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# CORPORATE PRESENTATION

June 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 Phase 3 trials of paltusotine in acromegaly, report data therefrom and the expected timing thereof; the potential for such Phase 3 program to support broad approval of paltusotine for all acromegaly patients who require pharmacotherapy; 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 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 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; 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 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.

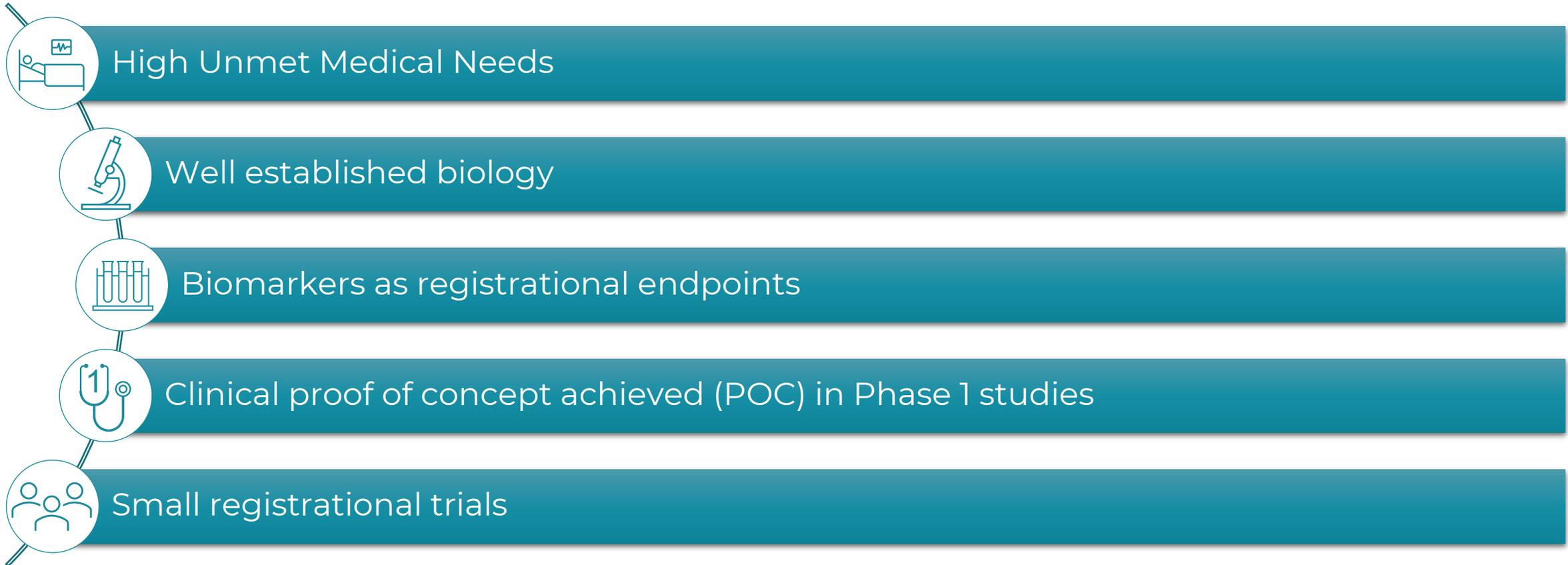
This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. 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.

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

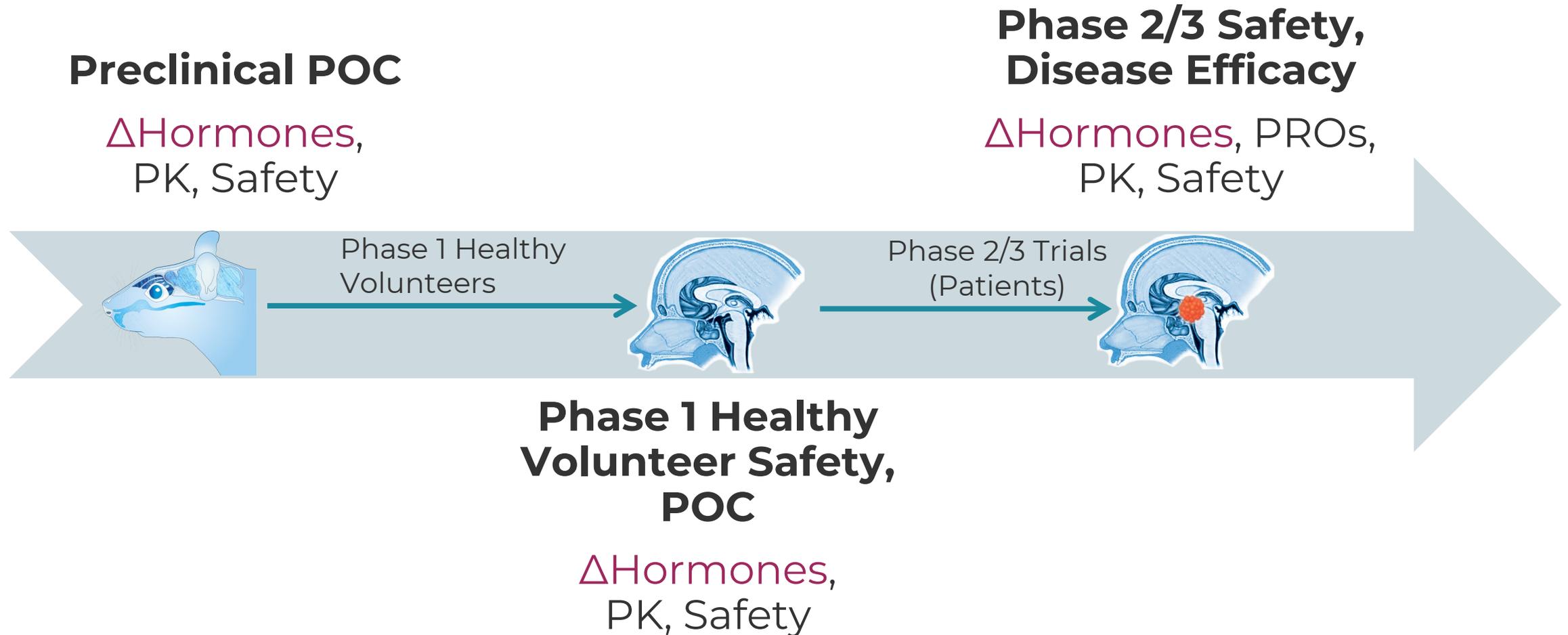


# Strategy: Drugs Built from Scratch for Purpose

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



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

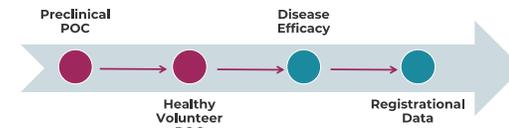


# Pipeline Targets Indications with Unmet Need

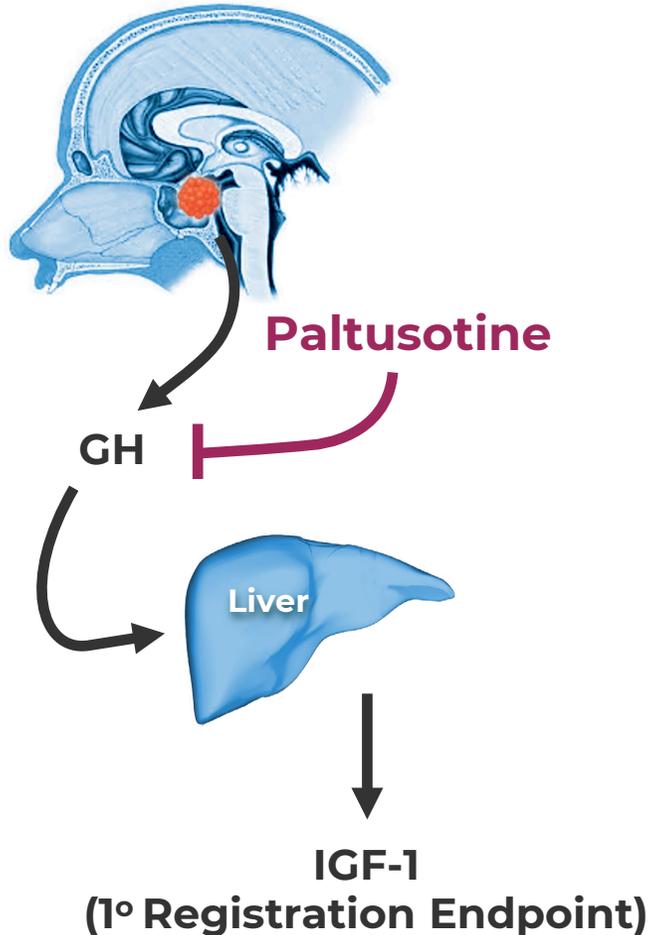
Well established biology has the potential to allow for the use of biomarkers as registration endpoints

PROGRAM	Development Stage				Registrational Endpoint	Prevalence	
	Preclin	Phase 1	Phase 2	Phase 3		US Total	Global Range per 100,000
<b>Paltusotine (SST2 agonist)</b>							
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
<b>CRN04894 (ACTH antagonist)</b>							
Cushing's Disease					Cortisol Levels	10K	2.5 – 3.8
Congenital Adrenal Hyperplasia (CAH)					Adrenal Androgens/ Glucocorticoid use	27K	6.7 – 10.0
<b>CRN04777 (SST5 agonist)</b>							
Congenital Hyperinsulinism (CHI)					Glucose Levels	2-4K	0.64 – 1.3
<b>US TOTAL</b>						<b>~236K</b>	

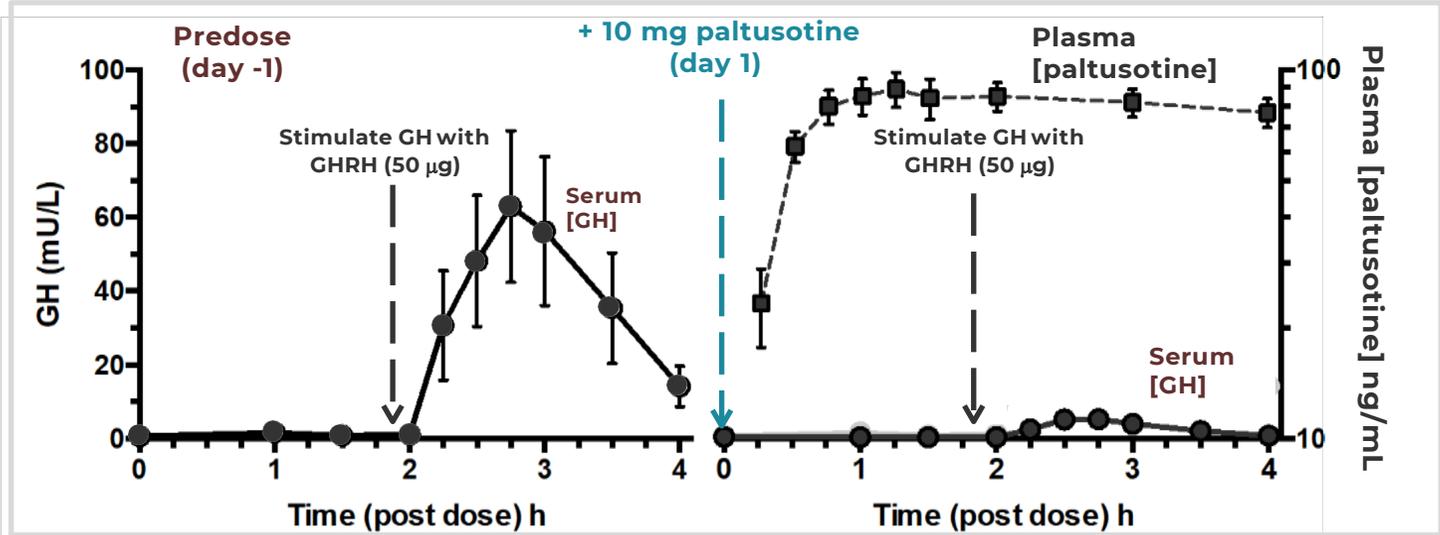
# Endocrinology Invented Biomarkers! Clinical Proof-of-Concept in Phase 1 is Our Goal



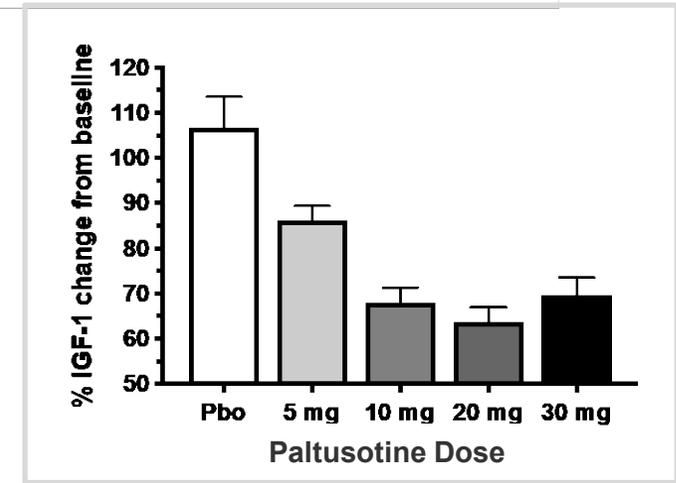
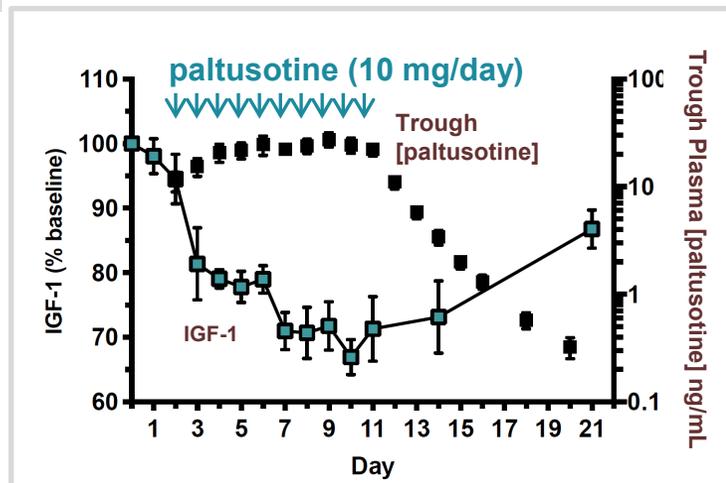
## Acromegaly



