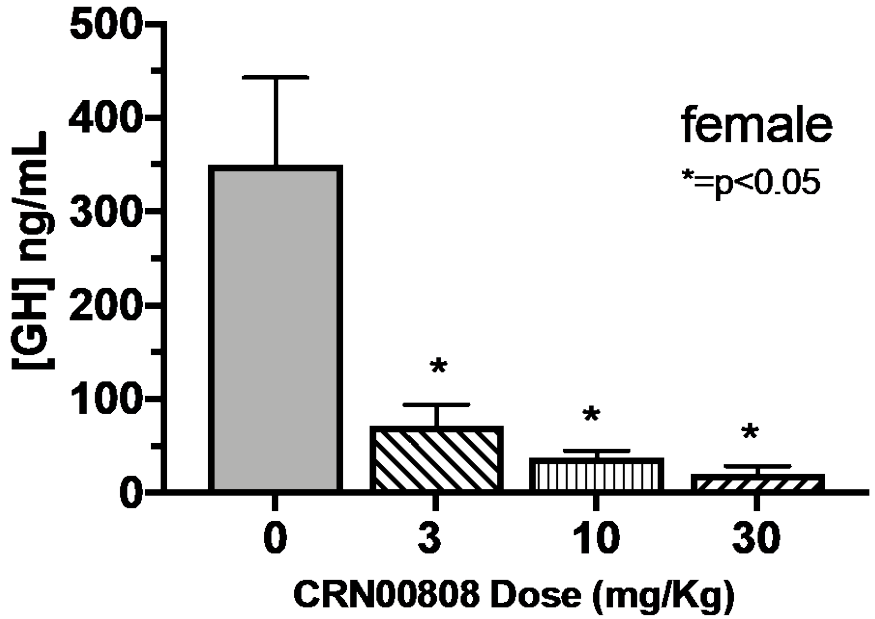
Paltusotine: In Vivo Proof-of-Concept in Healthy Rats





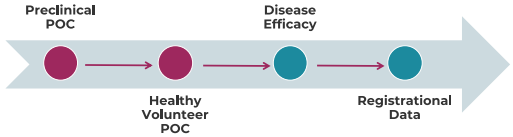
Suppression of GHRH stimulated GH secretion in male and female rats with oral paltusotine



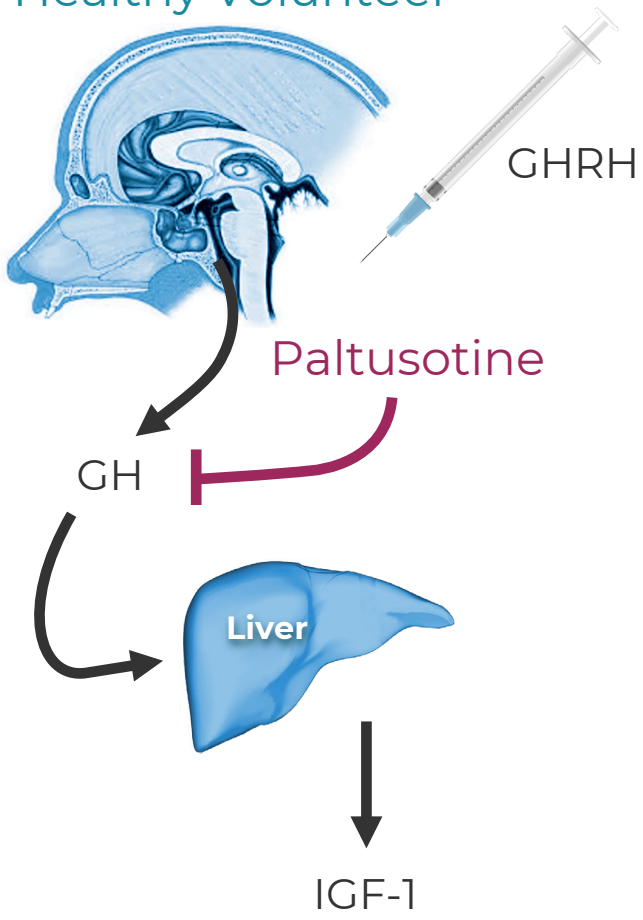


GHRH: Growth Hormone-Releasing Hormone

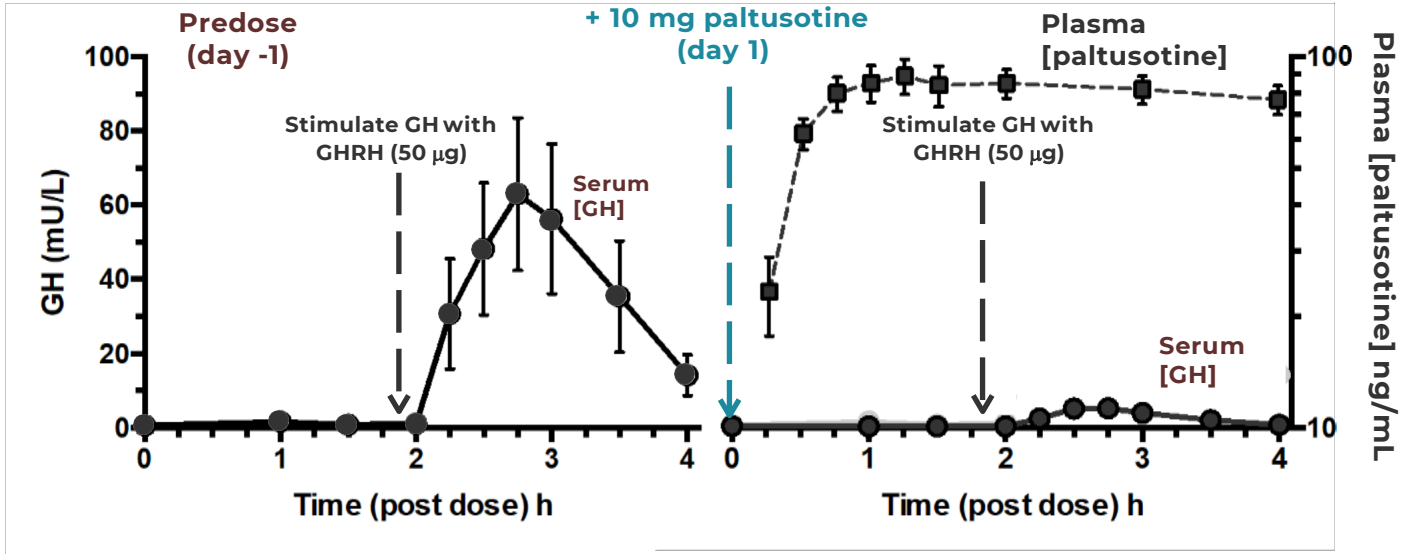
Paltusotine: Phase 1 Proof-of-Concept in Healthy Volunteers



Healthy Volunteer

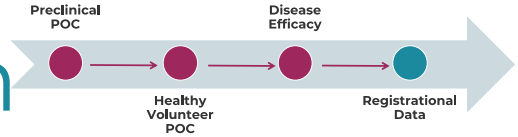


Suppression of GHRH stimulated GH secretion in healthy volunteers with oral paltusotine

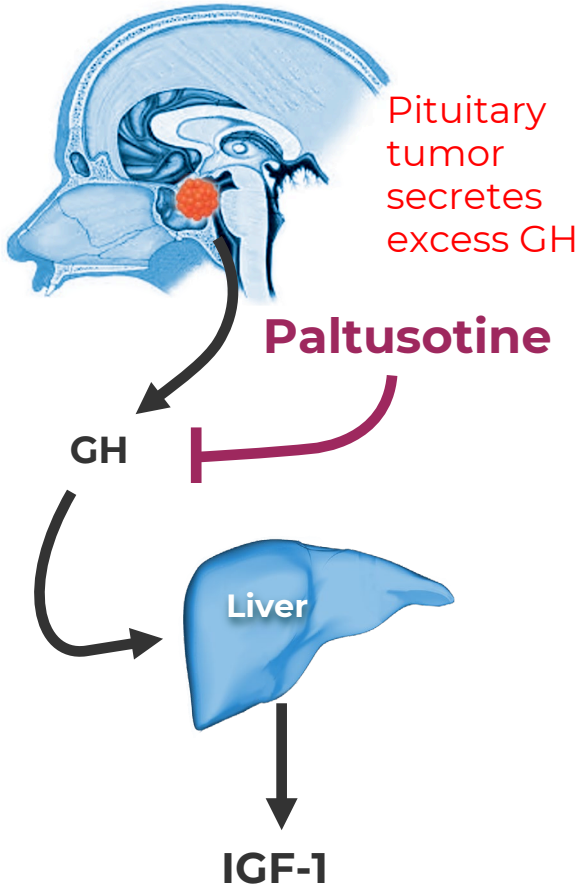


GHRH: Growth Hormone-Releasing Hormone

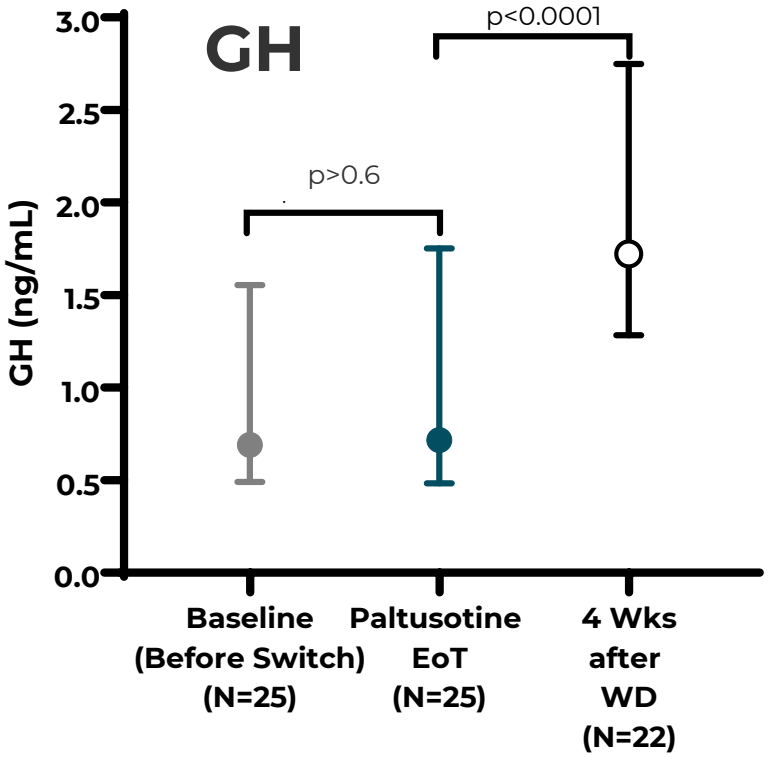
Paltusotine: GH and IGF-1 Suppression in Acromegaly Patients

