

INHIBITION OF BASAL AND ACTH-STIMULATED CORTISOL SECRETION IN HUMANS USING AN ORAL, NONPEPTIDE ACTH ANTAGONIST (CRN04894)

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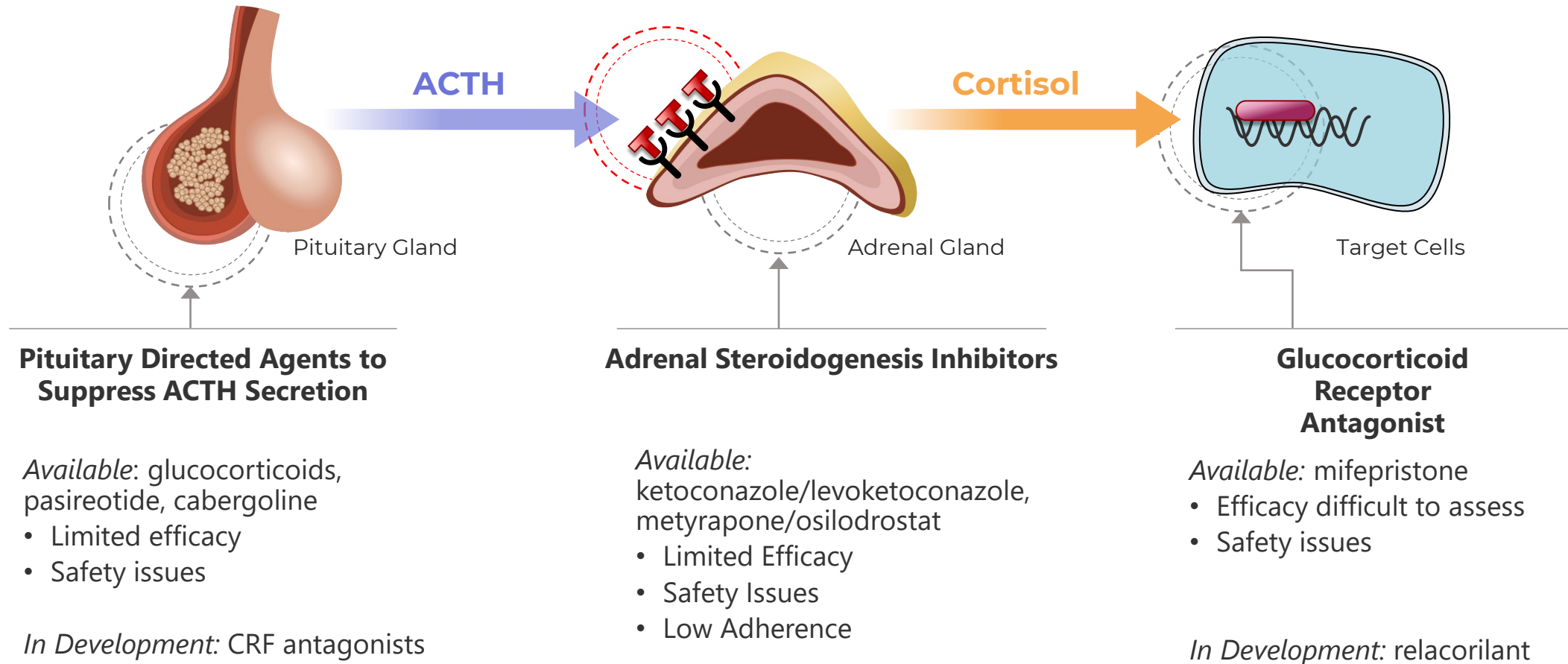
Disclosures

Crinetics Pharmaceuticals, Inc. is the sponsor and source of funding for the study of its investigational compound, CRN04894

- All other authors listed, except M. Hernandez-Illas and A. Madan, are employees of Crinetics
- A. Madan was an employee and is currently a consultant for Crinetics

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

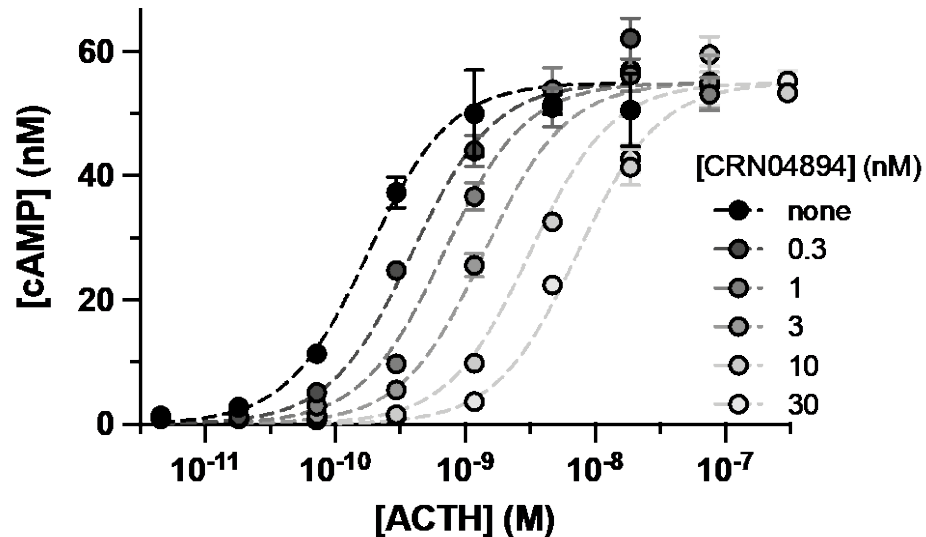
All currently approved therapies and agents in development act upstream or downstream of ACTH



