



NEWS RELEASE

CRINETICS REPORTS TOP-LINE CRN04894 MAD RESULTS FROM PHASE 1 STUDY

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SAN DIEGO – May 25, 2022 – **Crinetics Pharmaceuticals, Inc.** (Nasdaq: CRNX), a clinical stage pharmaceutical company focused on the discovery, development and commercialization of novel therapeutics for rare endocrine diseases and endocrine-related tumors, today announced positive results from the multiple-ascending dose (MAD) portion of a first-in-human Phase 1 clinical study of CRN04894, the company's first-in-class, investigational, oral, nonpeptide adrenocorticotrophic 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 design of our Phase 1 healthy volunteer study allowed us to demonstrate CRN04894's potent pharmacologic activity in the presence of ACTH levels that were in similar range to those seen in CAH and Cushing's disease patients," said **Alan Krasner, M.D.**, Crinetics' chief medical officer. "The observation of dose-dependent reductions in serum cortisol levels to below the normal range even in the presence of high ACTH indicates that CRN04894 was effective in blocking the key receptor responsible for regulating cortisol secretion. We believe this is an important finding that may be predictive of CRN04894's efficacy in patients."

ACTH is the key regulator of the hypothalamic-pituitary adrenal (HPA) axis controlling adrenal activation. It is regulated by cortisol via a negative feedback loop that acts to inhibit ACTH secretion. This feedback loop is dysregulated in diseases of excess ACTH. In Cushing's disease, a benign pituitary tumor drives excess ACTH secretion even in the presence of excess cortisol. While in CAH, an enzyme deficiency results in excess androgen synthesis without normal cortisol synthesis, allowing unchecked ACTH production and requiring lifelong

glucocorticoid use. In both diseases, excess ACTH drives over-stimulation of the adrenal gland and leads to a host of symptoms including infertility, adrenal rest tumors, and metabolic complications in CAH and, in Cushing's disease, symptoms include hypertension, central obesity, neuropsychiatric disorders and metabolic complications. To our knowledge, no other ACTH antagonists are currently in clinical development for diseases of ACTH excess such as Cushing's disease or CAH.

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.

"Due to its central position in HPA axis, ACTH is the obvious target for inhibiting excessive stimulation of the adrenal in diseases of ACTH excess. Even though the field of endocrinology has known about its clinical significance for more than 100 years, we are not aware of any other ACTH antagonist that has entered clinical development. This is an important milestone for endocrinology and for our company." said **Scott Struthers, Ph.D.**, founder and chief executive officer of Crinetics. "We are very excited to initiate patient studies in Cushing's disease and CAH with CRN04894, which will be our third home-grown NCE to demonstrate pharmacologic proof-of-concept and enter patient trials."

Crinetics plans to present additional details of safety, efficacy, and biomarker results from the CRN04894 Phase 1 study at an endocrinology-focused medical meeting in 2022.

Data Review Conference Call

Crinetics will hold a conference call and live audio webcast today, May 25, 2022, at 8:00 a.m. Eastern Time to discuss results from the MAD cohorts of the Phase 1 study of CRN04894. To participate, please dial 1-877-407-0789 (domestic) or 1-201-689-8562 (international) and refer to conference ID 13730000. To access the webcast, click [here](#). Following the live event, a replay will be available on the **Events** page of the Company's website.

About the CRN04894 Phase 1 Study

Crinetics has completed enrollment of the 88 healthy volunteers in this double-blind, randomized, placebo-controlled Phase 1 study. Participants were divided into multiple cohorts in the single ascending dose (n=39) and multiple ascending dose (n=49) portions of the study. In both the SAD and MAD portions of the study, safety and pharmacokinetics were assessed. In addition, pharmacodynamic responses were evaluated before and after challenges with injected synthetic ACTH to assess pharmacologic effects resulting from exposure to CRN04894.

About CRN04894

Adrenocorticotrophic hormone (ACTH) is synthesized and secreted by the pituitary gland and selectively binds to its receptor melanocortin type 2 receptor (MC2R), which is selectively expressed in the adrenal gland. This interaction of ACTH with MC2R activates the adrenal and results in production of cortisol, a stress hormone that is involved in the regulation of many physiologic systems. These include the regulation of blood sugar levels, metabolism, inflammation, blood pressure, and memory formulation. Diseases associated with excess of ACTH, therefore, can have significant impact on physical and mental health. Cushing's disease is characterized by chronically elevated cortisol levels caused by tumors that secrete excess ACTH and do not respond to negative feedback by even elevated glucocorticoid levels, resulting in hypertension, central obesity, neuropsychiatric disorders, and metabolic complications among other troubling symptoms. Congenital adrenal hyperplasia is caused by an enzyme deficiency in the normal cortisol synthesis pathway, resulting in a shunting of precursors to the formation of excess adrenal androgens. Excess adrenal androgen production can result in hirsutism, menstrual dysfunction, infertility in men and women, acne, cardiometabolic comorbidities and insulin resistance. Crinetics' ACTH antagonist, CRN04894, has exhibited strong binding affinity for MC2R in preclinical models and demonstrated suppression of adrenally derived glucocorticoids and androgens that are under the control of ACTH.

About Crinetics Pharmaceuticals

Crinetics Pharmaceuticals is a clinical stage pharmaceutical company focused on the discovery, development, and commercialization of novel therapeutics for rare endocrine diseases and endocrine-related tumors. The company's lead product candidate, **paltusotine**, is an investigational, oral, selective nonpeptide somatostatin receptor type 2 (SST2) biased agonist for the treatment of acromegaly, an orphan disease affecting more than 26,000 people in the United States. A Phase 3 clinical program in acromegaly with paltusotine is underway. Crinetics Pharmaceuticals is also developing paltusotine for the treatment of carcinoid syndrome associated with neuroendocrine tumors. The company is developing **CRN04777**, an investigational, oral, nonpeptide somatostatin receptor type 5 (SST5) agonist for congenital and other forms of hyperinsulinism, as well as CRN04894, an investigational, oral, nonpeptide adrenocorticotrophic hormone (ACTH) antagonist for the treatment of congenital adrenal hyperplasia, Cushing's disease and other diseases of excess ACTH. All of the company's drug candidates are new chemical entities resulting from in-house drug discovery efforts.

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 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 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.

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