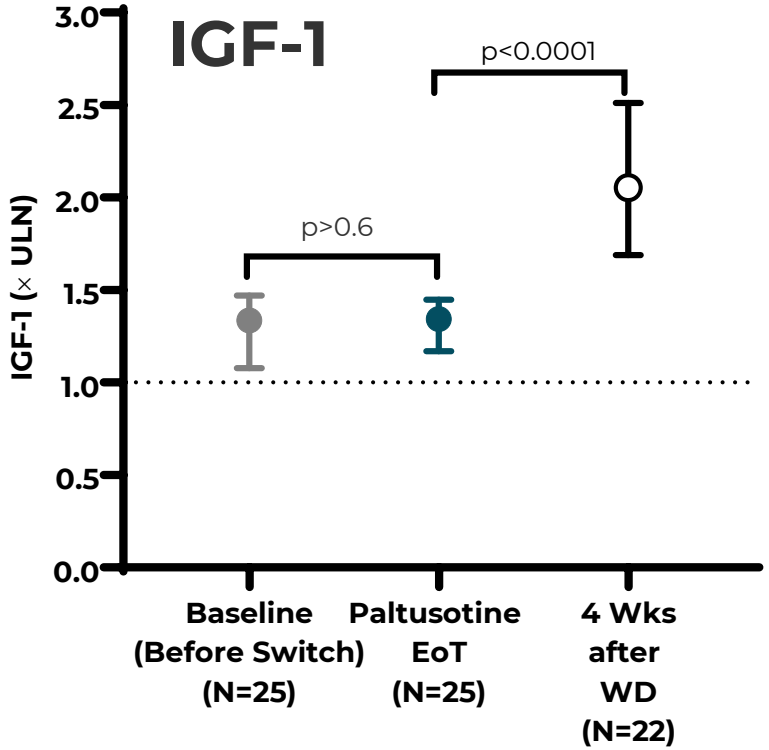


Acromegaly Patients



GH and IGF-1 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.

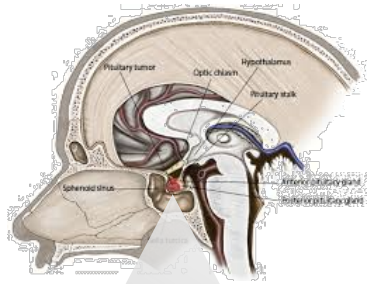
CRN04894: AN INVESTIGATIONAL, POTENTIAL FIRST-IN-CLASS, ORAL NONPEPTIDE ACTH ANTAGONIST

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



Stress

Hypothalamus

CRF

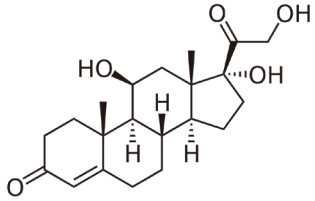
Optic Chiasma

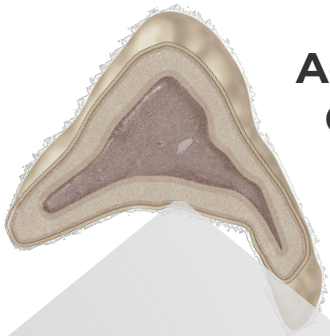
Pituitary

AVP

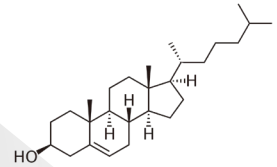
Adrenocorticotrophic hormone (ACTH)

Cortisol





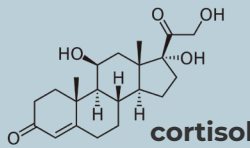
Adrenal Gland



cholesterol

MC2/MRAP

Adrenal Cortical Cell



cortisol

21-hydroxylase

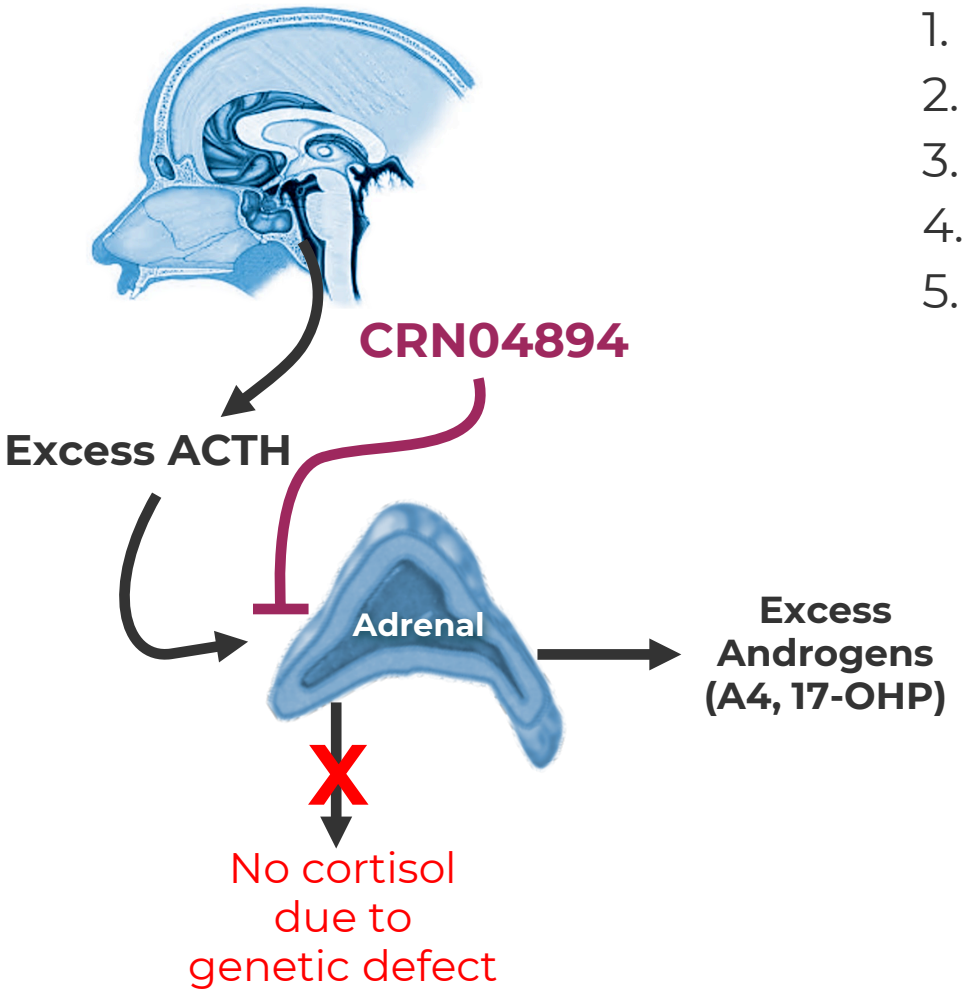
Adrenal Androgens (17-OHP, A_4)

mutated in CAH

(1) Cortisol provides negative feedback to pituitary
(2) Cortisol acts at peripheral target tissues (Glucocorticoid Receptor)

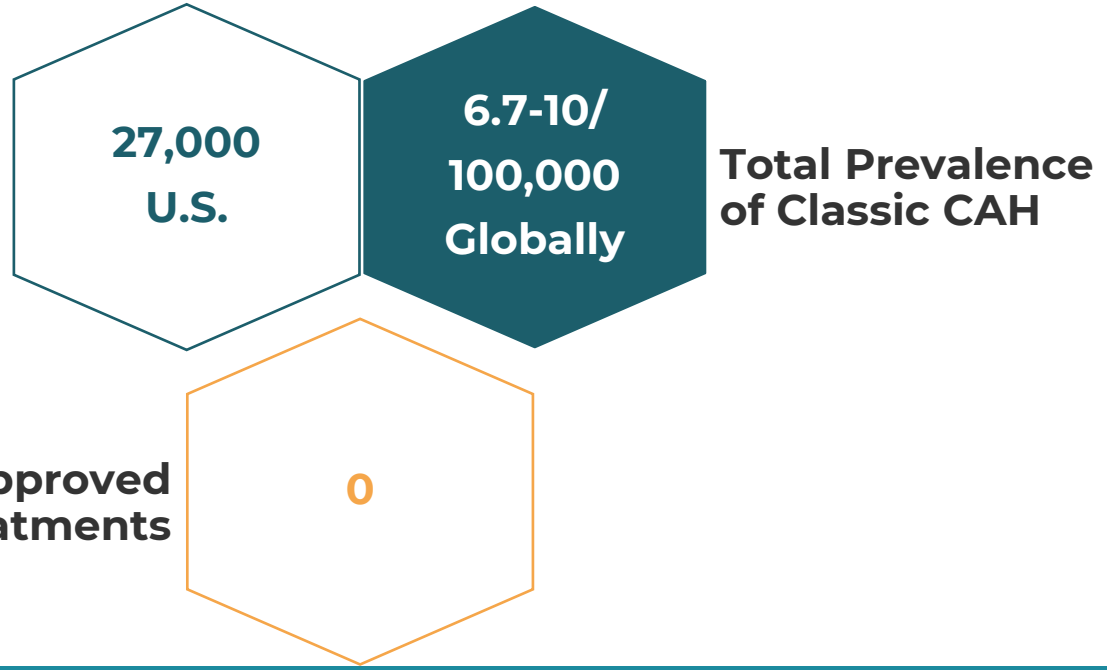
CRN04894, an ACTH Antagonist Designed to Block Excess ACTH Action in CAH Patients

CAH Patients



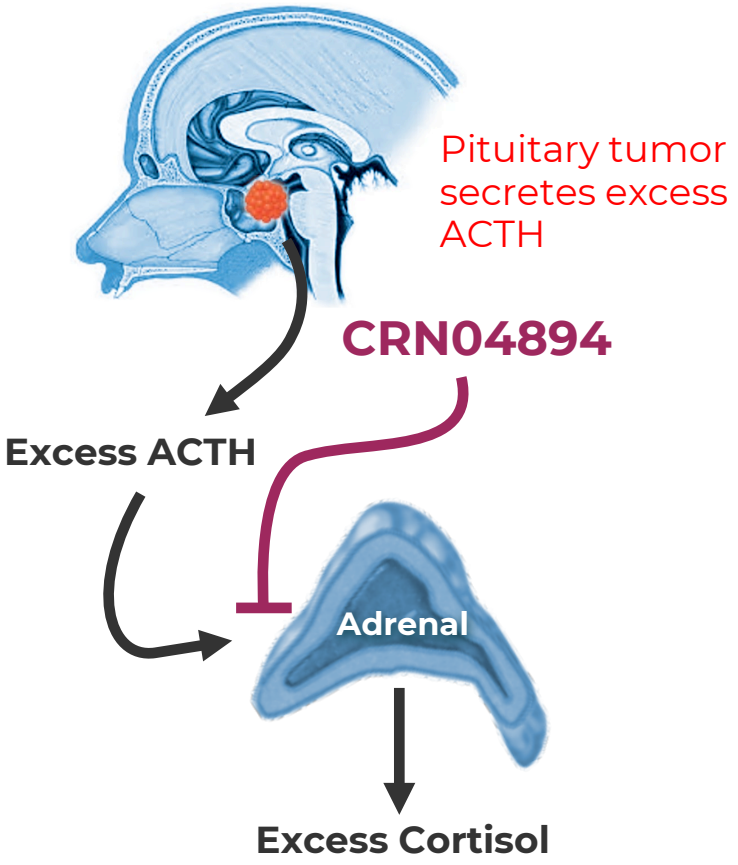
Loss of cortisol in CAH patients results in:

