# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION
**WASHINGTON, D.C. 20549**

# FORM 8-K

## CURRENT REPORT

**Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**

**Date of Report (Date of earliest event reported): May 25, 2022**

# Crinetics Pharmaceuticals, Inc.

**(Exact name of Registrant as Specified in Its Charter)**

| **Delaware** | **001-38583** | **26-3744114** |
|---|---|---|
| **(State or Other Jurisdiction of Incorporation)** | **(Commission File Number)** | **(IRS Employer Identification No.)** |

| | |
|---|---|
| **10222 Barnes Canyon Road, Bldg. #2**<br>**San Diego, California**<br>**(Address of Principal Executive Offices)** | **92121**<br>**(Zip Code)** |

**Registrant's Telephone Number, Including Area Code: (858) 450-6464**

**(Former Name or Former Address, if Changed Since Last Report)**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

**Securities registered pursuant to Section 12(b) of the Act:**

| Title of each class | Trading Symbol(s) | Name of each exchange on which registered |
|---|---|---|
| Common Stock, par value $0.001 per share | CRNX | NASDAQ Global Select Market |

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

**Item 7.01 Regulation FD Disclosure.**
The slides attached as Exhibit 99.1 to this Current Report contain certain additional information related to the clinical data results discussed in Item 8.01 below. Crinetics Pharmaceuticals, Inc. (the "Company" or "Crinetics") intends to present the slides during a conference call and live webcast with the investment community on May 25, 2022, at 8:00 a.m. Eastern Time.

The information contained in this Item 7.01, including in Exhibit 99.1 hereto, is being "furnished" and shall not be deemed "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended, is not subject to the liabilities of that section and is not deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, except as shall be expressly set forth by specific reference in such a filing.

**Item 8.01 Other Events.**
On May 25, 2022, Crinetics announced positive top-line data from the multiple-ascending dose (MAD) portion of a first-in-human Phase 1 clinical study with CRN04894 demonstrated pharmacologic proof-of-concept for Crinetics' investigational, oral, nonpeptide adrenocorticotropic hormone (ACTH) antagonist that is being developed for the treatment of Cushing's disease, congenital adrenal hyperplasia (CAH), and other conditions of excess ACTH. Following administration of CRN04894, results showed serum cortisol below normal levels and a marked reduction in 24-hour urine free cortisol excretion in the presence of sustained, disease-like ACTH concentrations.

The 49 healthy adults evaluated in the multiple ascending dose portion of the Phase 1 study were administered 40, 60 or 80 mg doses of CRN04894, or placebo, daily for 10 days. After 10 days of dosing was complete, evaluable participants were administered an ACTH challenge to stimulate adrenal activation to disease relevant levels. Safety and pharmacokinetic data were consistent with expectations from the single-ascending dose cohorts in the Phase 1 study. There were no discontinuations due to treatment related adverse events and no serious adverse events reported. Glucocorticoid deficiency was the most common treatment-related adverse event in the MAD cohorts. This was an expected extension of pharmacology given the mechanism of action of CRN04894. CRN04894 showed consistent oral bioavailability in the MAD cohorts with a half-life of approximately 24 hours, which is anticipated to support once-daily dosing.

Participants in the MAD cohorts who were administered once nightly CRN04894 experienced a dose-dependent suppression of adrenal function as measured by suppression of serum cortisol production of 17%, 29% and 37% on average from baseline over 24 hours for the 40, 60 or 80 mg dosing groups respectively, (despite requirement for glucocorticoid supplementation in some of these subjects to prevent clinical adrenal insufficiency), compared to an average 2% increase in serum cortisol for individuals receiving placebo. The strong, dose-dependent suppression of serum and urine free cortisol was achieved despite ACTH levels in subjects in the 60 and 80 mg cohorts similar to those typically seen in patients with CAH and Cushing's disease. Even when an additional exogenous ACTH challenge was administered on top of the already increased ACTH levels, cortisol levels remained below the normal range in subjects receiving CRN04894, indicating clinically significant suppression of adrenal activity.

**Forward-Looking Statements**
Crinetics cautions you that statements contained in this current report regarding matters that are not historical facts are forward-looking statements. These statements are based on the Company's current beliefs and expectations. Such forward-looking statements include, but are not limited to, statements regarding the potential benefits of CRN04894 for patients with Cushing's disease, congenital adrenal hyperplasia, and other conditions of excess ACTH; plans to meet with regulators and to advance CRN04894 into a clinical program in patients for the treatment of Cushing's disease, congenital adrenal hyperplasia, and other conditions of excess ACTH and the timing thereof and plans to advance other pipeline candidates. The inclusion of forward-looking statements should not be regarded as a representation by Crinetics that any of its plans will be achieved. Actual results may differ from those set forth in this current report due to the risks and uncertainties inherent in Crinetics' business, including, without limitation: top-line data that we report may change following a more comprehensive review of the data related to the clinical trials and such data may not accurately reflect the complete results of a clinical trial, and the FDA and other regulatory authorities may not agree with our interpretation of such results; advancement of CRN04894 into later stage trials is dependent on and subject to the receipt of further feedback from the FDA; we may not be able to obtain, maintain and enforce our patents and other intellectual property rights, and it may be prohibitively difficult or costly to protect such rights; the COVID-19 pandemic may disrupt Crinetics' business and that of the third parties on which it depends, including delaying or otherwise disrupting its clinical trials and preclinical studies, manufacturing and supply chain, or impairing employee productivity; the Company's dependence on third parties in connection with product manufacturing, research and preclinical and clinical testing; the success of Crinetics' clinical trials and nonclinical studies for paltusotine, CRN04894, CRN04777, and its other product candidates; regulatory developments in the United States and foreign countries; unexpected adverse side effects or inadequate efficacy of the Company's product candidates that may limit their development, regulatory approval and/or commercialization; Crinetics may use its capital resources sooner than it expects; and other risks described under the heading "Risk Factors" in documents the Company files from time to time with the Securities and Exchange Commission. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof, and Crinetics undertakes no

obligation to update such statements to reflect events that occur or circumstances that exist after the date hereof. 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.

**Item 9.01 Financial Statements and Exhibits.**

(d) Exhibits

| Exhibit No. | Description |
|---|---|
| 99.1 | CRN04894 Phase 1 Multiple Ascending Dose Data Presentation |
| 104 | Cover Page Interactive Data File (embedded within the Inline XBRL document) |

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Crinetics Pharmaceuticals, Inc.

Date: May 25, 2022

By: /s/ R. Scott Struthers, Ph.D.
R. Scott Struthers, Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 99.1


# CRN04894: PHASE 1 MULTIPLE ASCENDING DOSE (MAD) PRELIMINARY RESULTS

May 25, 2022

# Safe Harbor Statement

**This presentation contains forward-looking statements.**

Crinetics cautions you that statements contained in this presentation regarding matters that are not historical facts are forward-looking statements. These statements are based on the company's current beliefs and expectations. Such forward-looking statements include, but are not limited to, statements regarding: the potential benefits of CRN04894 for patients with Cushing's disease, congenital adrenal hyperplasia, and other conditions of excess ACTH; plans to meet with regulators and to advance CRN04894 into a clinical program in patients for the treatment of Cushing's disease, congenital adrenal hyperplasia, and other conditions of excess ACTH, and the timing thereof; and plans to advance other pipeline product candidates. The inclusion of forward-looking statements should not be regarded as a representation by Crinetics that any of its plans will be achieved. Actual results may differ from those set forth here due to the risks and uncertainties inherent in Crinetics' business, including, without limitation: preliminary data that we report may change following a more comprehensive review of the data related to the clinical trials and such data may not accurately reflect the complete results of a clinical trial, and the FDA and other regulatory authorities may not agree with our interpretation of such results; advancement of CRN04894 into later stage trials is dependent on and subject to the receipt of further feedback from the FDA; we may not be able to obtain, maintain and enforce our patents and other intellectual property rights, and it may be prohibitively difficult or costly to protect such rights; the COVID-19 pandemic may disrupt Crinetics' business and that of the third parties on which it depends; the success of Crinetics' clinical trials and nonclinical studies for paltusotine, CRN04894, CRN04777, and its other product candidates; regulatory developments in the United States and foreign countries; unexpected adverse side effects or inadequate efficacy of the company's product candidates that may limit their development, regulatory approval and/or commercialization; Crinetics may use its capital resources sooner than it expects; and other risks described under the heading "Risk Factors" in documents the company files from time to time with the Securities and Exchange Commission. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof, and Crinetics undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date hereof. 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.

