CRN04894: An Oral, Nonpeptide ACTH (MC2) Receptor Antagonist Decreased Basal and Stimulated Cortisol Secretion in Healthy Volunteers

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INTRODUCTION

- CRN04894 is a potent, orally bioavailable, nonpeptide melanocortin type 2 receptor (MC2R) antagonist that is >1000-fold selective for MC2R (exclusively expressed in the adrenal cortex) over other MCR subtypes
- This presentation reports the results of the first-in-human study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of CRN04894

DESIGN

- Phase 1, in-patient, Single Ascending Dose (SAD) and Multiple (10 day) Ascending Dose (MAD), double-blinded, placebo-controlled trial in healthy volunteers (male and female, age 18-55 y)
- SAD cohorts: 6 active, 2 placebo; MAD cohorts: 6 active, 3 placebo

Single ascending dose (250 µg ACTH test)

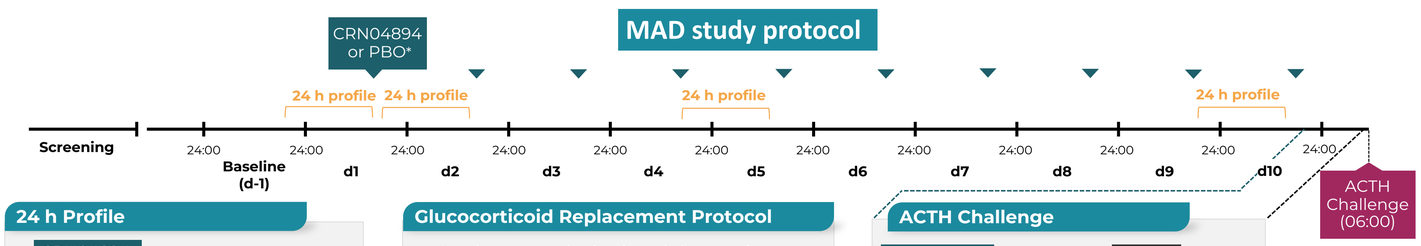
SAD1 10 mg at 08:00 h → SAD2 20 mg at 08:00 h → SAD3 40 mg at 08:00 h → SAD4 80 mg at 08:00 h → SAD5 80 mg at 08:00 h

Multiple ascending dose (1 µg ACTH test)

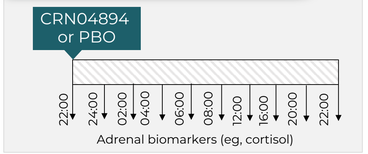
MAD1 40 mg at 08:00 h → MAD2 40 mg at 22:00 h → MAD3 60 mg at 22:00 h → MAD4 80 mg at 22:00 h → MAD5 40 mg BID at 08:00 h and 22:00 h

1 µg ACTH test cohort

MAD study protocol



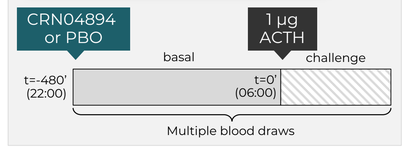
24 h Profile



Glucocorticoid Replacement Protocol

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

ACTH Challenge



*Timing of dosing cohort dependent.

RESULTS

Safety (combined SAD and MAD)

No serious adverse events (AEs); all AEs considered mild or moderate

Most Frequent TEAEs, n (%)*	CRN04894 (N=63)	Placebo (N=25)
Glucocorticoid deficiency	11 (17.5)	1 (4.0)
Headache	5 (7.9)	5 (20.0)
Contact dermatitis	5 (7.9)	0
COVID-19	3 (4.8)	1 (4.0)
URTI	3 (4.8)	1 (4.0)
Anxiety	2 (3.2)	1 (4.0)
Erythema	2 (3.2)	0
Palpitations	2 (3.2)	1 (4.0)
Pruritus	2 (3.2)	0

*Treatment-Emergent Adverse Events (TEAEs) in ≥2 CRN04894-treated patients.