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

CRN04894: Preclinical Evidence for ACTH Antagonism

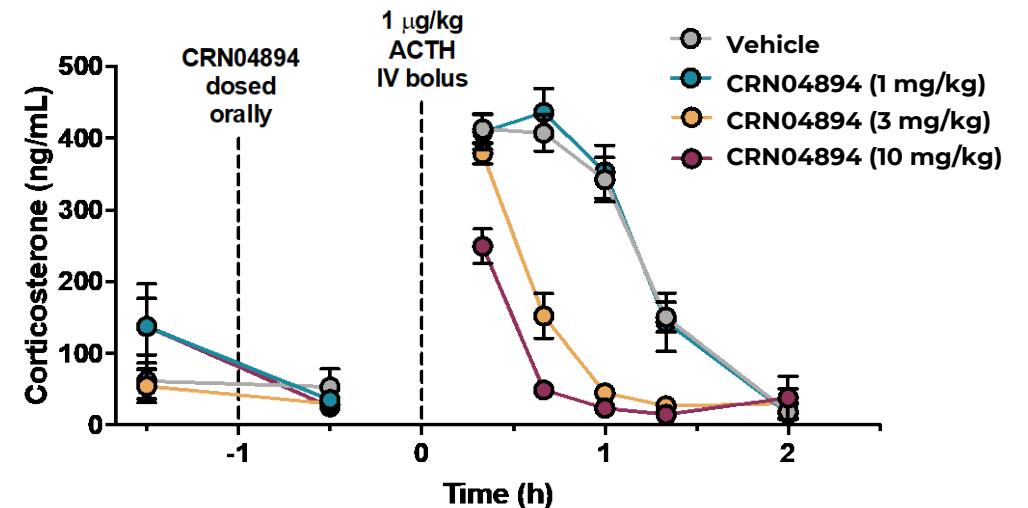
CRN04894 is a potent ($K_b = 0.4$ nM) competitive antagonist of ACTH signaling



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



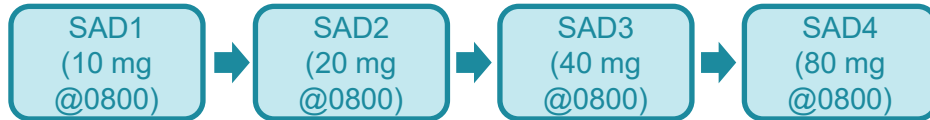
Experiment designed to mimic disease:

- 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

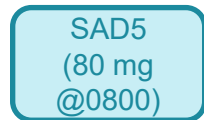
Phase 1, Randomized, Double Blind, Placebo-controlled SAD/MAD Trial in Healthy Volunteers

Design

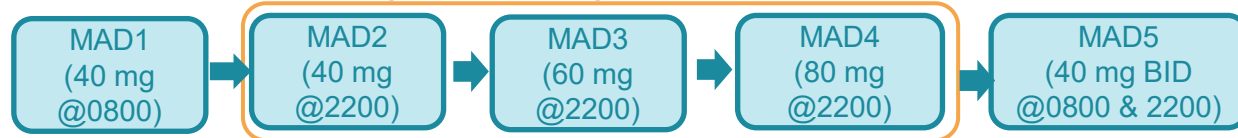
Single ascending dose (250 mcg ACTH stim)



Additional PD Cohorts (1 mcg ACTH stim)



Multiple ascending dose (1 mcg ACTH stim)



Objectives

Safety & tolerability

Pharmacokinetics

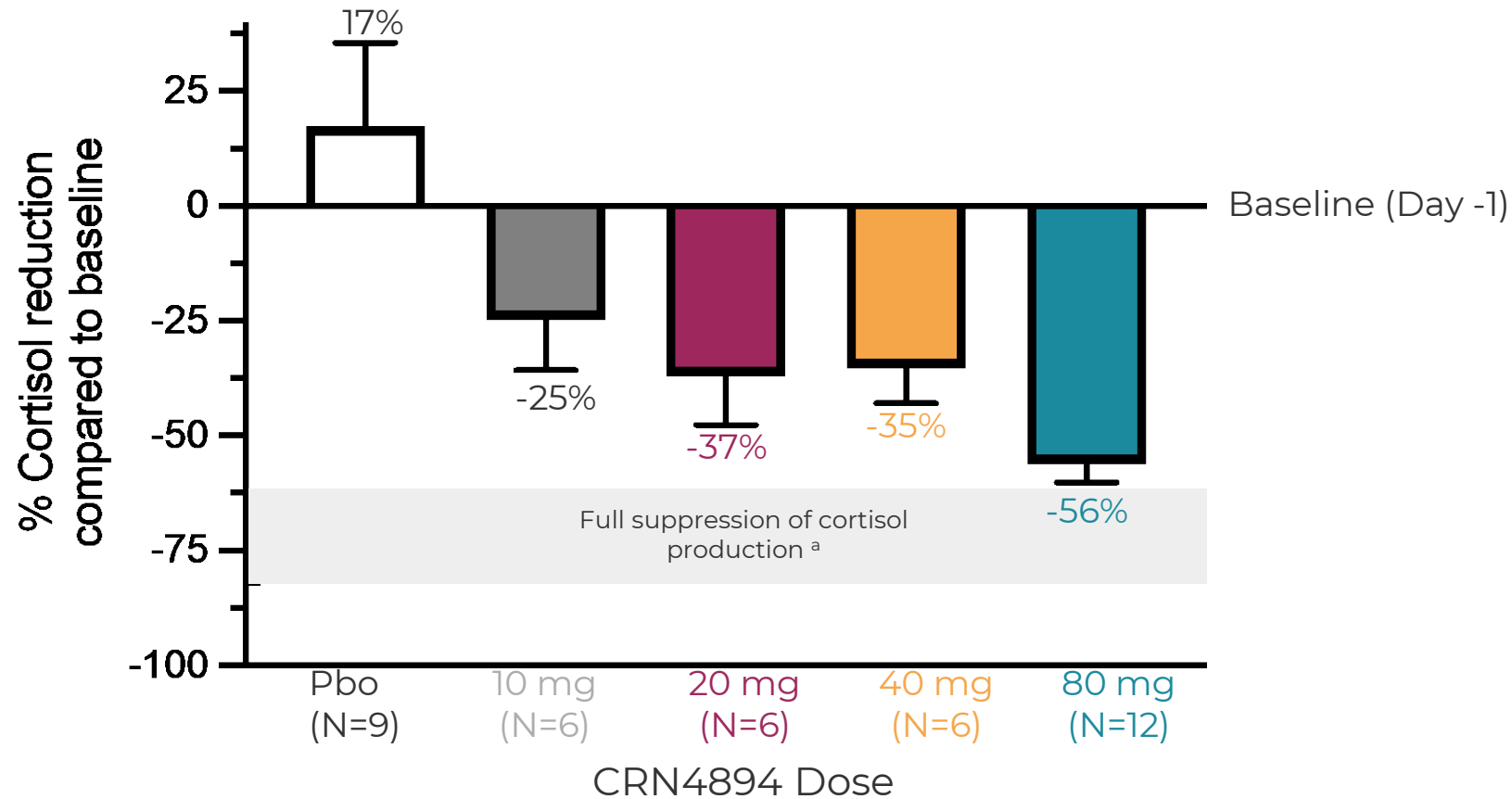
- After first dose and at steady state
- Daily pre- and post-dose