1. Adrenal insufficiency, loss of negative feedback to pituitary
2. Excess ACTH resulting in excess adrenal androgens
3. Precocious puberty, short stature, infertility, acne
4. Virilization, menstrual irregularities, hirsutism in women
5. Testicular adrenal rest tumors in men



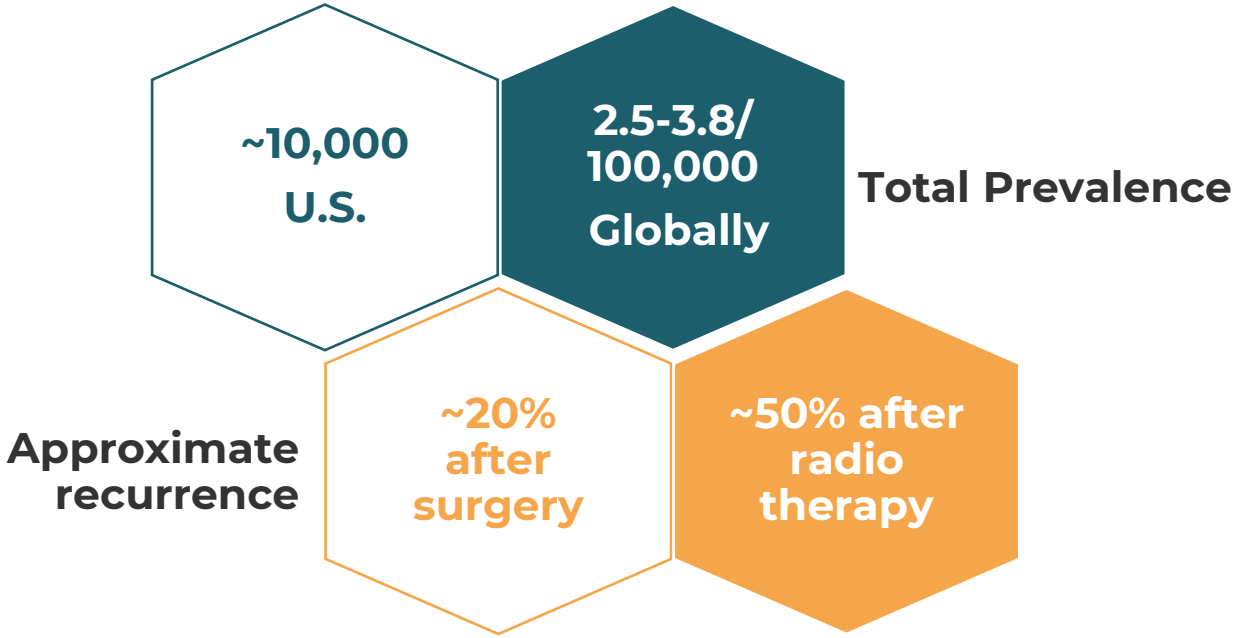
CRN04894, an ACTH Antagonist Designed to Block Excess ACTH Action in Cushing's Disease

Cushing's Disease Patients



Excess cortisol in Cushing's Disease patients results in:

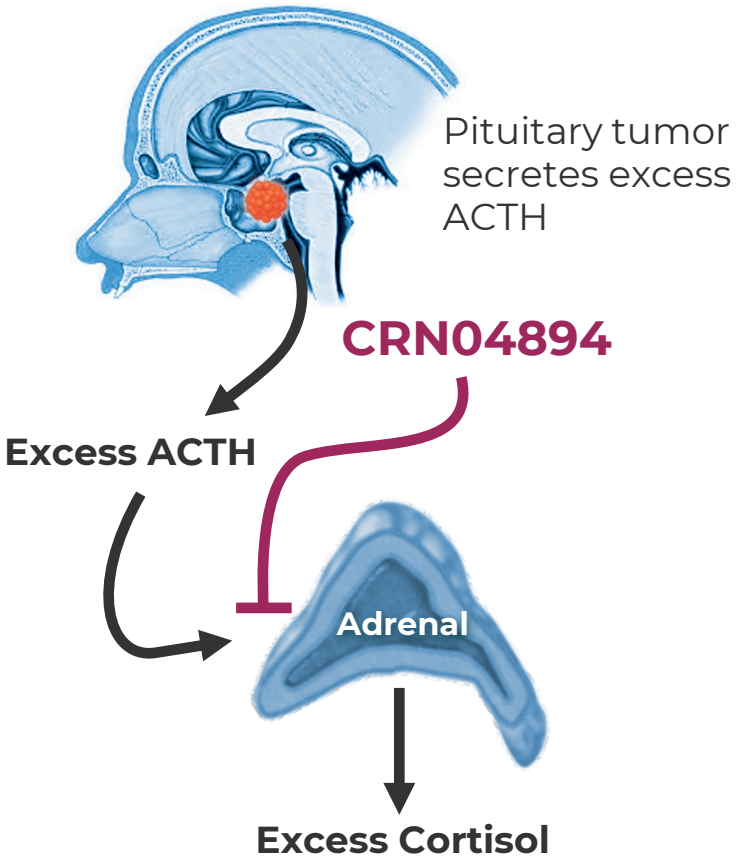
1. Central obesity and round face
2. Dorsal and supraclavicular fat pads
3. Hypertension; Stretch marks; Bone loss; Hyperglycemia
4. Psychiatric disturbances



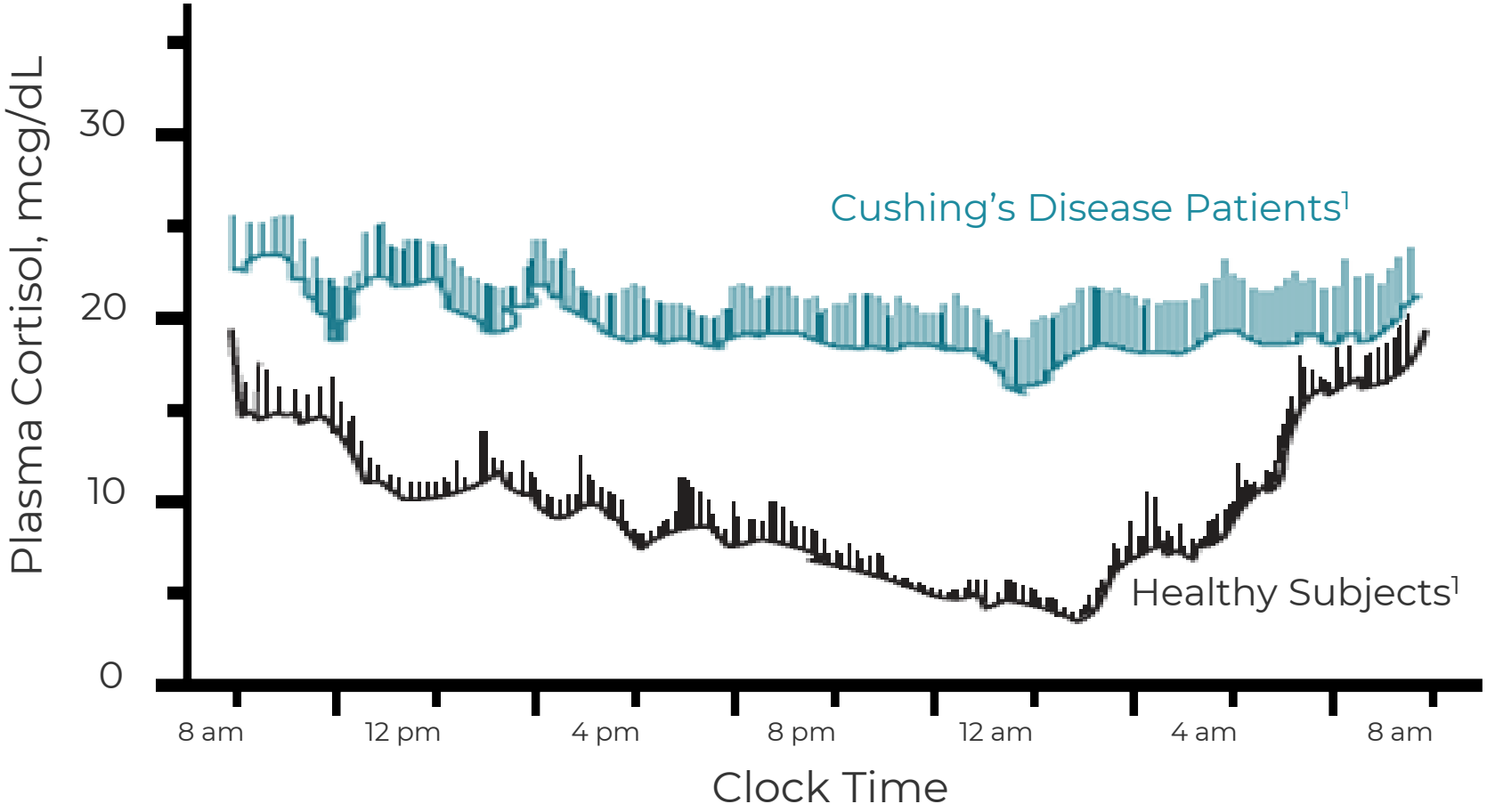
Korlym (2nd line Glucocorticoid Receptor antagonist) anticipated 2020 revenue = $355-365M

Pituitary Corticotroph Tumors Cause Cushing's Disease, an ACTH Dependent Cushing's Syndrome

