CRN04894, AN ORAL NONPEPTIDE ACTH RECEPTOR ANTAGONIST, REVERSES ACTH-STIMULATED GLUCOCORTICOID SECRETION IN RODENTS AND HUMANS

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Disclosures

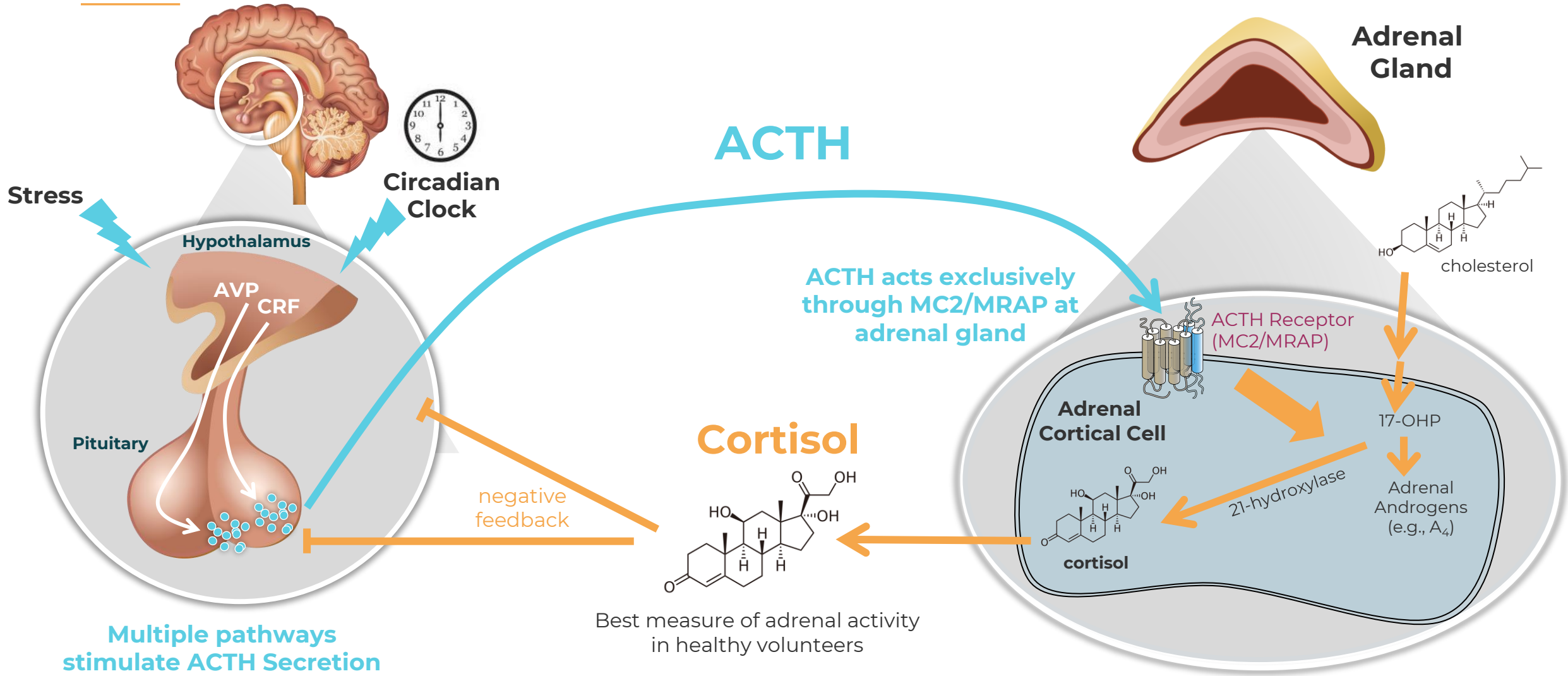
Crinetics Pharmaceuticals, Inc. is the sponsor and source of funding for the study of its investigational compound, CRN04894