Pharmacodynamics

- Serum cortisol, 24 hr. UFC, ACTH, A4, aldosterone
 - 24h circadian sampling: Baseline & multiple occasions postdose
 - ACTH stimulation tests performed in SAD and MAD

Single Doses of CRN04894 Rapidly Reduced Basal Cortisol Secretion from Adrenal Glands

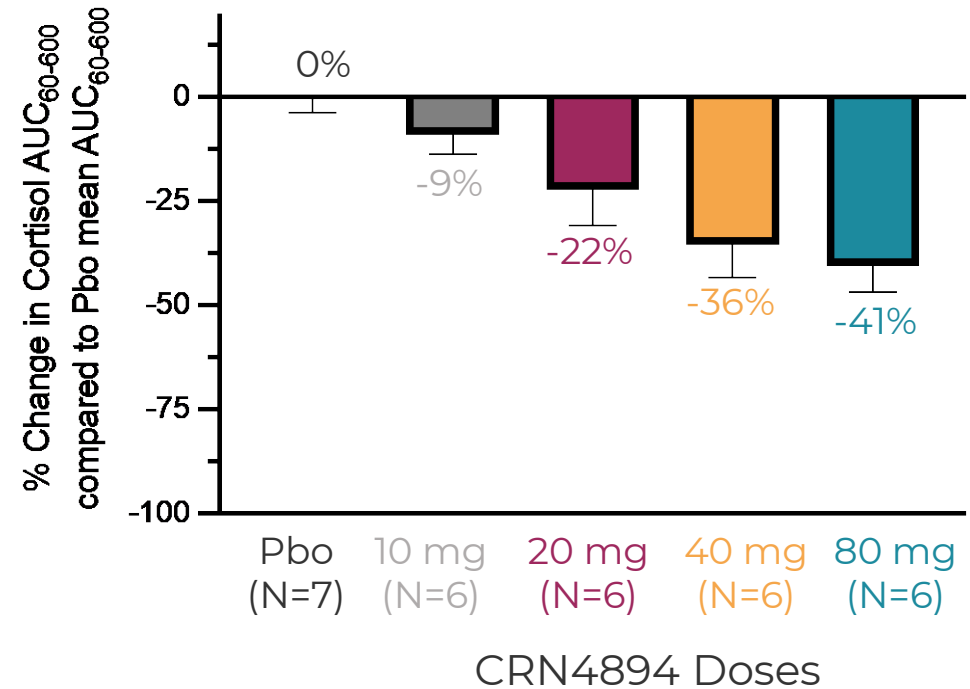
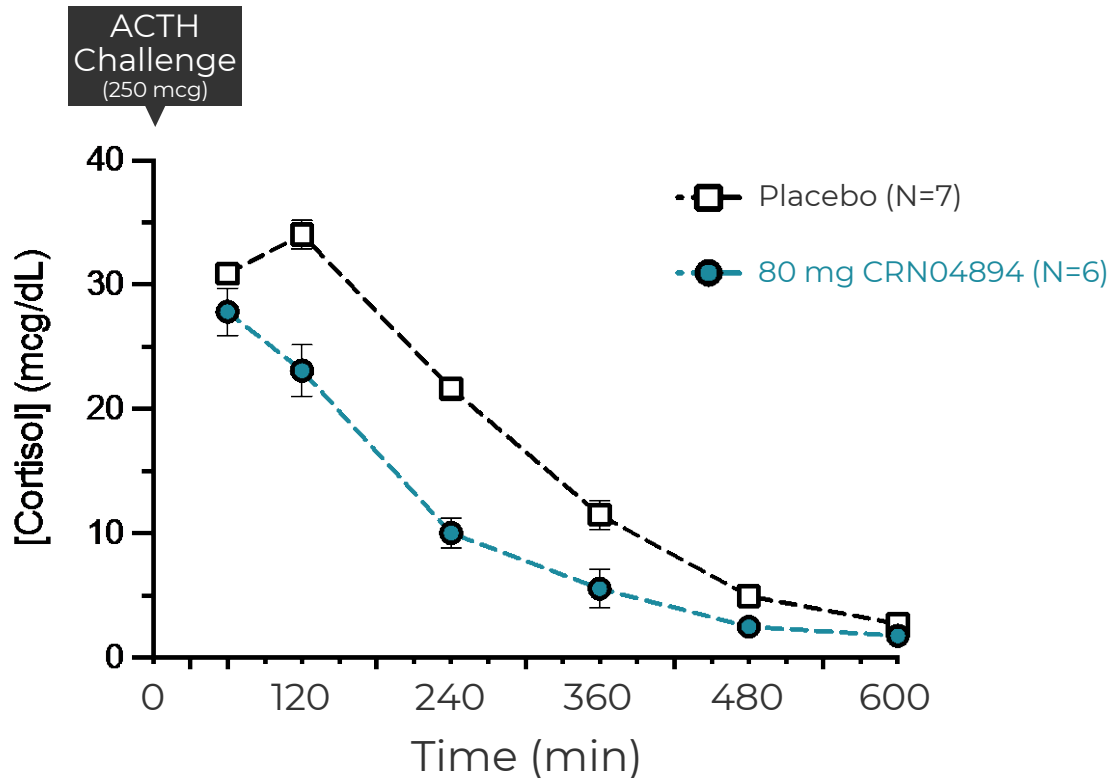
Acute reduction of basal cortisol (56% @ 80 mg) 2 hours after administration of CRN04894