# CRN04894 MAD Results Support Moving to Patient Studies in Both CAH and Cushing's

**Well tolerated at doses from 40 mg to 80 mg administered daily for 10 days**
- No Serious Adverse Events; All Adverse Events considered mild/moderate
- MTD not reached: may allow further dose escalation in some patients if necessary

**Favorable pharmacokinetics support goal of once daily dosing**
- Excellent oral bioavailability with ~24-hour half life
- PK results and exposures consistent with expectations from SAD data

**Confirmed pharmacologic POC & established starting dose range for patient studies**
- Substantial and dose-dependent reductions in adrenal activity (cortisol)
- Clinically-meaningful adrenal suppression following disease relevant ACTH challenge

**Next steps:**
- Advance clinical programs in CAH and Cushing's patients with QD dosing
- Engage with regulators on design of clinical programs in patients

MAD: Multiple-ascending dose SAD: Single-ascending dose; MTD: Maximum tolerated dose; POC: Proof-of-concept; PK: Pharmacokinetic; CAH: Congenital adrenal hyperplasia

# Crinetics' Endocrine Development Strategy: Hormone Levels from Preclinical to Approval

## Leveraging Highly Conserved Biology and Purpose-Built Molecules to Optimize Probability of Success in Diseases of High Unmet Need

**Preclinical POC**

ΔHormones, PK, Safety

Phase 1 Healthy Volunteers

**Phase 1 Healthy Volunteer Safety, Pharmacologic POC**

ΔHormones, PK, Safety

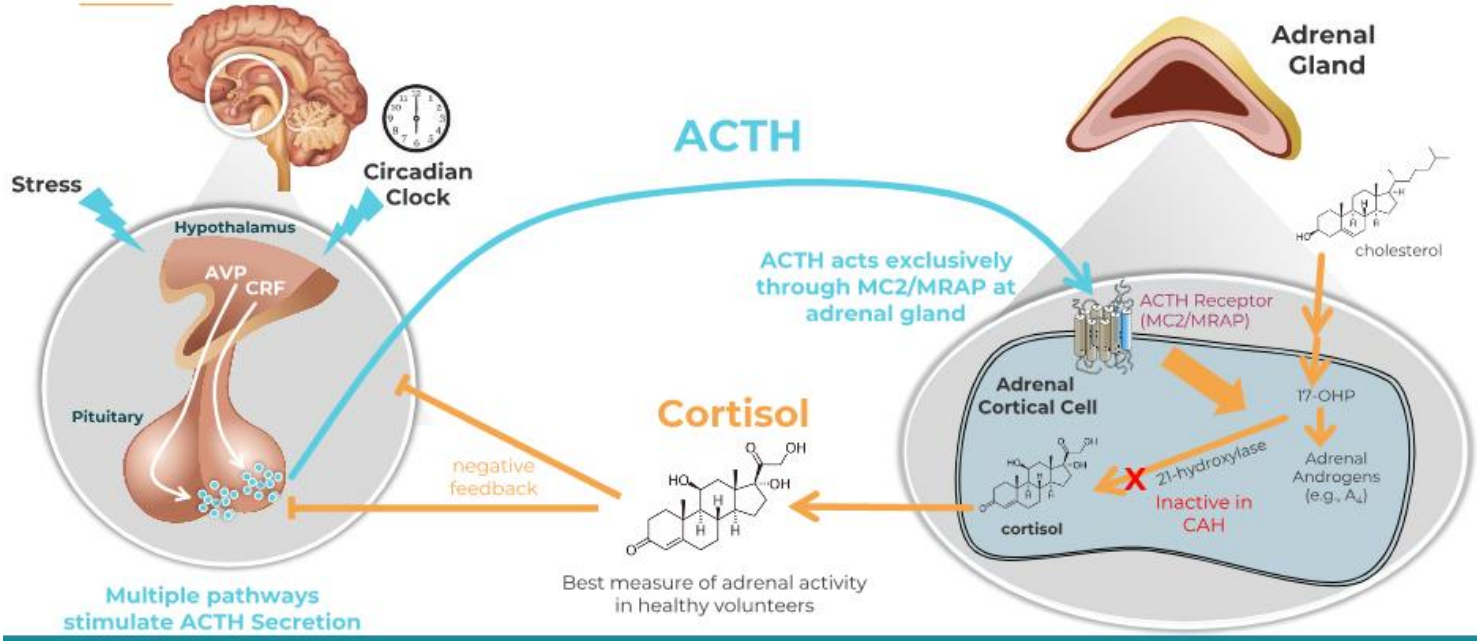
Phase 2/3 Trials (Patients)

**Phase 2,3 Safety, Disease Efficacy**

ΔHormones, PROs, PK, Safety

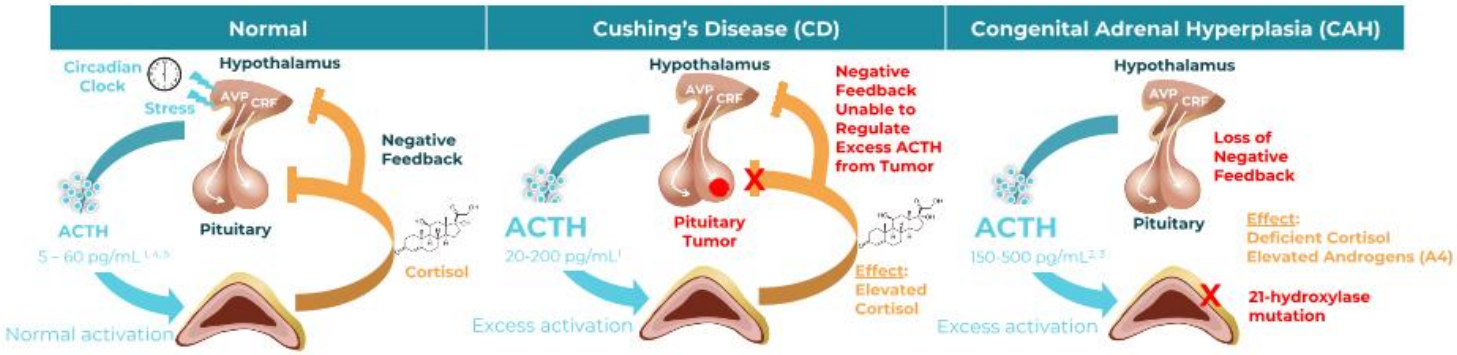
POC: Proof-of-concept; PK: Pharmacokinetic; PRO: Patient reported outcome