- All authors are employees & stockholders in Crinetics Pharmaceuticals except A. Madan who was an employee and is currently a consultant for Crinetics

Cortisol conversion factor

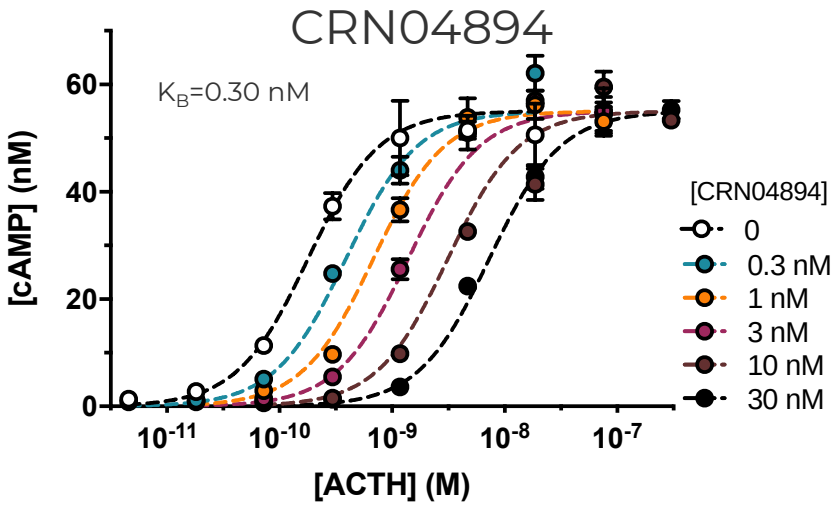
1 mcg/dl = 27.59 nmol/l

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

Potent and Selective MC2R Antagonist, CRN04894, Identified in In Vitro Assays



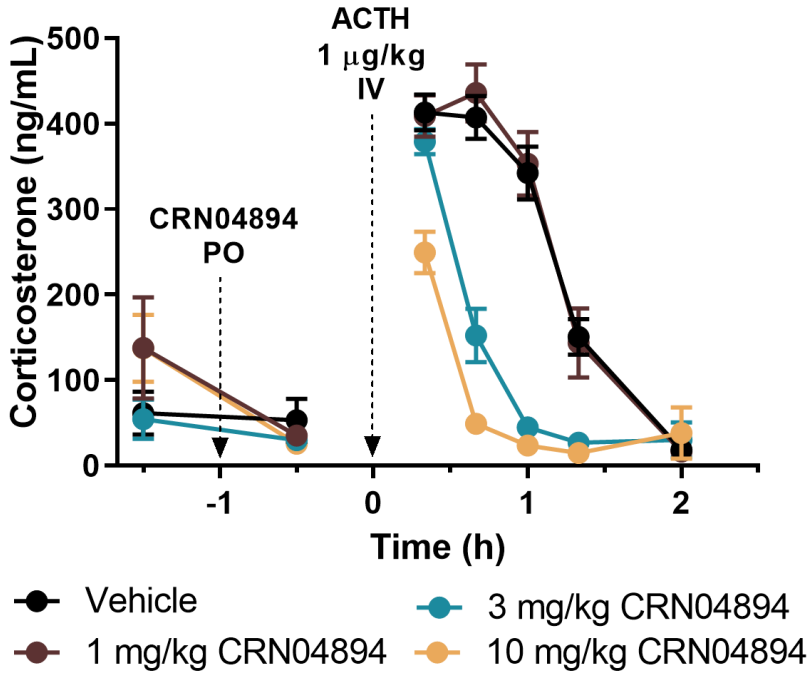
Compound	Human						Rat	Dog
	MC2R		MC1R	MC3R	MC4R	MC5R	MC2R	MC2R
	K_B (nM)[a]	K_i (nM)[b]	IC_{50} (nM)[c]	IC_{50} (nM)[c]	IC_{50} (nM)[c]	IC_{50} (nM)[c]	K_B (nM)[a]	K_B (nM)[a]
CRN04894	0.34	2.1	>10,000	>1,000	>10,000	>1,000	0.23	0.25