### Phase 1 SAD Data: Suppression of GH



### Phase 1 MAD Data: Suppression of IGF-1



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

Acromegaly

Carcinoid syndrome

Nonfunctional neuroendocrine tumors



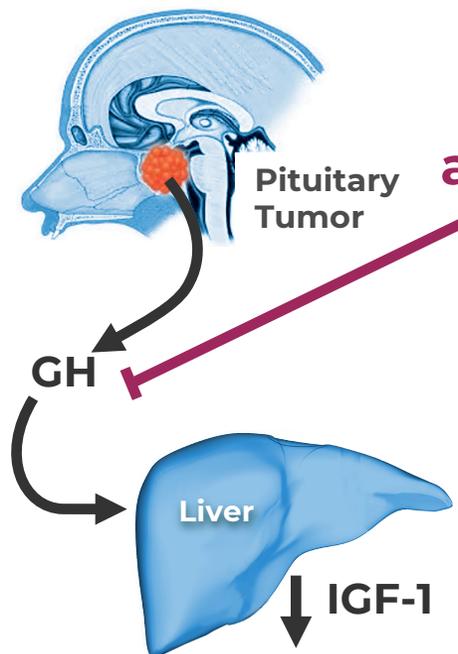
# Acromegaly and NETS are Currently Treated with Injected SST2 Peptide Agonists

## 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:

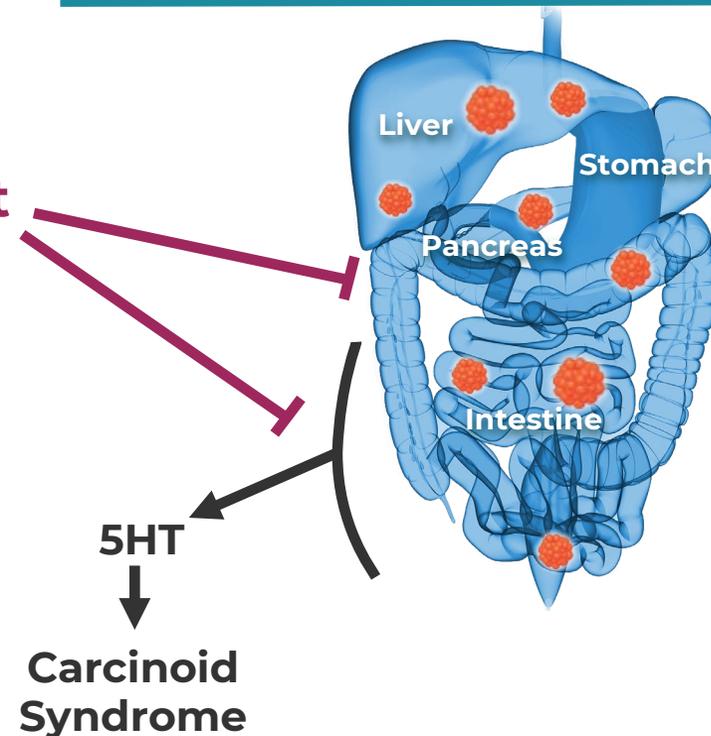
1. Bone and cartilage overgrowth
2. Organ enlargement
3. Changes in glucose and lipid metabolism
4. Abnormal growth of hands and feet
5. Alteration of facial features



US Prevalence: **26,000**

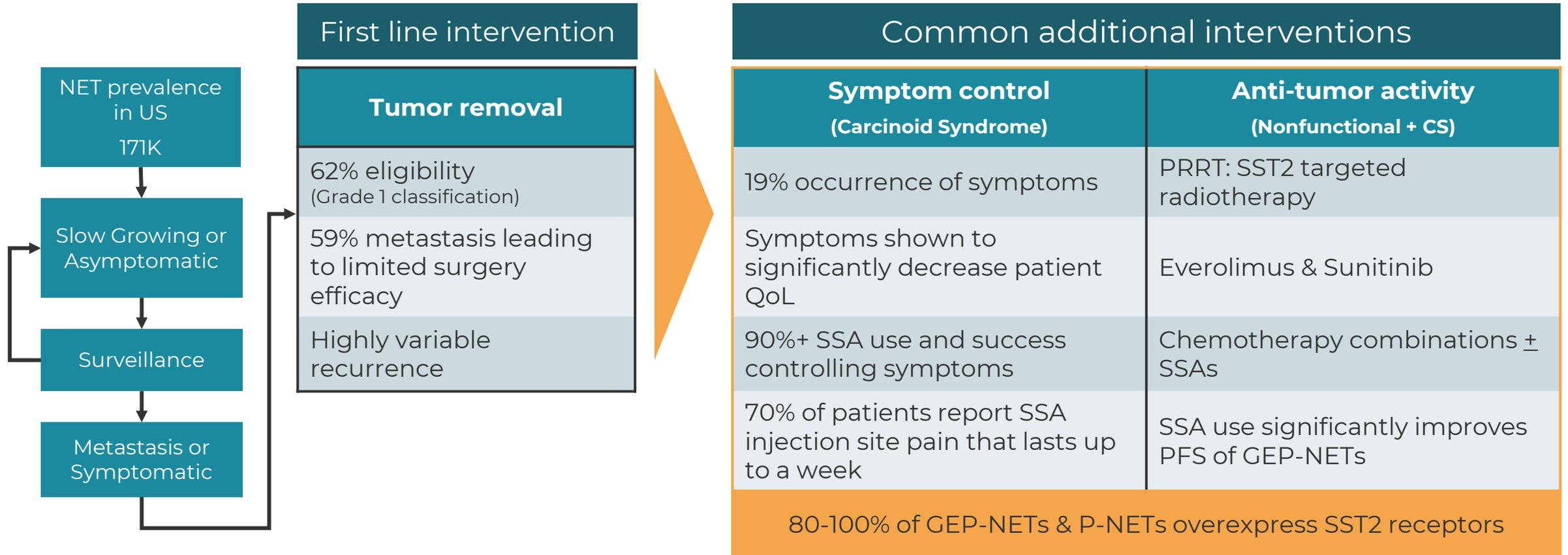
## Neuroendocrine Tumors (NETs)

- 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
<b>Total</b>	<b>171,000</b>

# NETs Treatment Considerations and Opportunities to Improve Current Standard of Care





# ~\$3B Market Despite Limitations of Current Therapies

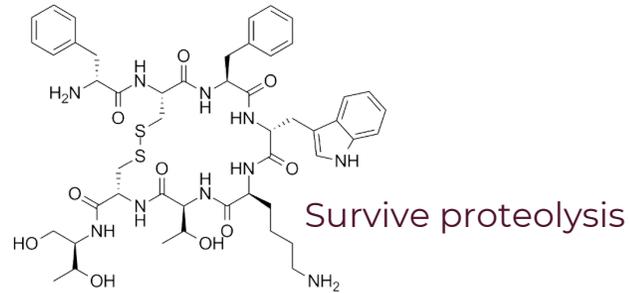


Sandostatin (octreotide)	Somatuline (lanreotide)	Somavert (pegvisomant)	MYCAPSSA (oral octreotide)
			
<p>\$1.4B</p> <p>Monthly intramuscular 5-mL vial; 1½” 19-gauge needle</p>	<p>\$1.4B</p> <p>Monthly deep subcutaneous .2-.5ml; 18-gauge needle</p>	<p>\$277M</p> <p>Daily injections 1 ml; 28 – 31- gauge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

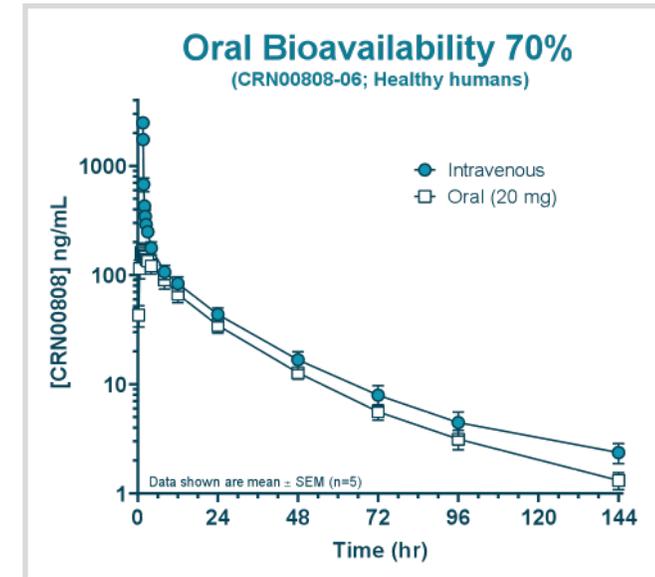
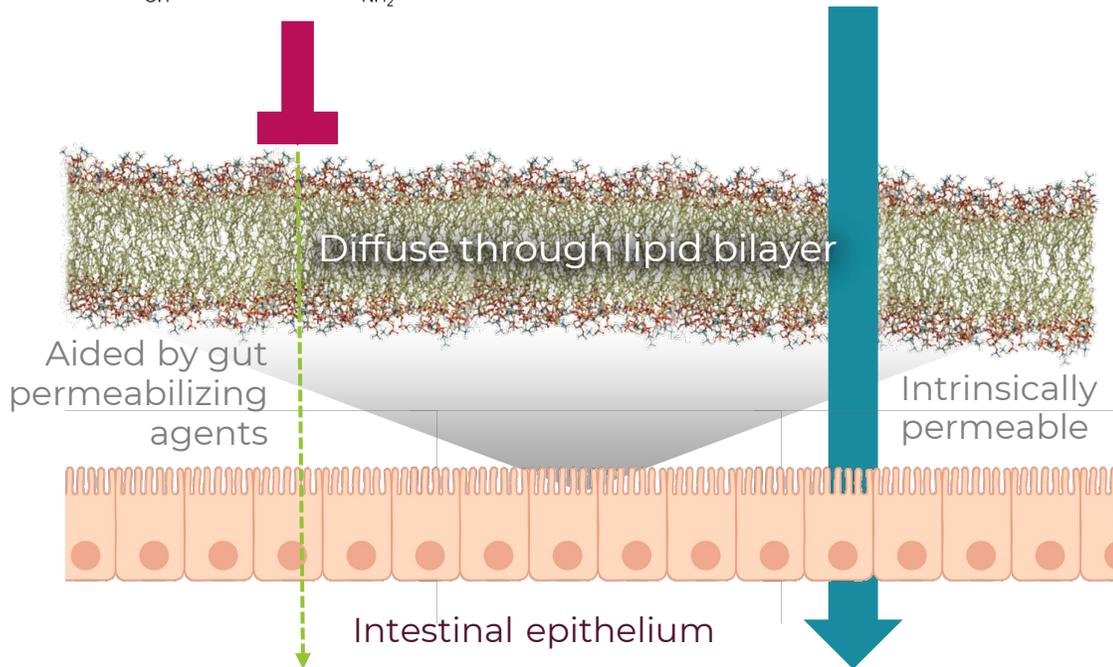
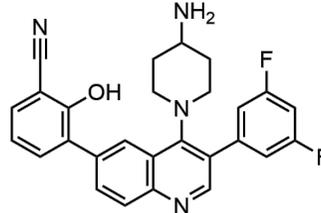
<sup>(1)</sup>MYCAPSSA Label

# Paltusotine Showed High Intrinsic Oral Bioavailability

## Peptide: Octreotide



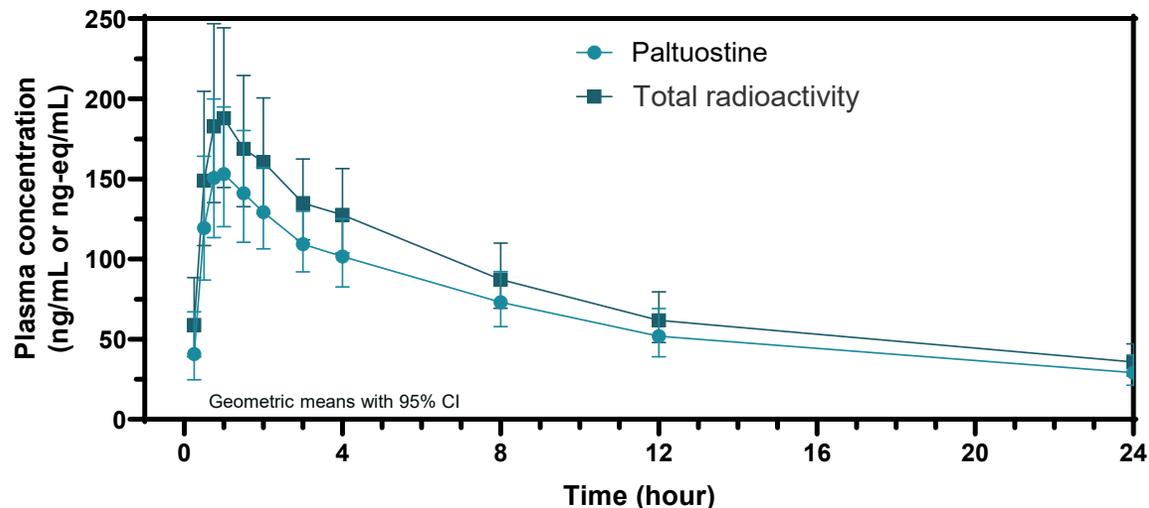
## Nonpeptide: paltusotine



	Paltusotine (CRN00808)
Oral Bioavailability	70%
Observed Half Life	42-50 hr.