Data shown are mean \pm SEM.

^a 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.

Single Doses of CRN04894 Resulted in Dose-Dependent Suppression of Cortisol Observed Following Pharmacologic Dose ACTH Challenge (250 mcg)



Data shown are mean ± SEM.

Safety Summary—Combined SAD and MAD

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.

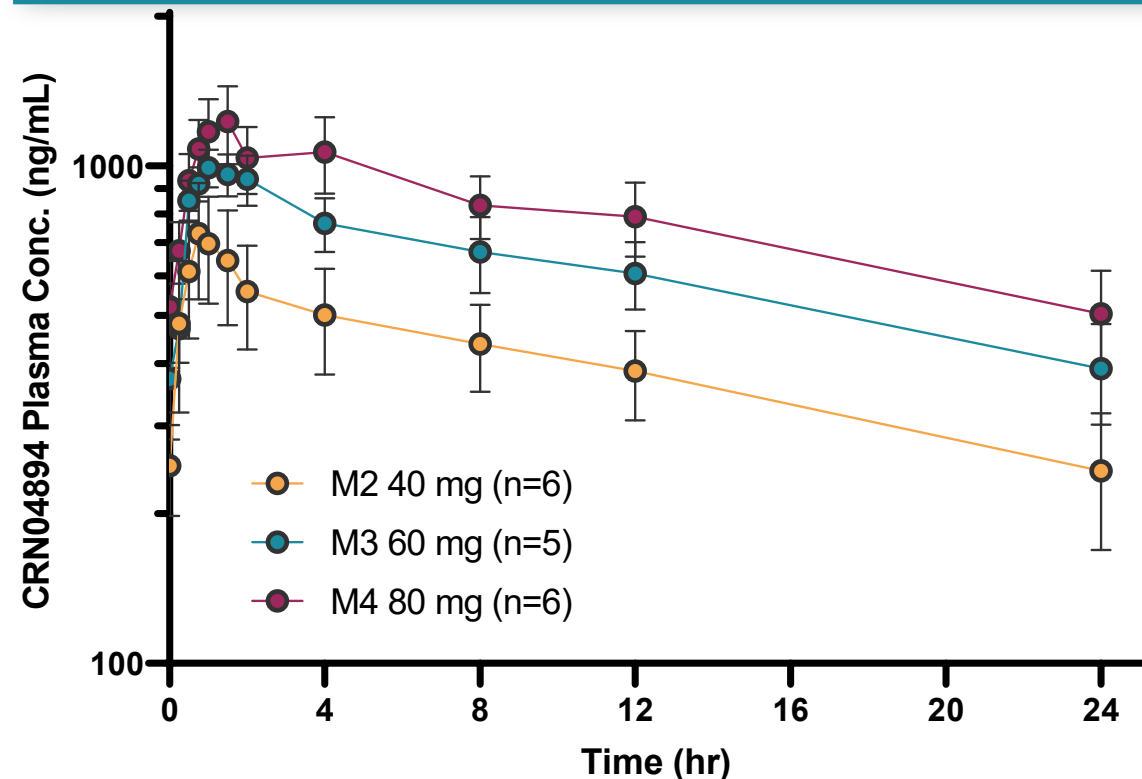
Pharmacokinetics of Night-Time (10 pm/2200) Dosing Cohorts in the MAD Portion of the Study