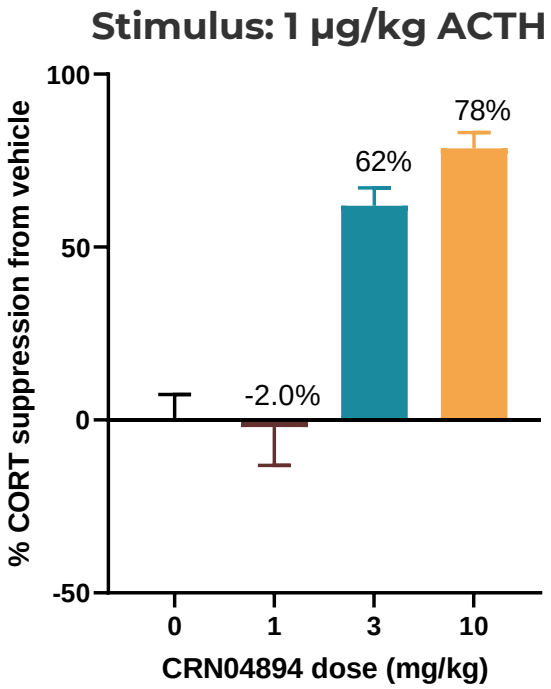
[a] avg equilibrium binding constant calculated from functional cell-based assays that measure the inhibition of ACTH-induced cellular cAMP levels
[b] avg equilibrium inhibitory constant calculated from the ability of compound to block binding of the radiolabeled ACTH to MC2R-containing membranes
[c] half-maximal inhibitory concentration of compound required to block binding of the radiolabeled α-MSH to MCR-containing membranes

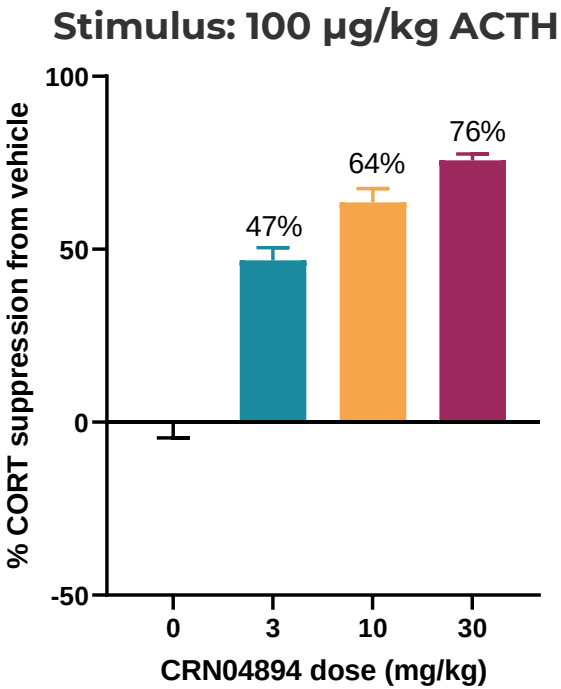
CRN04894 Suppresses ACTH-stimulated Corticosterone in Rats

Single oral administration of ≥3 mg/kg CRN04894 suppressed ACTH (1 µg/kg)-stimulated corticosterone in Sprague Dawley rats

- Higher dose of CRN04894 required to achieve >50% suppression of corticosterone with 100 µg/kg ACTH