# The Hypothalamic-Pituitary-Adrenal (HPA) Axis: The ACTH Receptor Is Key for Adrenal Activation



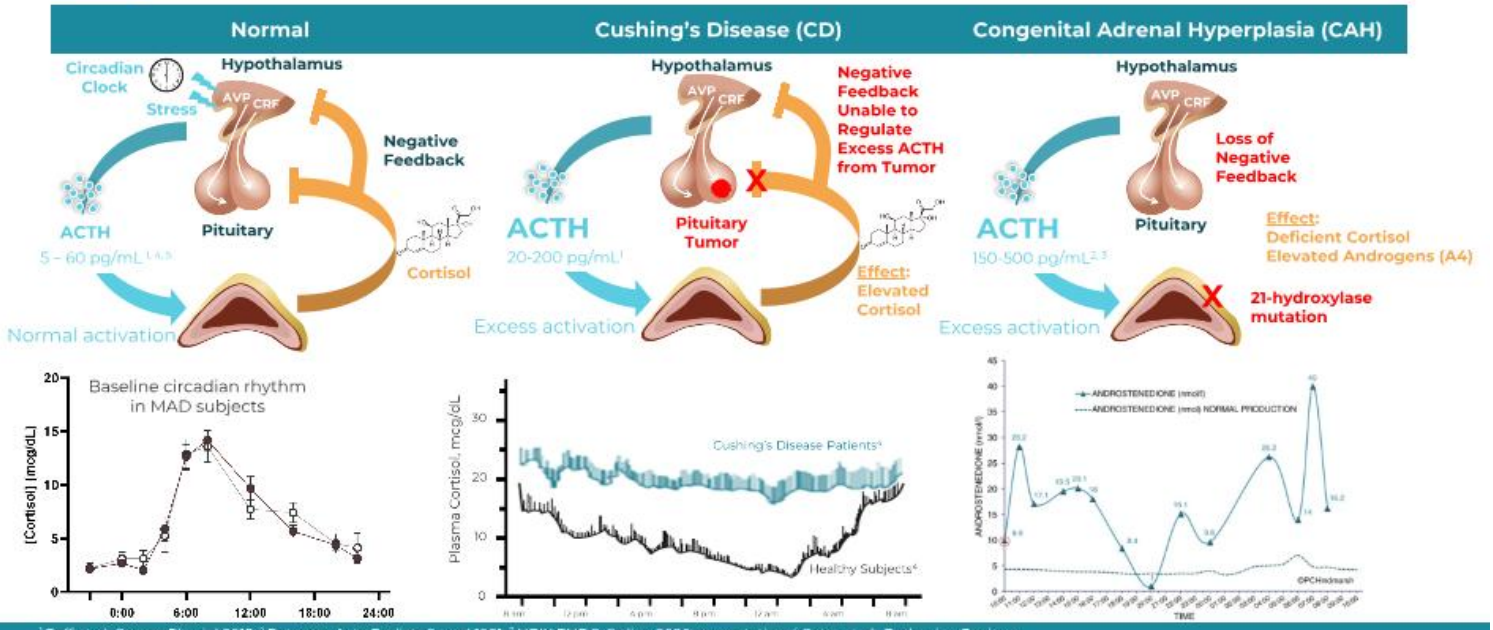

AVP: Arginine Vasopressin; CRF: Corticotrophin-Releasing Factor
Both AVP and CRF stimulate to ACTH secretion by the pituitary

# Disruptions in the HPA Axis Lead to Diseases of Excess ACTH and Excess Adrenal Activation




| | | |
|---|---|---|
| **Cause** | ACTH-secreting pituitary tumor | Inability to produce cortisol leads to loss of negative feedback & excess ACTH |
| **US Prevalence (global incidence per 100,000)** | 10k (2.5-3.8) | 27k (6.7-10.0) |
| **Symptoms** | Central obesity and round face; Dorsal and supraclavicular fat pads; Hypertension; Stretch marks; Bone loss; Hyperglycemia; Psychiatric disturbances | Adrenal insufficiency; Infertility; Hirsutism; Short stature; Precocious puberty; Adrenal rest tumors |

# Excess ACTH and Adrenal Activation Lead to Excess Cortisol in Cushing's and A4 in CAH







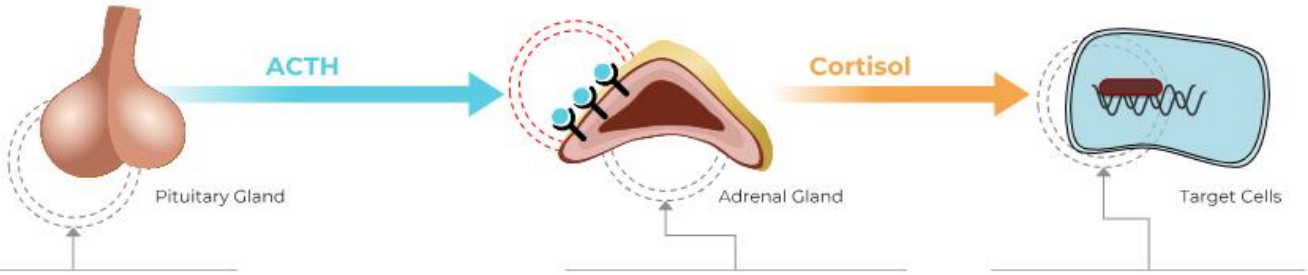






[1] Raff et al. Compr Physiol 2015, [2] Petersen Acta Pediatr Scand 1981, [3] NBIX ENDO Online 2020 presentation, [4] Oster et al., Endocrine Reviews 2017, [5] UpToDate Reference, [6] Oelkers et al, JCEM 1988, [6] Alia et. al Clinical Endocrinology 2006, Peter C. Hindmarsh, Kathy Geertsma, in Congenital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

# Current HPA Therapeutics Have Limited Efficacy and/or Safety Issues, Leaving High Unmet Need




**Pituitary Directed Agents to Suppress ACTH Secretion**

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

*In Development:* CRF antagonists (CAH only)

**Adrenal Steroidogenesis Inhibitors**

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

**Glucocorticoid Receptor Antagonist**

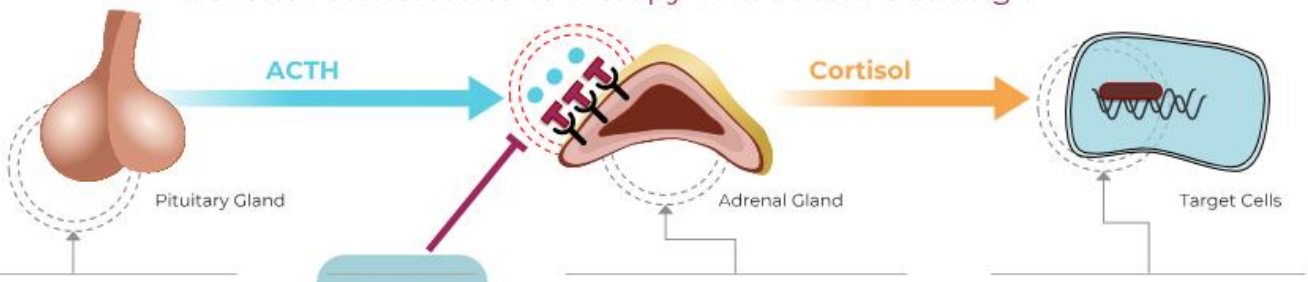
*Available:* mifepristone
- Efficacy difficult to assess
- Safety issues

*In Development:* relacorilant

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

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

Targeting the ACTH receptor blocks the key chokepoint of HPA signaling, and could become cornerstone of therapy in CAH and Cushing's

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**ACTH Receptor Antagonist**

**CRN04894**

**Adrenal Steroidogenesis Inhibitors**

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# CRN04894 Healthy Volunteer MAD Study Designed to Build on SAD Pharmacologic POC Data