MAD PK consistent with expectations from SAD data at the same doses

Steady State PK

- Oral bioavailability
- 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

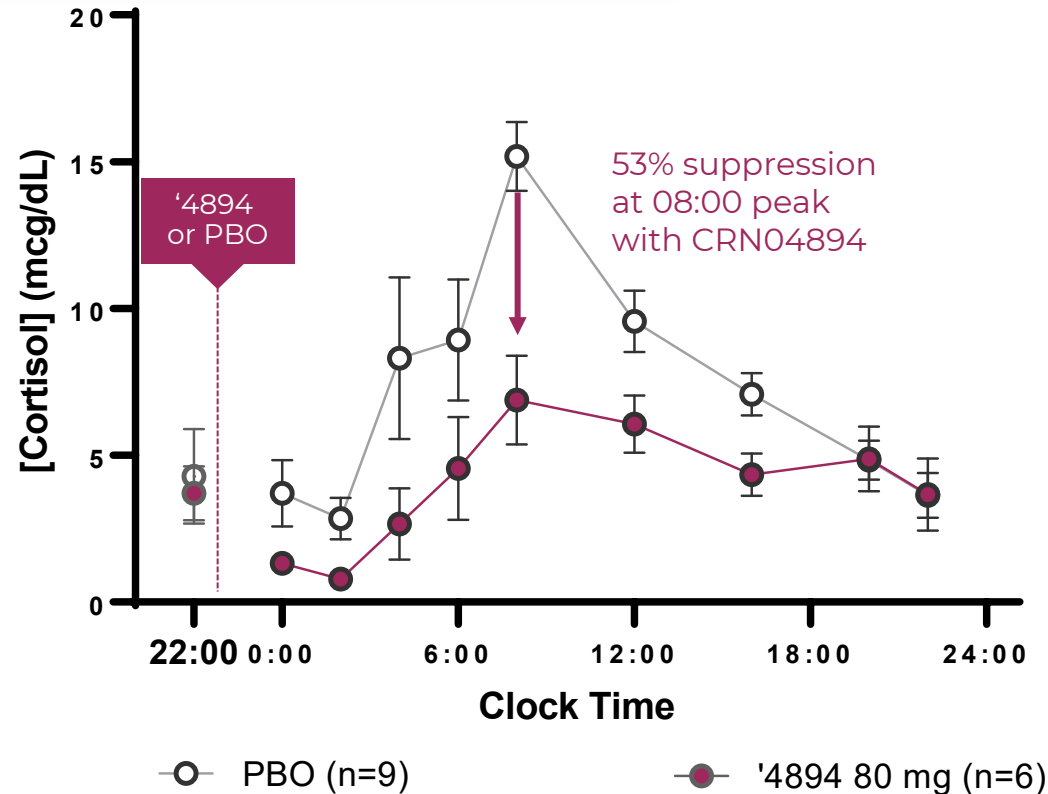
Concentration-Time Profile at Steady State (Day 10)



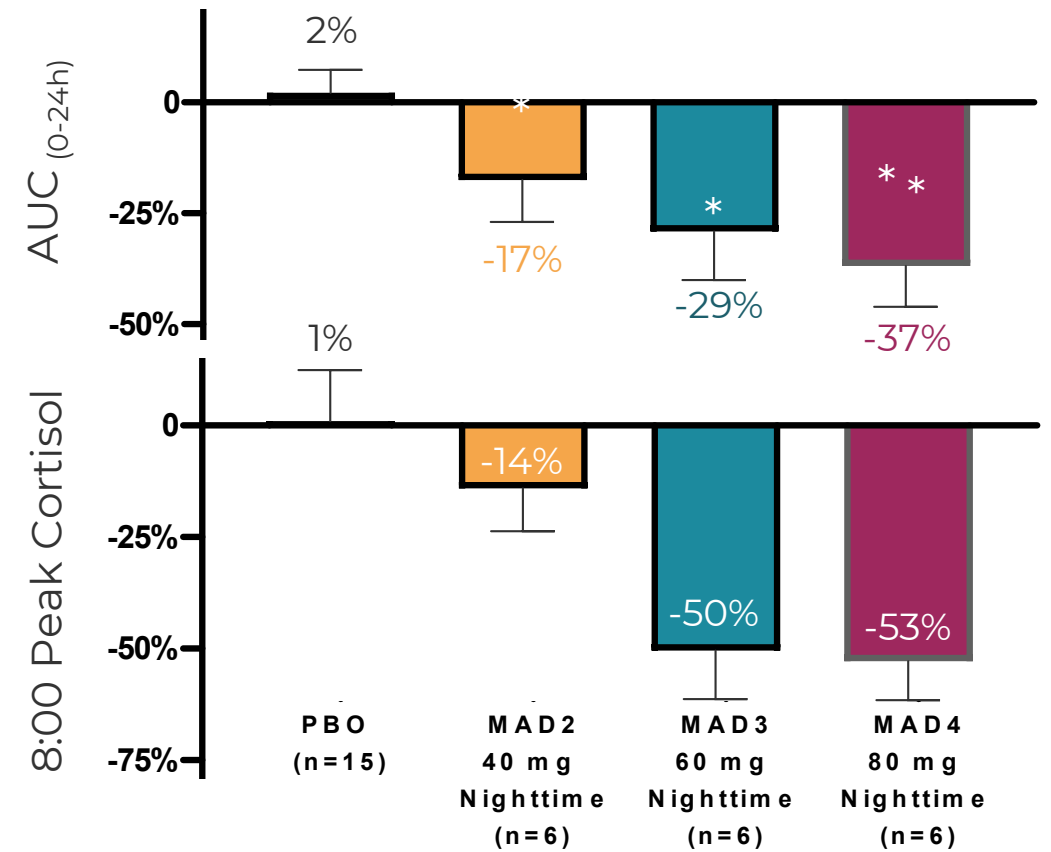
Data shown are mean \pm SEM. N=1 subject was an outlier and excluded in 60 mg cohort; MAD: Multiple-ascending dose; SAD: Single-ascending dose; PK: Pharmacokinetics; BID: Twice daily.