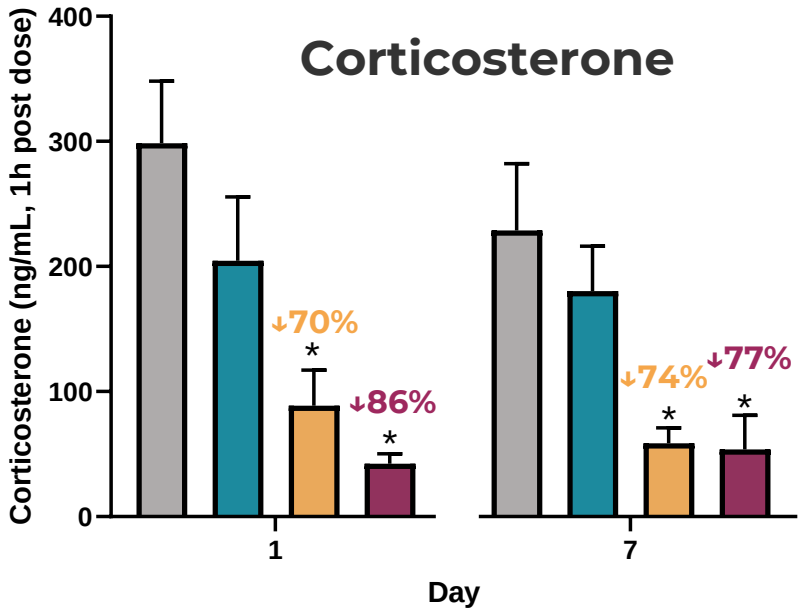


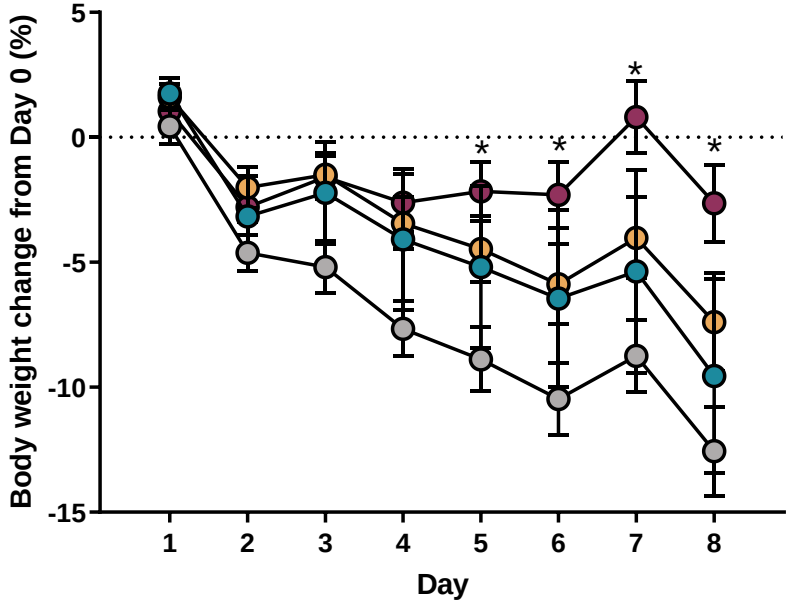


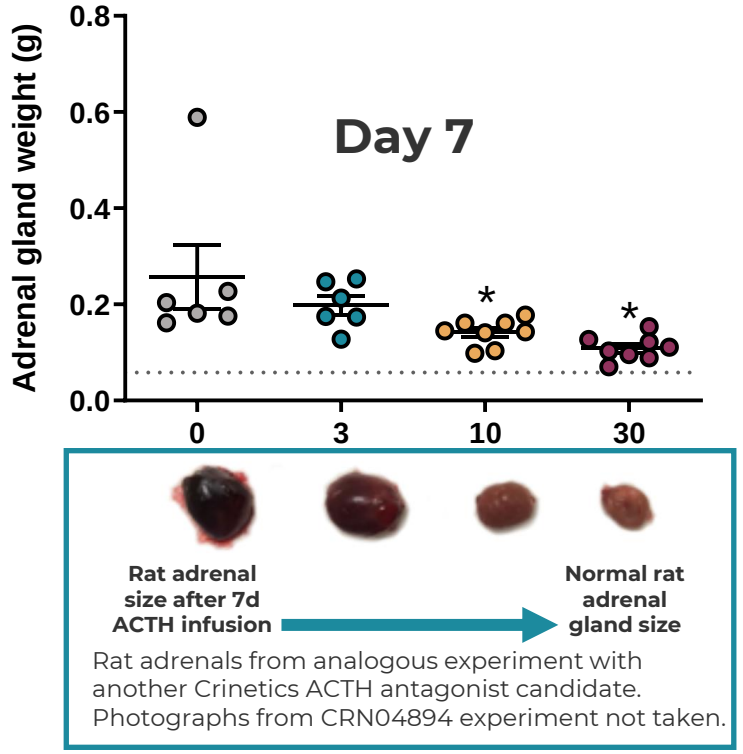
CRN04894 Suppresses Corticosterone and Reverses Adrenal Gland Hypertrophy in Rat Model of ACTH Excess