Cushing's Disease Patients

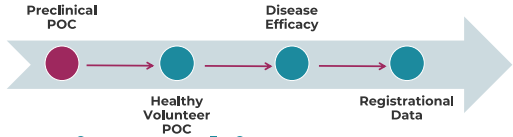


Time course of plasma cortisol levels over a diurnal cycle

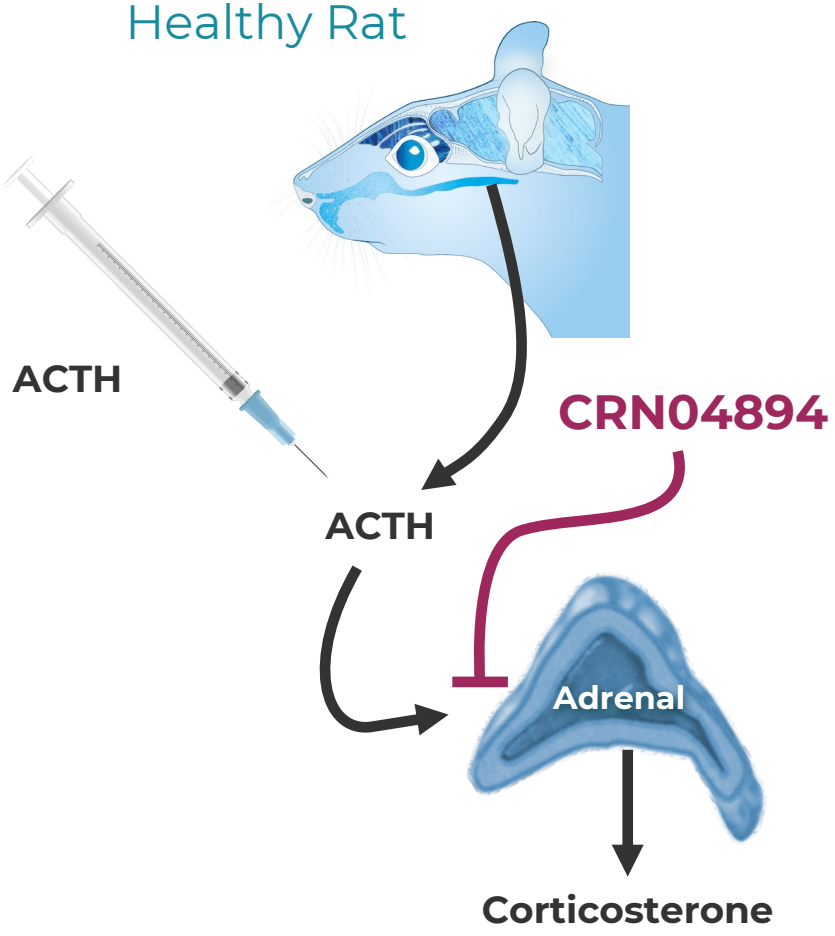


[1] Data from Oster et al., Endocrine Reviews 2017 (data shown are mean ± SEM, N=8-10)

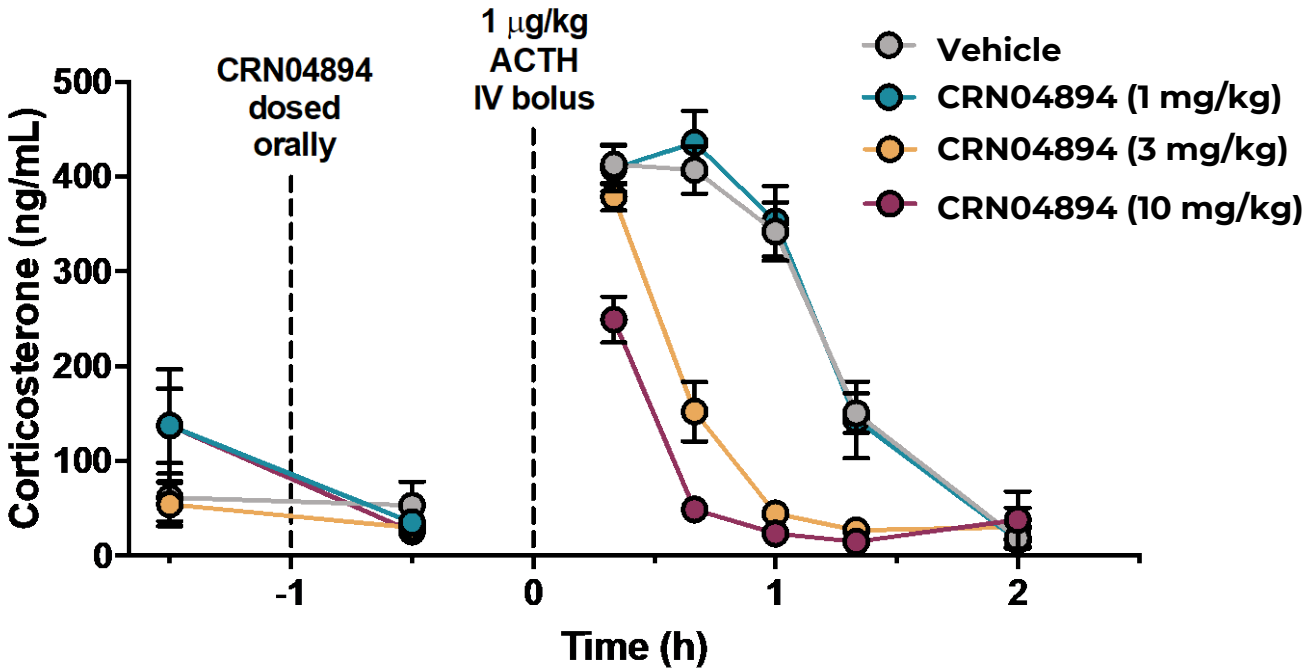
CRN04894: In Vivo Proof-of-Concept in Healthy Rats with Induced Hypercortisolism



Healthy Rat



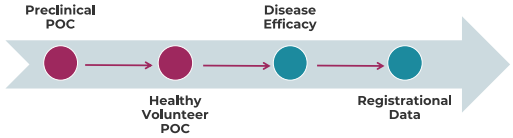
CRN04894 suppression of ACTH-induced corticosterone secretion in rats



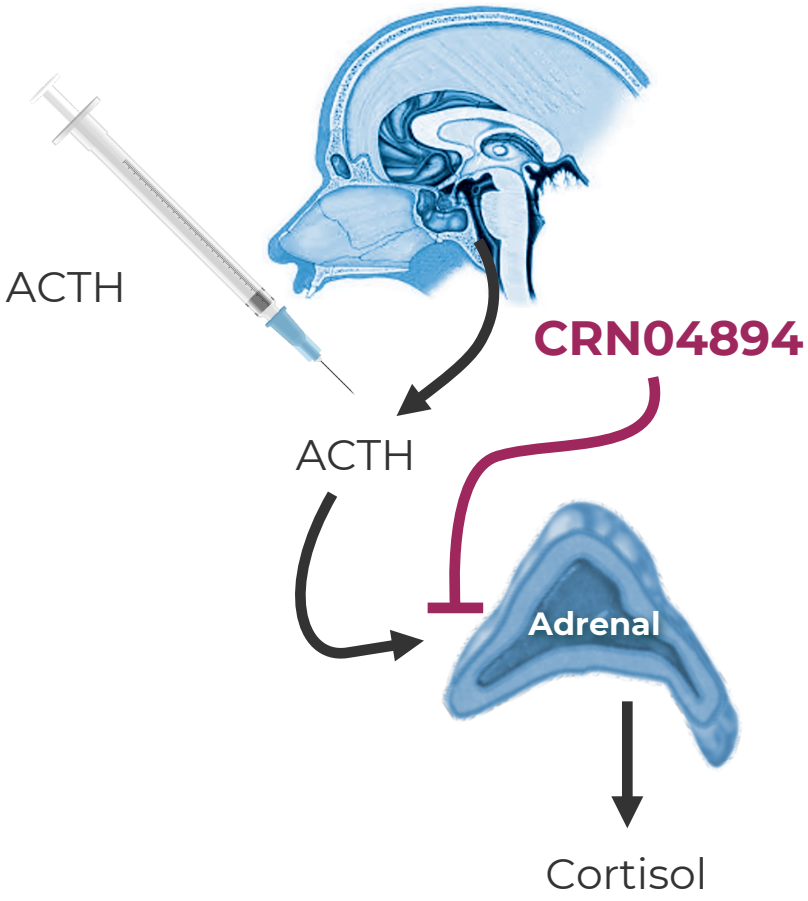
Experiment designed to mimic disease:

- 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: Phase 1 Proof-of-Concept in Healthy Volunteers with Induced Hypercortisolism



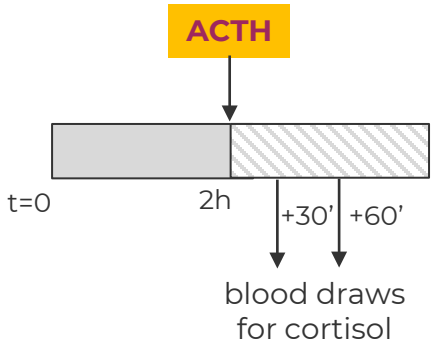
Healthy Volunteers



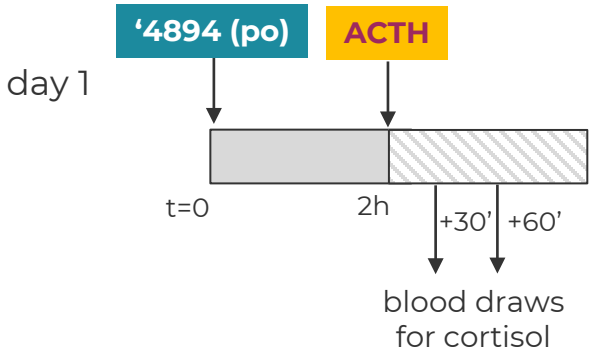
Evaluation of CRN04894 suppression of ACTH-induced cortisol secretion in healthy volunteers

ACTH Stimulation Test

Baseline (day -1)

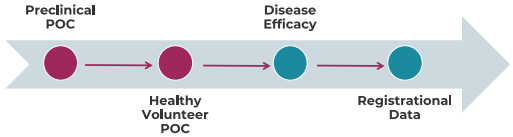


Treated (SAD day 1; MAD day 10)



Proof-of-Concept: Dose dependent suppression of ACTH-stimulated peak cortisol with CRN04894 vs baseline

CRN04894: Ongoing Phase 1 Proof-of-Concept in Healthy Volunteers



Single Ascending Dose (SAD) Cohorts

S1 (10 mg) → S2 → S3 → S4 → S5 → S6 (optional) → S7 (optional) → S8 (optional)

SAD Cohorts

Key Endpoint

- ACTH stimulated peak cortisol Day 1 vs. baseline (± CRN04894)

Additional Efficacy Endpoints

- Basal and ACTH stimulated 17-OHP, androstenedione, DHEA, aldosterone

Safety

Pharmacokinetics

Multiple Ascending Dose (MAD) Cohorts

M1 10d → M2 10d → M3 (optional) → M4 (optional)

MAD Cohorts

Key Endpoints

- Basal (8 am) cortisol D10 vs. baseline
- ACTH stimulated peak cortisol D10 vs. baseline

Additional Efficacy Endpoints

- 24-hour serum profiles for cortisol, 17-OHP, androstenedione, ACTH
- 24-hour salivary cortisol profiles (including LNSC)
- 24-hour urine free cortisol
- Basal and ACTH stimulated 17-OHP, androstenedione, DHEA, aldosterone