Dose-Dependent Suppression of Serum Cortisol Below Normal Levels

Day 9 Cortisol Profiles



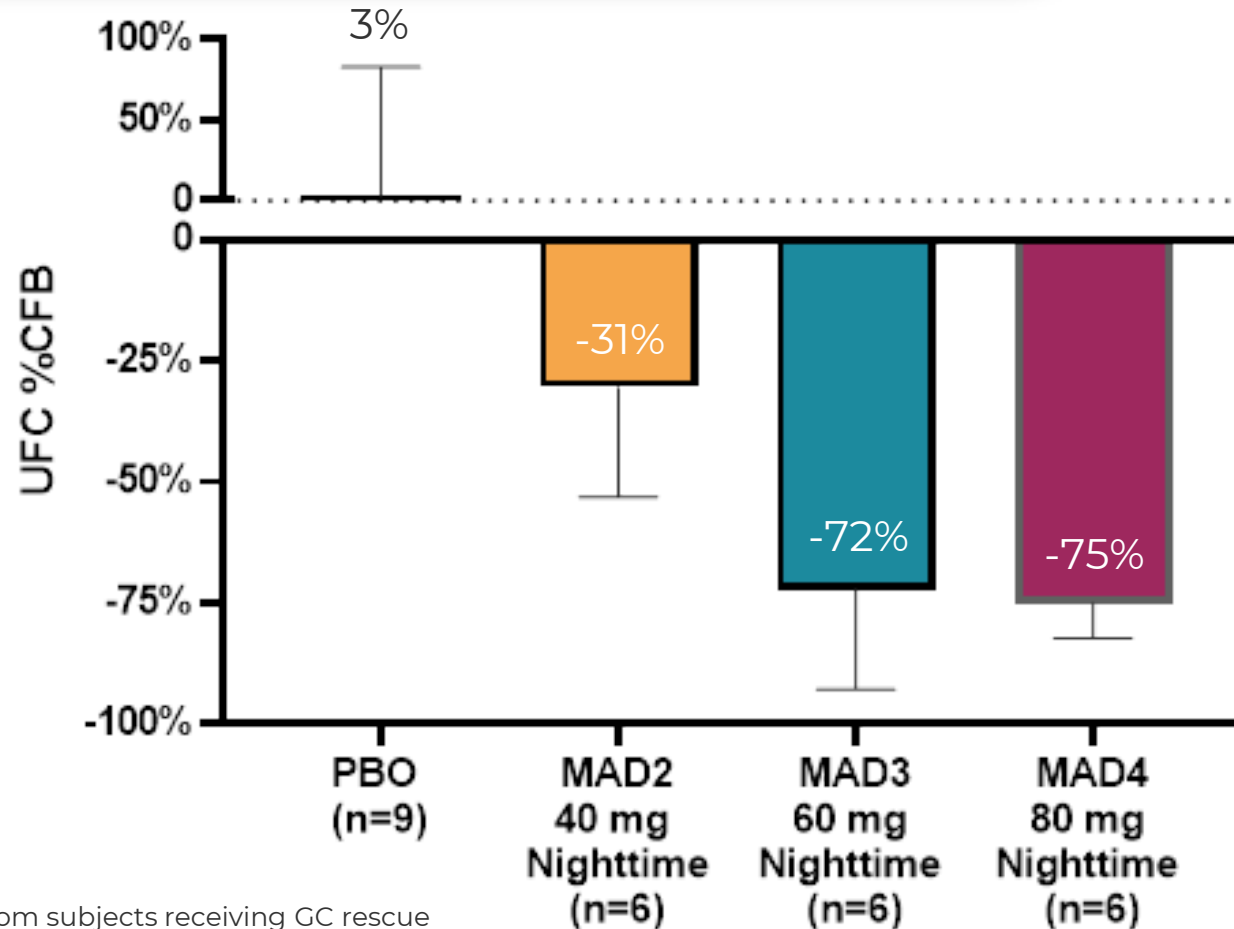
Change in Cortisol from Baseline



Data shown are mean \pm 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.

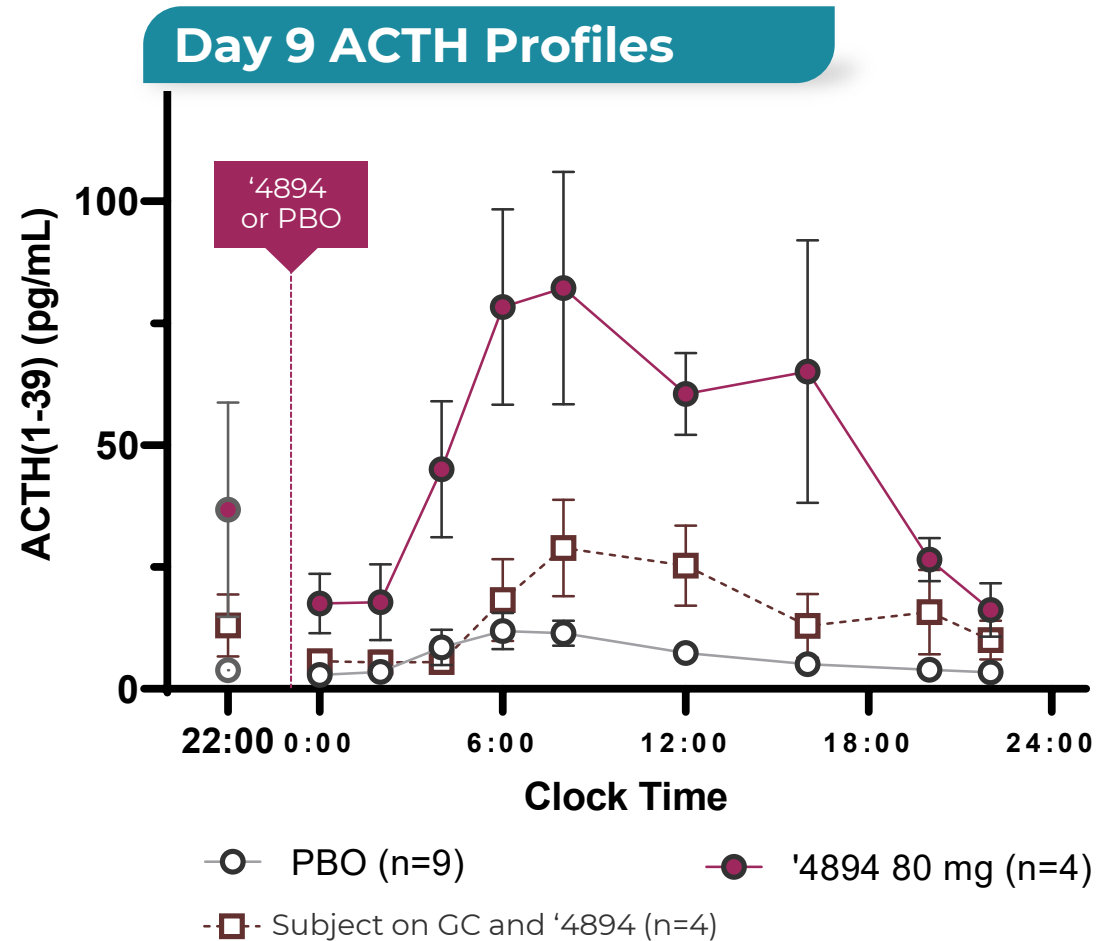
CRN04894 Potently Suppressed Adrenal Activity as Measured by Urinary Free Cortisol