Continuous subcutaneous administration of 100 µg/kg/day ACTH(1-24) over 7 days causes increased plasma corticosterone levels and adrenal gland hypertrophy in rats

Oral administration of CRN04894 for 7 days dose dependently suppressed corticosterone levels and rescued body weight effects and adrenal gland hypertrophy in the rat model of excess ACTH







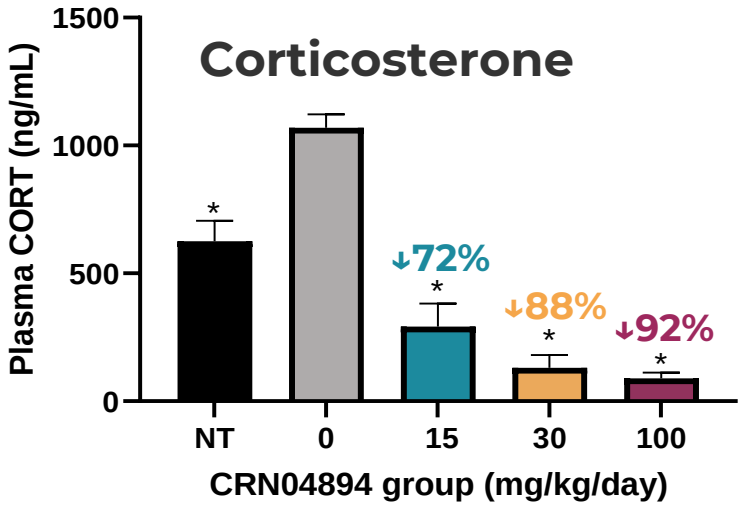
Vehicle | 3 mg/kg/day CRN04894 | 10 mg/kg/day CRN04894 | 30 mg/kg/day CRN04894

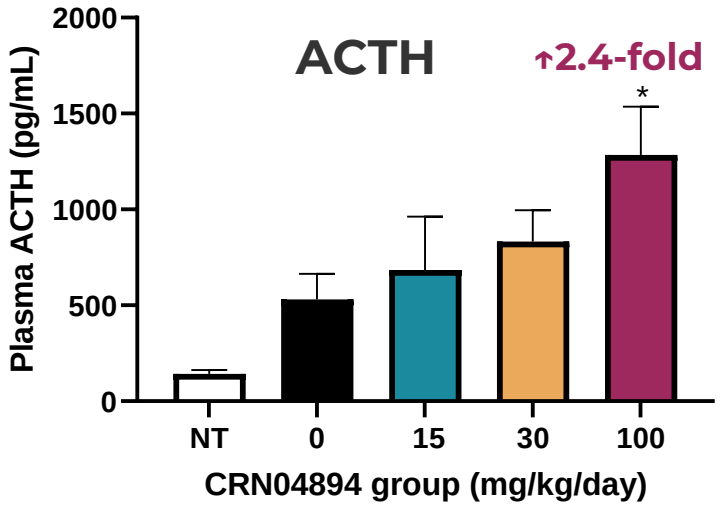
Oral Administration of CRN04894 Suppresses Corticosterone Levels in AtT-20 Tumor Bearing Mice