Safety

Pharmacokinetics

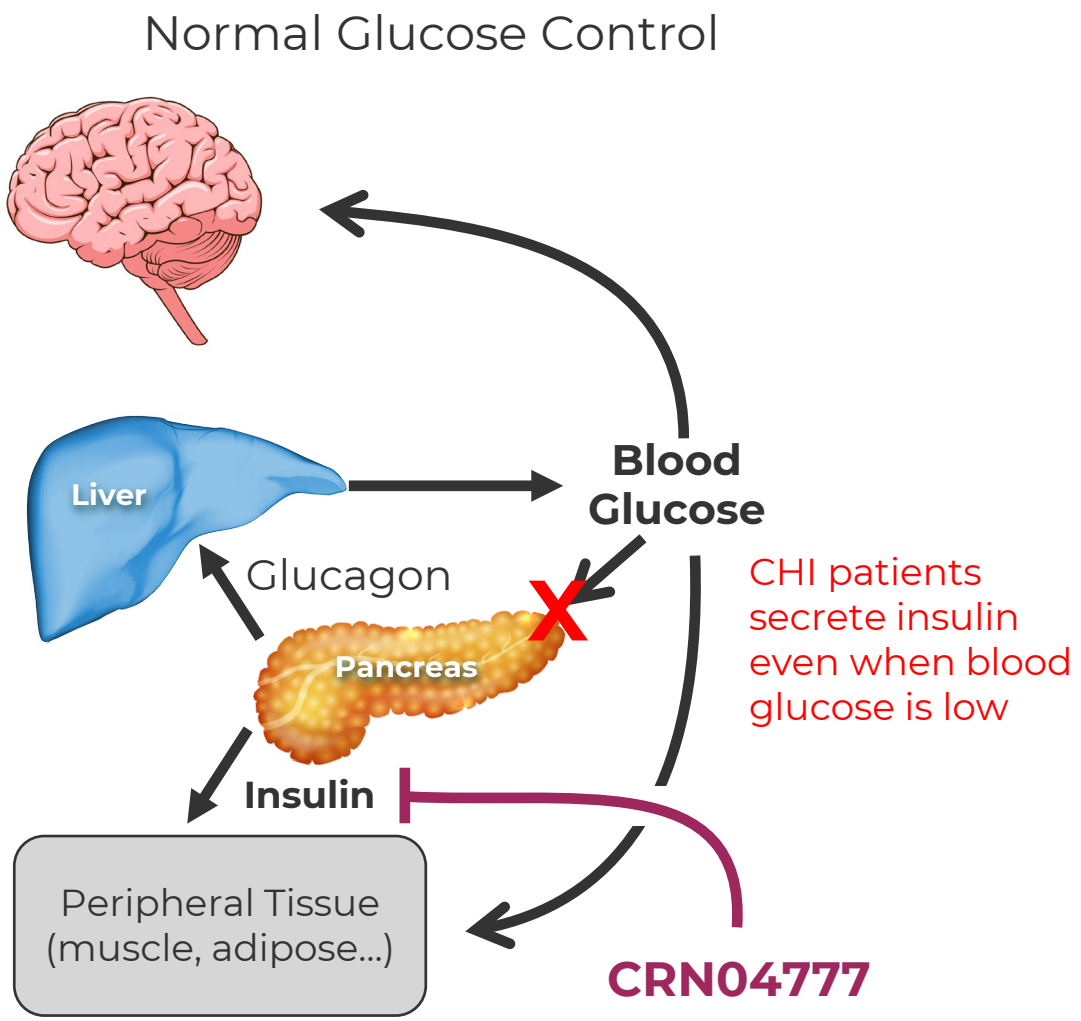
All volunteers will be monitored continuously in a clinical research unit for the advent of clinical or biochemical adrenal insufficiency.

Protocol defined criteria for glucocorticoid replacement verified by biochemical hypocortisolism (whenever possible) will be in place

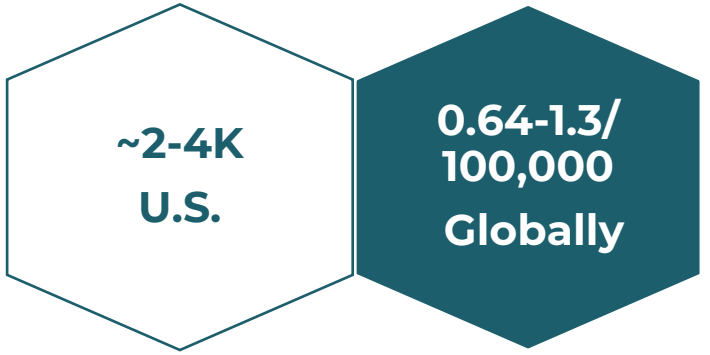
CRN04777: AN INVESTIGATIONAL, POTENTIAL FIRST-IN-CLASS, ORAL NONPEPTIDE SST5 AGONIST

Congenital hyperinsulinism (CHI)

Inappropriate Insulin Secretion Causes Life Threatening Recurrent Hypoglycemia in CHI



Congenital Hyperinsulinism



- Genetic defect results in excess insulin secretion when blood glucose is low
- Excess insulin causes hypoglycemia
- Untreated hypoglycemia can result in neurodevelopment disorders and death
- Early identification and intensive glucose management are critical

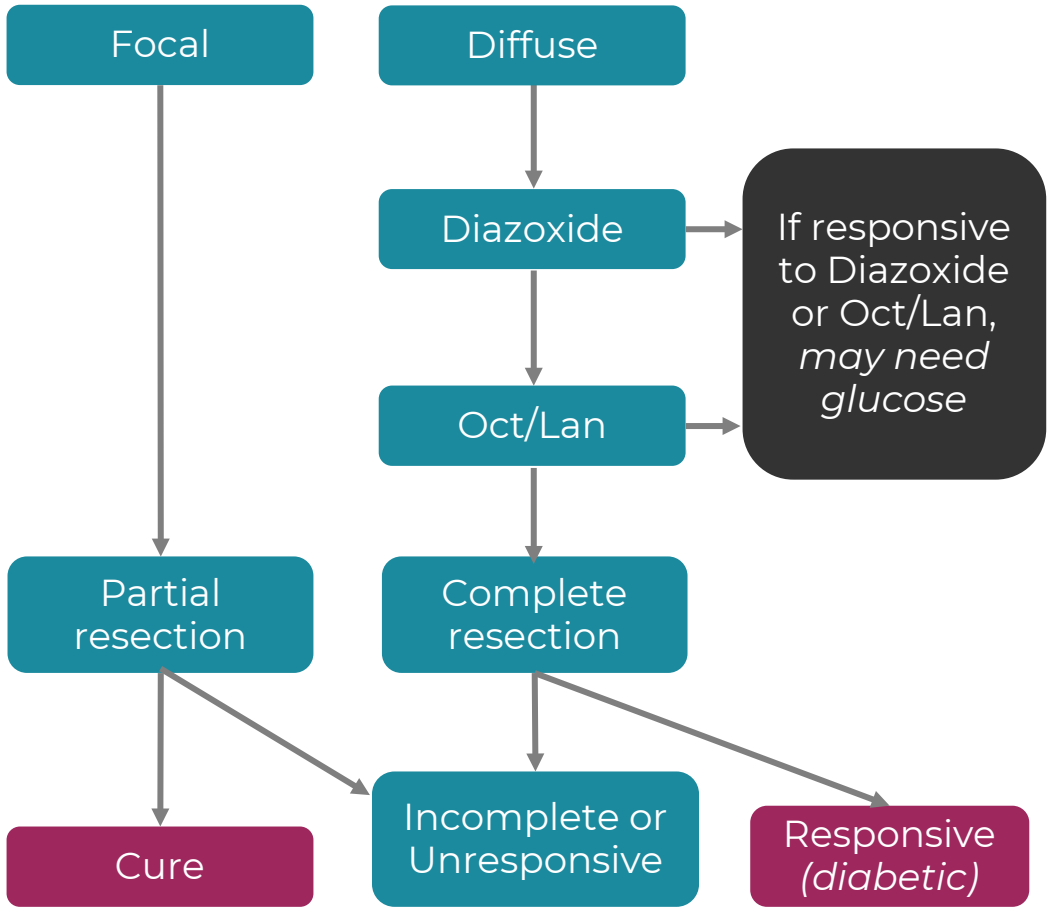
Robust global patient advocacy

- Congenital Hyperinsulinism International (www.congenitalhi.org)

Excruciating Unmet Medical Needs in CHI

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

Current Standard of Care for CHI

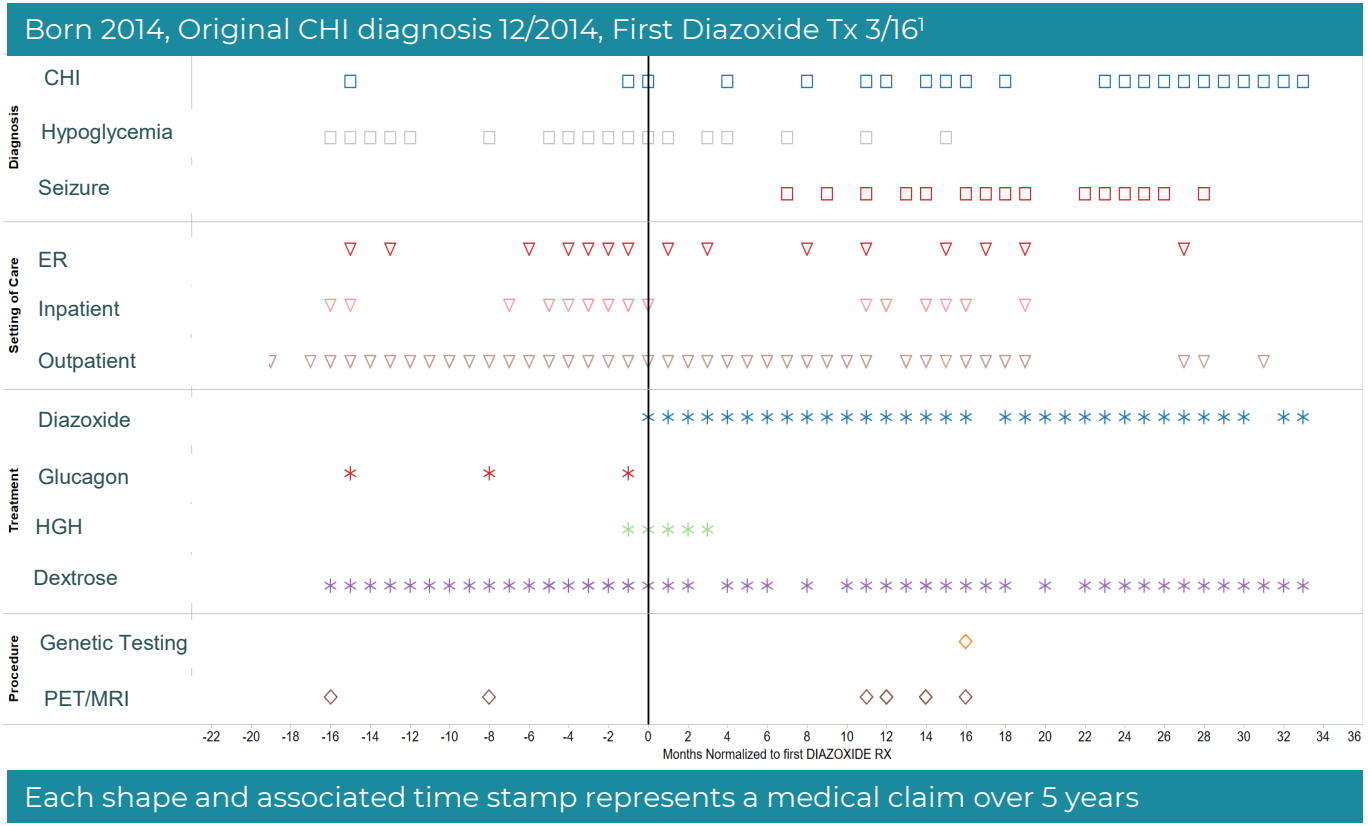


Patient & Parent Goals

- ✓ Put child to bed knowing they will wake up in the morning
- ✓ Avoid neurological damage
- ✓ Eliminate the glucose tube and backpack
- ✓ Reduce injections and glucose sticks
- ✓ Avoid pancreatectomy
- ✓ Medical management until HI resolves
- ✓ Be a kid not a patient