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

## MAD Study Goals

- Evaluate safety and tolerability with repeat dosing
- Evaluate pharmacokinetics at steady state
- Explore optimal dosing regimen given the circadian rhythm of adrenal activation levels measured by cortisol in healthy volunteers
- Evaluate PD on basal adrenal activity (cortisol) with repeat dosing
- Evaluate PD after disease relevant (1 mcg) ACTH challenge
- Select dosing regimen and range for patient studies

## Evaluated Dosing Regimens

- QD 08:00 (8 am) dosing: 40 mg
- **QD 22:00 (10 pm) dosing: 40, 60, & 80 mg**
- BID dosing: 40 mg (total of 80 mg daily)

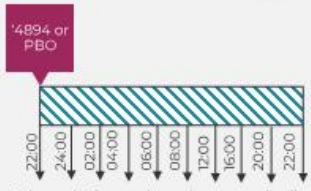
## Proof-of-Concept

- Dose dependent suppression of basal and ACTH-induced adrenal activity (measured by cortisol) with CRN04894

MAD cohorts include 6 treated and 3 placebo per cohort
MAD: Multiple-ascending dose; SAD: Single-ascending dose; POC: Proof-of-concept; PD: Pharmacodynamic; QD: Once daily; BID: Twice daily

# CRN04894 Healthy Volunteer MAD Study Designed to Build on SAD Pharmacologic POC Data


## 24h Profile




## GC Replacement Protocol

- Study protocol stipulated that subjects with suppression of 08:00 cortisol below 5 mcg/dL were to receive hydrocortisone (cortisol) add back (10 mg @ 08:00 and 5 mg @ 14:00).

## ACTH Challenge


MAD: Multiple-ascending dose; SAD: Single-ascending dose; POC: Proof-of-concept PBO: Placebo, GC: Glucocorticoid; *PM doses given orally at 22:00 (10:00 pm); In subjects requiring GC replacement, blood draws for biomarker profiles were taken prior to administration of short-acting oral GC. 8 am cortisol levels drawn 18 hours after last dose of oral GC (half-life of ~1.5 hours).

# CRN04894 was Well Tolerated: No Study Drug Discontinuations due to Treatment Related AEs

## No Serious Adverse Events. All Adverse events considered mild/moderate

Treatment emergent adverse events in ≥2 '4894 treated subjects

| Most Frequent TEAEs* | Placebo (SAD+MAD) (N=25) n (%) | '4894 (SAD+MAD) (N=63) n (%) |
|---|---|---|
| Glucocorticoid deficiency | 1 (4.0%) | 11 ( 17.5%) |
| Headache | 5 ( 20.0%) | 6 ( 9.5%) |
| Dermatitis contact | 0 | 5 ( 7.9%) |
| COVID-19 | 1 (4.0%) | 3 (4.8%) |
| Upper respiratory tract infection | 1 (4.0%) | 3 (4.8%) |
| Anxiety | 1 ( 4.0%) | 2 ( 3.2%) |
| Erythema | 0 | 2 ( 3.2%) |
| Palpitations | 1 ( 4.0%) | 2 ( 3.2%) |
| Pruritus | 0 | 2 ( 3.2%) |

- As expected, glucocorticoid deficiency, defined as 08:00 cortisol level <5 mcg/dL, was the most common treatment related adverse event and seen only in MAD cohorts (8 during dosing, 4 after completion of dosing)
  - These subjects experienced no symptoms suggestive of clinical adrenal insufficiency
  - Physiologic replacement glucocorticoid was co-administered with continued study drug per protocol
- No study drug discontinuations due to treatment related AEs
- 4 subjects with new COVID-19 infections were sent home after 4 days of dosing during the MAD.
  - Make up subjects were subsequently enrolled and evaluated for the full 10 days of dosing
- No safety signals seen with vital signs, laboratory testing, ECGs

AE: Adverse event; TEAE: Treatment emergent adverse event; SAD: Single-ascending dose; MAD: Multiple-ascending dose; ECG: Electrocardiogram

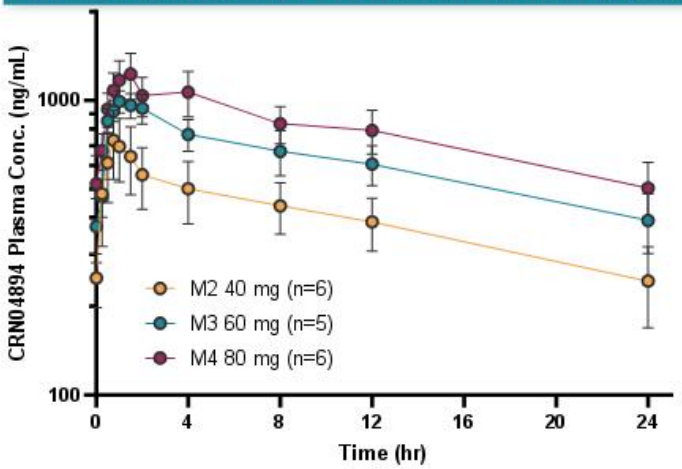
# PK Supports Goal of Once Daily Oral Dosing

MAD PK Consistent with Expectations from SAD Data at the Same Doses

## Steady State PK

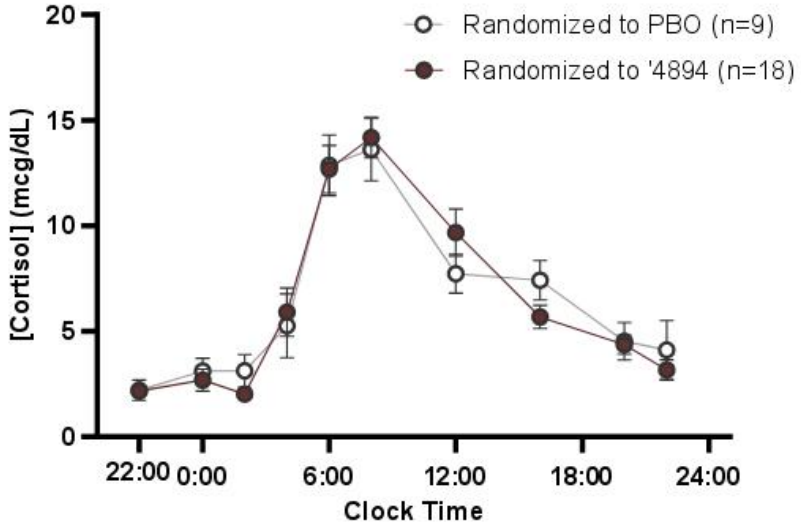
- Oral bioavailability
- Favorable half-life of ~24 hours
- Rapidly absorbed with a $t_{max}$ of ~1-2 hours
- Dose proportional exposure
- PK profile is consistent with morning, nighttime, or BID dosing