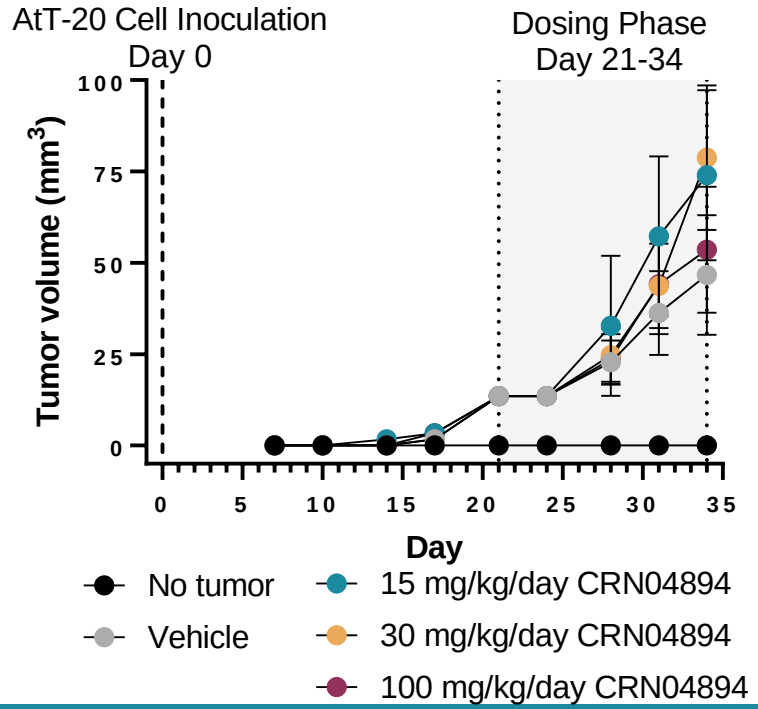
Subcutaneous implantation of an ACTH-secreting mouse pituitary cell line (AtT-20) into female Balb/c nude mice leads to formation of tumors and increased plasma ACTH and corticosterone by 34 days post inoculation

Oral administration of the ACTH antagonist, CRN04894, for 14 days dose dependently suppressed corticosterone levels in AtT-20 tumor bearing mice

- Increased plasma ACTH levels observed with 100 mg/kg/day CRN04894 compared to vehicle treatment
- No difference in tumor volume between CRN04894 and vehicle treated mice







