Crinetics Pharmaceuticals

# Corporate Presentation

*August 2019*

# Safe harbor statement

This presentation contains forward-looking statements. All statements other than statements of historical facts contained in this presentation, including statements regarding our future results of operations and financial position, business strategy, prospective products, product approvals, research and development costs, timing and likelihood of success, plans and objectives of management for future operations, and future results of current and anticipated products, are forward-looking statements. 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. These known risks and uncertainties are described in detail in our filings made with the Securities and Exchange Commission from time to time. 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.

# OUR VISION

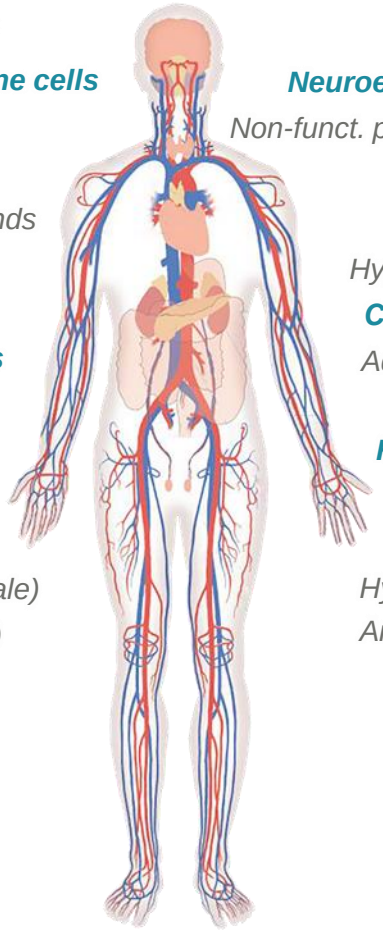
To build the leading endocrine company that consistently pioneers new therapeutics to help patients better control their disease and improve their daily lives

# Our Strategy: Discover, develop and commercialize across multiple rare endocrine diseases and endocrine-related tumors

- Ongoing in-house discovery of novel drug-candidates
- Focus on endocrine diseases and related tumors with:
  - High unmet medical need
  - Established biology
  - Biomarker endpoints
  - POC in Phase 1
  - Small registration trials
- Rapidly advance clinical pipeline of multiple drug candidates in parallel
- Retain commercialization rights in core therapeutic areas and regions
- Nurture an entrepreneurial, scientifically rigorous, collaborative and inclusive company culture

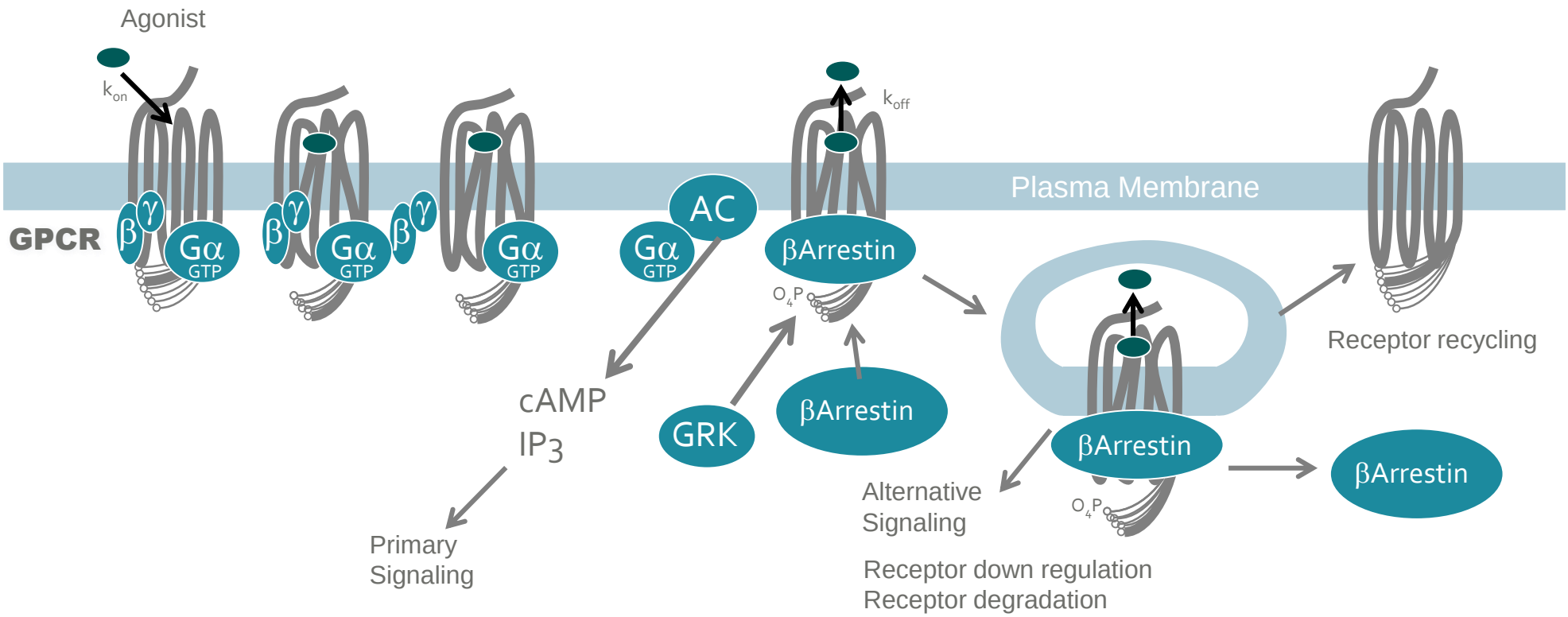
## The endocrine therapeutic area

| Endocrine system: | Multiple indications: |
|---|---|
| ***Pituitary gland*** | ***Acromegaly*** |
| ***Enteroendocrine cells*** | ***Neuroendocrine tumors*** |
| *Hypothalamus* | *Non-funct. pituitary adenomas* |
| *Pineal gland* | *GH deficiency* |
| *Parathyroid glands* | *Grave's disease* |
| *Thyroid gland* | *Hyperparathyroidism* |
| *Thymus* | ***Cushing's disease*** |
| ***Adrenal glands*** | *Adrenal hyperplasia* |
| *Kidneys* | *Adrenal cancer* |
| ***Pancreas*** | ***Hyperinsulinemia*** |
| *Liver* | *Insulinoma* |
| *Placenta* | *Thyroid cancer* |
| *Ovaries (in female)* | *Hypoparathyroidism* |
| *Testes (in male)* | *Androgen deficiency* |
| | *Infertility* |



***Targeting today /*** *Future opportunity*

# Our approach: Tailor ligands to regulate dynamic GPCR behaviors and ultimately improve patient outcomes




***Ligand binding kinetics conformational changes***

***Receptor signaling***

***Receptor trafficking***

***Our understanding of the complex GPCR signaling pathways enables us to develop oral, small molecule, product candidates that modulate GPCR dynamic behaviors***

# Pipeline:

Building a rare disease franchise in endocrinology and endocrine oncology

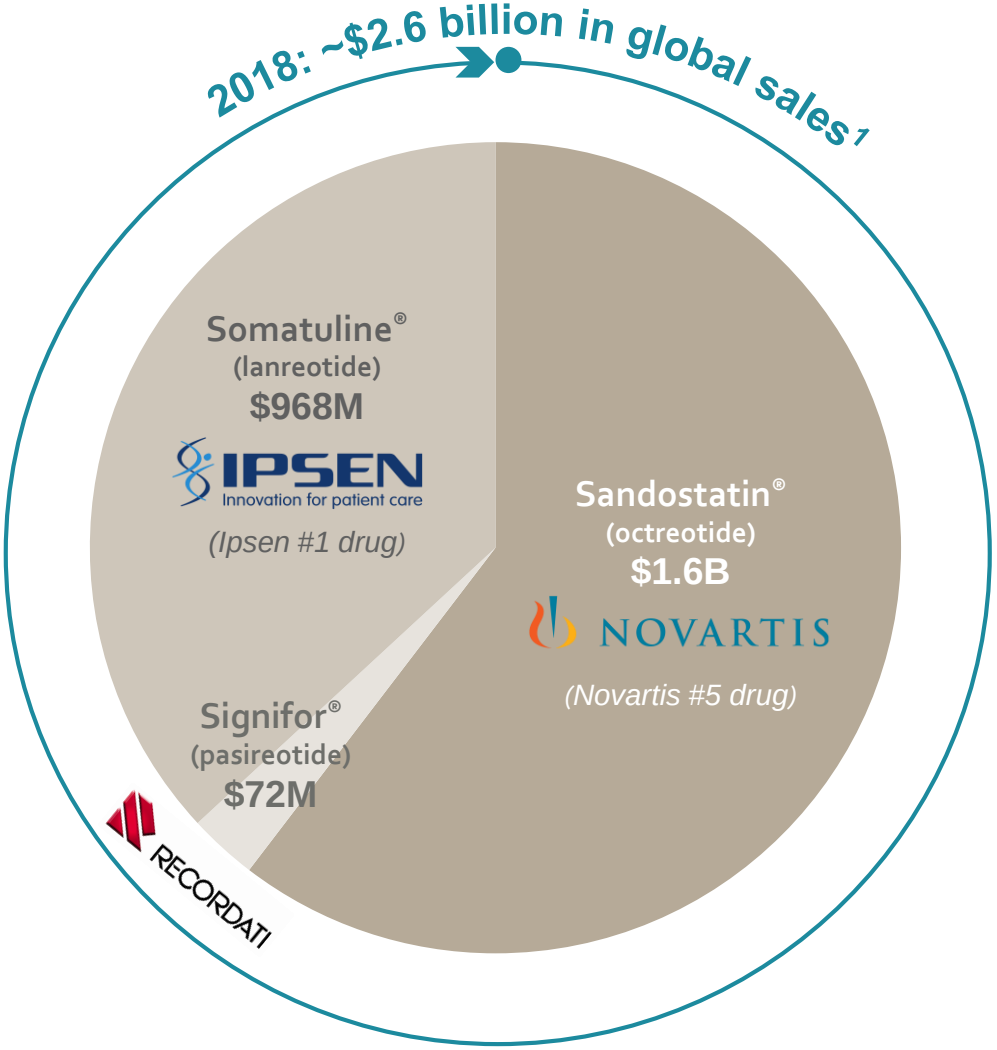
| PROGRAM | DISCOVERY | PRECLIN | PHASE 1 | PHASE 2 | PHASE 3 |
|---|---|---|---|---|---|
| **CRN00808** **(Oral sst2 Agonist)** Acromegaly | | | | | |
| **CRN01941** **(Oral sst2 Agonist)** Neuroendocrine Tumors (NETs) | | | | | |
| **Oral sst5 Agonist** Hyperinsulinemia | | | | | |
| **Oral ACTH Antagonist** Cushing's Disease | | | | | |