# Paltusotine was Designed to Avoid Drug-Drug Interactions and Be Easy to Prescribe

Mass-balance (<sup>14</sup>C) study in healthy volunteers



*Unchanged paltusotine was the primary circulating species (>75%)*

Excretion Summary	Fraction in Urine (%)	Fraction in Feces (%)	Total Recovery (%)
Mean (%CV)	3.9 (29.9)	90 (2.5)	94 (1.1)

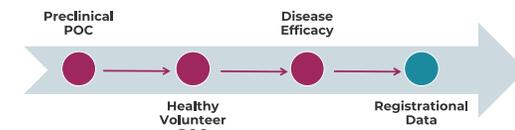
Paltusotine has not shown clinically meaningful inhibition or induction of drug metabolizing enzymes

- Dose adjustment may not be required for co-administered drugs

Low risk for drug interactions from inhibition of drug-metabolizing enzymes by co-administered drugs

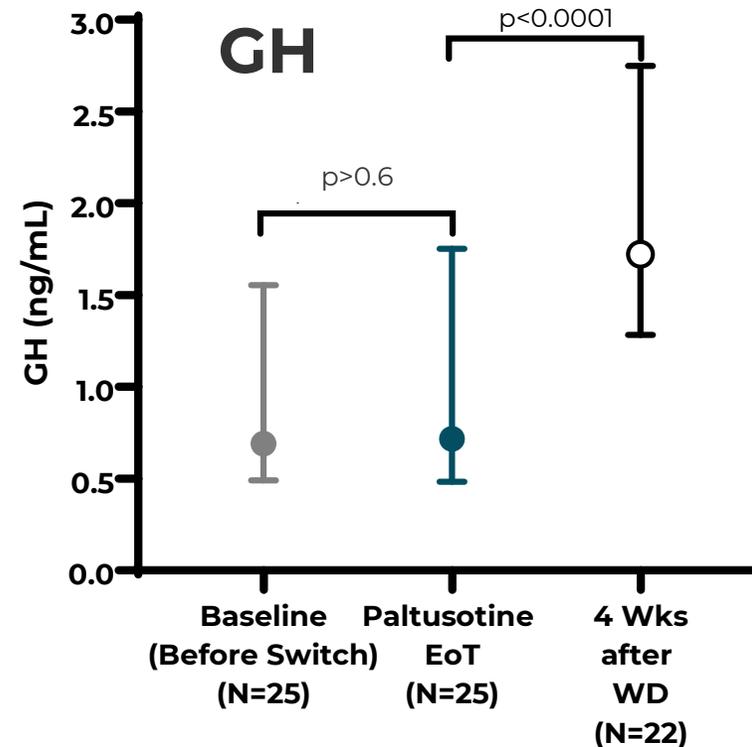
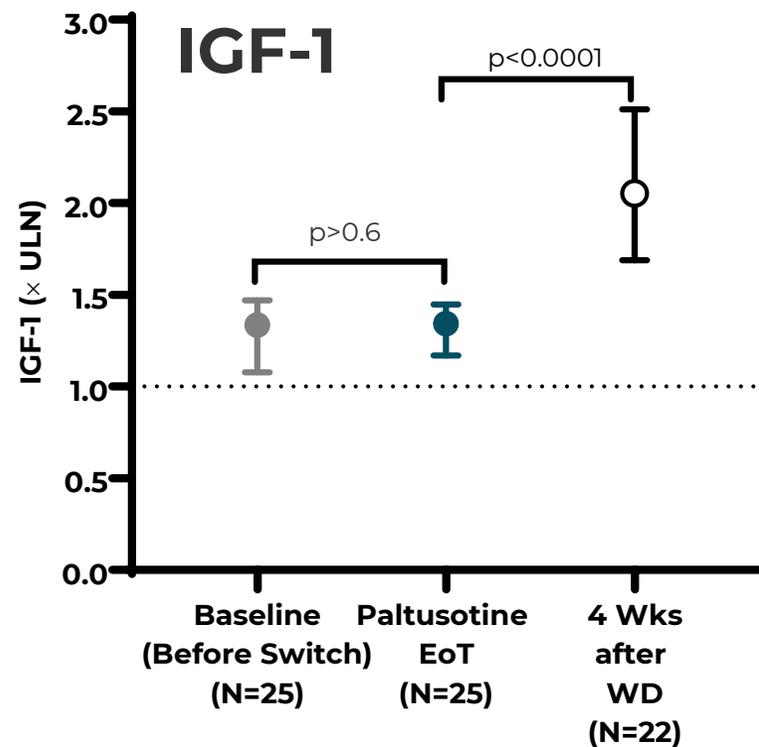
- Paltusotine is eliminated via the liver
- Multiple potential metabolic pathways
  - Glucuronidation and CYP-dependent metabolism
  - No single pathway is dominant

No excipients that may influence permeability of co-administered drugs



# Phase 2 ACROBAT Edge Study Met Primary Endpoint

Hormone suppression maintained after switching from injected SOC to oral paltusotine

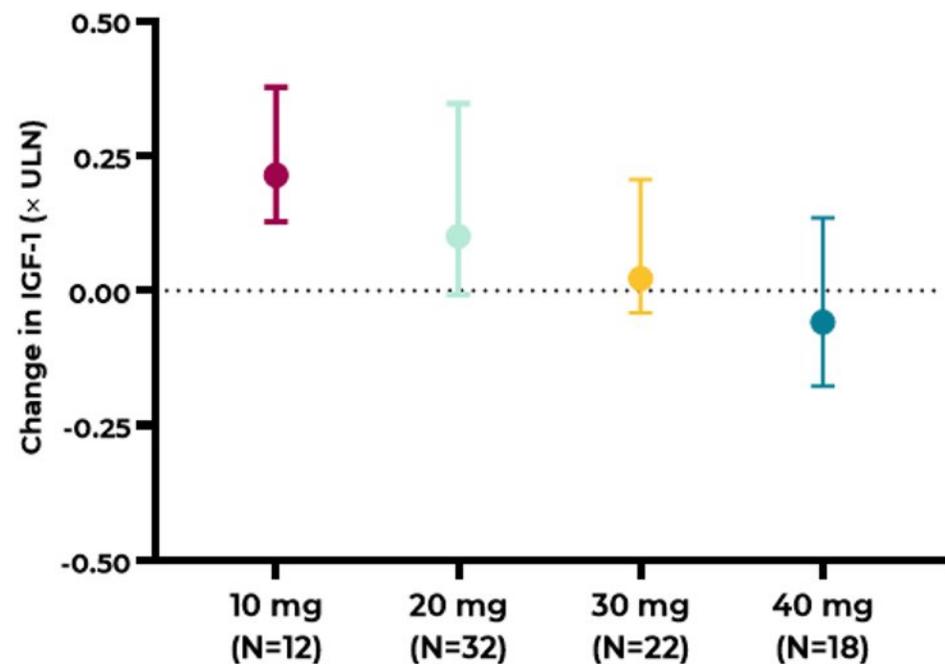


Data presented are median (Interquartile Range [IQR]: 25th percentile, 75th percentile) from the EDGE study's primary analysis population. EoT = End of Treatment defined as Week 13 (Visit 14) or last on treatment value carried forward (LOCF). Wks after WD is defined as Week 17 or result at least 22 days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

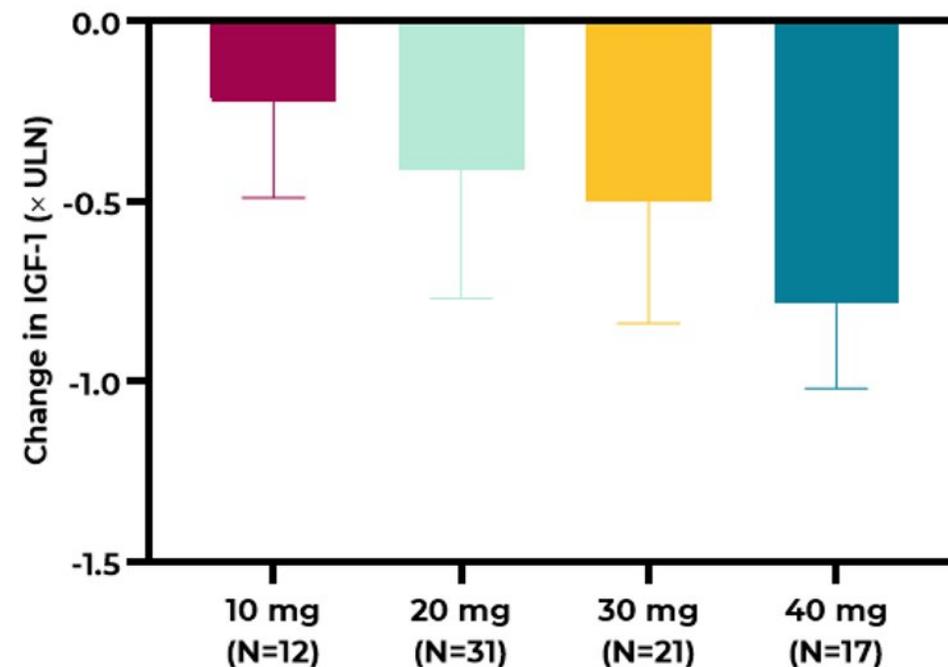


# Evidence of Dose Response from Phase 2 Program

Results from Switching to Paltusotine: Change in IGF-1 from Baseline to Steady State at Indicated Dose



Magnitude of Paltusotine Activity: Change in IGF-1 from Steady State to 4 Weeks After Withdrawal



Post-hoc analysis of data from EDGE primary analysis population and EVOLVE patients

Steady state IGF-1 at the indicated dose: Patients were on the indicated dose for at least 12 days. Data prior to Week 7 were excluded because of insufficient washout of depot injection during this window. Data are shown from Week 7, Week 10, and Week 13.

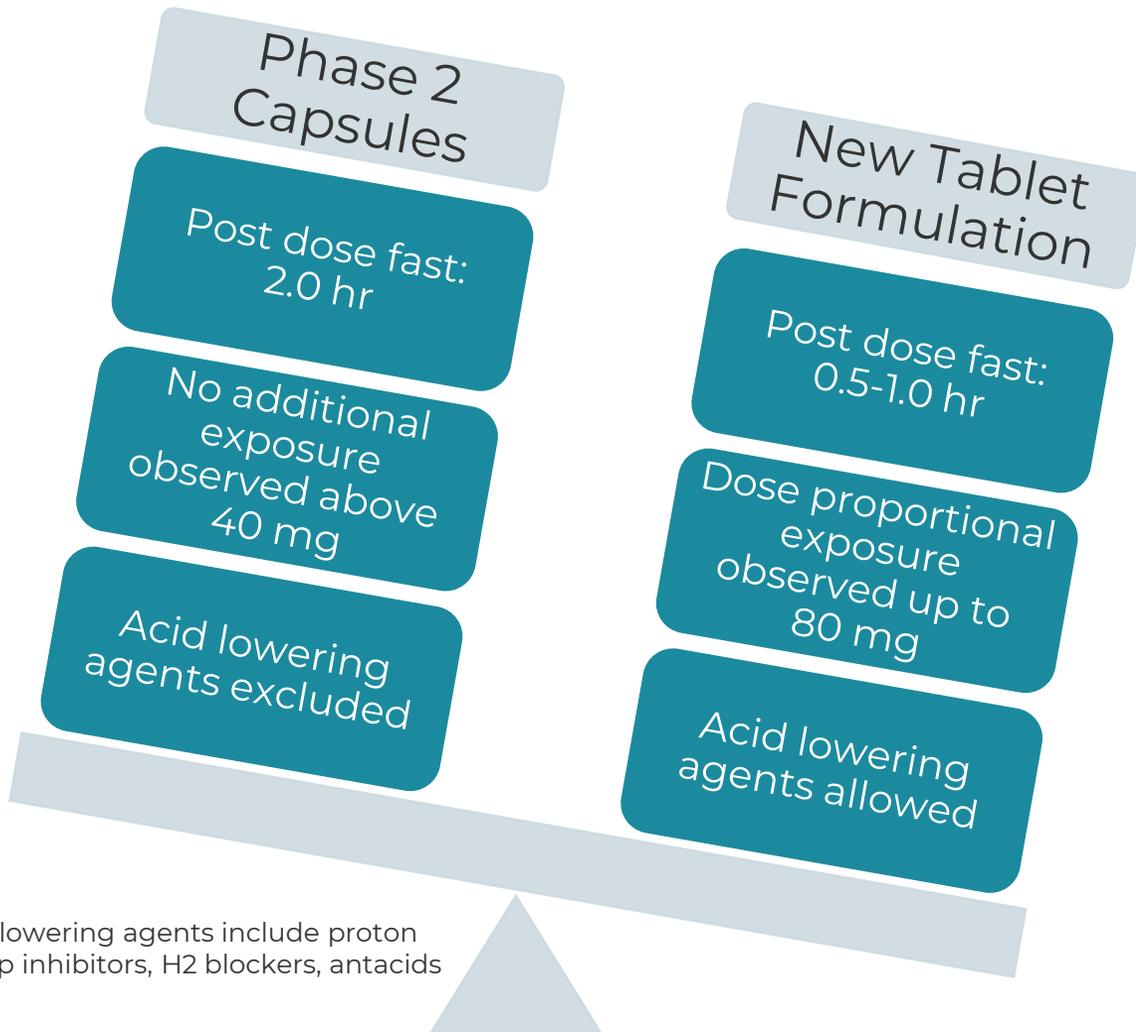
Data presented are median +/- IQR. EoT = End of Treatment defined as Week 13 (Visit 14) or last on treatment value carried forward (LOCF).

WD = Withdrawal, where 2 Wks after WD is defined as Week 15 or result within 7-21 days after last dose and 4 Wks after WD is defined as Week 17 or result at least 22 days after last dose. One subject is missing 4 Weeks after withdrawal observation.

Octreotide and lanreotide concentrations were measured 17 weeks after depot dose (W13 of the treatment period). Octreotide was completely washed out. Lanreotide concentrations were >75% reduced from baseline.