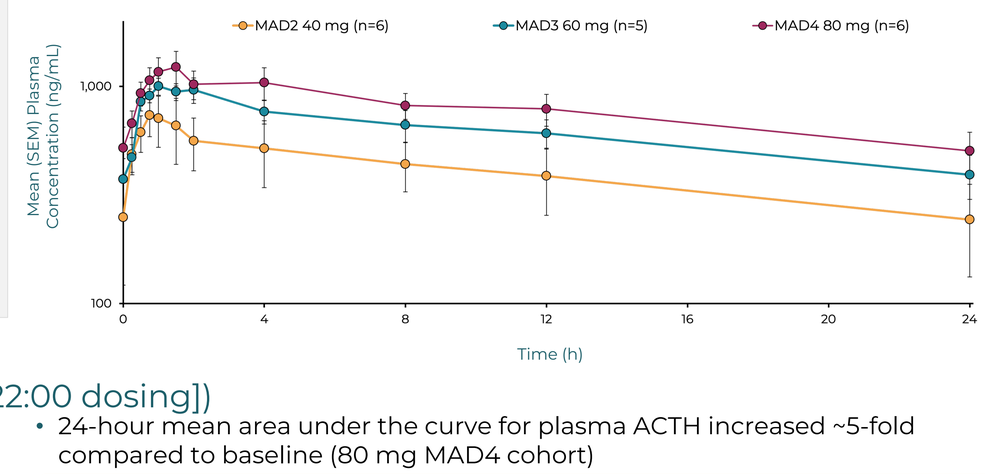
- As expected, glucocorticoid deficiency, defined as 08:00 h cortisol level <5 µg/dL, was the most common treatment-related AE and seen only in MAD cohorts (8 during dosing, 4 after completion of dosing)
  - These patients experienced no symptoms suggestive of clinical adrenal insufficiency
  - Physiologic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

Pharmacokinetics (MAD 2, 3, and 4 cohorts [22:00 dosing])

Steady State PK

- Oral bioavailability
- Half-life of ~24 h
- Rapidly absorbed with a t_{max} of ~1-2 h
- Dose proportional exposure
- PK profile is consistent morning, nighttime, or twice-daily dosing

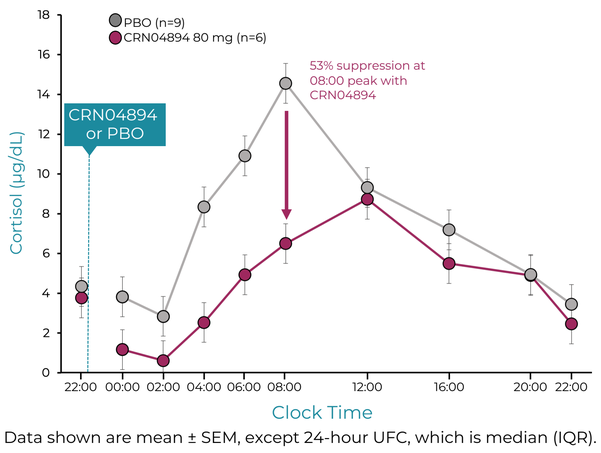
Concentration-Time Profile at Steady State (Day 10)



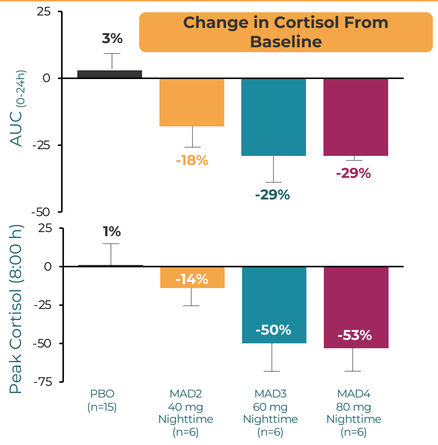
Pharmacodynamics (MAD 2, 3, and 4 cohorts [22:00 dosing])