***All product candidates discovered and developed internally***
***Global rights retained and no licensing obligations***
***Composition of matter for CRN00808 through 2037***

# CRN00808

## for the treatment of acromegaly

# Established commercial opportunity for injectable somatostatin peptides despite significant limitations




## Limitations of current somatostatin peptide analogs

- ***Painful*** intramuscular/deep sc injections every month (octreotide, lanreotide)
  - Hardness, bruising and swelling at injection site
- ***Inconvenient*** / frequent physician office visits
  - Complex reconstitution of depot dosing regimens and prone to error (octreotide)
- Limited efficacy – ***only half of patients are fully controlled*** (reduce excess GH secretion and normalize IGF-1 levels) throughout the treatment period
- A majority of ***patients experience increased glucose levels*** within the first 2-3 weeks of treatment with pasireotide

***CRN00808 pioneers a new class of oral selective non-peptide sst2 biased agonists***

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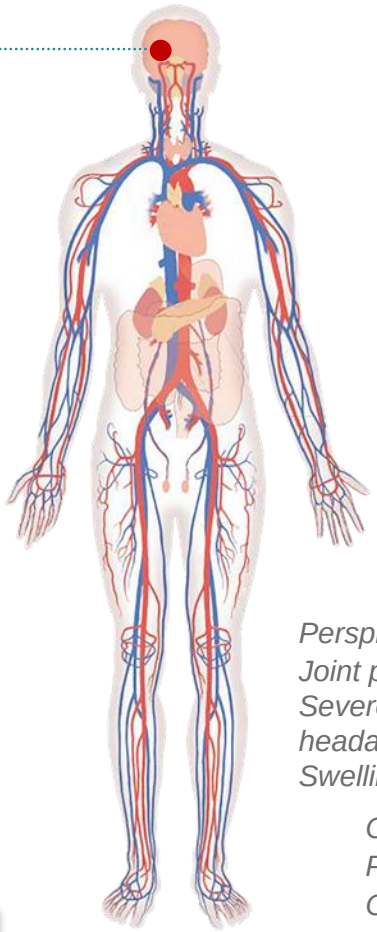
Sources: Company earnings and equity research analyst reports
[1] Includes acromegaly, neuroendocrine tumors and other uses

# Acromegaly: disease overview and treatment paradigm

## ~25,000 people in the U.S. suffer from acromegaly

**Acromegaly** is caused by a benign pituitary tumor



***Increased GH*** results in ***excess downstream secretion of IGF-1*** from the liver

***GH and IGF-1 promote tissue growth*** and other metabolic effects

*Perspiration, Joint pain, Severe headache, Swelling*

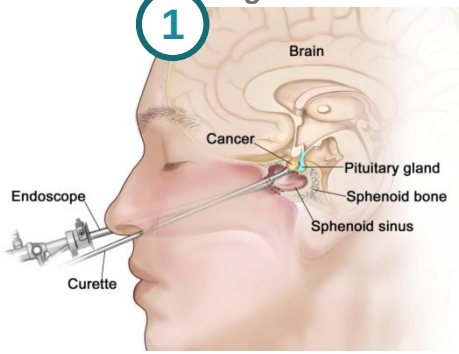
*Hypertension, Hepatomegaly, Impaired glucose, Thyroid hypertrophy*

*Changed facial features, Prognathism, Enlarged hands, Carpal tunnel, Arthritis*

***Uncontrolled acromegaly is debilitating and increases the risk of early death***

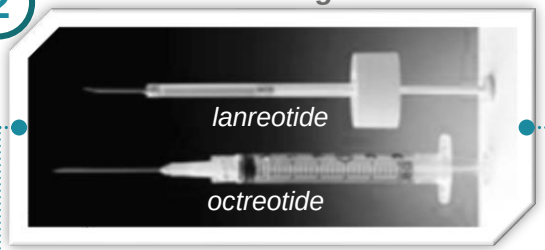
## Current treatment options for patients

**1** ***Surgical resection*** **of tumor for eligible patients**




*40-60% of acromegaly patients are candidates for chronic pharmacological intervention*

**2** ***Somatostatin analog***




*Not controlled*

**3** ***Dopamine Agonist***
***GH Receptor Antagonist***
***+/- Somatostatin Analog***

*Controlled*

*Controlled*

***Estimated 10-15K acromegaly patients in the U.S. on life long therapy***

# CRN00808 – Target product candidate profile

- A new class of oral selective nonpeptide sst2 biased agonist designed for the treatment of acromegaly
- First agent in its class with reported clinical results

**PRODUCT CANDIDATE TAILORED TO DELIVER KEY BENEFITS**

| CHARACTERISTICS | PRIMARY BENEFITS |
|---|---|
| **Orally bioavailable nonpeptide (small molecule)** | Lack of injections/pain<br>Administration at home<br>Rapid dose optimization<br>Consistent exposure over time<br>Lower COGS and admin costs |
| **Long half life (42-50 hrs)** | Once daily dosing |
| **Reduced desensitization** | Potential improved responder rates |
| **Selectivity for sst2** | Glucose control (avoid sst5 mediated hyperglycemia) |

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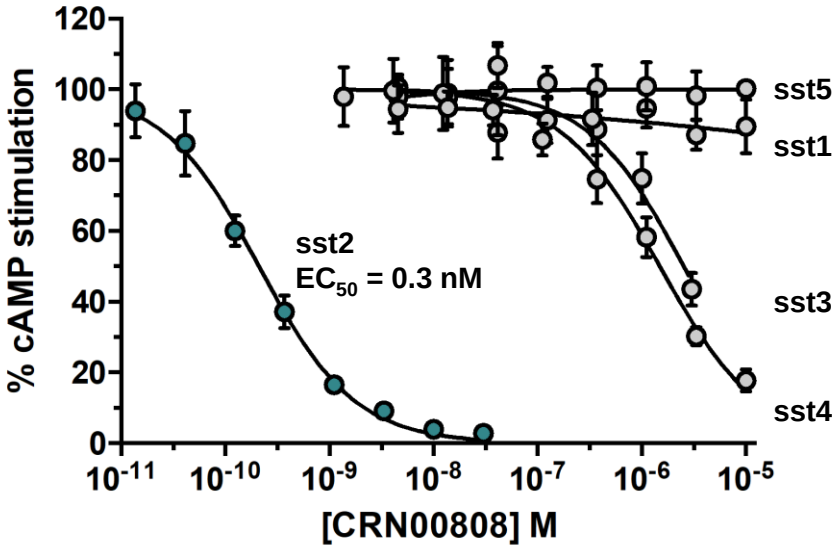
# CRN00808 is a potent and selective nonpeptide sst2 agonist

***In vitro*** **selectivity profile at all five somatostatin receptor subtypes for CRN00808**




***In vitro*** **selectivity profile at all five somatostatin receptor subtypes for CRN00808 and SSA peptides**

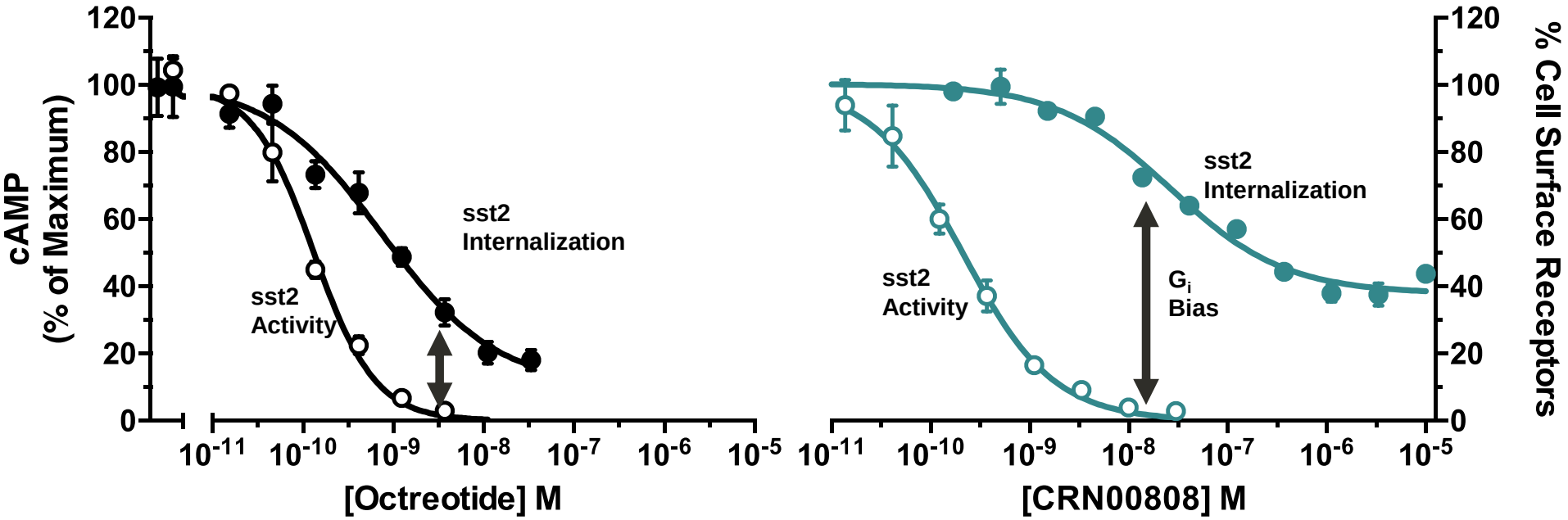
| | Human $EC_{50}$ (nM) | | | | |
|---|---|---|---|---|---|
| AGONIST | sst2 | sst1 | sst3 | sst4 | sst5 |
| CRN00808 | 0.25 | >10000 | 3300 | 1100 | >10000 |
| lanreotide | 0.10 | 1900 | 200 | 820 | 19 |
| octreotide | 0.061 | > 10000 | 7.9 | 470 | 2.1 |
| pasireotide | 0.59 | 23 | 0.78 | 6300 | 0.076 |
| native SS14 | 0.14 | 0.83 | 0.17 | 0.21 | 0.065 |