# Paltusotine New Tablet Formulation Incorporates Multiple Improvements

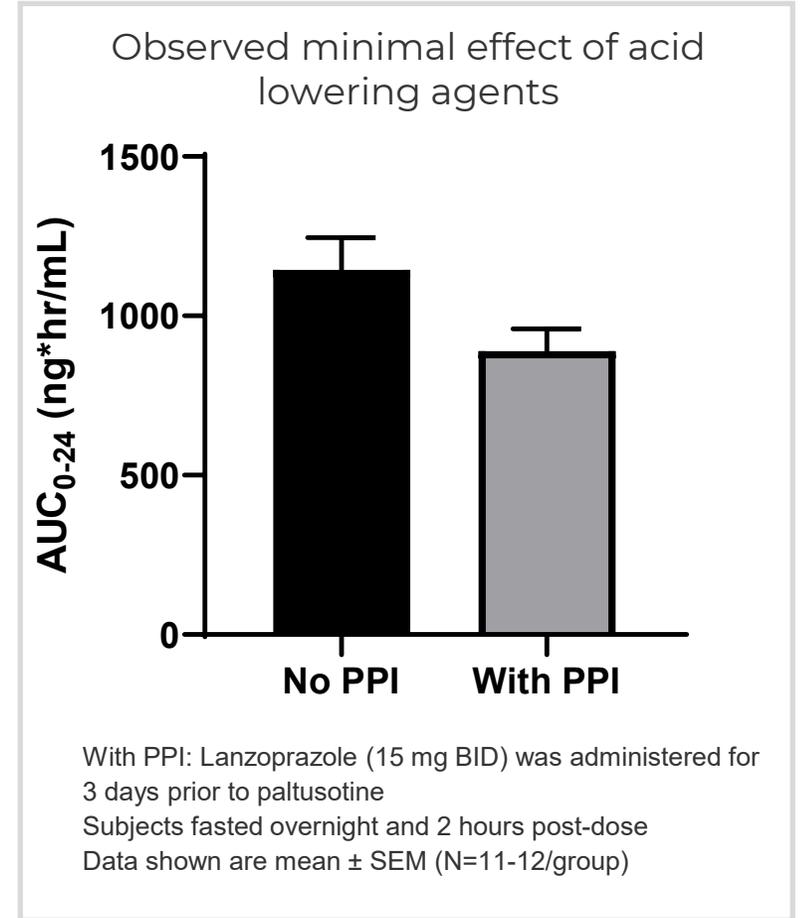
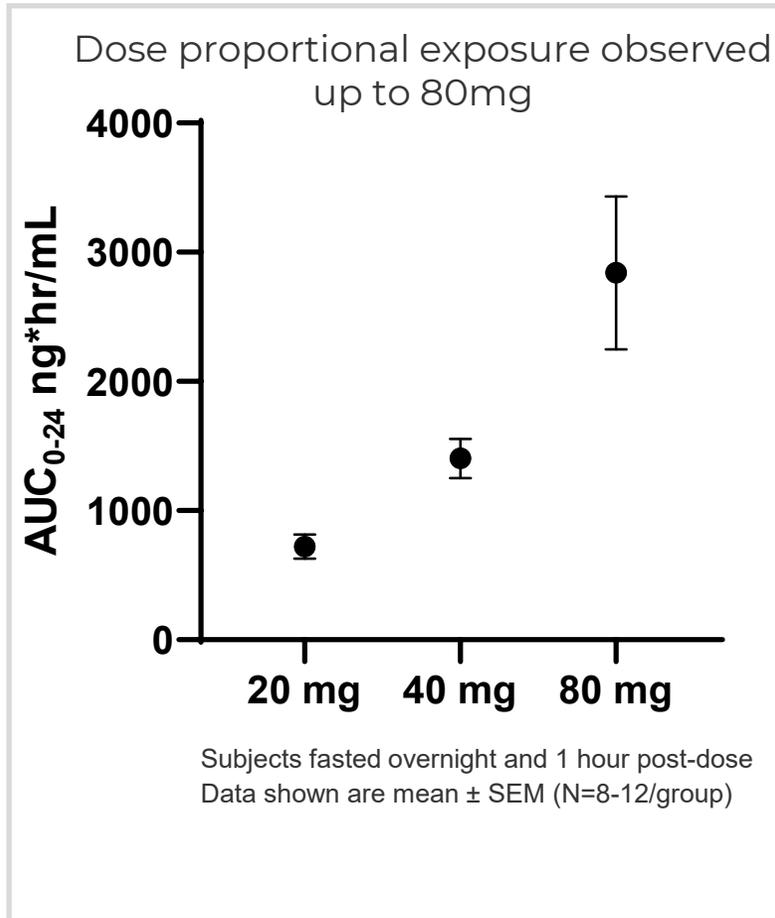
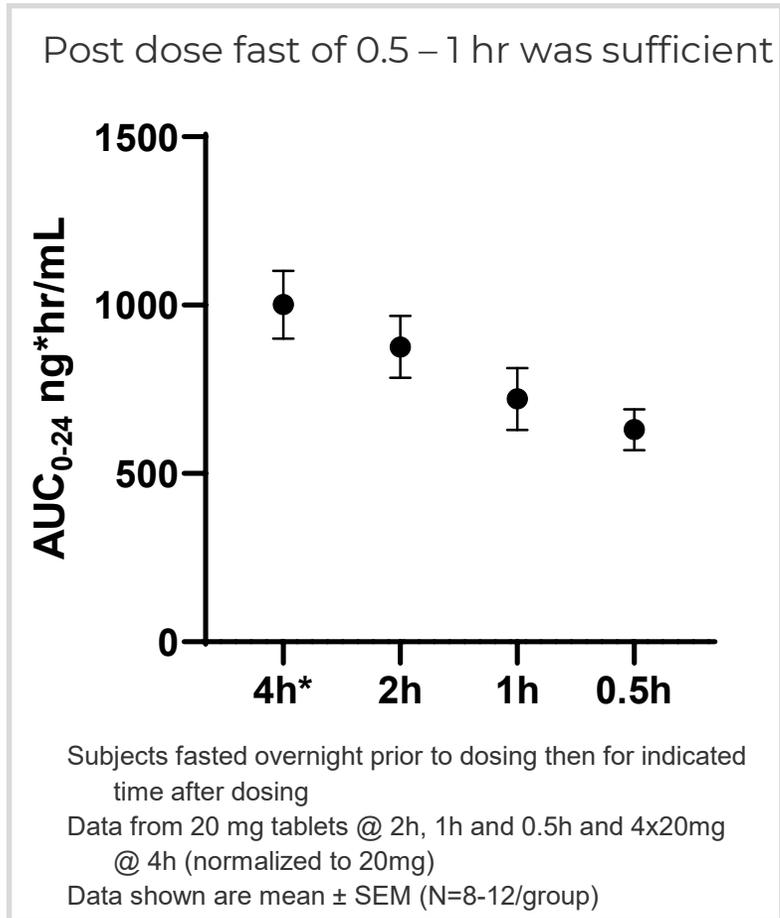
New tablet formulation to be used in Phase 3  
(and commercially, if approved)



Expected ambient shipping and storage

Data to be presented at ENDO (March 20-23, 2021)

# Improved Performance of New Tablet Formulation Observed in Healthy Volunteers



Data to be presented at ENDO (March 20-23, 2021)



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

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

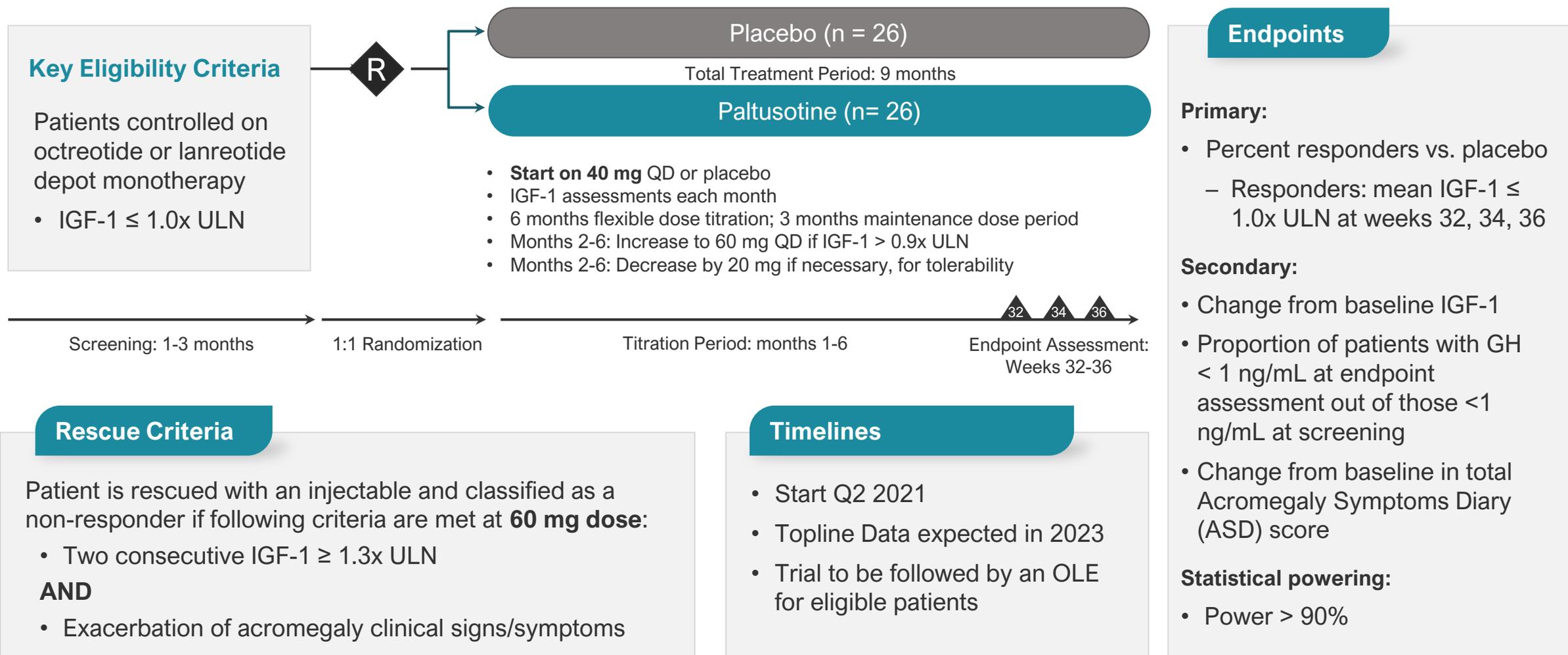
## **PATHFNDR-1: Switching from SOC**

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

## **PATHFNDR-2: Untreated Patients**

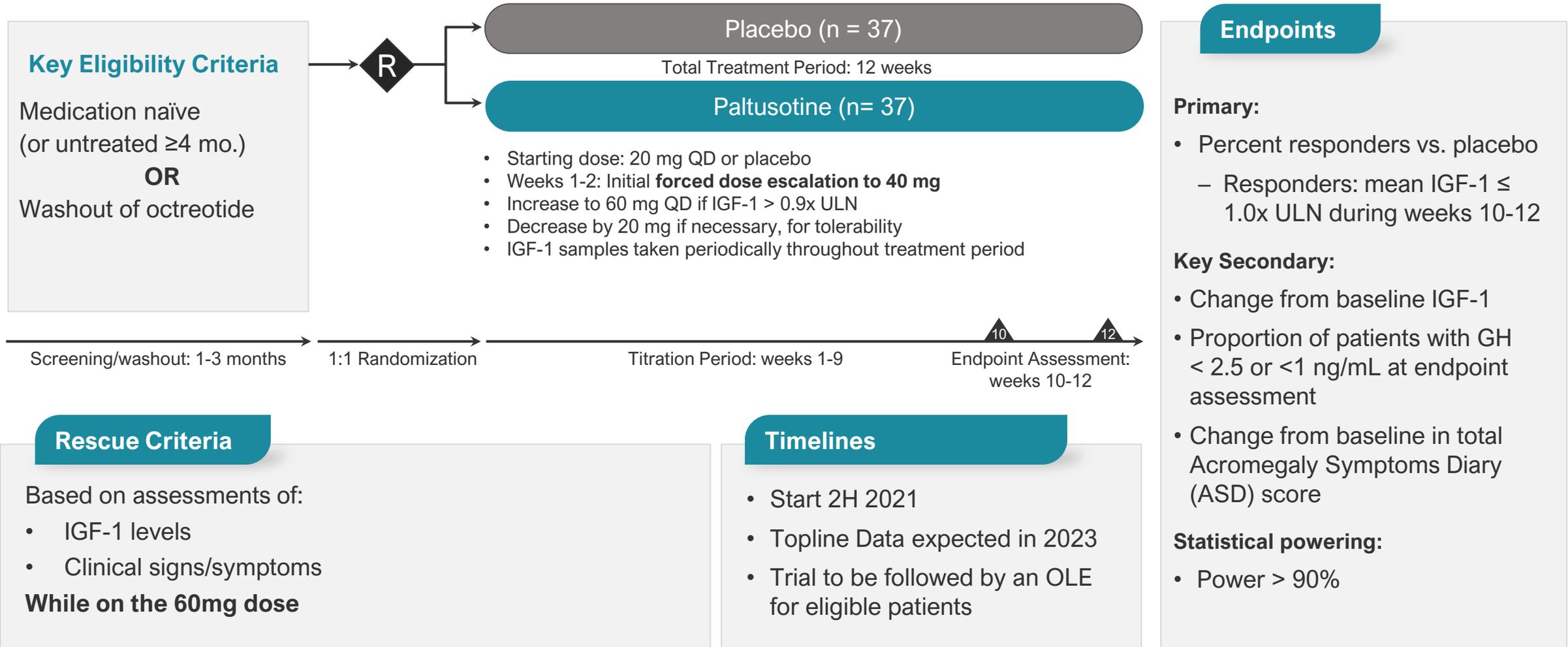
Evaluate safety and efficacy of paltusotine in untreated acromegaly patients who are *biochemically uncontrolled*