## Concentration-Time Profile at Steady State (Day 10)



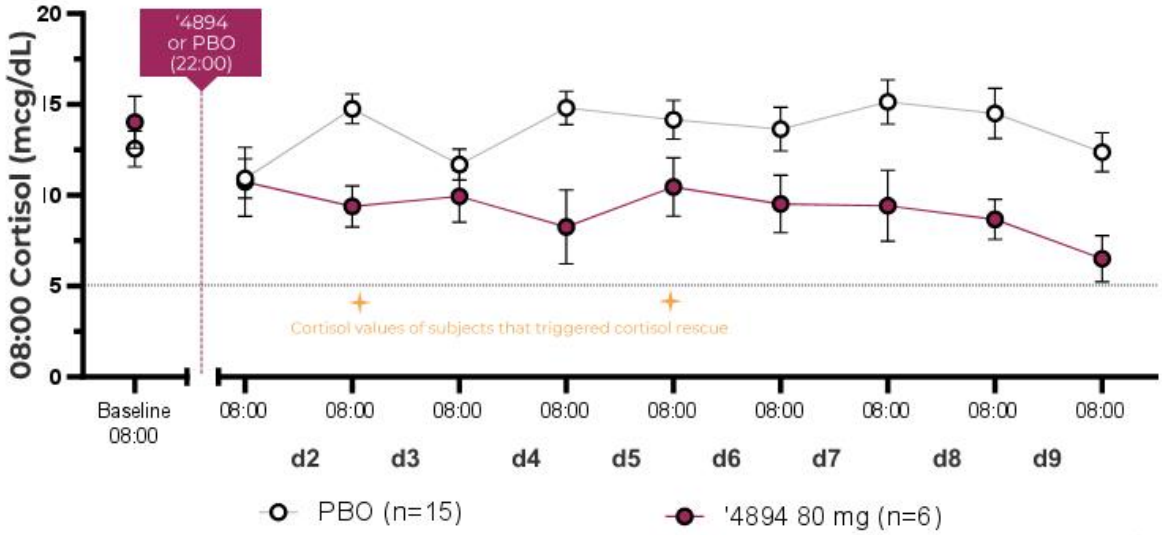

Data represent mean ± SEM. N=1 subject was an outlier and excluded in 60 mg cohort; MAD: Multiple-ascending dose; SAD: Single-ascending dose; PK: Pharmacokinetics; BID: Twice daily

# Healthy Volunteers Have Expected Circadian Rhythm of Adrenal Activity (Cortisol) at Baseline




Data represent mean ± SEM. Excluding subjects (n=1 in PBO, n=3 in active) with COVID-19 infection. PBO=placebo

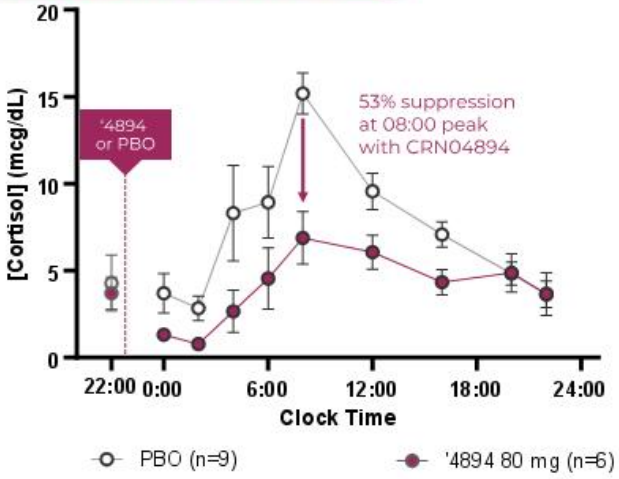
# Administration of CRN04894 Suppressed Peak Adrenal Activity Below Normal Levels in HVs



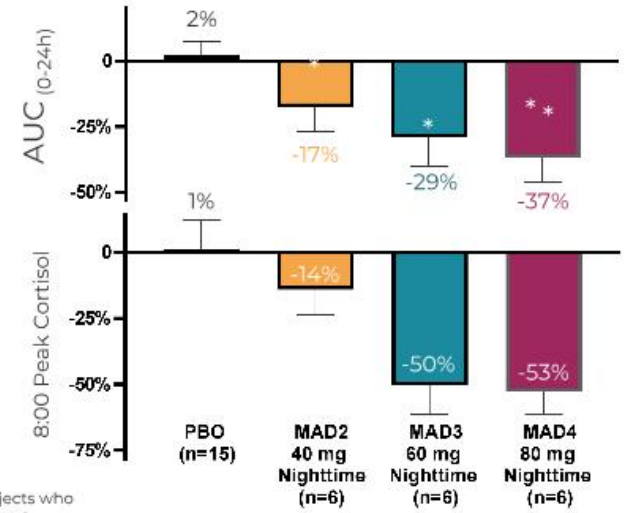

Data represent mean ± SEM. Includes data from two subjects that required glucocorticoid replacement as per protocol (AM cortisol less than 5 mcg/dL) Cortisol (Hydrocortisone) (10 mg @ 08:00 and 5 mg @ 14:00) starting on day 2 for one subject and starting on day 5 for second subject; cortisol values measured before the morning dose of GC. HVs: Healthy volunteers; PBO: Placebo

# Dose-Dependent Suppression of Serum Cortisol Below Normal Levels

## Day 9 Cortisol Profiles



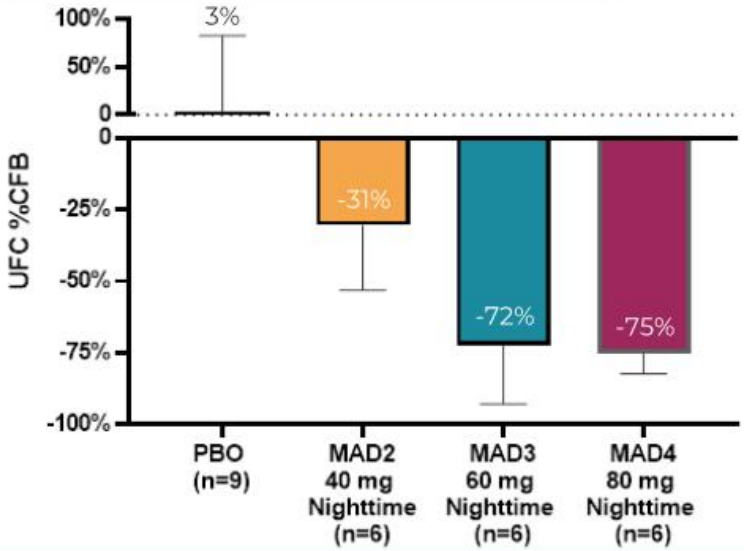

## Change in Cortisol from Baseline




Data represent mean ± SEM. White asterisks in graph on upper right represent values for subjects who received glucocorticoid rescue; since GC add-back last administered at 14:00 it is expected to not contribute to 08:00 plasma levels. PBO: Placebo; HV: Healthy volunteers

# CRN04894 Potently Suppressed Adrenal Activity as Measured by Urinary Free Cortisol

**24-Hour Urinary Free Cortisol (day 9)**

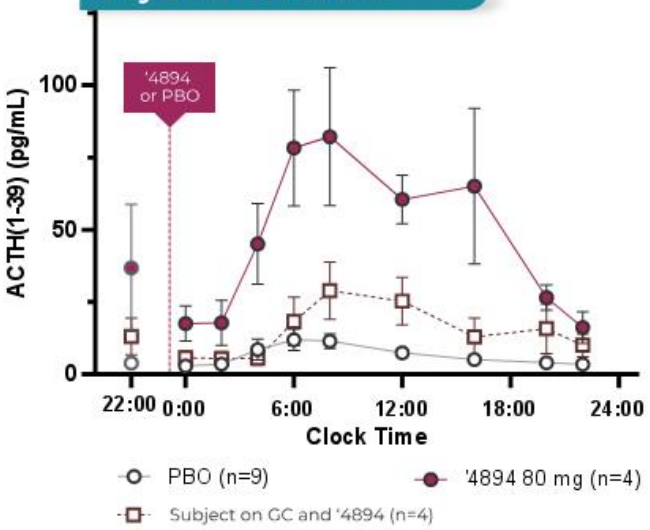



Normalization of 24-hour urinary free cortisol has been the registrational endpoint for previously approved Cushing's disease drugs