**Potency was measured by inhibition of cAMP in cells stably expressing the indicated human receptor**

***CRN00808's potency for sst2 is 4,000 times greater than for other subtypes***

# CRN00808 is designed with $G_i$ bias to reduce internalization and desensitization of sst2

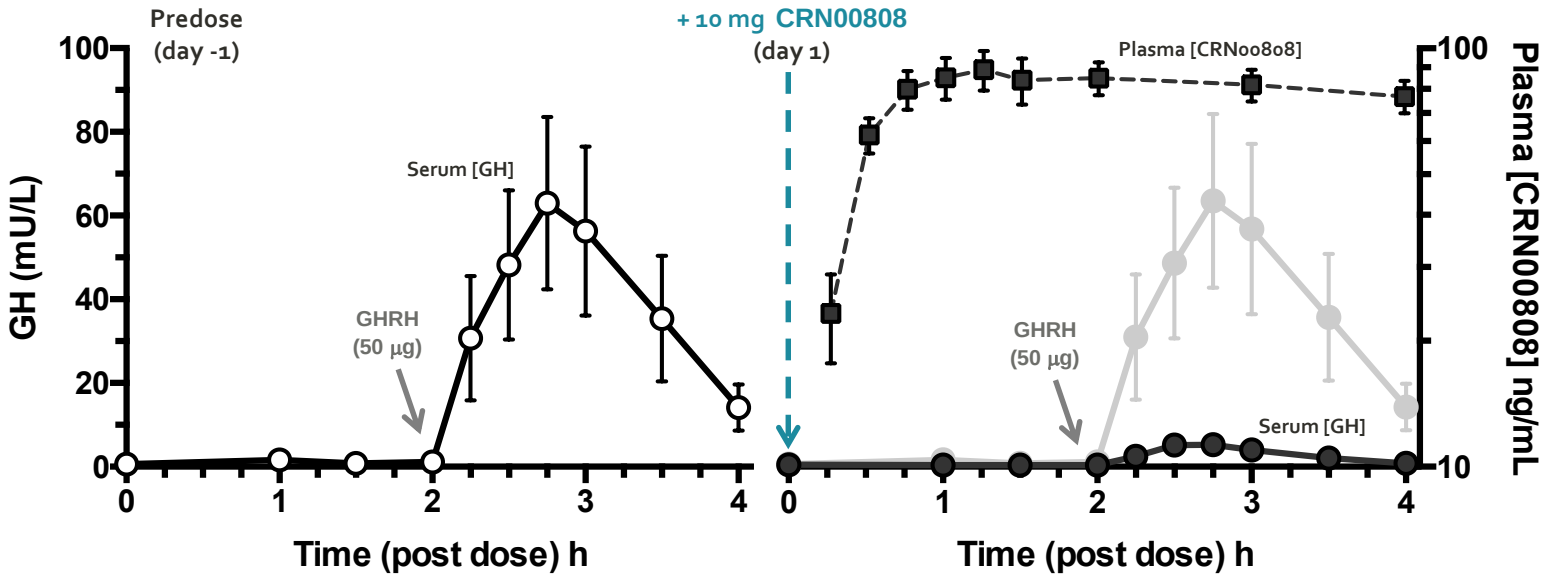
> ***In vitro*** **studies have shown CRN00808 was** ***75 times more potent*** **for cAMP inhibition than receptor internalization**



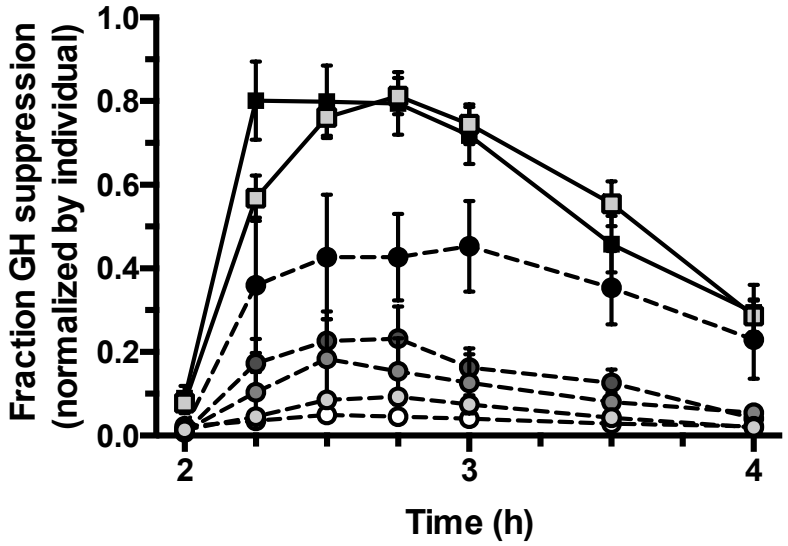

Dose response curves are shown from individual representative experiments. All points are the mean ± standard error of either triplicate or quadruplicate readings. White circles are from a cAMP assay measuring sst2 activation. Filled circles are from an internalization assay measuring the amount of cell surface receptors.

# Phase 1 SAD arm: PK/PD analysis

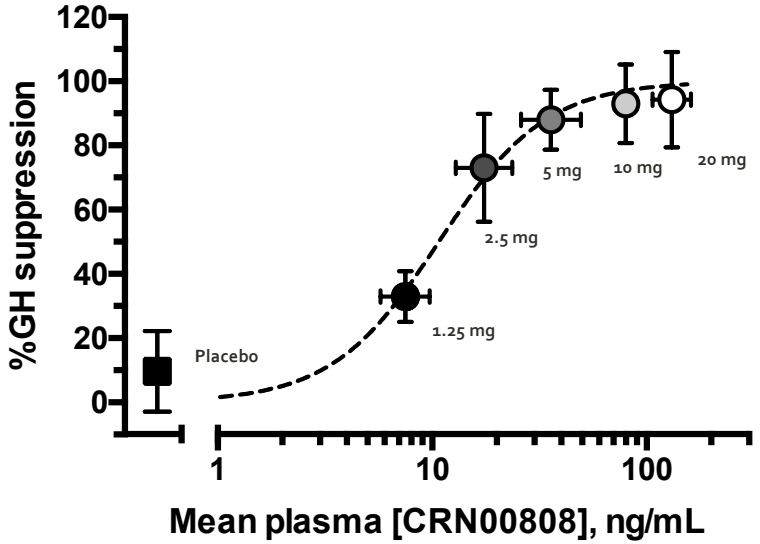
## Suppression of GHRH stimulated GH secretion by 10 mg of CRN00808




## Dose response of GH suppression




## Exposure response of GH suppression

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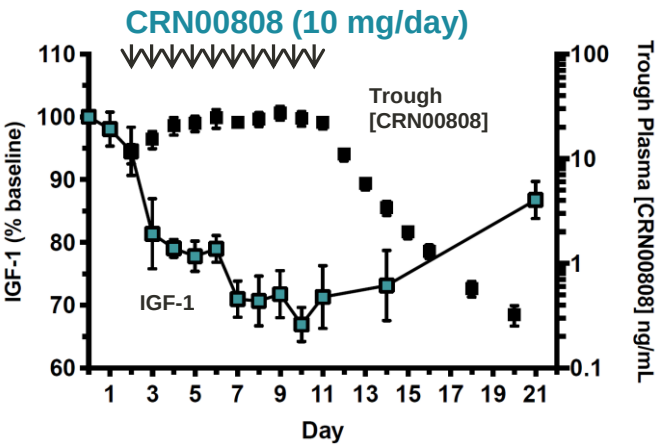
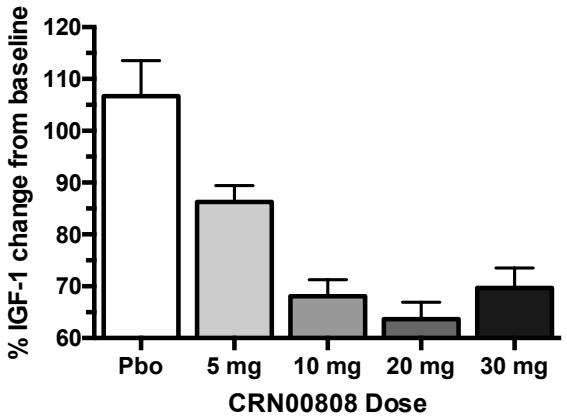
# Phase 1 MAD arm: PK/PD analysis

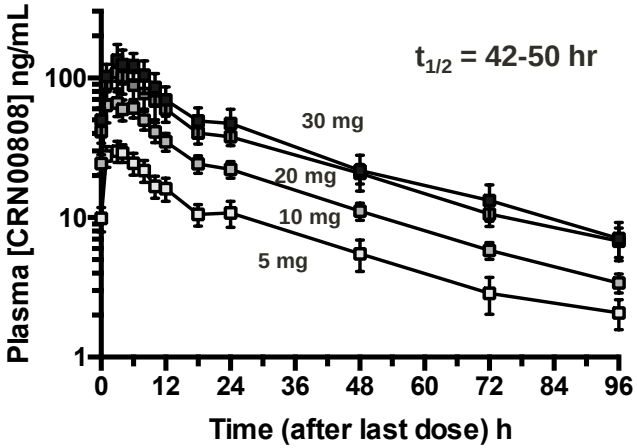
**Time-course of plasma CRN00808 trough and IGF-1 concentrations**