# PATHFNDR-1: Enabling Switching from SOC



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

# PATHFNDR-2: Enabling Use in Untreated Patients



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

# Anticipated Paltusotine Milestones

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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

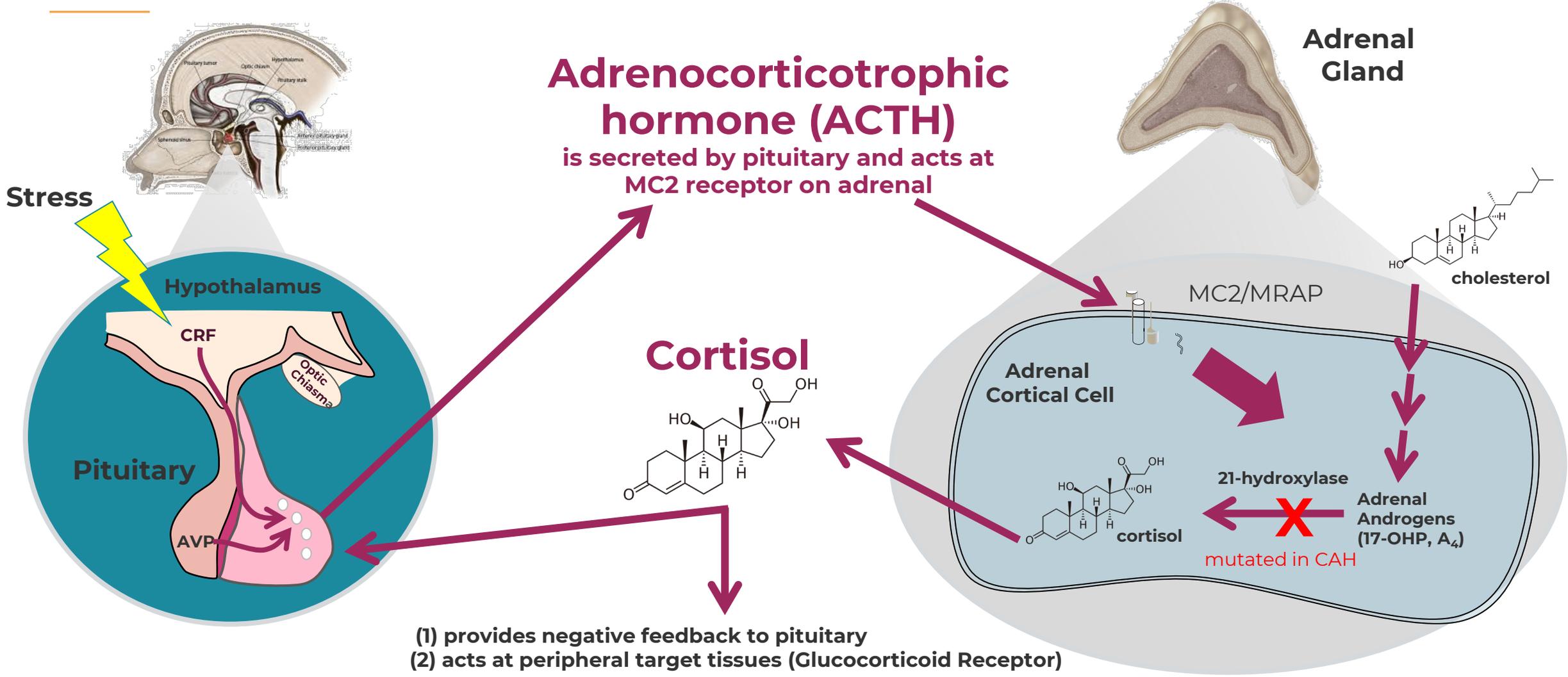
Congenital adrenal hyperplasia (CAH)

Cushing's disease (CD)

Other conditions of ACTH excess



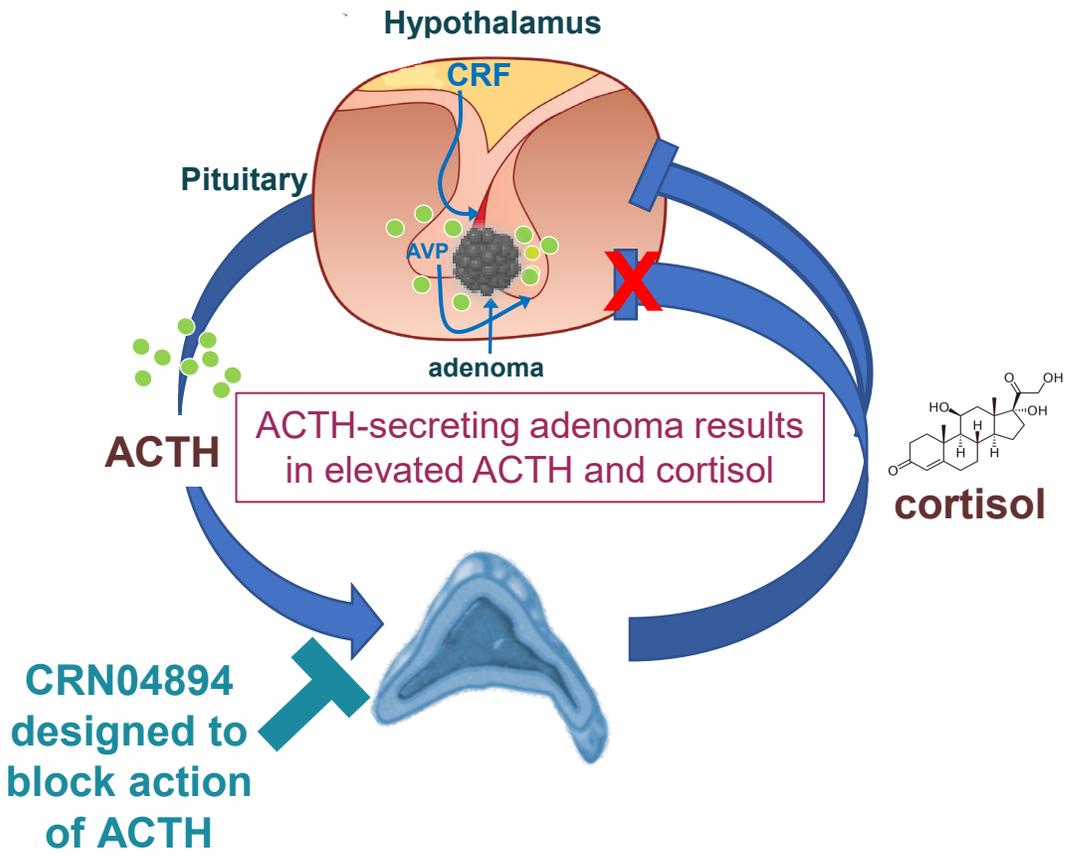
# The Hypothalamic-Pituitary-Adrenal (HPA) Axis is the Body's Emergency Response System for Stress





# CRN04894, an ACTH Antagonist Designed to Treat Cushing's Disease at the Source

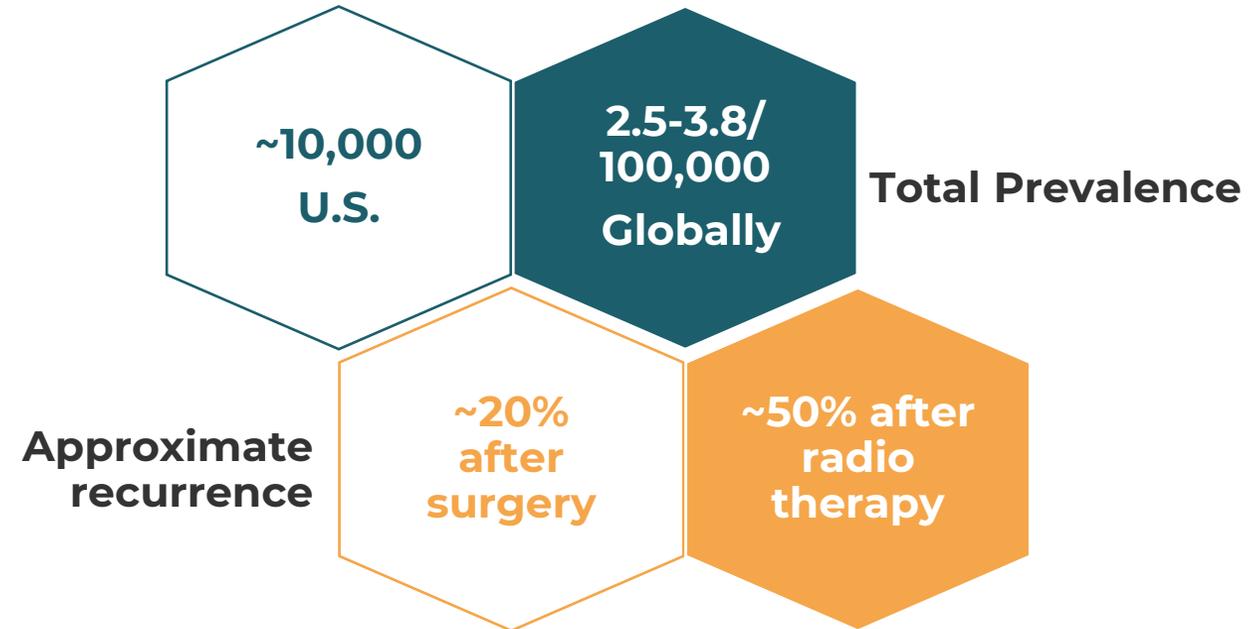
## Cushing's Disease



**Excess ACTH 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

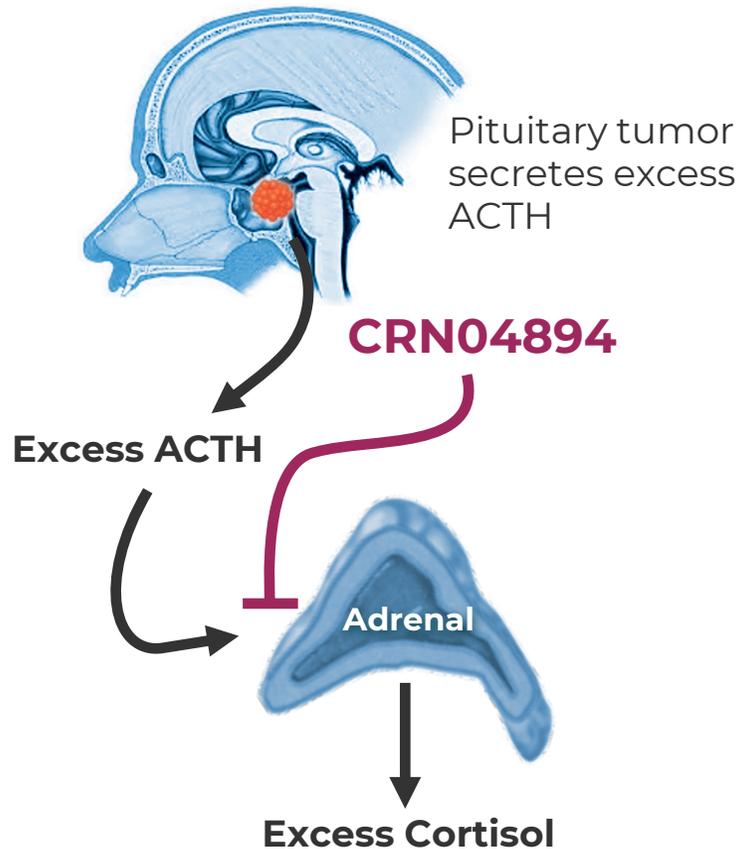
**Biomarkers: Elevated ACTH, elevated Cortisol**



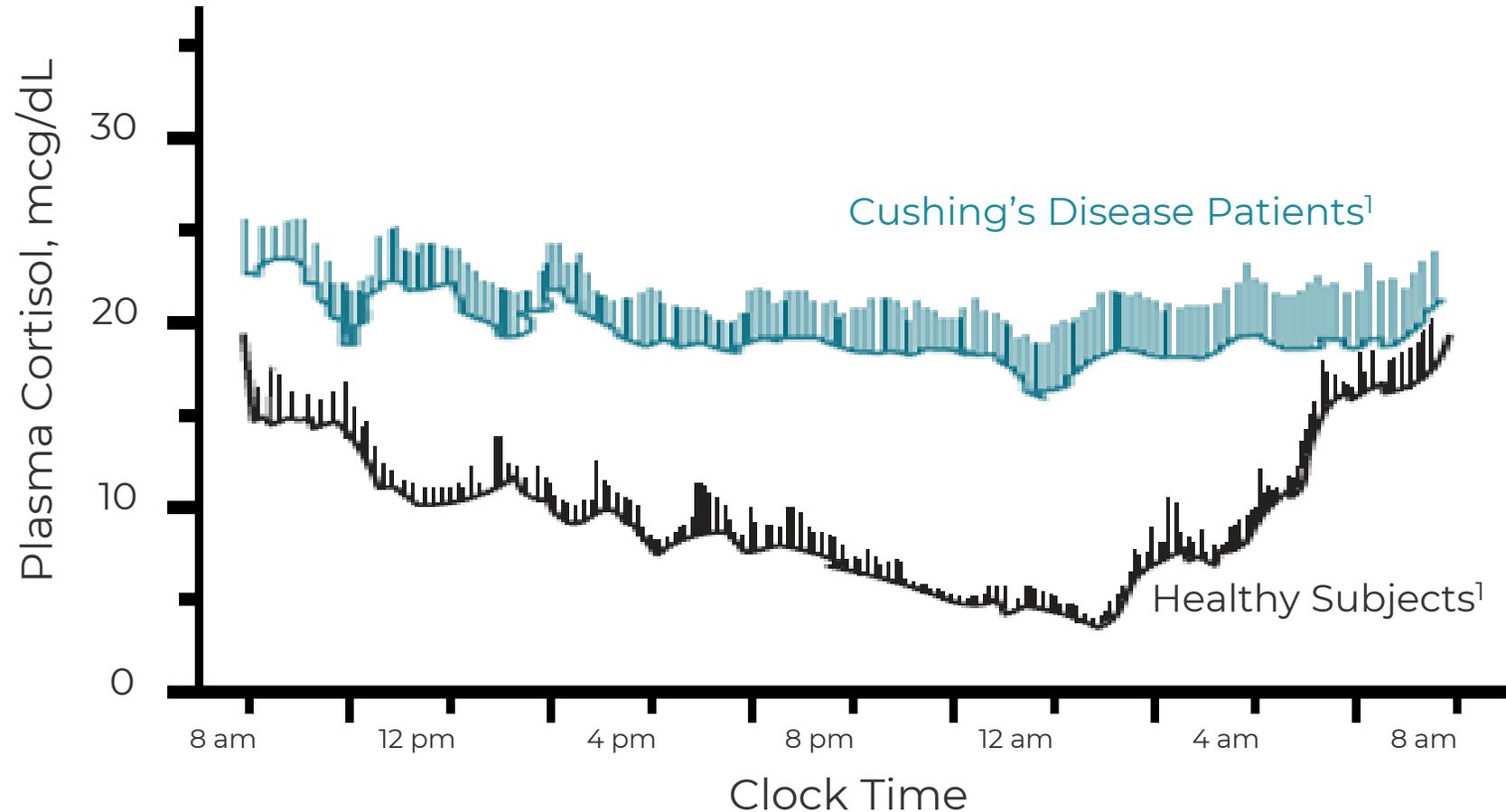
Korlym (2<sup>nd</sup> line Glucocorticoid Receptor antagonist) anticipated 2020 revenue = \$355-365M