Data shown are median ± IQR. Includes data from subjects receiving GC rescue

# Loss of Cortisol Negative Feedback Resulted in HV ACTH Comparable to That Seen in Disease States

## Day 9 ACTH Profiles




## Healthy Volunteer HPA Axis

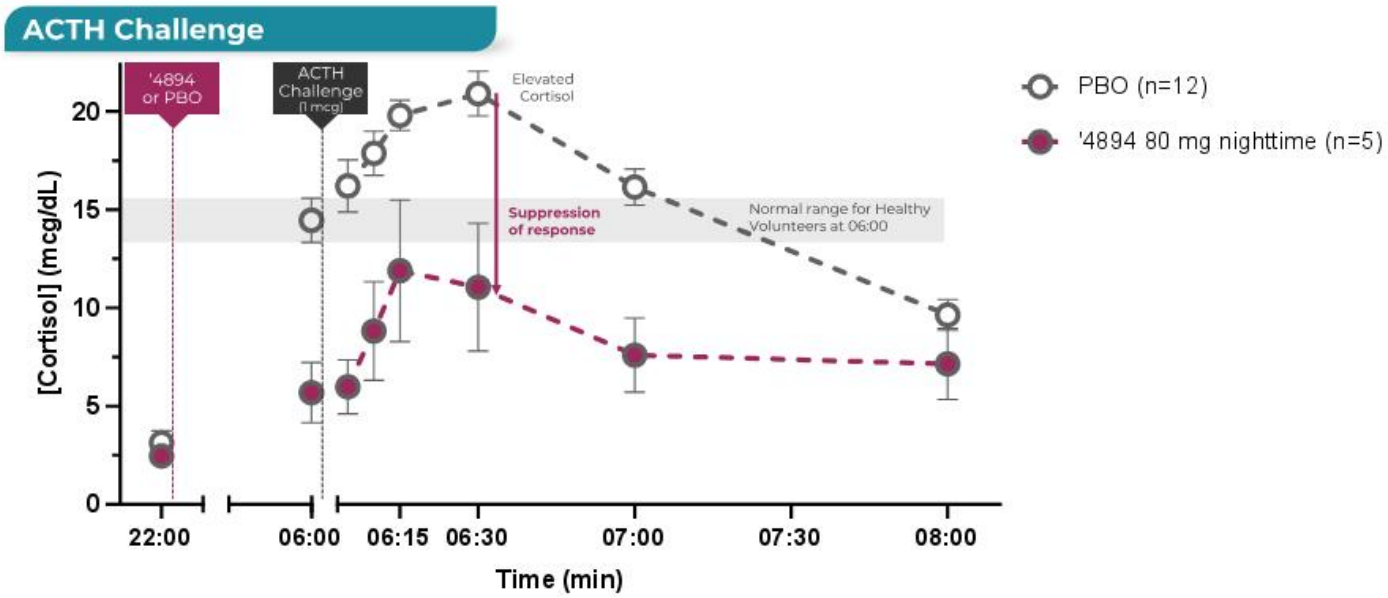
- Expected rise in ACTH was due to reduction of negative feedback with reduced cortisol levels
- Continued cortisol suppression in face of elevated ACTH demonstrated CRN04894's pharmacologic activity


## Disease-like ACTH Levels

- ACTH levels at 60 and 80 mg were in the disease-relevant range in CAH and Cushing's disease patients[1-3]
- Cortisol (hydrocortisone) replacement reduced ACTH levels

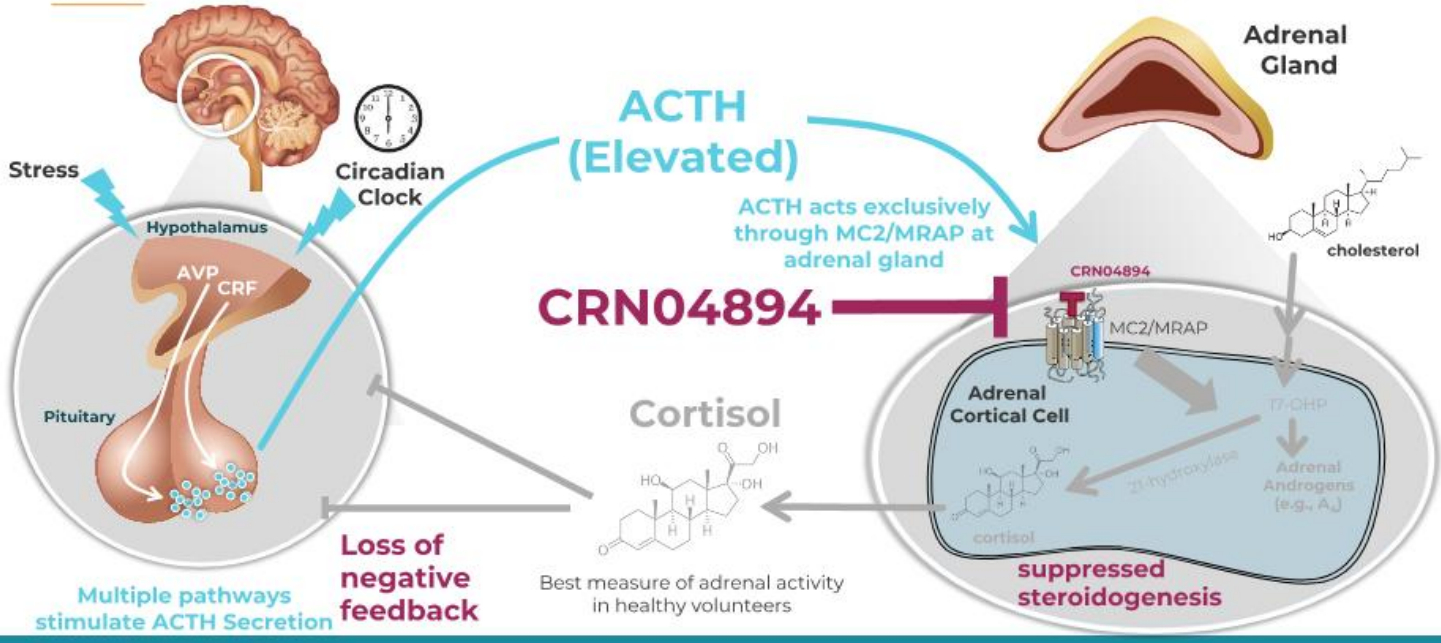
Data shown are mean±SEM using **Luminex assay which reports values ~3.9-fold lower than more commonly used clinical Roche assay**. All subjects receiving GC add back (in addition to '4894) are pooled across cohorts and depicted as a separate group; 1. Raff et al. Compr Physiol 2015, 2. Petersen Acta Pediatr Scand 1981, 3. NBIX ENDO Online 2020 presentation; HV: Healthy volunteer PBO: Placebo; GC: glucocorticoid

# CRN04894 Maintained Cortisol Below Normal Levels After ACTH Challenge Test on Top of Sustained Elevated ACTH




Data shown are mean ± SEM; one subject in 80 mg MAD arm did not receive ACTH challenge; Placebo

# CRN04894 Suppressed Adrenal Activity in Presence of Sustained, Disease-like ACTH Levels




AVP: Arginine Vasopressin; CRF: Corticotrophin-Releasing Factor

# Results from Completed CRN04894 Phase 1 Program (SAD & MAD Cohorts)

**Objectives**

- Evaluate safety and tolerability
- Evaluate drug-like Pharmacokinetics
- Evaluate PK/PD for suppression of ACTH-induced adrenal activity
- Enable patient clinical studies

**CRN04894 was well tolerated in the Phase 1 program**

**Achieved targeted pharmacokinetic profile**

- Rapidly absorbed after oral administration ($t_{max}$ ~1-2 hrs)
- Dose proportional exposure from 10 to 80 mg
- Favorable half-life of ~24 hours

