CRN04894: FIRST IN HUMAN SINGLE ASCENDING DOSE (SAD) PRELIMINARY RESULTS
August 10, 2021
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This presentation contains forward-looking statements. Crinetics cautions you that statements contained in this press release 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 CRN04984 for patients with conditions of ACTH excess, including Cushing’s disease and congenital adrenal hyperplasia; the design and timing of data from the Phase 1 clinical trial of CRN04984; plans to advance paltusotine into a Phase 2 trial for the treatment of carcinoid syndrome associated with neuroendocrine tumors; and plans to advance other pipeline product candidates and to invest in the small molecule discovery approach. 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 press release 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 are 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; unanticipated 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.

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.
## Phase 1 Pharmacologic Proof-of-Concept for CRN04894 in Healthy Volunteers

<table>
<thead>
<tr>
<th>PK Results</th>
<th>• Orally bioavailable, dose proportional pharmacokinetics</th>
</tr>
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<tbody>
<tr>
<td>Safety Results</td>
<td>• Well-tolerated</td>
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<tr>
<td></td>
<td>• No Serious Adverse Events (SAEs)</td>
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<td></td>
<td>• All Adverse Events (AEs) considered mild</td>
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<tr>
<td>Pharmacology Results</td>
<td>• Dose-dependent reduction of basal cortisol levels</td>
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<tr>
<td></td>
<td>• Dose-dependent suppression of cortisol following ACTH challenge</td>
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<td></td>
<td>• Evidence of clinically meaningful cortisol suppression</td>
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<tr>
<td>Next Steps</td>
<td>• Multiple Ascending Dose data expected in Q4</td>
</tr>
</tbody>
</table>
Crinetics’ Endocrine Development Strategy: Hormone Levels from Preclinical to Approval

**Preclinical POC**
- ΔHormones, PK, Safety

**Phase 1 Healthy Volunteers**

**Phase 1 Healthy Volunteer Safety, Pharmacologic POC**
- ΔHormones, PK, Safety

**Phase 2,3 Safety, Disease Efficacy**
- ΔHormones, PROs, PK, Safety

**Phase 2/3 Trials (Patients)**
The Hypothalamic-Pituitary-Adrenal (HPA) Axis is the Body’s Emergency Response System for Stress

- **Stress**
  - Hypothalamus
    - CRF
    - AVP
    - negative feedback to pituitary
- Pituitary
  - ACTH
  - peripheral target tissues (Glucocorticoid Receptor)
- Adrenal Gland
  - MC2/MRAP
  - cholesterol to cortisol
  - 21-hydroxylase
  - Adrenal Androgens (17-OHP, A4)
Hypothalamic-Pituitary-Adrenal (HPA) Axis: Cortisol Levels Rise and Fall in a Diurnal Rhythm

**Normal Biology**

ACTH

Pituitary gland secretes ACTH

Adrenal

Cortisol

**Time course of plasma cortisol levels over a diurnal cycle**

<table>
<thead>
<tr>
<th>Clock Time</th>
<th>Plasma Cortisol, mcg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 am</td>
<td>0</td>
</tr>
<tr>
<td>12 pm</td>
<td>10</td>
</tr>
<tr>
<td>4 pm</td>
<td>20</td>
</tr>
<tr>
<td>8 pm</td>
<td>30</td>
</tr>
<tr>
<td>12 am</td>
<td>20</td>
</tr>
<tr>
<td>4 am</td>
<td>10</td>
</tr>
<tr>
<td>8 am</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Data from Oster et al., Endocrine Reviews 2017 (data shown are mean ± SEM, N=8-10)
Hypothesis: An Oral, Selective ACTH Antagonist Will Have Utility in Treating Diseases of ACTH Excess

<table>
<thead>
<tr>
<th>Normal</th>
<th>Cushing’s Disease (CD)</th>
<th>Congenital Adrenal Hyperplasia (CAH)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagram" /></td>
<td><img src="image" alt="Diagram" /></td>
<td><img src="image" alt="Diagram" /></td>
</tr>
</tbody>
</table>

### Cause
- **ACTH-secreting pituitary tumor**
- **Inability to produce cortisol leads to loss of negative feedback & excess ACTH**

<table>
<thead>
<tr>
<th>US Prevalence (global incidence per 100,000)</th>
<th>ACTH Range = 5 – 60 pg/mL</th>
<th>ACTH Range = 20-200 pg/mL</th>
<th>ACTH Range = 150-500 pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>10k (2.5-3.8)</td>
<td></td>
<td>27k (6.7-10.0)</td>
<td></td>
</tr>
</tbody>
</table>

### 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**

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

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

**Pituitary Directed Agents to Suppress ACTH Secretion**
- Available: glucocorticoids, pasireotide, cabergoline
  - Limited efficacy
  - Safety issues
- In Development: CRF antagonists