CHI Patient Care is a High Burden on Healthcare Systems

Healthcare utilization by a baby girl with CHI



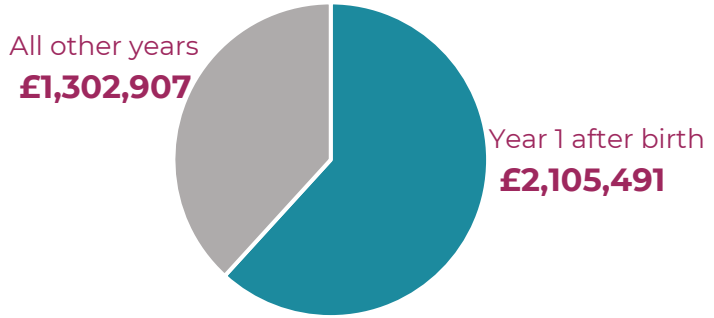
Current Challenges

- 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

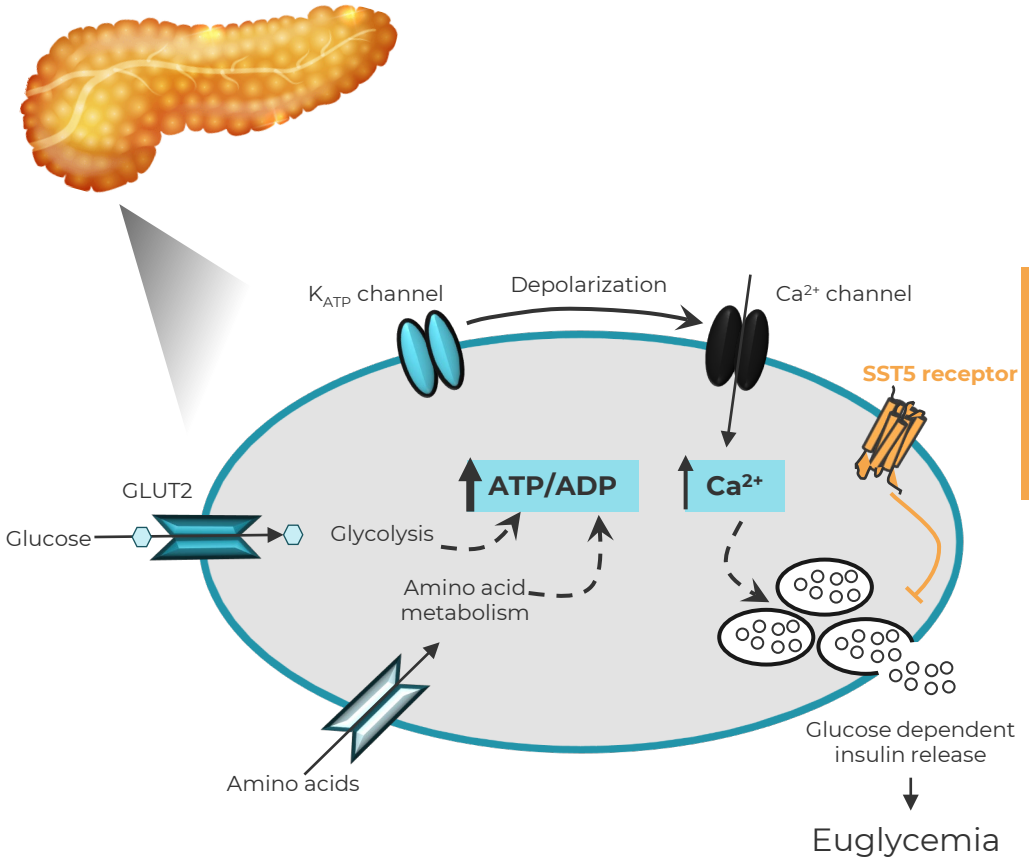


Patients unresponsive to first-line drug therapy (diazoxide) represented the greatest driver of costs

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

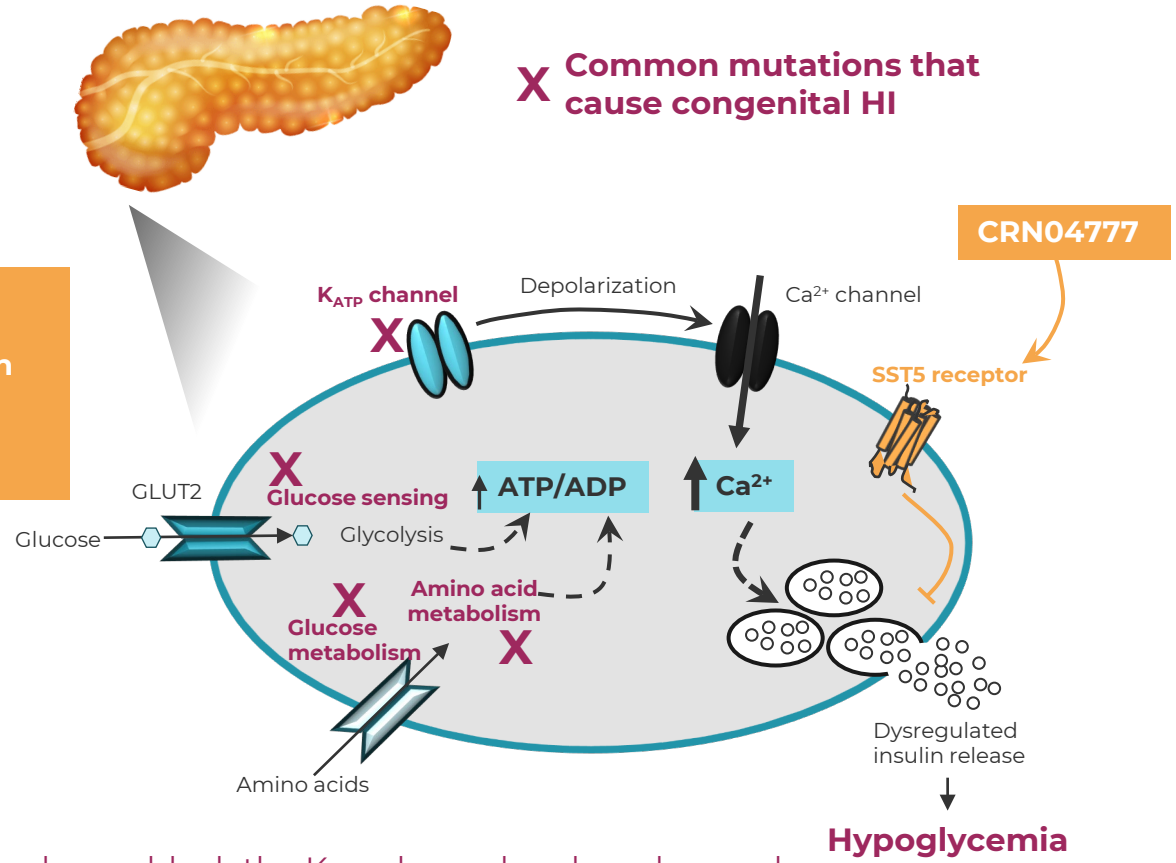
SST5 Agonists Should Be Universally Effective Against Various Forms of Congenital HI

Healthy pancreatic β-cells



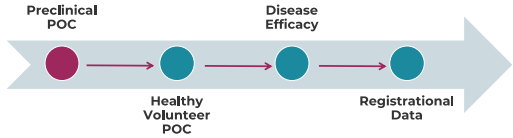
SST5 receptor activation inhibits insulin secretion via multiple pathways

Congenital HI pancreatic β-cells

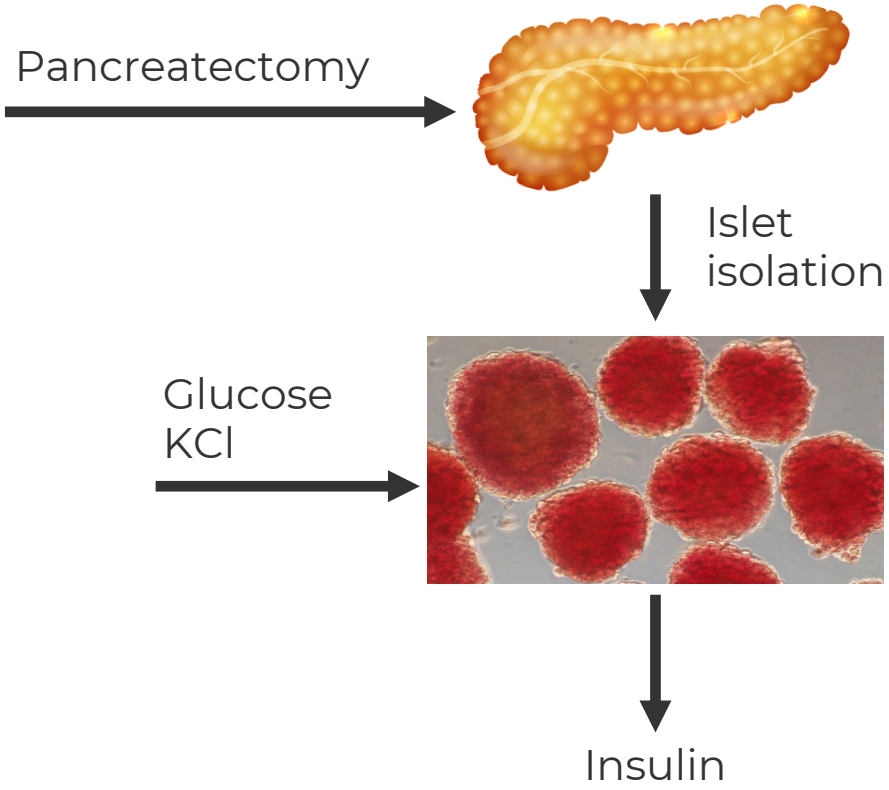


Sulfonylureas block the K_{ATP} channel and can be used to mimic the genetic defect in many CHI patients