# 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

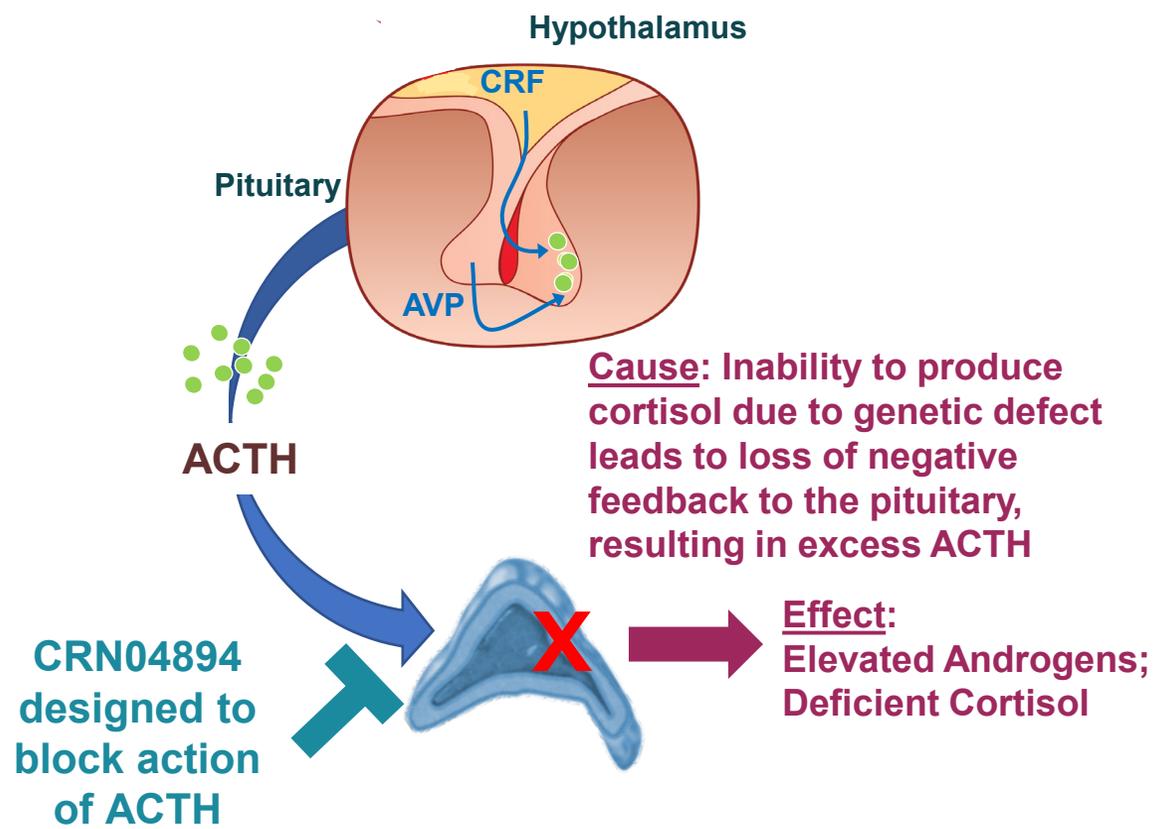


<sup>1</sup> Data from Oster et al., Endocrine Reviews 2017 (data shown are mean  $\pm$  SEM, N=8-10)

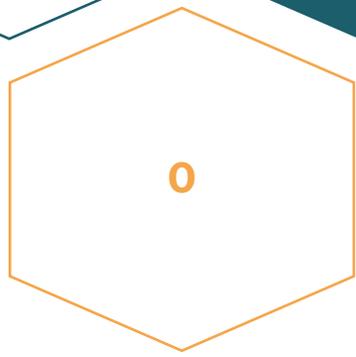


# CRN04894, an ACTH Antagonist Designed to Provide Predictable Steroid Administration for CAH Patients

## Congenital Adrenal Hyperplasia



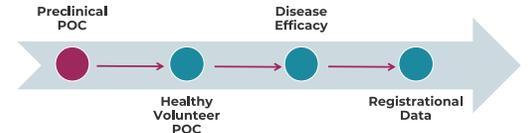
No approved treatments



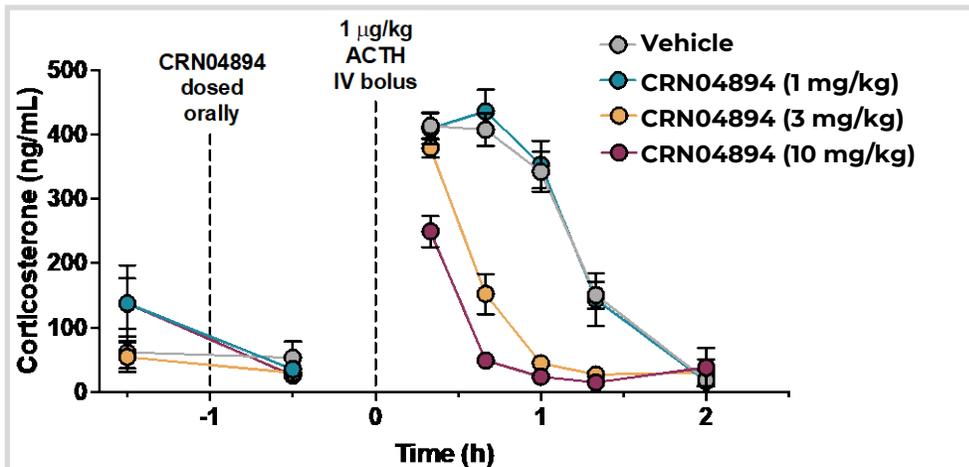
**Current Therapies: Limitations and High Burden**

Balancing glucocorticoid replacement and adrenal hormone suppression requires continuous oversight

# CRN04894 Showed Activity in Preclinical Models



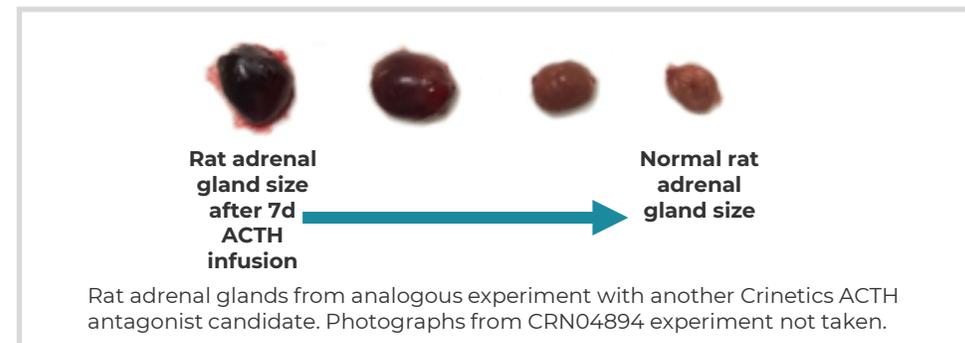
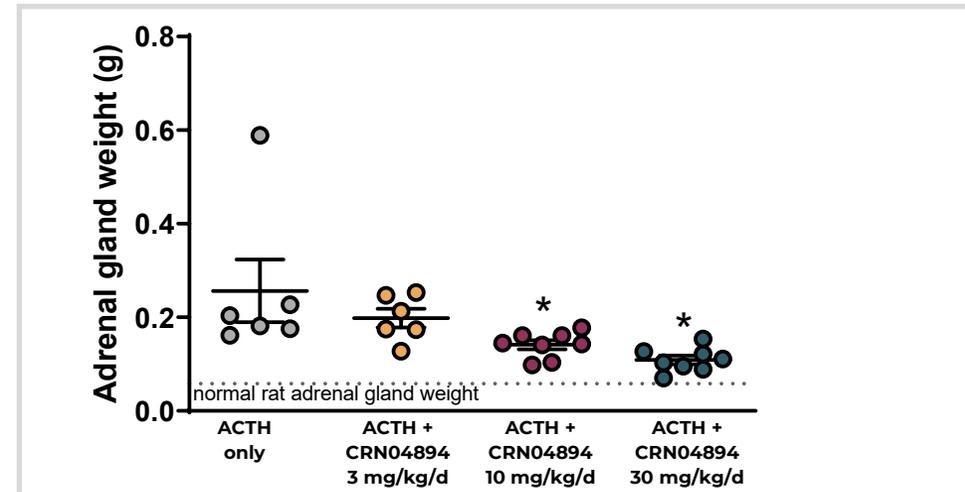
## Acute suppression of ACTH-induced corticosterone observed in rats



### 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

## Repeat CRN04894 dosing (7d) prevented adrenal hypertrophy from chronic ACTH infusion



Preclinical characterization of CRN04894 selected for oral presentation at ENDO (March 20-23, 2021)

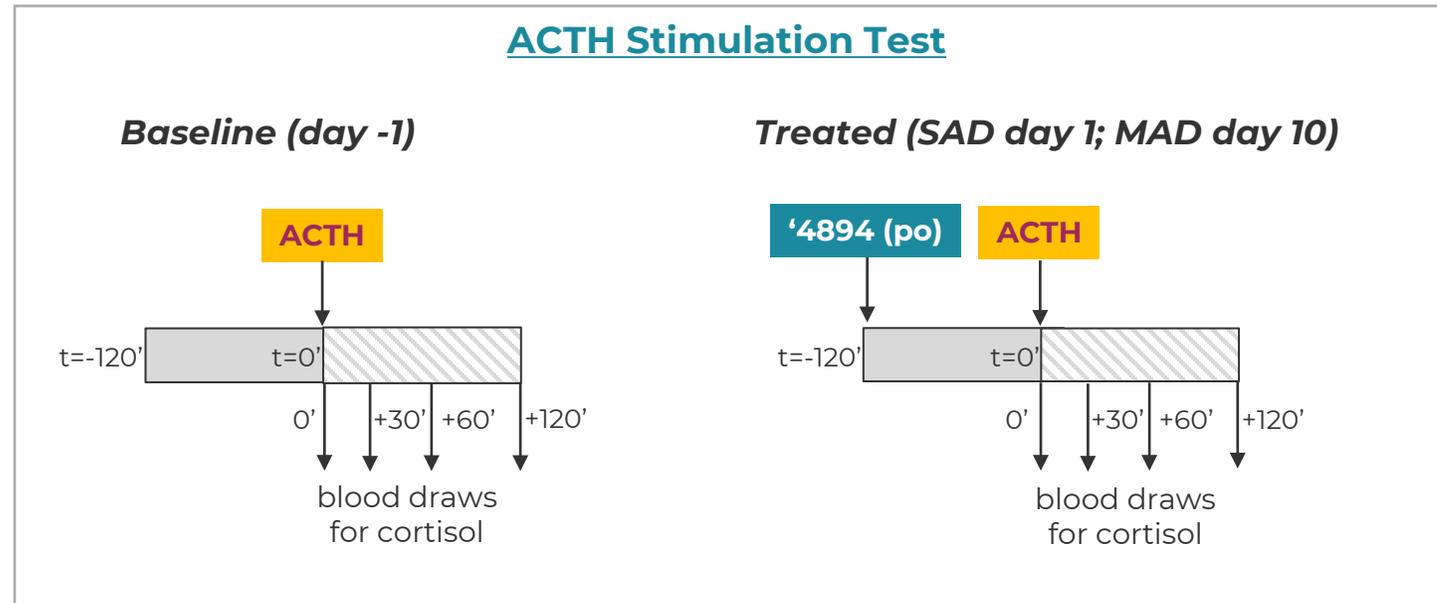
# CRN04894 Phase 1 Clinical POC Cushing's Disease and CAH – Adrenal Suppression

Healthy volunteers: SAD data expected mid-2021; MAD data expected 2H 2021

## Objectives

- Safety and tolerability
- Pharmacokinetics
- PK/PD for suppression of ACTH-induced adrenal activity
- Dose selection for patient studies

## ACTH Stimulation Test



**Proof of concept: dose dependent suppression of ACTH-stimulated peak cortisol with CRN04894**

# 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 (expected mid-2021)
- 4 Report Phase 1 MAD data (expected 2H 2021)