**Confirmed pharmacologic POC & established starting dose range for patient studies (40 to >80 mg QD)**

- Strong and dose-dependent suppression of basal adrenal function
- Clinically-meaningful suppression of cortisol following disease relevant ACTH challenge

PK: Pharmacokinetics; PD: Pharmacodynamics; POC: Proof-of-concept

# Key Treatment Goal for Cushing's Disease Patients

## Goal: prevent complications of excessive cortisol secretion

### CD Treatment Objective

Inhibit excessive cortisol secretion, which is associated with serious complications such as:

- Weight gain, obesity
- Insulin resistance, diabetes mellitus
- Hypertension
- Muscle weakness
- Neuropsychiatric disorders
- Impaired reproductive health
- Estimated 5-year survival of 50% if untreated

**Registrational endpoint:** Twenty-four-hour urinary free cortisol

### Select Comorbidities Associated with CD

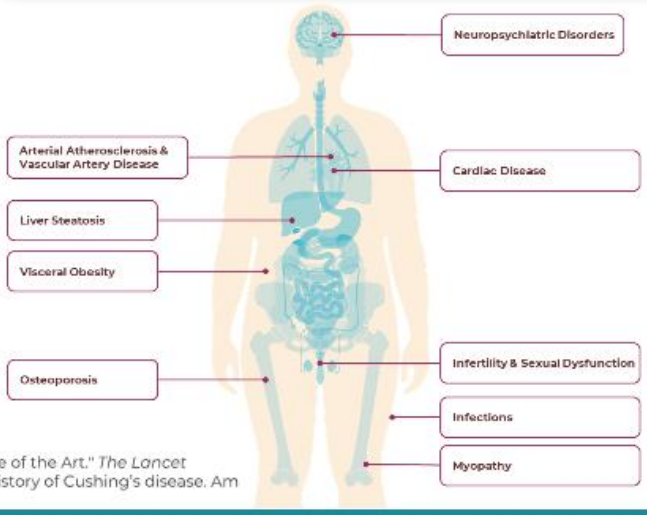



Figure adapted from: Pivonello, Rosario, et al. "Complications of Cushing's Syndrome: State of the Art." *The Lancet Diabetes & Endocrinology* 4.7 (2016): 611-629. Plotz D, Knowlton AI, Ragan C: The natural history of Cushing's disease. Am J Med 1952;13:597–614. CD: Cushing's Disease

# Key Treatment Goals for CAH Patients

## Goal: reduce symptoms of androgen excess and excess glucocorticoid treatment-related complications

### CAH Treatment Objectives

- Normalization of adrenal androgens (e.g., androstenedione ($A_4$))
- Reduce dose of glucocorticoids needed for disease control
- Achieving both of these may improve signs and symptoms of adrenal hyperandrogenism (e.g., hirsutism, menstrual disorders, adrenal rest tumors) and of glucocorticoid overexposure (e.g., central weight gain, hyperglycemia, osteoporosis).
- **Expected registrational endpoints:** Glucocorticoid sparing; $A_4$ reduction

### CAH Symptoms/Complications

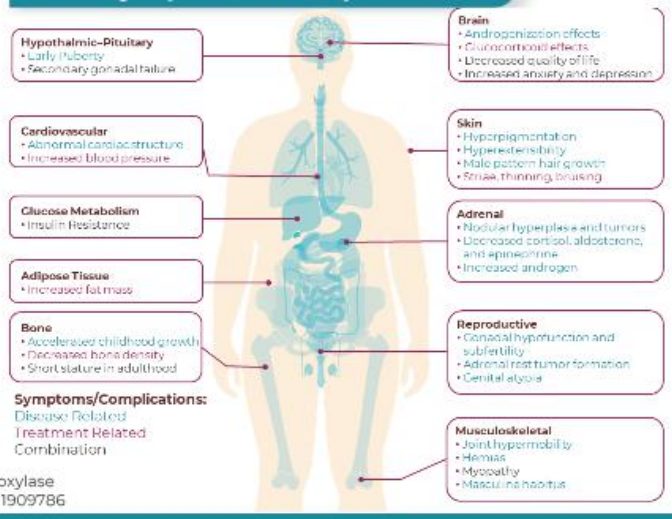



Figure adapted from: Merke D, Auchus R. Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency. New England Journal of Medicine. 2020;383(13):1248-1261.DOI: 10.1056 / NEJMra1909786

# Phase I Data Supports Advancing to Studies in Both CAH and Cushing's Disease Patients

## Next Steps

1. Review '4894 data package and discuss patient program with global regulators
   - Seek confirmation of proposed dose range (40 to >80mg QD)
   - Feedback on P2 trial designs
   - Seek guidance on registration requirements

2. Initiate clinical program in patients (anticipated 2H22)
   - CAH: Targeting single efficacious QD dose
   - Cushing's Disease: Targeting patient specific QD dose range

CAH: Congenital adrenal hyperplasia; CD: Cushing's disease

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

## NCE patent portfolio expected to provide protection into the 2040s

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

Radionetics Oncology

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

NETs: Neuroendocrine tumors; GIR: Glucose infusion rate; GC: Glucocorticoid; A4: Androstenedione; HHM: Humoral hypercalcemia of malignancy; NCE: New chemical entity

# 2021 Accomplishments and Anticipated 2022 Milestones

## 2021 Accomplishments

- Initiated Ph 3 PATHFNDR program of paltusotine in acromegaly
- Phase 1 POC data for CRN04894
- Phase 1 POC data for CRN04777
- Launched Radionetics Oncology spinout
- Strengthened balance sheet
- Identified potential development candidate PTHR1 antagonists for hyperparathyroidism and HHM

## 2022 Accomplishments & Anticipated Milestones

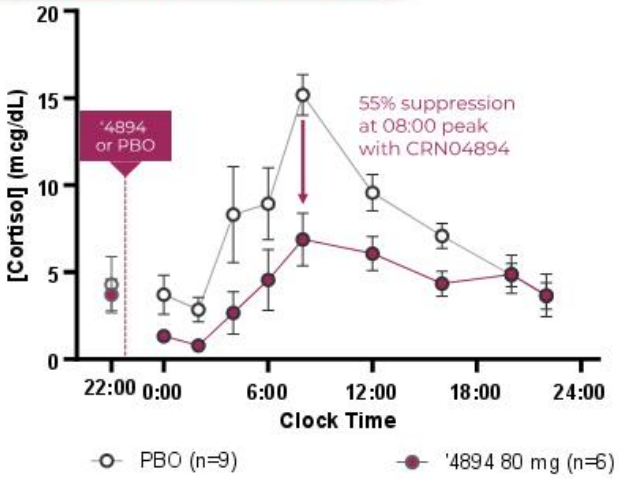
- Strategic partnership for paltusotine in Japan
- CRN04777 MAD data in 1Q22
- CRN04894 MAD data in 2Q22
- Strengthened balance sheet
- CRN04777 patient program initiation in 2H22
- CRN04894 patient program initiation in 2H22
- Initiate IND enabling studies for PTHR1 antagonist