**Dose response of IGF-1 suppression**




**Plasma concentration on the last day of dosing**




## Safety & tolerability across phase 1

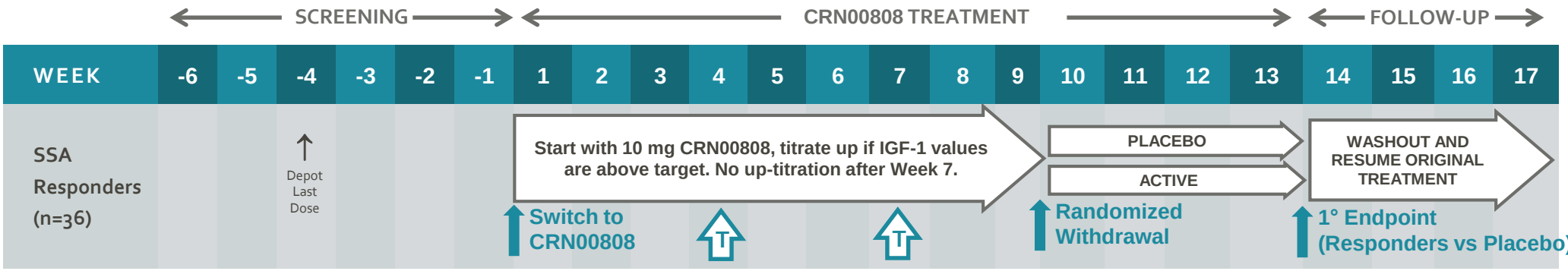
- Tolerability and AE profile was generally consistent with approved peptide somatostatin analogs (abdominal pain, flatulence, abdominal distension, and diarrhea in approximately 30% of subjects and mild elevations of pancreatic enzymes in approximately 10% of subjects)
- Additional adverse events included: headache, dizziness and cardiac rhythm abnormalities (including NSVT). One serious adverse event of moderate NSVT was observed following a single 1.25 mg dose and was considered unlikely to be related to CRN00808. These AEs were not dose dependent and were also observed in placebo subjects and/or prior to dosing.

***10 mg selected as the initial dose in Phase 2 trials***

# Acromegaly Phase 2 Trial for SSA Monotherapy Responders

ACROBAT EVOLVE

**Evaluation of CRN00808 vs placebo in patients controlled on injected SSA monotherapy**




Entry Criteria: IGF ≤ ULN on SSA depot monotherapy (octreotide LAR or lanreotide)

T Titrate up if two consecutive IGF-1 values are above ULN.

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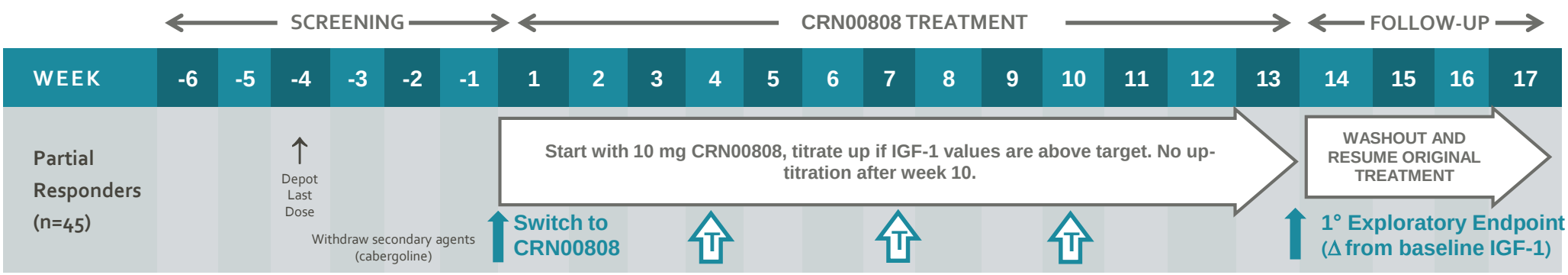
# Acromegaly Phase 2 Trial for Partial Responders to SSAs

ACROBAT EDGE

## Exploration of CRN00808 in patients inadequately controlled on injected SSA monotherapy




Entry Criteria: Partial responders on SSA monotherapy or when combined with dopamine agonist. Complete and partial responders on second line and combination therapies

Titrate up if two consecutive IGF-1 values are above ULN.

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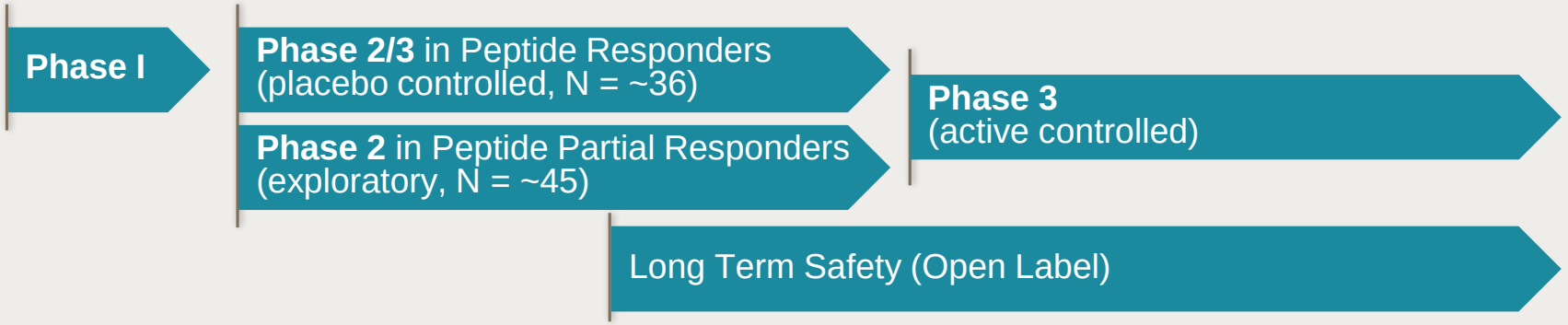
# CRN00808: Established clinical development strategy based on other approved products

## Planned clinical development path outline

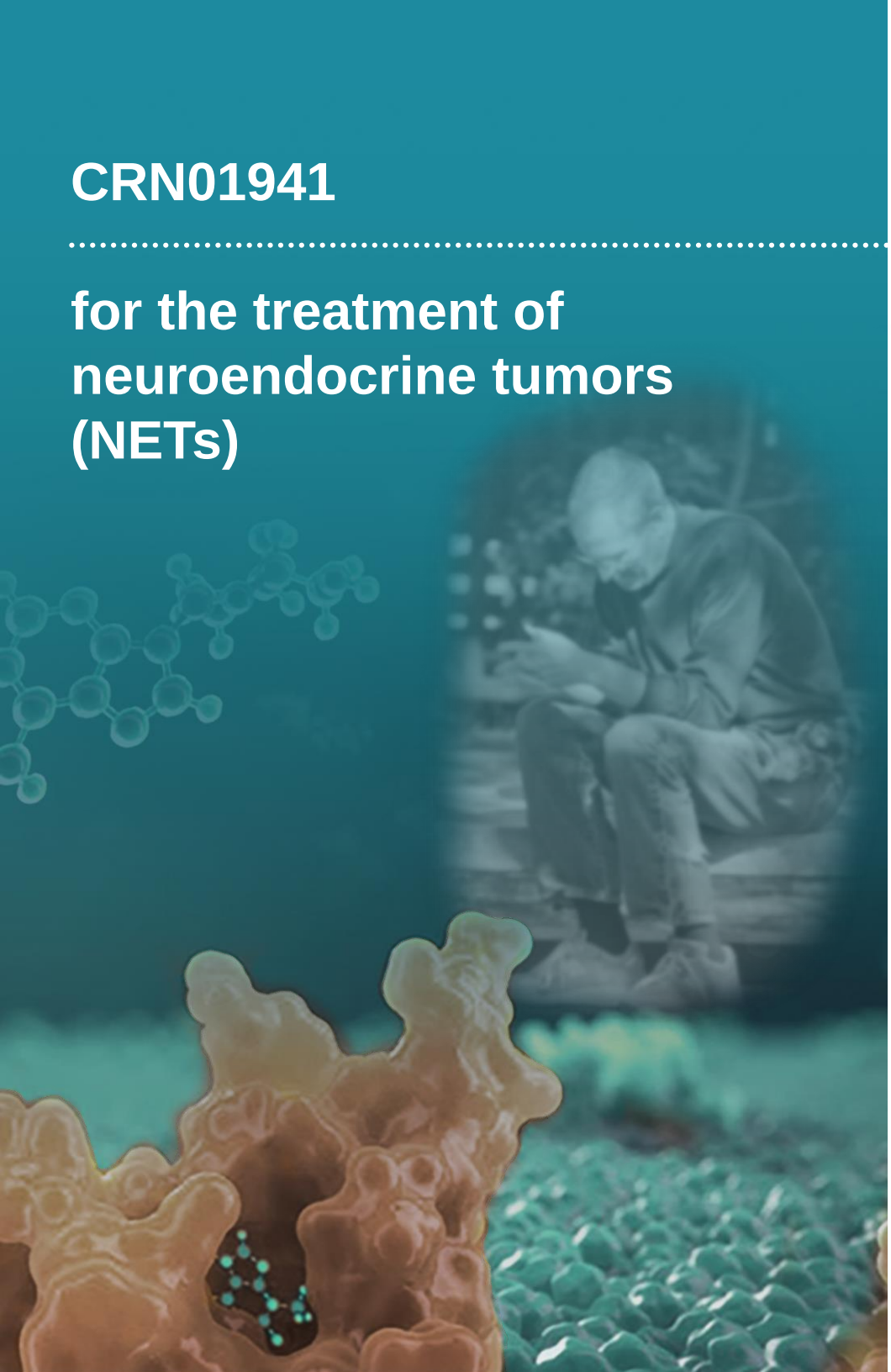



## Summary of acromegaly registration trials for other products

| DRUG (TRIAL) | COMPARATOR | N | PRIMARY ENDPOINT |
|---|---|---|---|
| Somatuline® Depot (lanreotide) Injection | placebo | 107 | 50% GH ↓ @ 4 weeks |
| | none | 63 | IGF normalization @ week 48 |
| Oral octreotide | baseline | 155 | IGF normalization @ month 7 |
| | placebo | 56 | IGF normalization @ month 9 |
| | octreotide/lanreotide | 150 | TWA IGF-1 over 9 months |
| Signifor (pasireotide) Injection 0.3 mg/mL, 0.6 mg/mL, 0.9 mg/mL | octreotide/lanreotide | 198 | GH + IGF normalization @ week 12 |
| | octreotide | 358 | GH + IGF normalization @ month 12 |
| SOMAVERT® pegvisomant | placebo | 112 | IGF reduction / normalization @ week 12 |