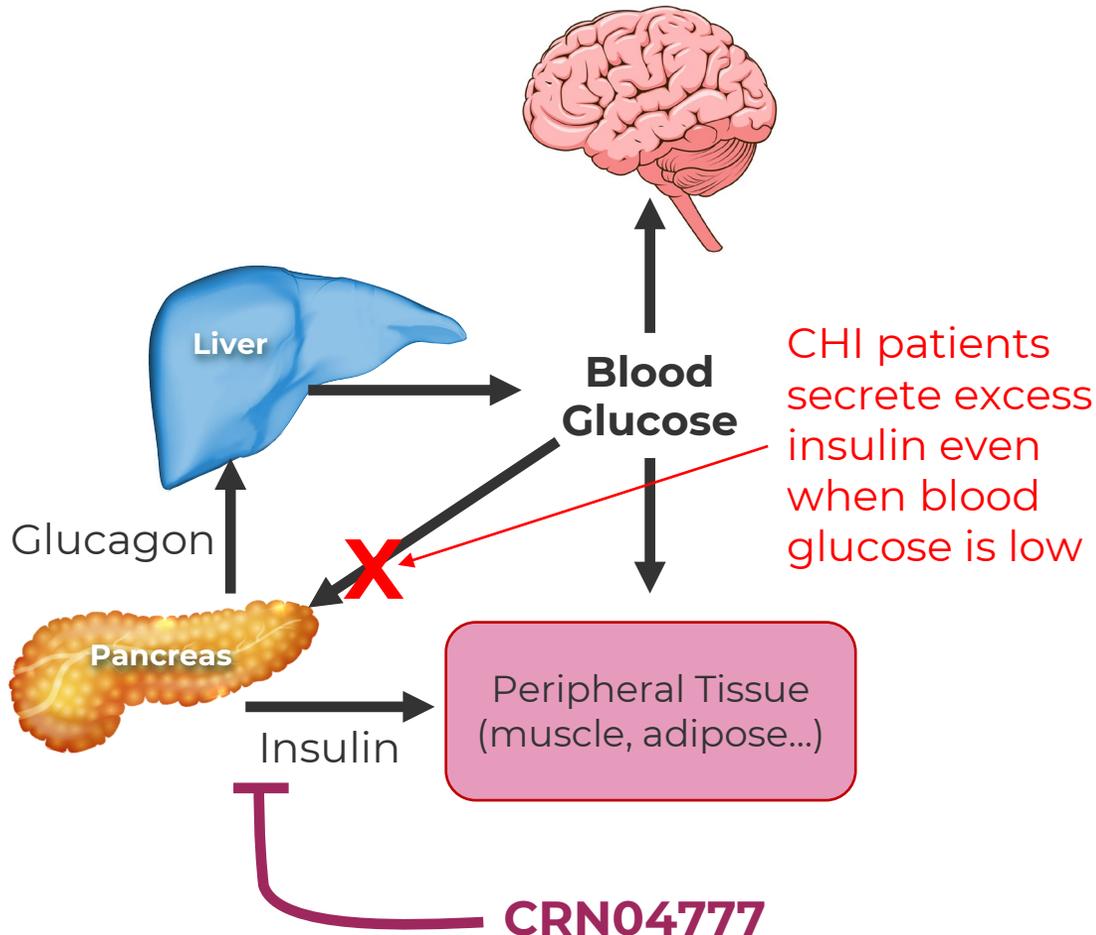
# CRN04777: AN INVESTIGATIONAL, POTENTIAL FIRST-IN-CLASS, ORAL NONPEPTIDE SST5 AGONIST

Congenital hyperinsulinism (CHI)



# Inappropriate Insulin Secretion Causes Life Threatening Recurrent Hypoglycemia in CHI

## Normal Glucose Control



## 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

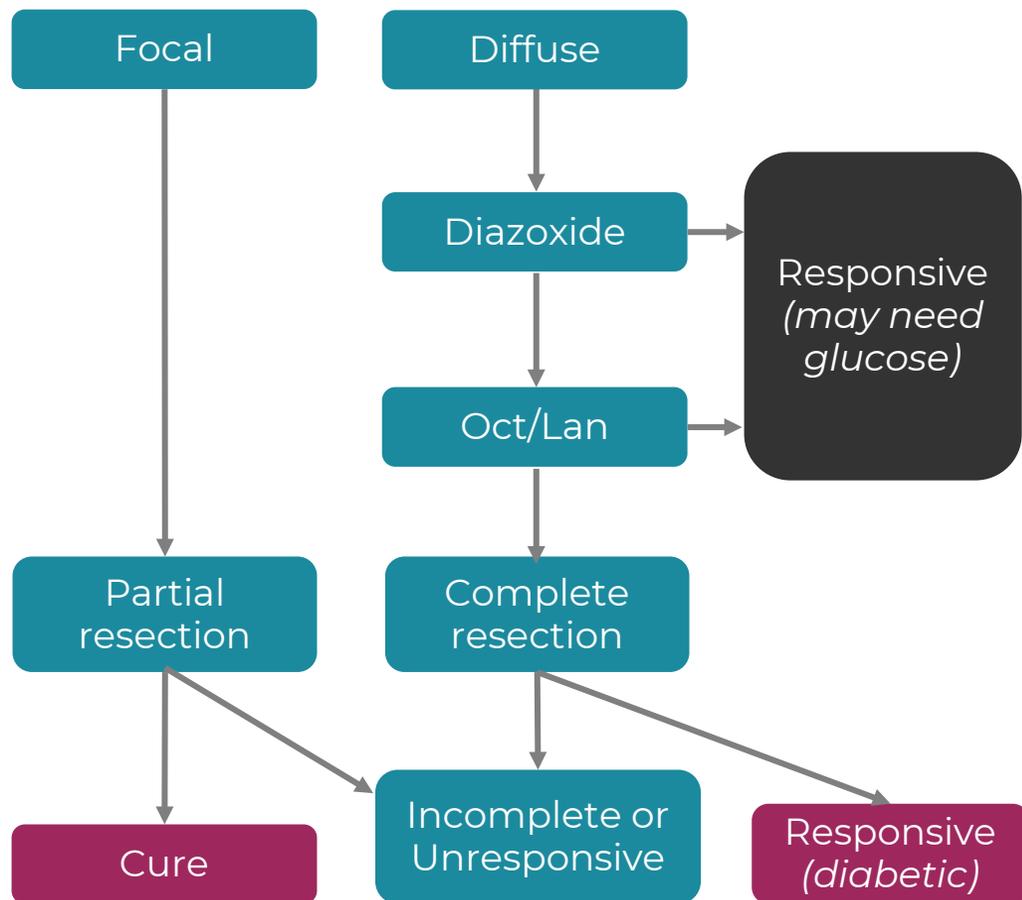
- Congenital Hyperinsulinism International ([www.congenitalhi.org](http://www.congenitalhi.org))



# Excruciating Unmet Medical Needs in CHI

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

## Current Standard of Care for CHI



## Patient & Parent Goals

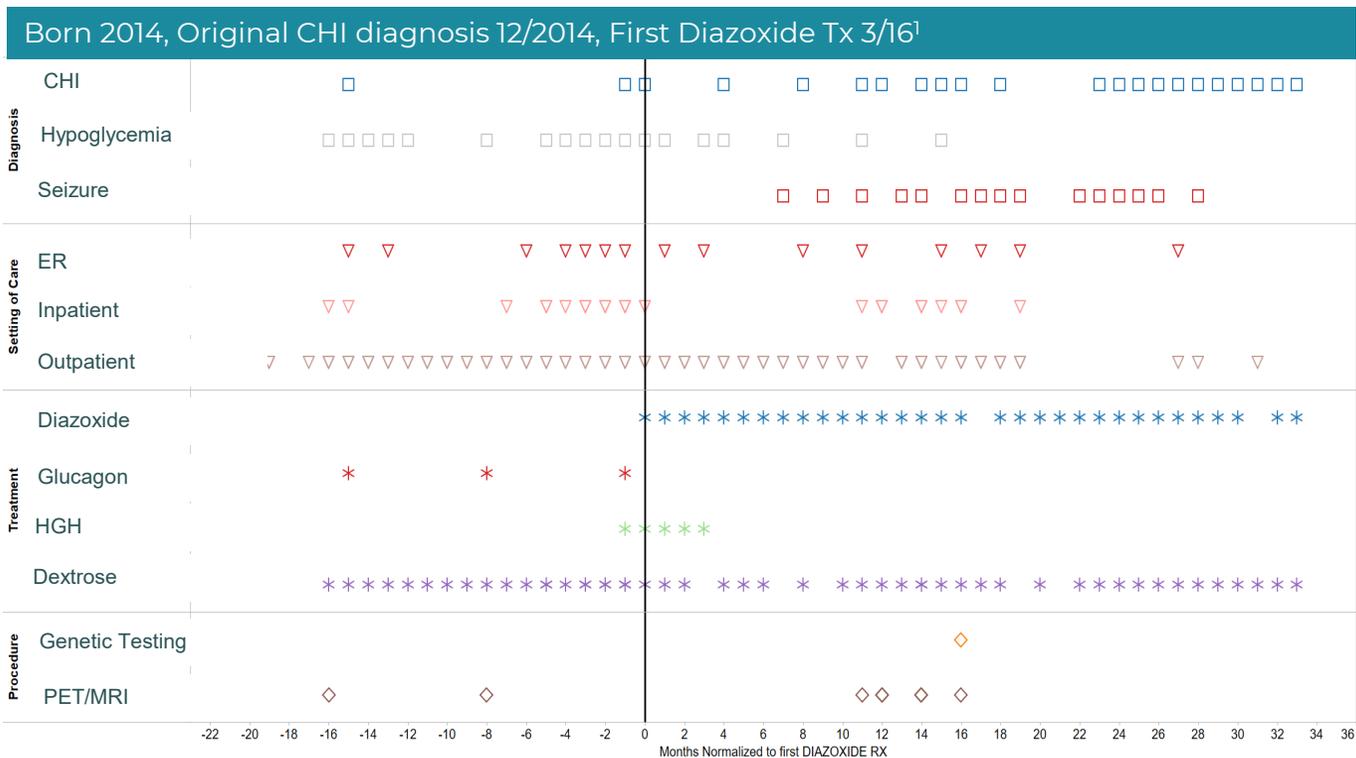
- ✓ Put child to bed knowing they will wake up in the morning
- ✓ Avoid neurological damage
- ✓ Eliminate the glucose tube and backpack
- ✓ Reduce injections and glucose sticks
- ✓ Avoid pancreatectomy
- ✓ Medical management until HI resolves
- ✓ Be a kid not a patient





# CHI Patient Care is a High Burden on Healthcare Systems

## Healthcare utilization by a baby girl with CHI



Each shape and associated time stamp represents a medical claim over 5 years

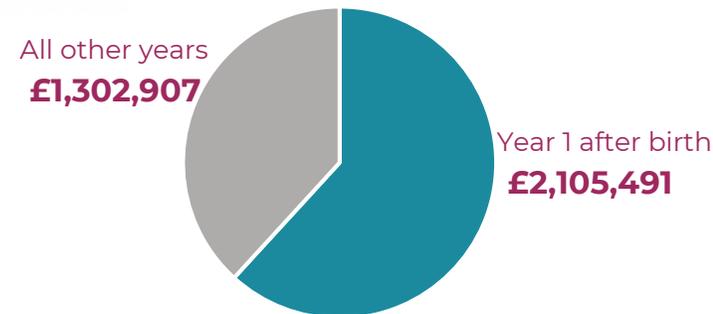
### Current Challenges

- 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<sup>2</sup>, £ 3,408,398 (\$4,630,939): first 11 years of life**

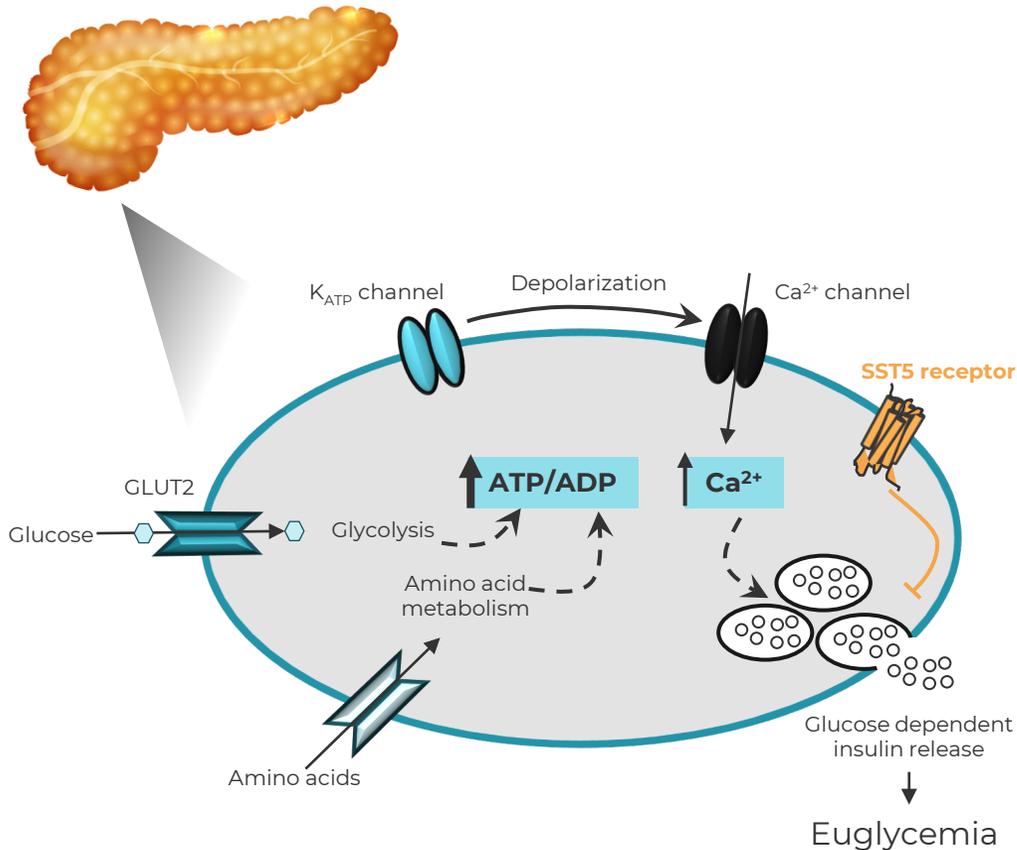


Patients unresponsive to first-line drug therapy (diazoxide) represented the greatest driver of costs