24-Hour Urinary Free Cortisol (day 9)



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

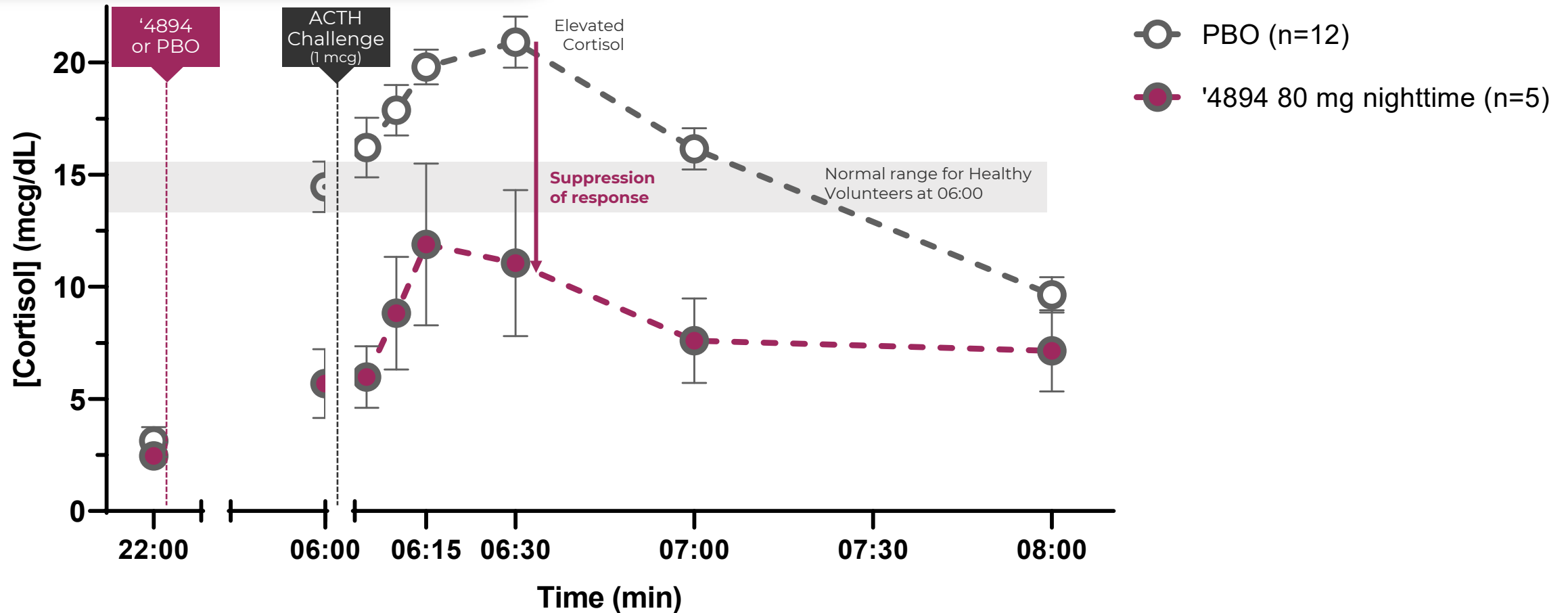
Loss of Cortisol Negative Feedback Resulted in HV ACTH Comparable to That Seen in Disease States



Data shown are mean \pm 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 Paediatr Scand* 1981, 3. NBIX ENDO Online 2020 presentation; HV: Healthy volunteer PBO: Placebo; GC: glucocorticoid.