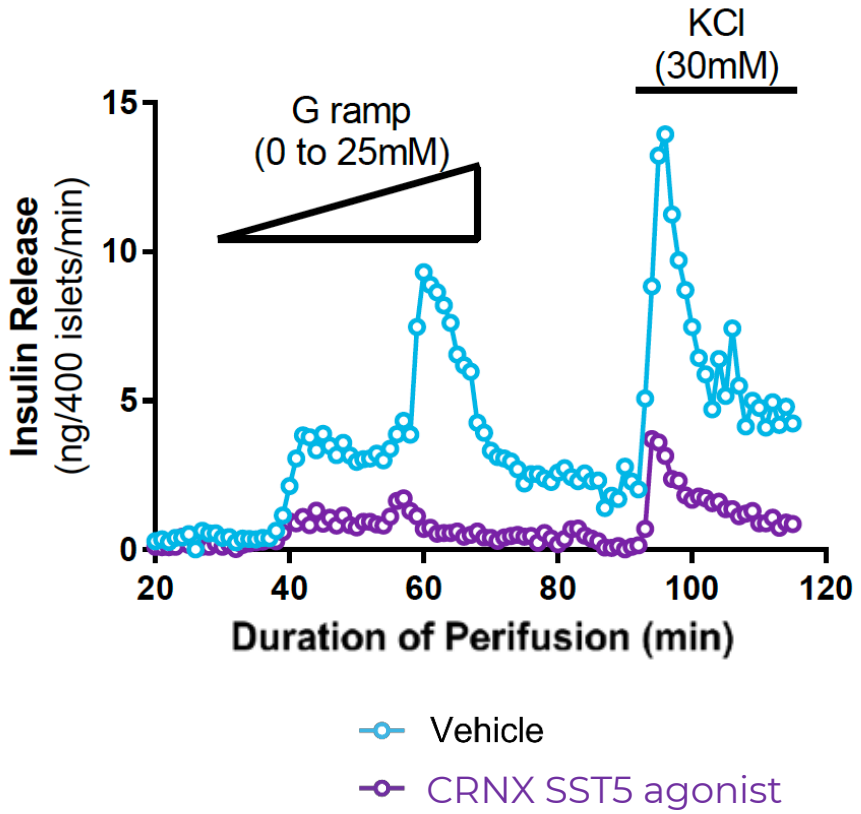
CRN04777: Ex-Vivo Proof-of-Concept with Pancreatic Islets from CHI Donor



Congenital HI pancreas

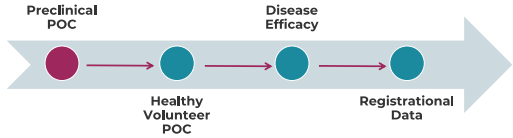


CRNX SST5 agonist suppressed insulin from islets isolated from patient with Beckwith-Wiedemann Syndrome

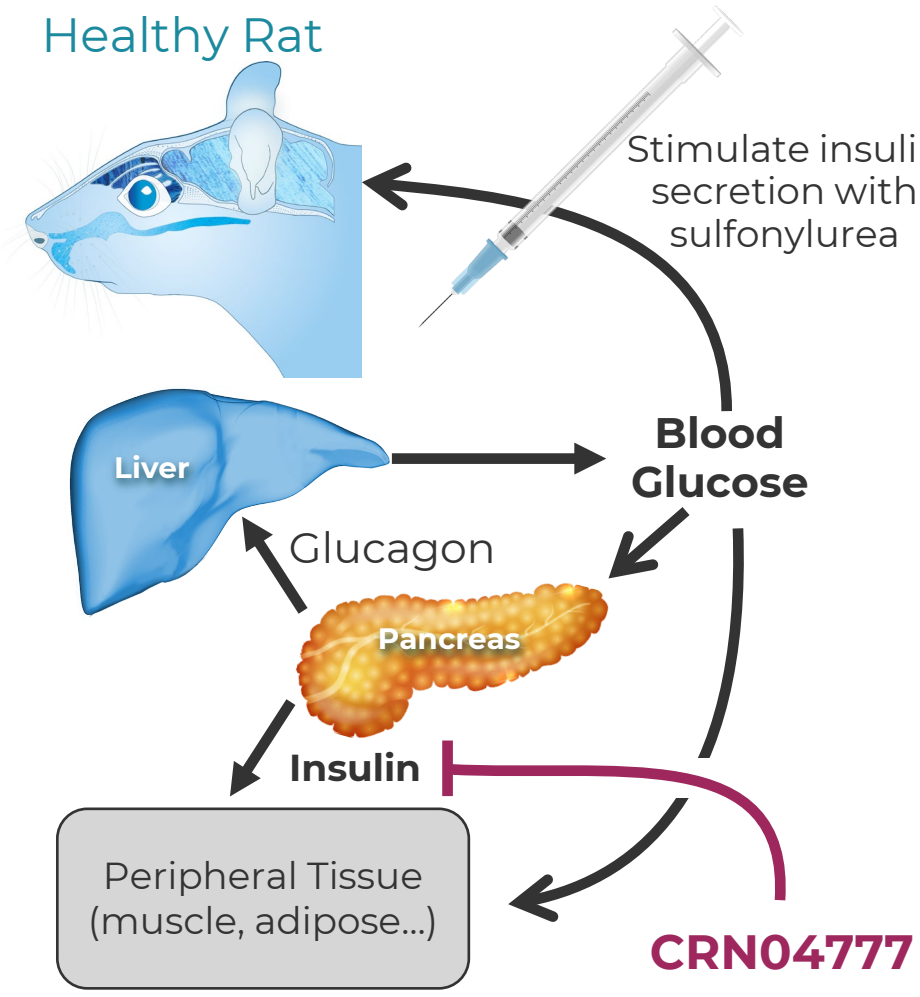


Islet data was obtained using another Crinetics SST5 agonist candidate before CRN04777 had been selected for development

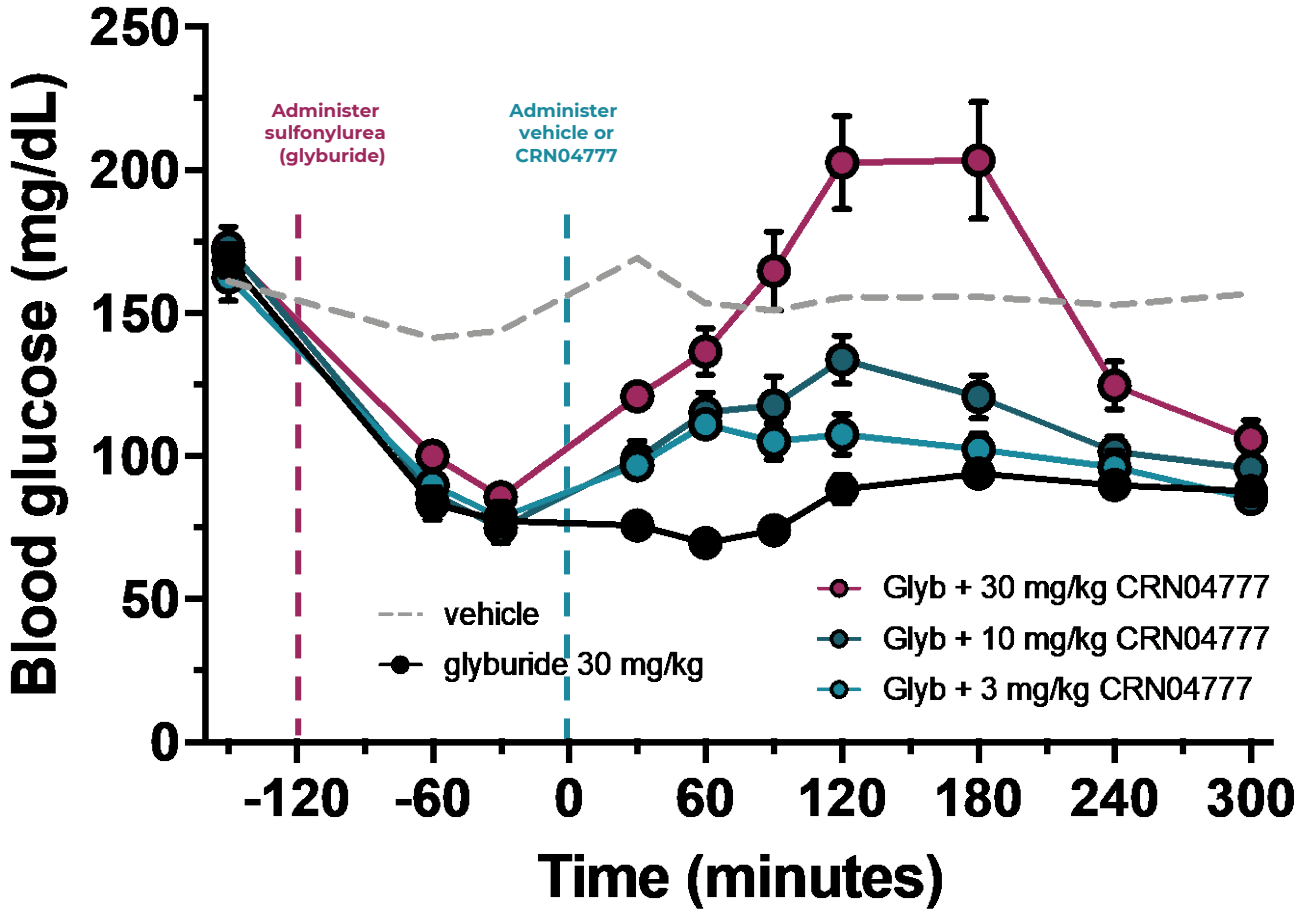
CRN04777: In Vivo Proof-of-Concept in Healthy Rats with Induced Hyperinsulinism