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

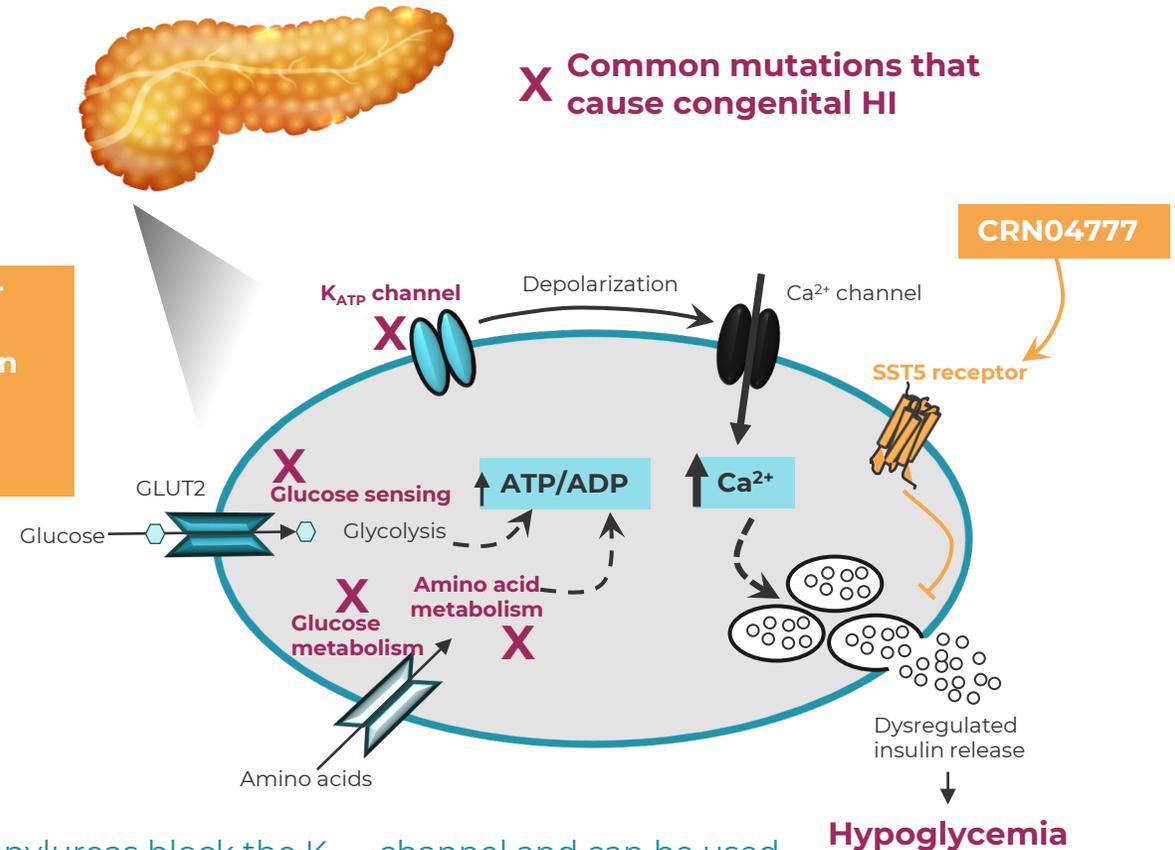
# SST5 Agonists Should Be Universally Effective Against Various Forms of Congenital HI

Healthy pancreatic  $\beta$ -cells



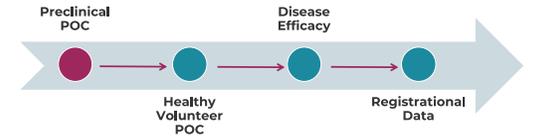
Congenital HI pancreatic  $\beta$ -cells

SST5 receptor activation inhibits insulin secretion via multiple pathways

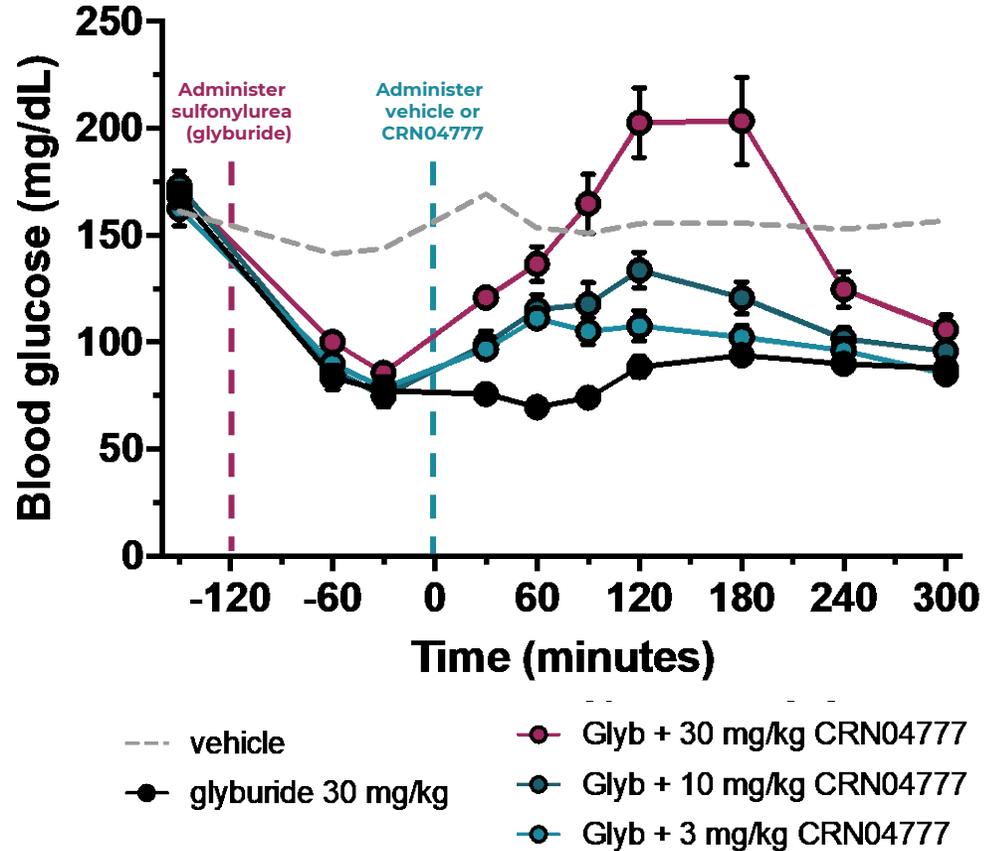


Sulfonylureas block the  $K_{ATP}$  channel and can be used to mimic the genetic defect in many CHI patients

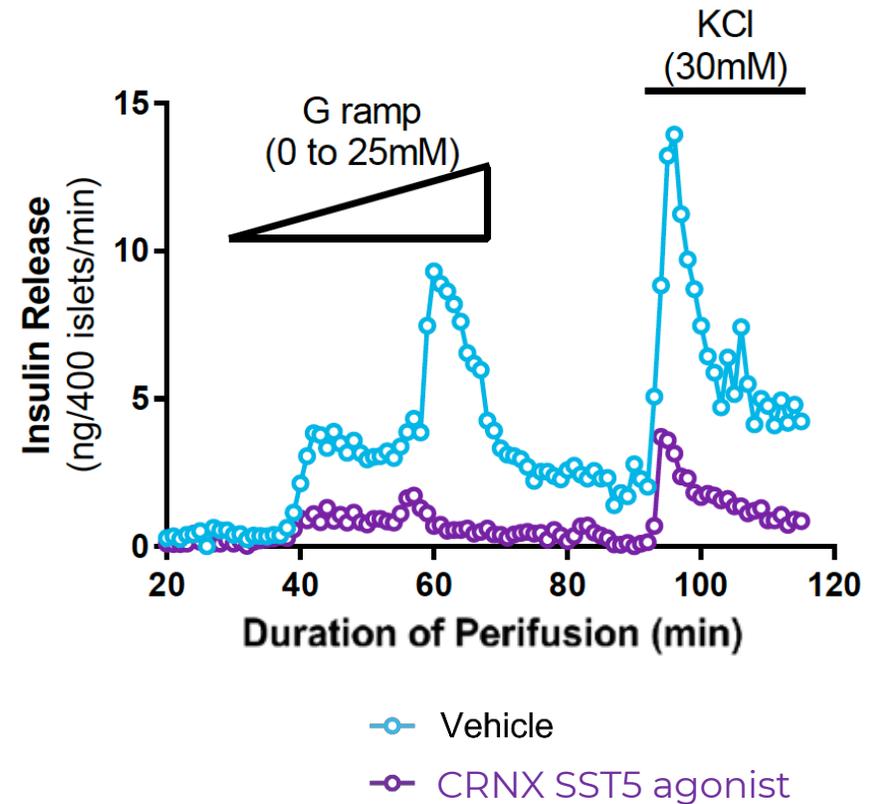
# Proof of Mechanism Achieved in Animal Models and Patient Islets



CRN04777 rescued sulfonylurea-induced 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 Phase 1 Clinical POC Congenital Hyperinsulinism – Insulin Suppression

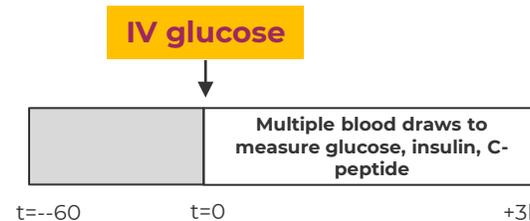
Healthy volunteers: SAD data expected mid-2021; MAD data expected 2H 2021

## Objectives

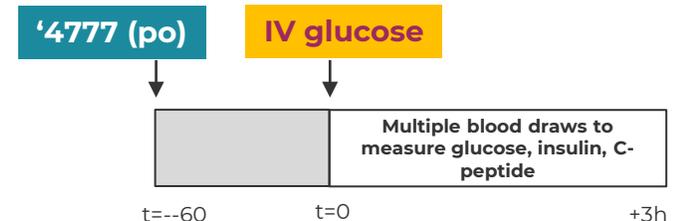
- Safety and tolerability
- Pharmacokinetics
- PK/PD for suppression of stimulated insulin secretion
- Dose selection for patient studies

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

*Baseline (day -1)*

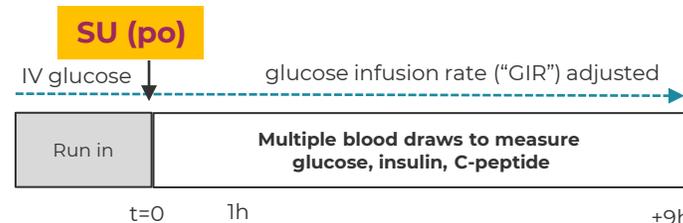


*Treated (SAD day 1)*

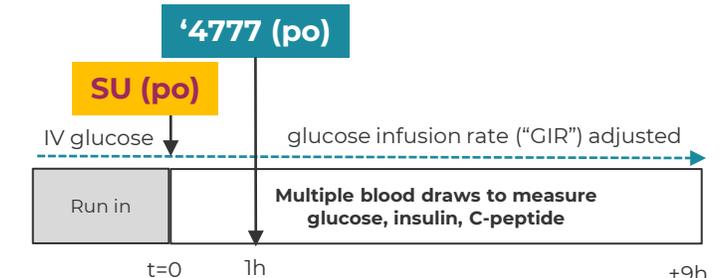


### 2. Sulfonylurea (SU) Challenge Test (Glucose Clamp)

*Baseline (SAD day -1; MAD day -2)*



*Treated (SAD day 1; MAD day 10)*



**Proof of concept: dose dependent suppression of glucose- or sulfonylurea-induced insulin secretion with CRN04777**

# 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 (expected mid-2021)
- 4 Report Phase 1 MAD data (expected 2H 2021)

# 2021 Goal: Three Programs with Clinical POC

Poised for steady cadence of milestones in 2021

	Q1	Q2	Q3	Q4
<b>Paltusotine</b> SST2 Agonist for Acromegaly & NETs	Initiate PATHFND-1		Initiate PATHFND-2	
			Initiate Phase 2 NETs Trial in Carcinoid Syndrome	
<b>CRN04894</b> ACTH Antagonist for Cushing's Disease & CAH	Initiate Phase 1	Phase 1 SAD Data		
			Phase 1 MAD Data	
<b>CRN04777</b> SST5 Agonist for Congenital HI	Initiate Phase 1	Phase 1 SAD Data		
			Phase 1 MAD Data	

'4894 and '4777 programs follow our development strategy validated by paltusotine

# 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	<b>Granted in:</b> U.S. AU <b>Pending in:</b> 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	<b>Granted in:</b> U.S. <b>Pending in:</b> 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	<b>Granted in:</b> U.S. <b>Pending in:</b> TW <b>To be filed in:</b> 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	<b>Pending in:</b> PCT, U.S., TW, AR, VE	Aug 2019	Aug 2040

# Leadership Team

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**Frank Zhu, PhD** VP of Chemistry, Founder



Shanghai Institute of Organic Chemistry  
Chinese Academy of Sciences

**Steve Betz, PhD** VP of Biology, Founder



**Ajay Madan, PhD** Chief Development Officer



**Marc Wilson** Chief Financial Officer



**Alan Krasner** Chief Medical Officer



**Gina Ford** VP, Corporate Strategy & Commercial Planning



**Adriana Cabré** VP, Human Resources



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