**Adrenal Steroidogenesis Inhibitors**
- Available: ketoconazole, metyrapone/осилодростат
  - Limited Efficacy
  - Safety Issues
  - Low Adherence
- In Development: levoketoconazole

**Glucocorticoid Receptor Antagonist**
- Available: mifepristone
  - Efficacy difficult to assess
  - Safety issues
- In Development: relacorilant

CRN04894 is the Only ACTH Antagonist in Clinical Development

CRN04894 was carefully crafted by Crinetics in-house discovery team

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

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

Acute suppression of ACTH-induced corticosterone observed in rats

Experiment designed to mimic disease:
- CRN04894 orally administered
- Administer IV bolus of ACTH after 60 minutes
- Marked suppression of ACTH with increasing doses of CRN04894
- Analogous ACTH challenge in Phase 1 POC
CRN04894 SAD Study Design to Establish Pharmacologic Proof-of-Concept

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

**Study Goals**

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

**ACTH Challenge Test**

**Baseline (Day -1)**

- Blood draws for cortisol
- Basal t=-120', challenge t=0'

**Treated (Day 1)**

- Blood draws for cortisol
- Basal t=-120', t=0'

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

**Proof of concept:** dose dependent suppression of basal cortisol and ACTH-stimulated cortisol with CRN04894
PK Results: CRN04894 Showed Oral Bioavailability With Dose-Proportional Exposure

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

Data shown are mean±SEM
CRN04894 Rapidly Reduced Basal Cortisol Output from Adrenal Glands

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

Data shown are mean ± SEM

Full suppression of cortisol production assumes no more cortisol is produced at time of CRN04894 dose and cortisol half-life is 66 ±18 min from McKay LI, Cidlowski JA. Pharmacokinetics of Corticosteroids. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON); 2003
Dose-Dependent Suppression of Cortisol Observed Following Supra-Pathophysiologic ACTH Challenge (250 mcg)

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

Data shown are mean±SEM.
Clinically Meaningful Cortisol Suppression Observed in Response to Disease-relevant ACTH Challenge (1 mcg)

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

Data shown are mean±SEM
Conclusions from CRN04894 SAD Results

**Objectives**

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

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

**Achieved targeted pharmacokinetic profile**

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

**Demonstrated pharmacologic proof-of-concept for ACTH antagonism**

- Strong suppression of basal cortisol (56%)
- Dose-dependent, strong cortisol suppression (41%) following supra-pathophysiologic ACTH (250 mcg) challenge
- Maintains normal cortisol levels for the Phase 1 participants in face of disease-relevant ACTH (1 mcg) challenge
CRN04894: First-in-Class ACTH Antagonist for ACTH Driven Diseases

- Pituitary Gland
  - ACTH
  - ACTH Receptor Antagonist
    - CRN04894 in Phase 1
  - Pituitary Directed Agents to Suppress ACTH Secretion
    - Limited efficacy
    - Safety issues

- Adrenal Gland
  - Cortisol
  - Adrenal Steroidogenesis Inhibitors
    - Limited Efficacy
    - Safety Issues
    - Low Adherence

- Target Cells
  - GC Receptor Antagonist
    - Efficacy difficult to assess
    - Safety issues
## Pipeline With Two Candidates Beyond Pharmacologic Proof-of-Concept

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>Development Stage</th>
<th>Registralional Endpoint</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td><strong>Paltusotine (SST2 agonist)</strong></td>
<td>Preclin</td>
<td>Phase 1</td>
<td>Phase 2</td>
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<tr>
<td>Acromegaly</td>
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<td>Carcinoid Syndrome</td>
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<td>Nonfunctional NETs</td>
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<tr>
<td><strong>CRN04894 (ACTH antagonist)</strong></td>
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<tr>
<td><strong>CRN04777 (SST5 agonist)</strong></td>
<td>Preclin</td>
<td>Phase 1</td>
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<tr>
<td>Congenital Hyperinsulinism (CHI)</td>
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<td><strong>US TOTAL</strong></td>
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On Track to Achieve 2021 Goal of Three Programs with Proof-of-Concept Demonstrated in the Clinic

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
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</thead>
</table>
| **Paltusotine**  
SST2 Agonist for Acromegaly & NETs  
POC Achieved |  |  | Initiate PATHFNDR-1 ✓ | Initiate PATHFNDR-2 |
| **CRN04894**  
ACTH Antagonist for Cushing’s Disease & CAH  
POC Achieved |  | Initiate Phase 1 ✓ |  | Initiate Phase 2 NETs Trial in Carcinoid Syndrome |
| **CRN04777**  
SST5 Agonist for Congenital HI  
Phase 1 Underway |  | Initiate Phase 1 ✓ |  |  |

‘4777 program follows development strategy validated by paltusotine and ‘4894

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