- Dose-dependent suppression of serum and urinary free cortisol
- 24-hour mean area under the curve for plasma ACTH increased ~5-fold compared to baseline (80 mg MAD4 cohort)

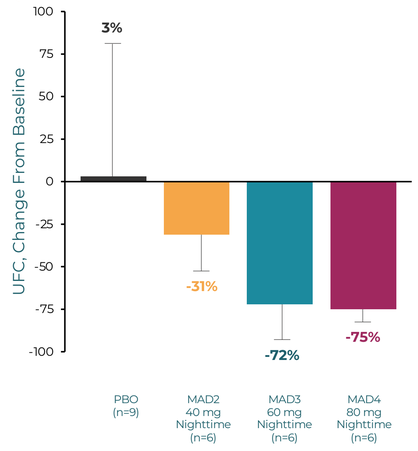
Cortisol Profiles (Day 9)



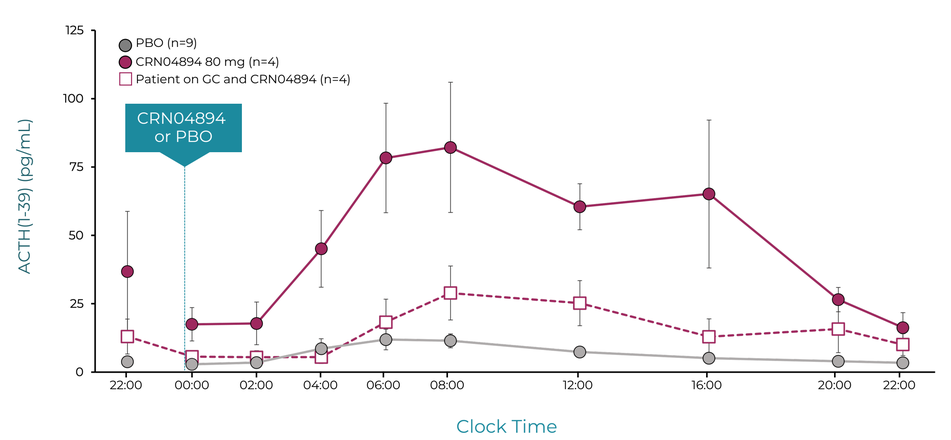
Change in Cortisol From Baseline



24-Hour UFC (Day 9)



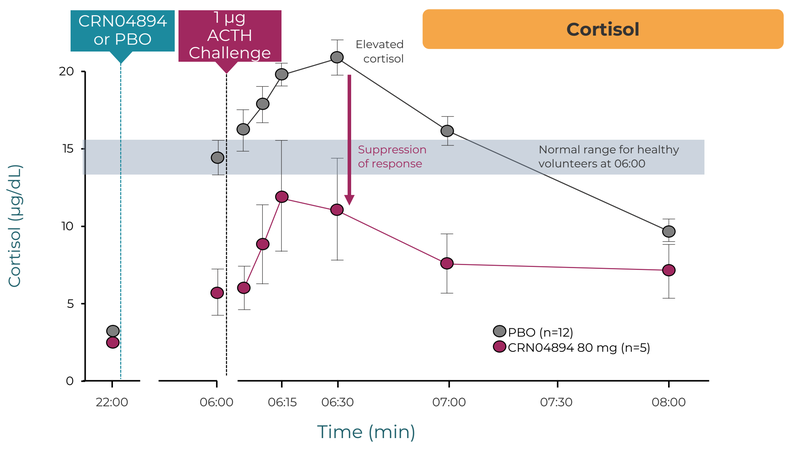
ACTH Profiles (Day 9)