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

Objectives

Safety & tolerability

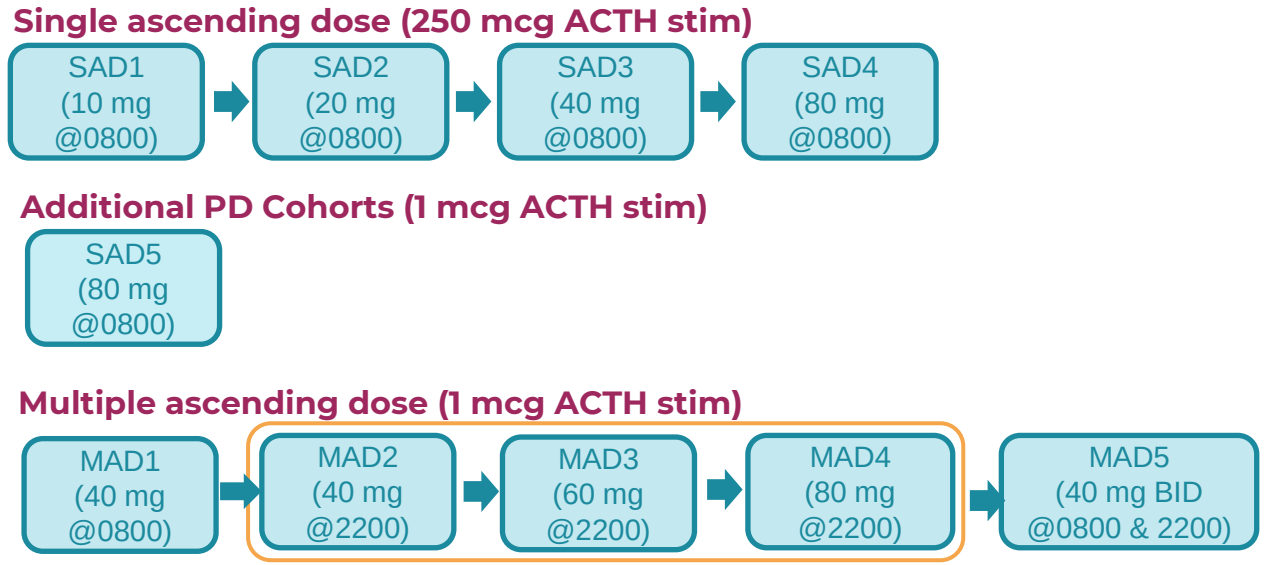
Pharmacokinetics

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

Pharmacodynamics

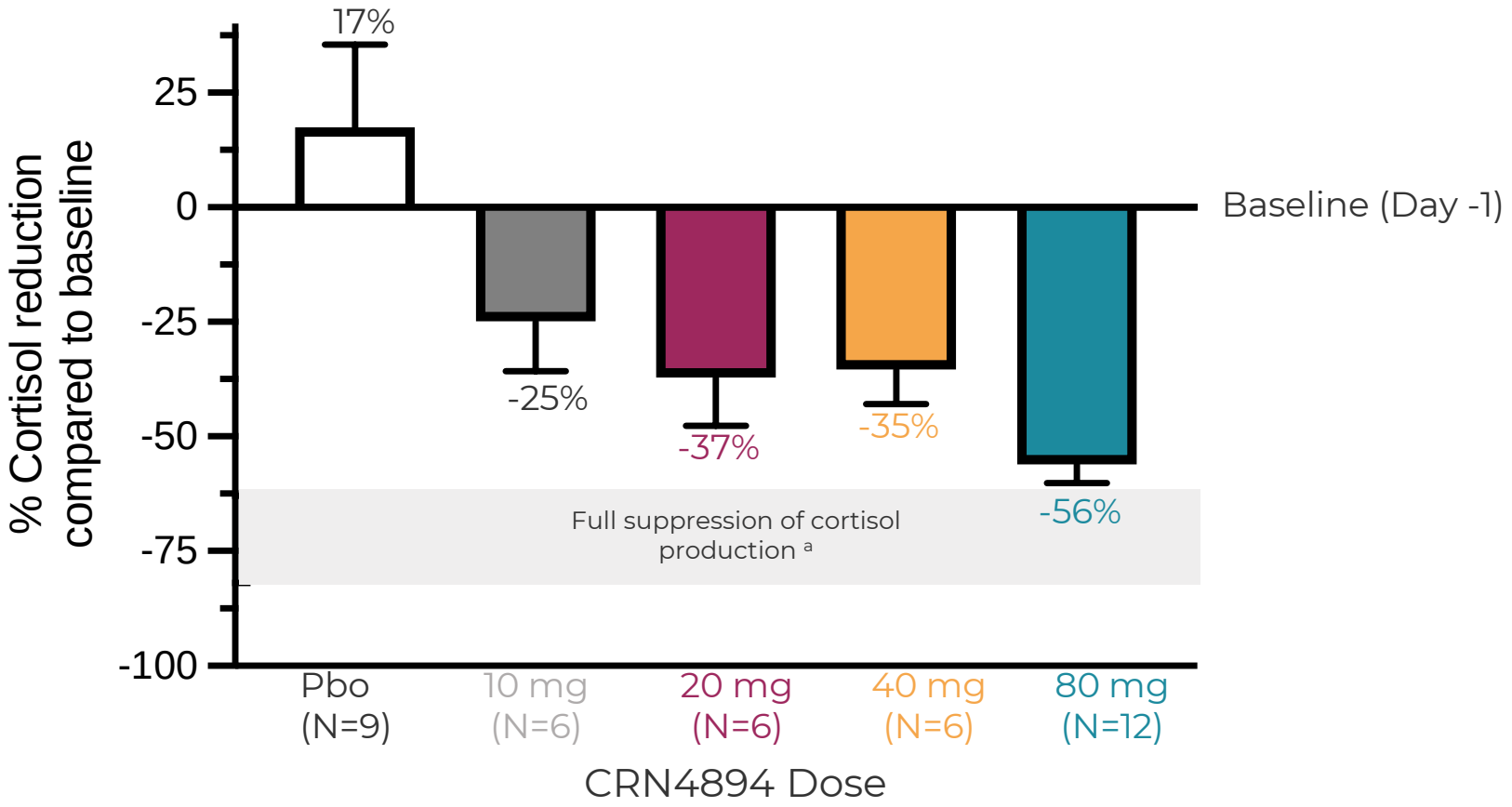
- Serum cortisol, 24 hr. UFC, ACTH, A4, aldosterone
  - 24h circadian sampling: Baseline & multiple occasions postdose
  - ACTH stimulation tests performed in SAD and MAD