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

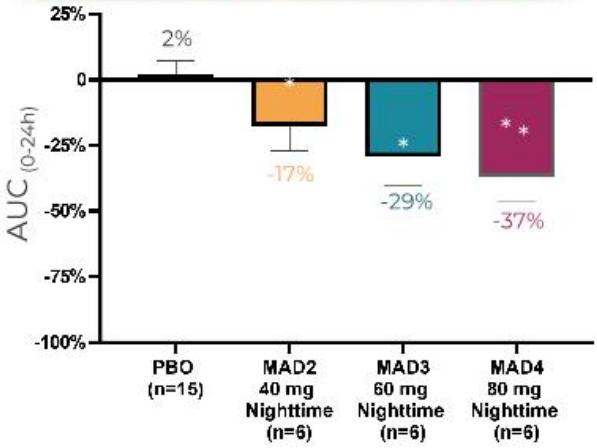
# UNUSED

# Dose-Dependent Suppression of Cortisol Below Normal Levels Despite Elevated ACTH

## Day 9 Cortisol Profiles



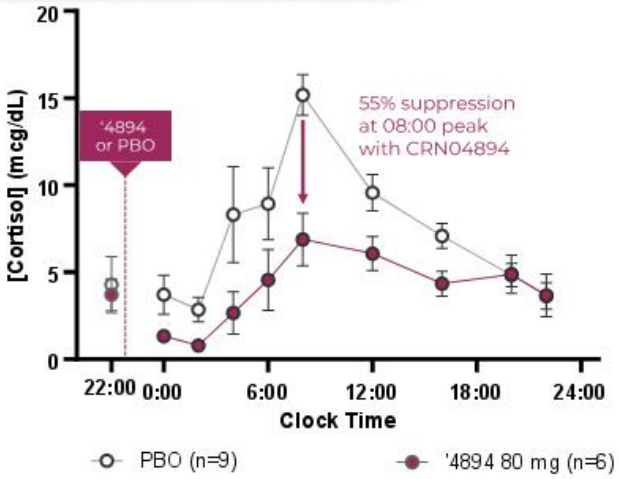

## Change in Cortisol from Baseline



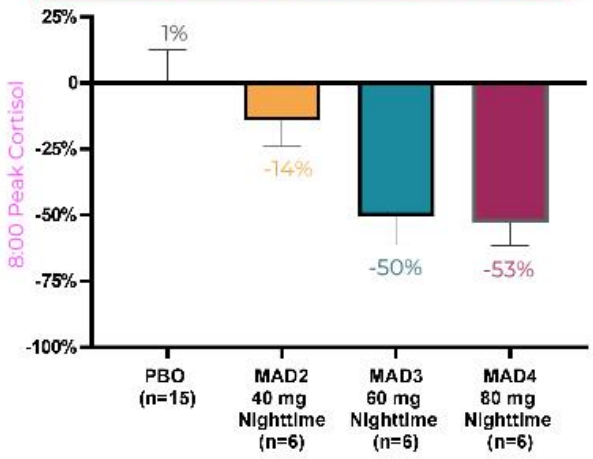

Data represent mean ± SEM. White asterisks in graph on right represent values for subjects who received glucocorticoid rescue; PBO: Placebo; HV: Healthy volunteers

# Dose-Dependent Suppression of Cortisol Below Normal Levels Despite Elevated ACTH

## Day 9 Cortisol Profiles

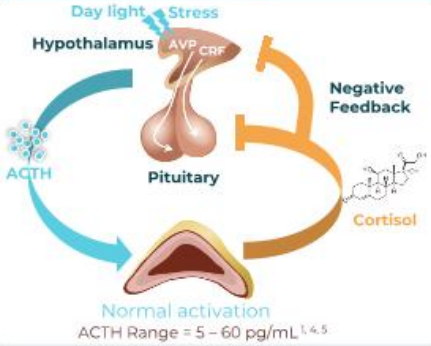
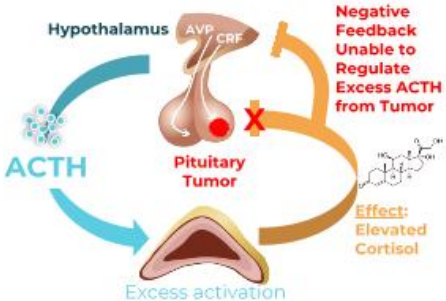
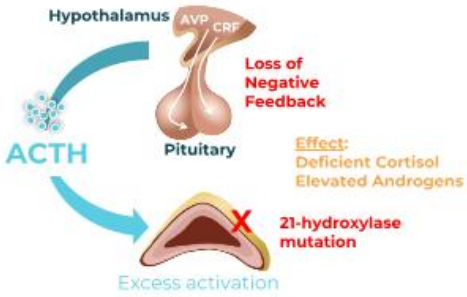



## Change in Cortisol from Baseline




Data represent mean ± SEM. White asterisks in graph on right represent values for subjects who received glucocorticoid rescue; PBO: Placebo; HV: Healthy volunteers

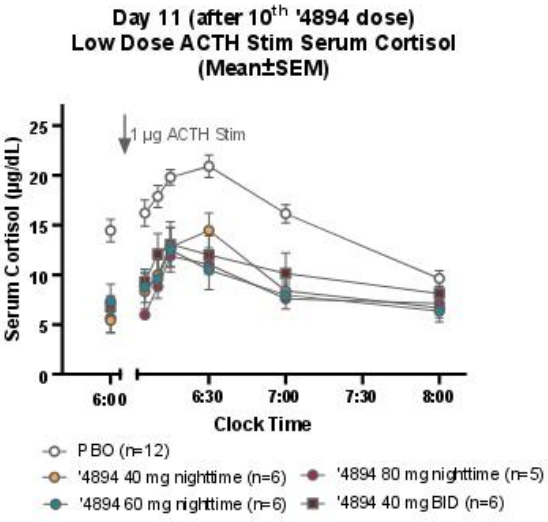
# Disruptions in the HPA Axis Lead to Diseases of Excess Hormone Secretion

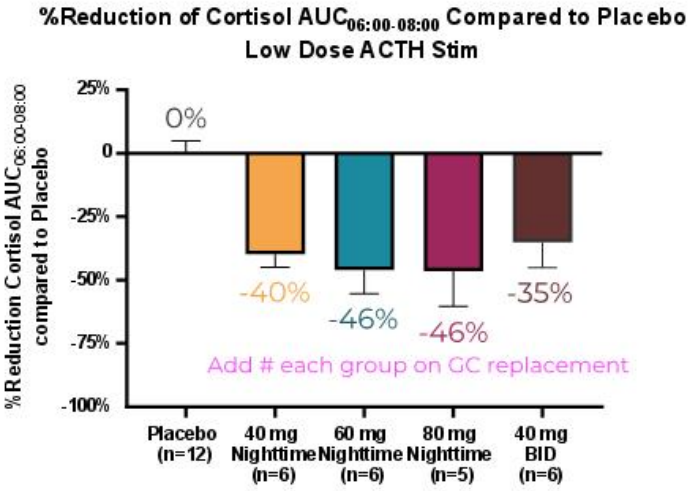
| Normal | Cushing's Disease (CD) | Congenital Adrenal Hyperplasia (CAH) |
|---|---|---|
|  |  |  |
| ACTH Range = 5 – 60 pg/mL[1,4,5] | Untreated ACTH Range = 20-200 pg/mL[1] | Untreated ACTH Range = 150-500 pg/mL[2,3] |
| **Cause** | ACTH-secreting pituitary tumor | Inability to produce cortisol leads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

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

# CRN04894 Suppresses ACTH-Stimulated Cortisol Production

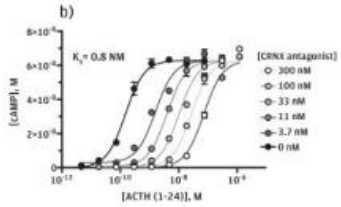
Add 40 mg AM dosing



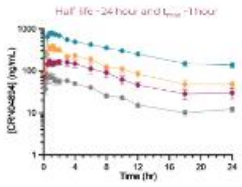



# Consider re-introducing 4894 as did in SAD

**Preclinical potency**




**Ph1 SAD PK**




**Ph1 SAD PD <u>at 2 hrs</u>**