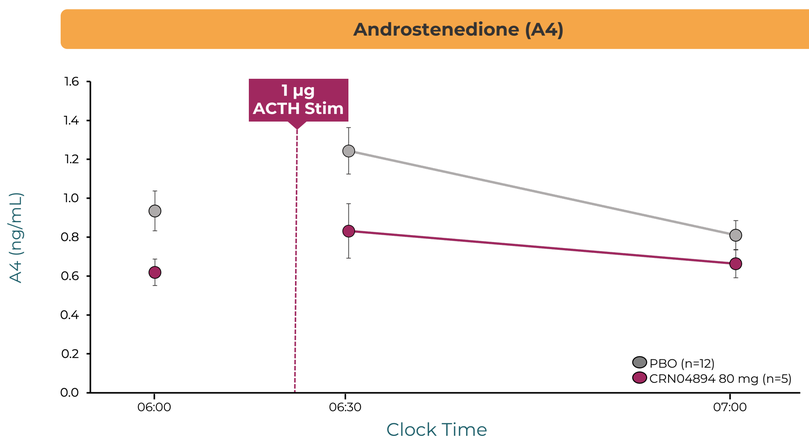
Data shown are mean ± SEM, except 24-hour UFC, which is median (IQR).

ACTH Challenge

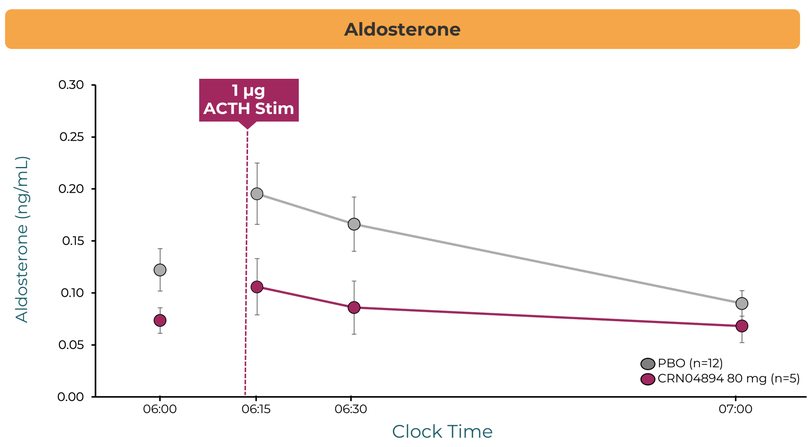
Cortisol



Androstenedione (A4)



Aldosterone



- In the 80-mg cohort (MAD4), the median peak cortisol in response to the Day 11, one µg ACTH stimulation test was 12 µg/dL (330 nmol/L) and in all patients was <18 µg/dL (500 nmol/L)

CONCLUSIONS

SAFETY

- CRN04894 was well tolerated in healthy volunteers

PHARMACOKINETICS

- Rapidly absorbed after oral administration (t_{max} ~1-2 h)
- Dose proportional increases in exposure from 10 to 80 mg
- Half-life of approximately 24 hours, expected to be suitable for once-daily dosing

PHARMACODYNAMICS

- Dose-dependent suppression of adrenocortical function (serum cortisol, 24-h urinary free cortisol, androstenedione, and aldosterone) in healthy volunteers
- Negative feedback-induced rise in plasma ACTH, with no evidence of loss of efficacy

Patients treated with 80 mg for 10 days had a biochemical picture compatible with insidious primary adrenal failure.

Phase 2 trials are currently under development for patients with classical congenital adrenal hyperplasia and ACTH-dependent Cushing's syndrome.

Acknowledgments

This study was funded by Crinetics Pharmaceuticals, Inc. We thank the trial participants and drug discovery and development professionals who made this study possible. Editorial assistance was provided under the direction of the authors by Synchrony Medical Communications, LLC, West Chester, PA, USA, and funded by Crinetics Pharmaceuticals, Inc.

Disclosures

PJT, CF-C, AA, RL, SM, YW, RSS, SFB, and AK are employees of Crinetics Pharmaceuticals, Inc. MH-I is an employee of QPS Miami.

Society for Endocrinology BES 2022 | 14–16 November, 2022 | Harrogate, England

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