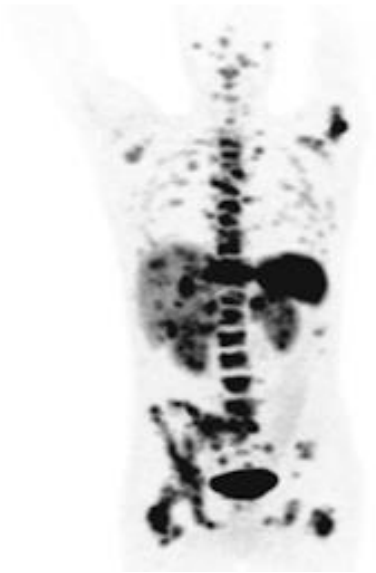
# CRN01941

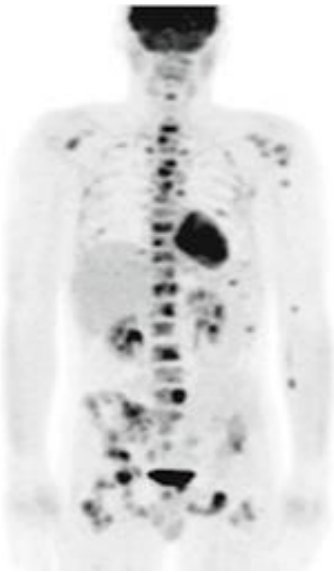
## for the treatment of neuroendocrine tumors (NETs)



## NETs Background

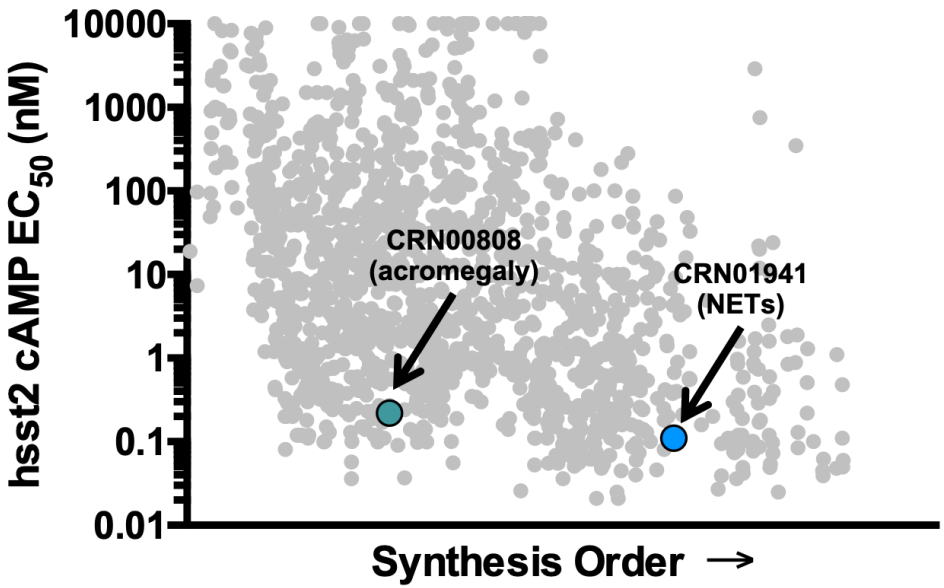
- Prevalence: ~171,000 patients (U.S.)
- Arise from enteroendocrine cells in the GI tract, lung, pancreas
  - Commonly overexpress sst2 receptors
- Somatostatin analogs (SSAs) are a standard of care
  - Historically indicated only for carcinoid syndrome (~10% of NETs patients)
  - Recently, positive impact on progression free survival demonstrated
  - Guidelines now outline SSAs as first line for a large segment of NETs patients





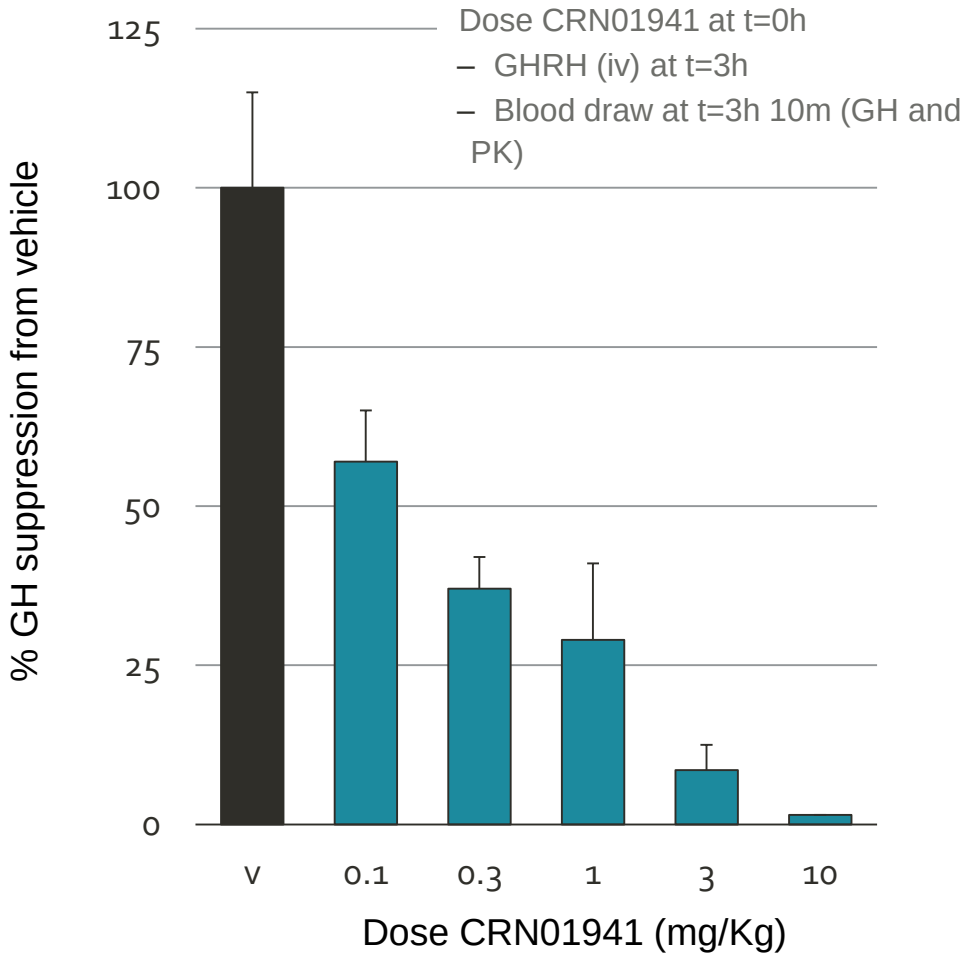
# CRN01941:

**CRN01941 is a novel molecule from a separate chemical series**




| | hSST2 $EC_{50}$ | rSST2 $EC_{50}$ | In vivo $EC_{50}$ |
|---|---|---|---|
| CRN00808 | 0.27 nM | 1.1 nM | 11 ng/mL |
| CRN01941 | 0.11 nM | 0.38 nM | 1 ng/mL |

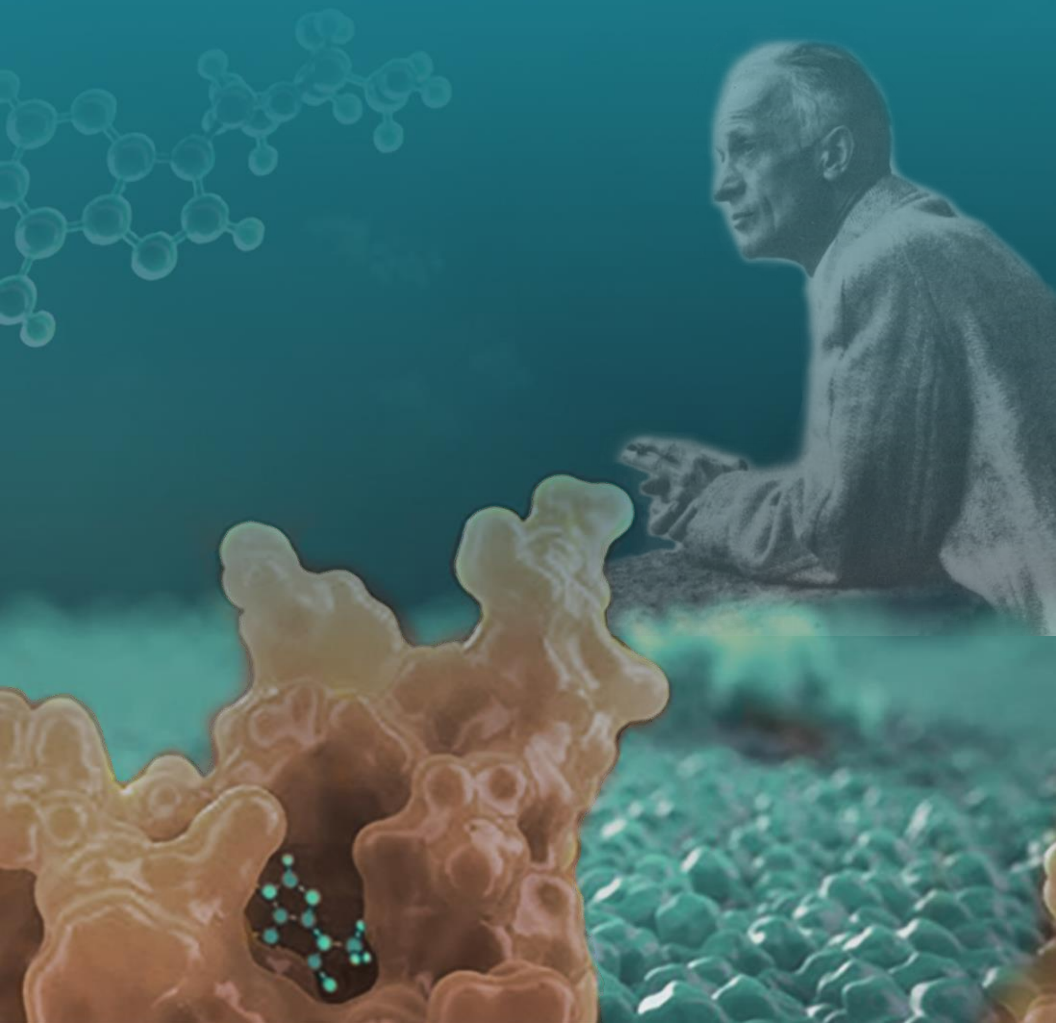
**Demonstrated suppression of GHRH-induced GH in preclinical models**