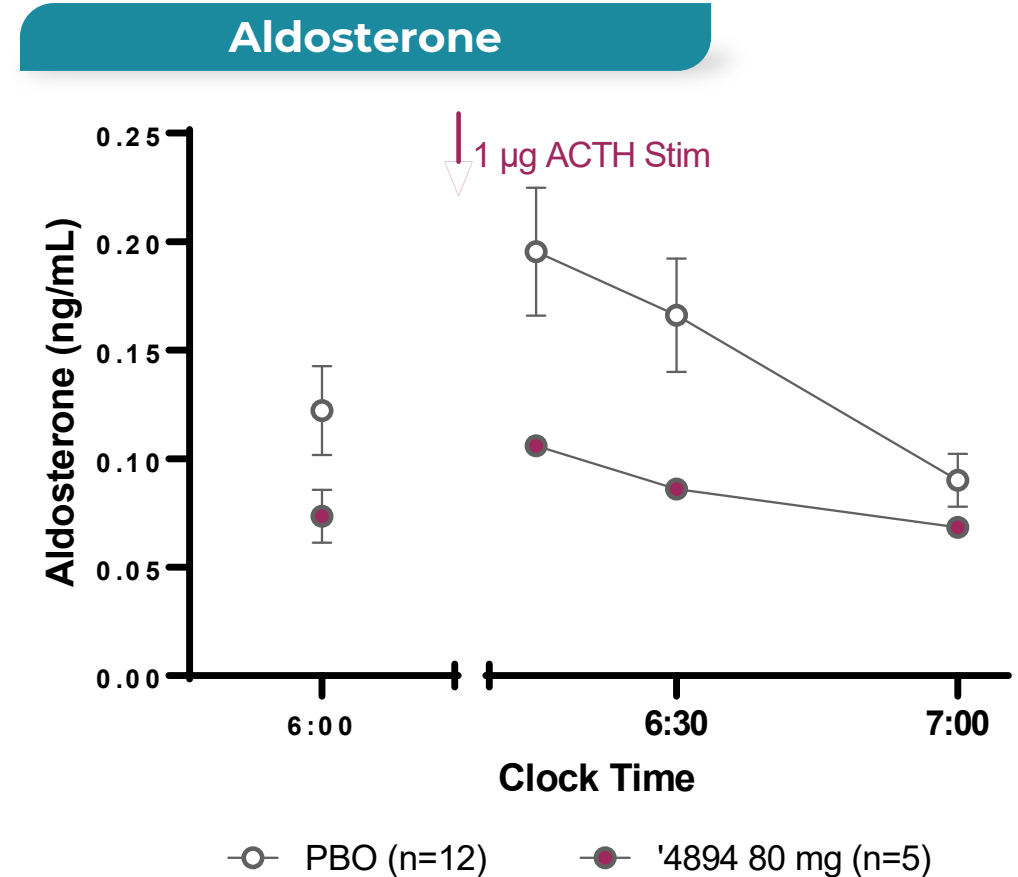
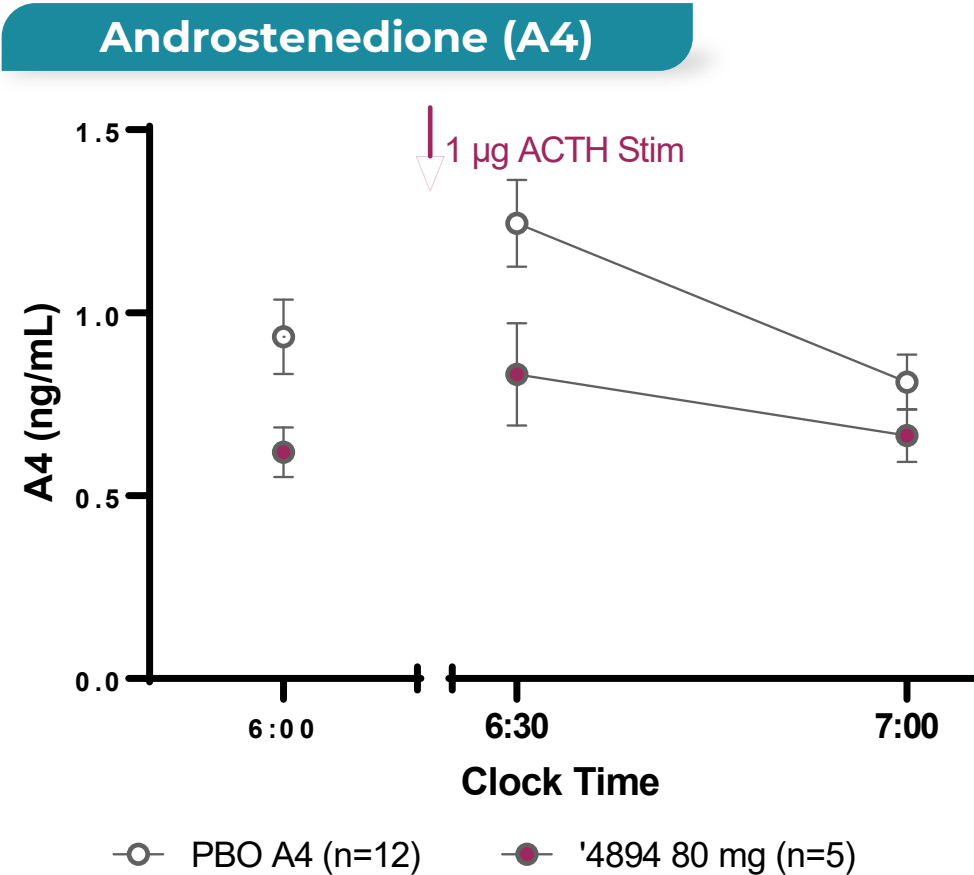
CRN04894 Maintained Cortisol Below Normal Levels After ACTH Challenge Test on Top of Sustained Elevated ACTH

ACTH Challenge



Data shown are mean \pm SEM; one subject in 80 mg MAD arm did not receive ACTH challenge.

Suppression of Basal and ACTH Stimulated Androstenedione and Aldosterone



Data shown are mean \pm SEM. One subject in 80 mg MAD arm did not receive an ACTH challenge at end of study.

Conclusions

- Safety:
 - CRN04894 was well tolerated in healthy volunteers
- Pharmacokinetic profile:
 - Rapidly absorbed after oral administration (t_{\max} ~1-2 hrs)
 - Dose proportional increases in exposure from 10 to 80 mg
 - Half-life of ~24 hours, expected to be suitable for once daily dosing
- Pharmacodynamics:
 - Dose-dependent suppression of adrenal function (serum cortisol, 24 hr. UFC, androstenedione, aldosterone) in healthy volunteers
- Phase 2 trials currently under development for patients with classic Congenital Adrenal Hyperplasia and ACTH dependent Cushing's syndrome

Acknowledgements

Thank you to the clinical trial volunteers and the drug discovery and development professionals who made this study possible