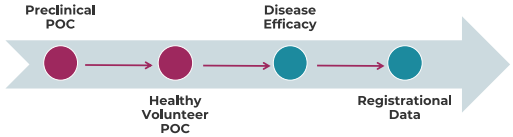
Healthy Rat



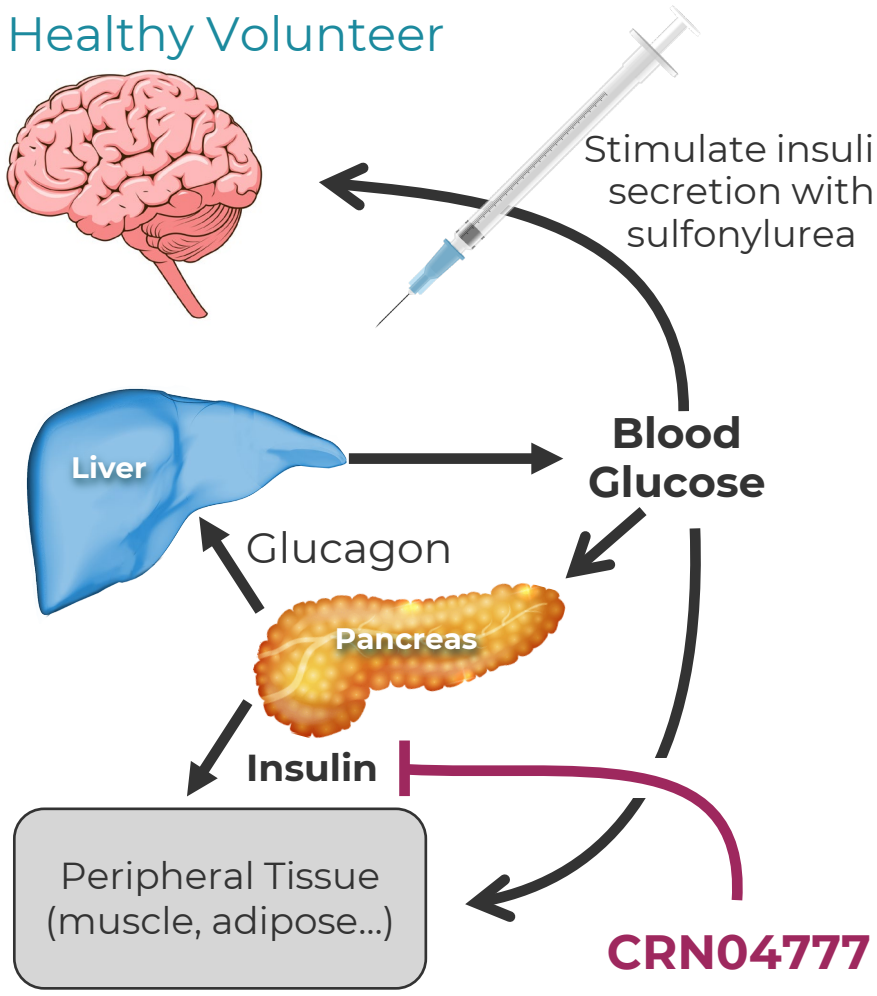
CRN04777 suppression of sulfonylurea-induced insulin secretion and hypoglycemia in rats



CRN04777: Phase 1 Proof-of-Concept in Healthy Volunteers with Induced Hyperinsulinism

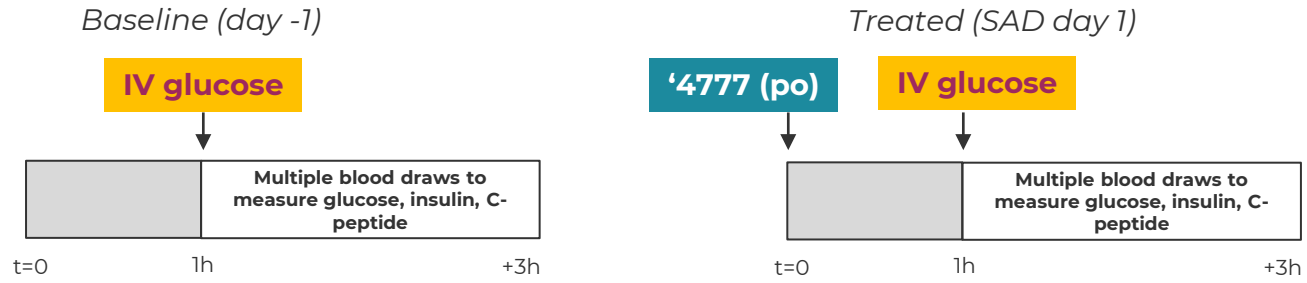


Healthy Volunteer

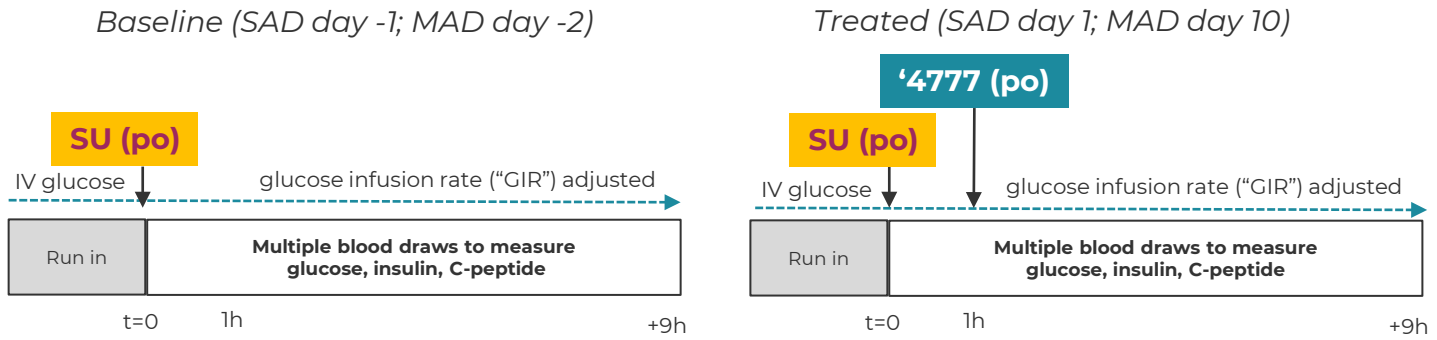


Evaluation of CRN04777 suppression of glucose and sulphonylurea induced insulin secretion in healthy volunteers

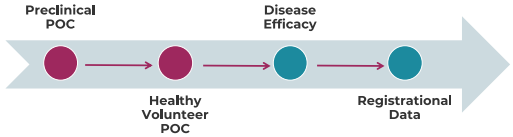
1. IV Glucose Tolerance Test (IVGTT)



2. Sulfonylurea (SU) Challenge Test (Glucose Clamp)



CRN04777: Ongoing Phase 1 Proof-of-Concept in Healthy Volunteers



Single Ascending Dose (SAD) Cohorts

Sa1 (0.5 mg) → Sa2 → Sa3 → Sa4 → Sa5 → Sa6

IV Glucose Tolerance Test (IVGTT)

Sb1 → Sb2

Sulfonylurea challenge

Sc1

Food effect on bioavailability

SAD (3 parts)

SAD A (n=8/cohort, up to 6 cohorts)
- IVGTT: Measure plasma glucose, insulin, C-peptide AUC Day 1 vs baseline
- Measure fasting plasma glucose, insulin, C-peptide vs baseline
- Determines dose for SAD bc and MAD

SAD B (n=8/cohort, 2 cohorts)
- Sulfonylurea challenge (Glucose Clamp)
- Measure GIR, plasma glucose, and C-peptide during euglycemic Day 1 vs baseline

SAD C (n=6/cohort, 1 cohort)
- Food effect on bioavailability

Safety/PK

Multiple Ascending Dose (MAD) Cohorts

M1 10d → M2 10d → M3 10d → M4 10d → M5 10d

Sulfonylurea challenge

MAD (n=9/cohort, up to 5 cohorts)

Key Endpoints:
- Sulfonylurea challenge (Glucose Clamp)
  - Measure: GIR, plasma glucose, and C-peptide during euglycemic Day 1 vs baseline
- Mixed Meal Test: Measure plasma glucose, insulin, C-peptide, GLP-1 AUC Day 1 vs baseline

Safety/PK

Abbreviations: GIR: glucose infusion rate

2020 Accomplishments and Anticipated 2021-2022 Milestones

2020 Accomplishments

- ✓ Positive paltusotine acromegaly Phase 2 data
- ✓ Improved paltusotine tablet formulation
- ✓ CRN04894 (ACTH antagonist) IND open for FIH study
- ✓ CRN04777 US Rare Pediatric Disease Designation & EU Orphan Drug Designation
- ✓ CRN04777 (SST5 agonist) regulatory approval for FIH study in Germany

2021 Anticipated Milestones

CRN04894 SAD POC data in 1H2021

CRN04777 SAD POC data in mid-2021

Paltusotine acromegaly Phase 3 start (1H2021)

Paltusotine NETs program start (2021)

2022 Goals

Paltusotine Phase 3 enrollment complete for acromegaly

CRN04777 Phase 2/3 start

CRN04894 Phase 2 start

New Preclinical Candidates

- Hyperparathyroidism
- Nonfunctional pituitary adenomas
- Polycystic kidney disease
- Other


Crinetics
Pharmaceuticals

APPENDICES

Key Patent Families Anchor a Robust IP Portfolio

Paltusotine Portfolio				
Patent Family Subject Matter	**Patent Nos.**	**Status**	**Priority Date**	**Estimated Expiration**
Composition of Matter	U.S. 10,562,884 U.S. 10,604,507 U.S. 10,766,877 U.S. 10,875,839	**Granted in**: U.S. AU **Pending in**: EA, EP, BR, CA, CN, IL, IN, JP, KR, MX, NZ, SG, ZA, TW, HK, ID, UA, VE	July 2016	July 2037
HCl Salt and its Polymorph Form	U.S. 10,464,918	**Granted in:** U.S. **Pending in:** EA, EP, AU, BR, CA, CN, IL, IN, JP, KR, MX, NZ, SG, ZA, TW, ID, UA, VE	January 2018	January 2039
New Formulation	N/A	Pending	Sep 2020	September 2041
ACTH Antagonist Portfolio				
Patent Family Subject Matter	**Patent Nos.**	**Status**	**Priority Date**	**Estimated Expiration**
Composition of Matter	U.S. 10,562,884 U.S. 10,604,507 U.S. 10,766,877	**Granted in:** U.S. **Pending in:** TW **To be filed in:** EA, EP, AU, BR, CA, CN, IL, IN, JP, KR, MX, NZ, SG, UA, ZA	June 2018	June 2039
SST5 Agonist Portfolio				
Patent Family Subject Matter	**Patent Nos.**	**Status**	**Priority Date**	**Estimated Expiration**
Composition of Matter	N/A	**Pending in:** PCT, U.S., TW, AR, VE	Aug 2019	Aug 2040

Leadership Team

Scott Struthers, PhD	President & CEO, Founder	Neurocrine Biosciences; ScienceMedia; BIOSYM Technologies; salk. Where cures begin.
Frank Zhu, PhD	VP of Chemistry, Founder	Neurocrine Biosciences; UC San Diego; Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
Steve Betz, PhD	VP of Biology, Founder	Neurocrine Biosciences; Abbott; DU PONT MERCK
Ajay Madan, PhD	Chief Development Officer	Neurocrine Biosciences; UC San Diego; XenoTech, Uncommon Science | Uncommon Service
Marc Wilson	Chief Financial Officer	CIDARA Therapeutics; Trius Therapeutics; Neurocrine Biosciences; pwc
Alan Krasner	Chief Medical Officer	Shire; BIODEL; Pfizer; Johns Hopkins School of Medicine
Gina Ford	VP, Corporate Strategy & Commercial Planning	AcelRx Pharmaceuticals, Inc.; IPSEN, Innovation for patient care; SOLSTICE NEUROSCIENCES; élan
Adriana Cabré	VP, Human Resources	National University; MedImpact; AMYLIN; CooperVision

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