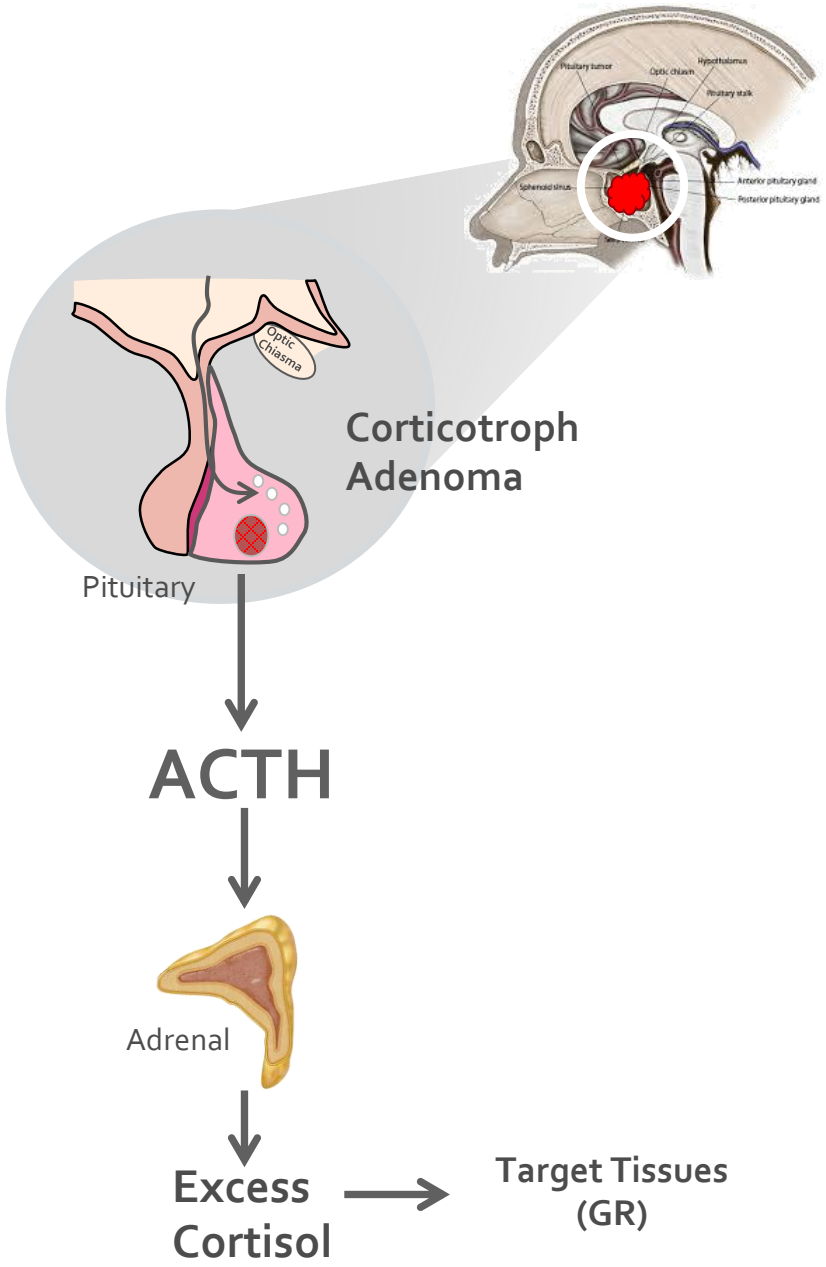

***Goal: Initiate a Phase 1 human proof-of-concept clinical trial in the first half of 2019 with results expected in late 2019 / early 2020***

# ACTH Antagonists

## for the treatment of Cushing's disease and other conditions of ACTH excess



## Cushing's Etiology

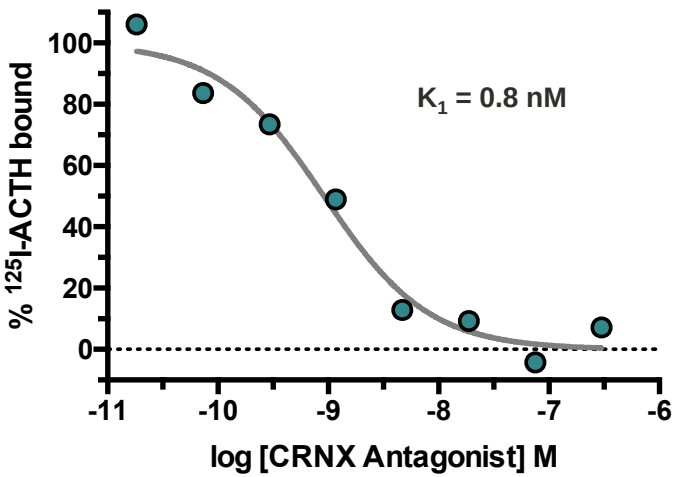



Cushing's Disease Standardized Mortality Ratio = 2.4 (95% CI, 1.2-3.9)

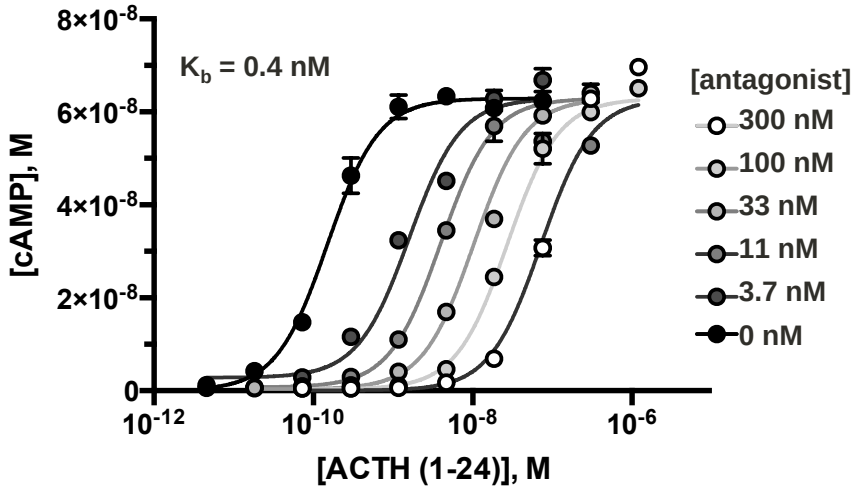
Source: Dekkers et al (2007) 1210, 2006-2012

# A prototype ACTH antagonist

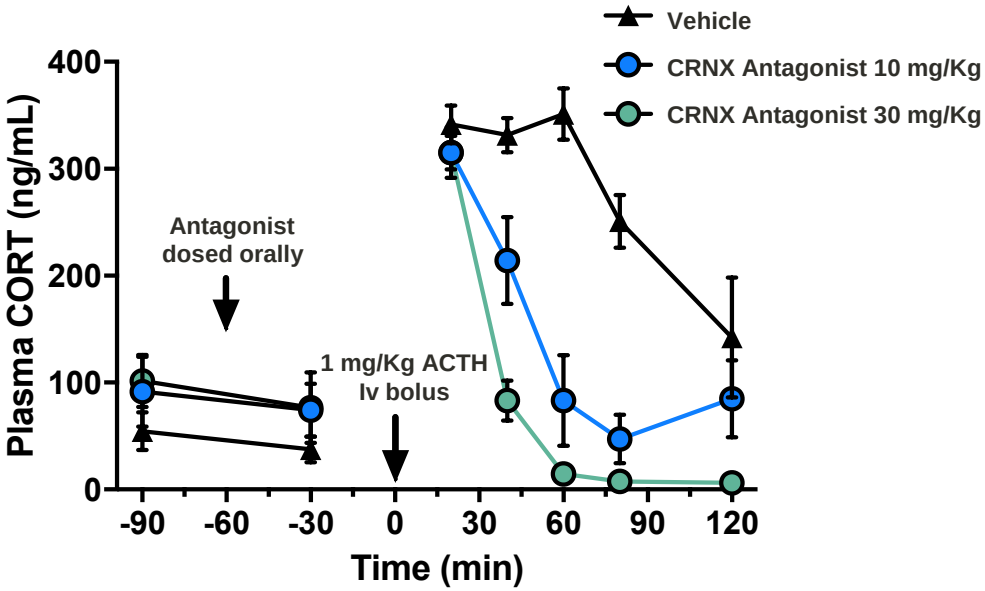
## Competition radio-ligand binding assay



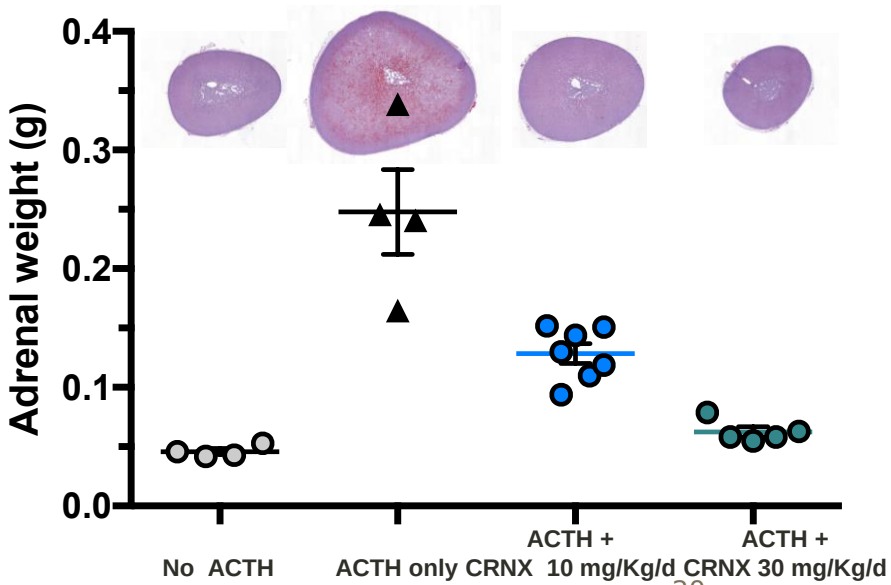

## Schild analysis of functional antagonism




## In vivo POC: acute suppression of ACTH-induced corticosterone in rats




## In vivo POC: repeat antagonist dosing (7d) rescues adrenal hypertrophy from chronic ACTH infusion

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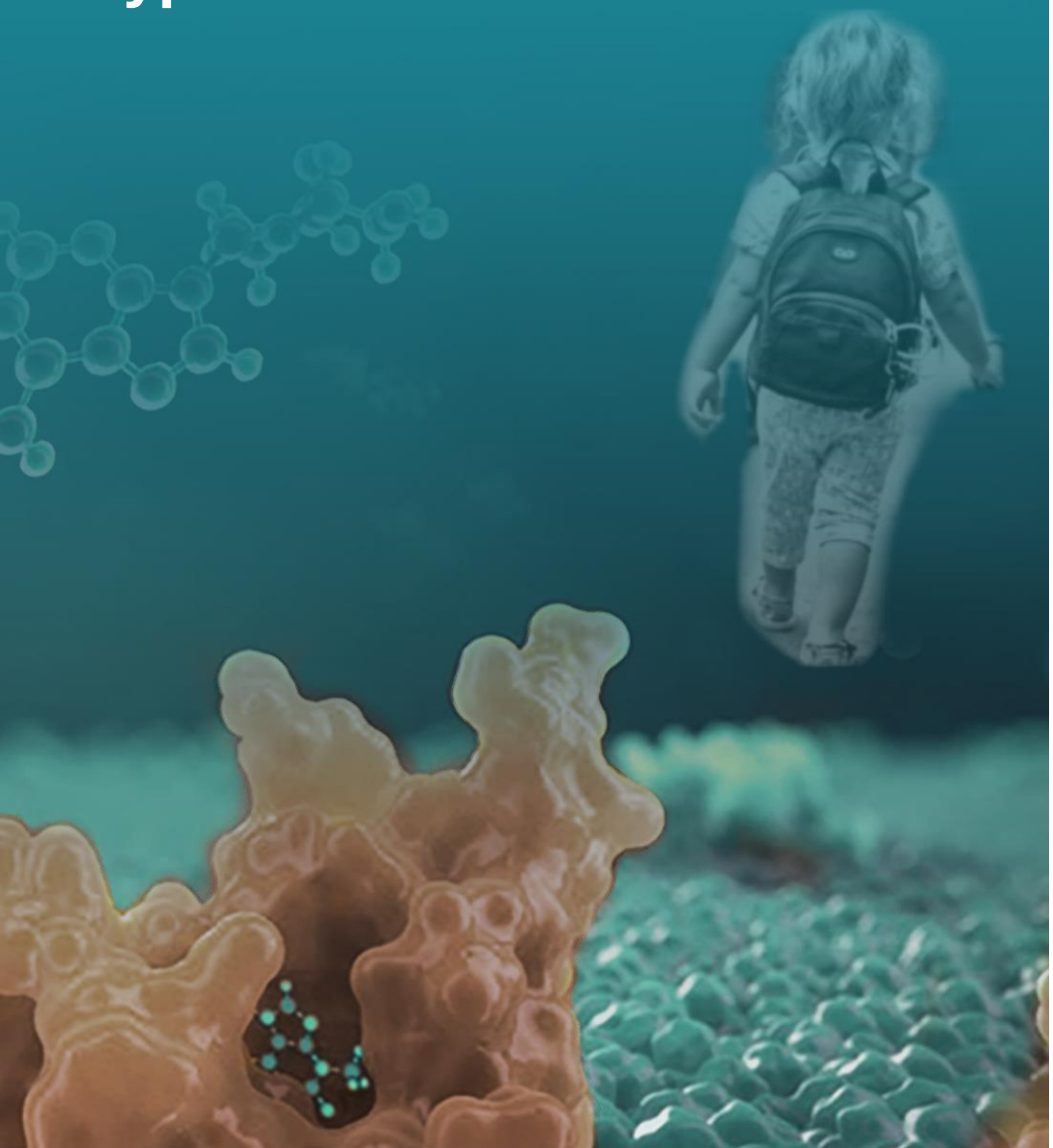
# sst5 Agonists

## for the treatment of hyperinsulinism



## Congenital Hyperinsulinism

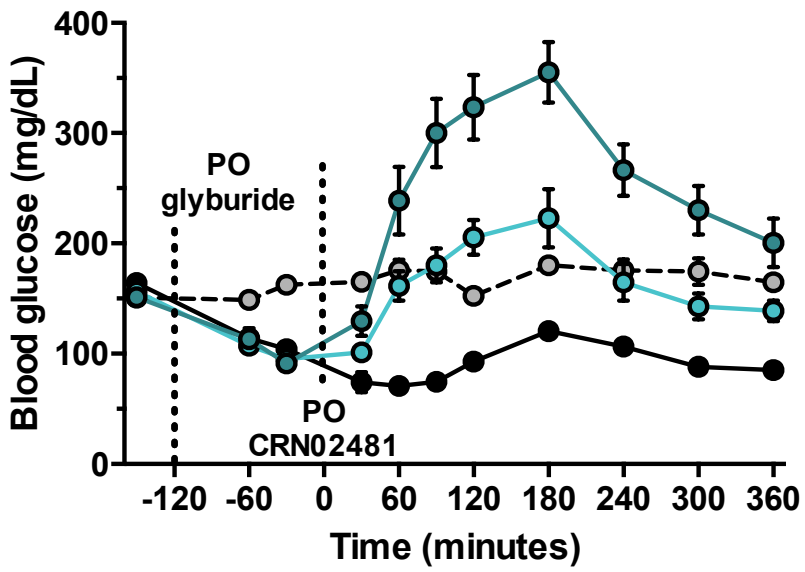
- Etiology
  - Genetic defects (e.g. $K_{ATP}$ channel) results in excess insulin secretion and profound hypoglycemia
  - Incidence: 1:30,000 to 1:50,000 births (U.S.)
- Treatment Goals
  - Avoid pancreatectomy
  - Prevent cognitive / developmental problems
  - Reduce injections and glucose sticks
  - Medical management until HI is resolved
  - Live a normal life

## Other Potential Indications

- Post-bariatric surgery hypoglycemia
- Insulinoma
  - Insulin secreting neuroendocrine tumor
  - Ultra-rare

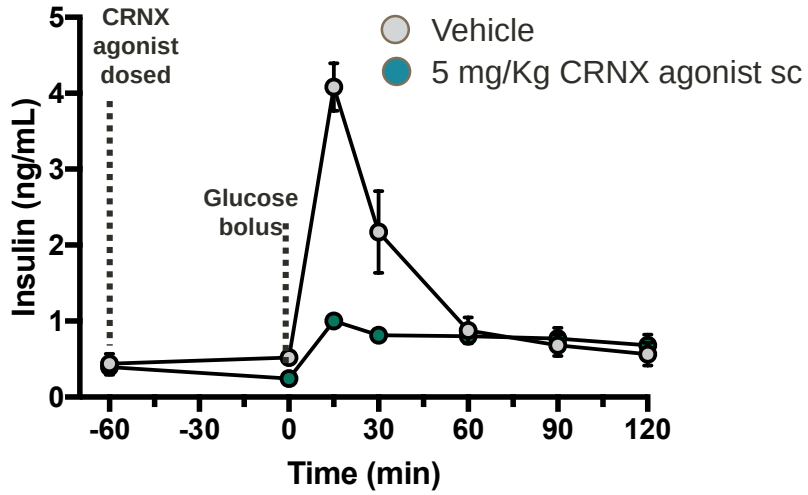
# sst5 Agonists: Preclinical results

## Rescue of hypoglycemia in rats induced by treatment with sulfonylurea glyburide

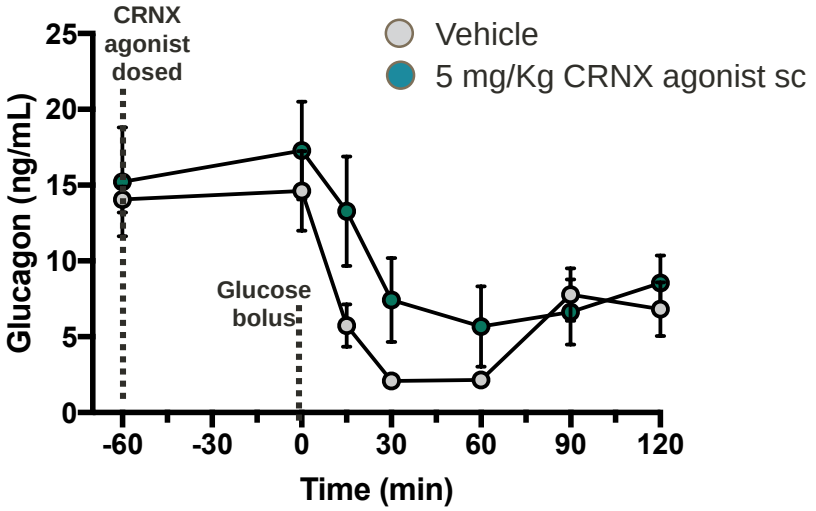



- Glyb + 10 mg/Kg CRN02481
- Glyb + 3 mg/Kg CRN02481
- Vehicle
- 30 mg/Kg glyburide

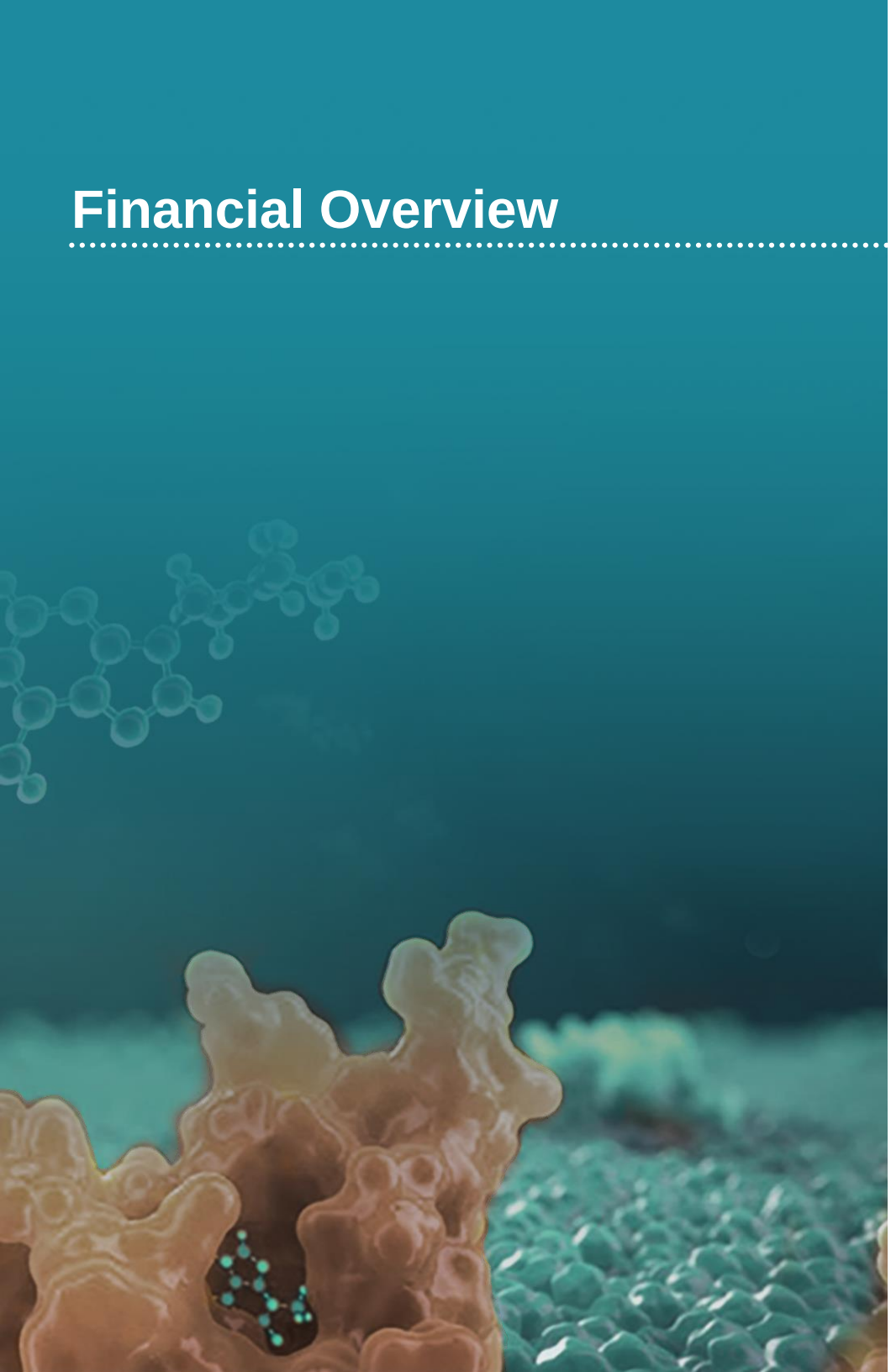
## In an OGTT, CRNX agonist suppressed insulin…




## …while maintaining glucagon levels



# Financial Overview



## As of June 30, 2019

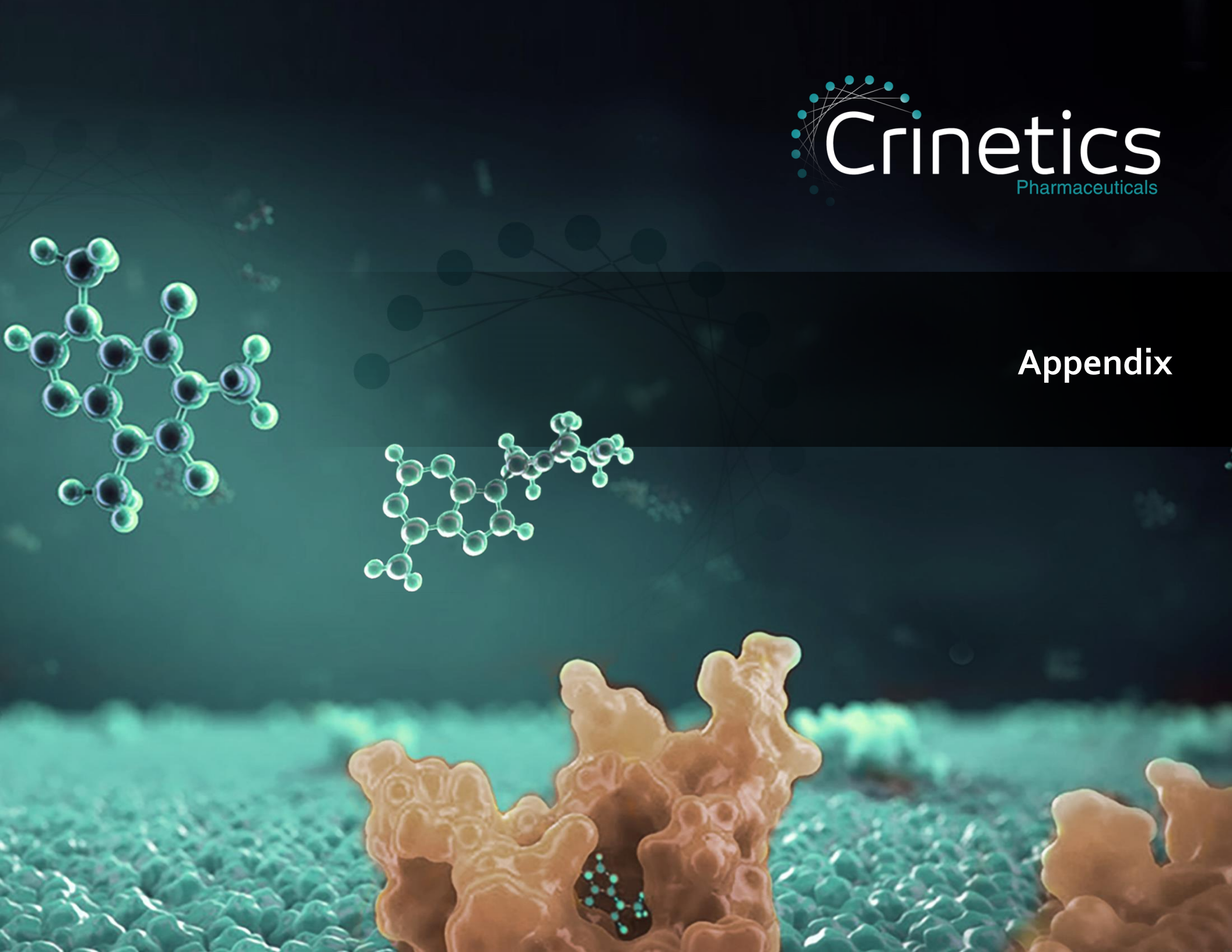
- $145.0 million cash and investments
- No debt
- 24.2 million common shares outstanding

## 2019 Goals

- *Enroll CRN00808 Phase II trials*
- *Initiate CRN01941 Phase I study*
- *Continue to advance sst5 for hyperinsulinism and ACTH antagonist programs towards the clinic*

Crinetics
Pharmaceuticals

# Appendix



# Leadership Team

| | |
|---|---|
| **Scott Struthers, PhD** | President & CEO, Founder |
| **Frank Zhu, PhD** | VP of Chemistry, Founder |
| **Steve Betz, PhD** | VP of Biology, Founder |
| **Ajay Madan, PhD** | VP of Development |
| **Marc Wilson** | Chief Financial Officer |
| **Alan Krasner** | Chief Medical Officer |
| **Gina Ford** | VP, Corporate Strategy & Commercial Planning |

# Directors and Advisory Board

## BOARD OF DIRECTORS

| | |
|---|---|
| **Wendell Wierenga, PhD** | Chairman (Former EVP R&D, Santarus) |
| **Scott Struthers, PhD** | Founder & CEO |
| **Steve Kaldor, PhD** | Former CEO, Quanticel |
| **Matt Fust** | Former CFO, Onyx |
| **Jack Nielsen** | Managing Director, Vivo Capital |
| **Weston Nichols, PhD** | Analyst, Perceptive Advisors |

## SCIENTIFIC ADVISORY BOARD

| | |
|---|---|
| **David Clemmons, MD** | Professor of Medicine at UNC, Chapel Hill |
| **Anne Klibanski, MD** | Chief of Neuroendocrine Unit at MGH & Professor of Medicine at Harvard |