Design



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

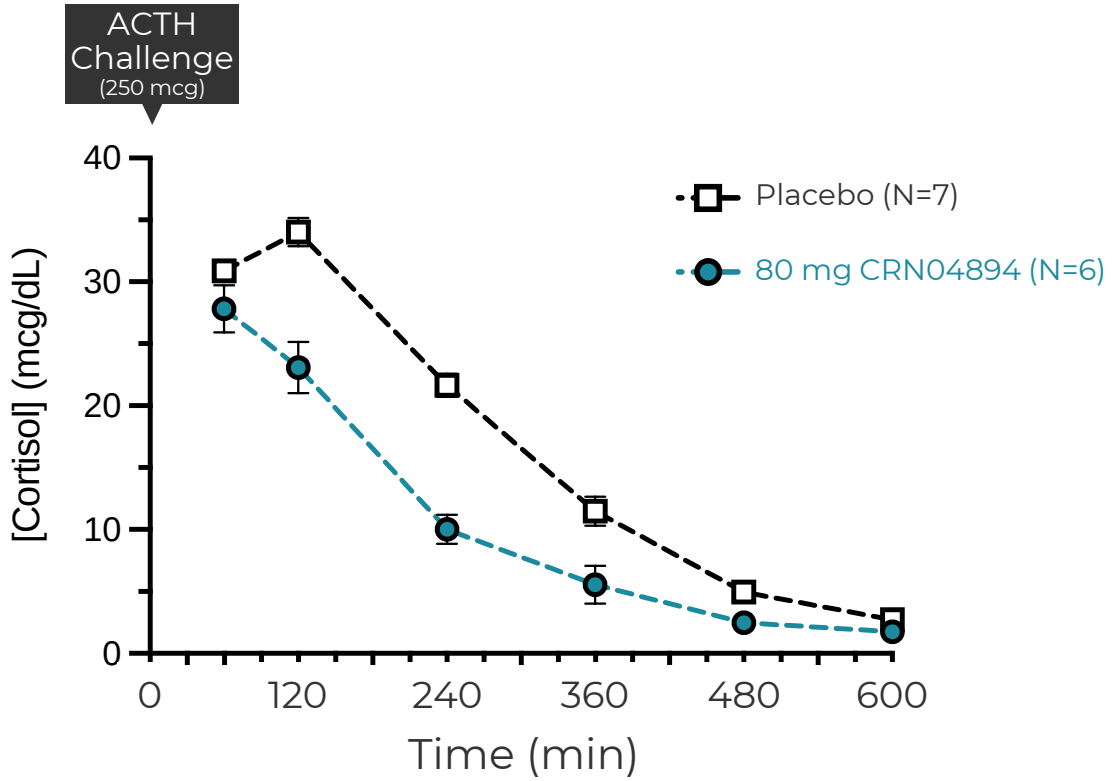
Acute reduction of basal cortisol (56% @ 80 mg) 2 hours after administration of CRN04894

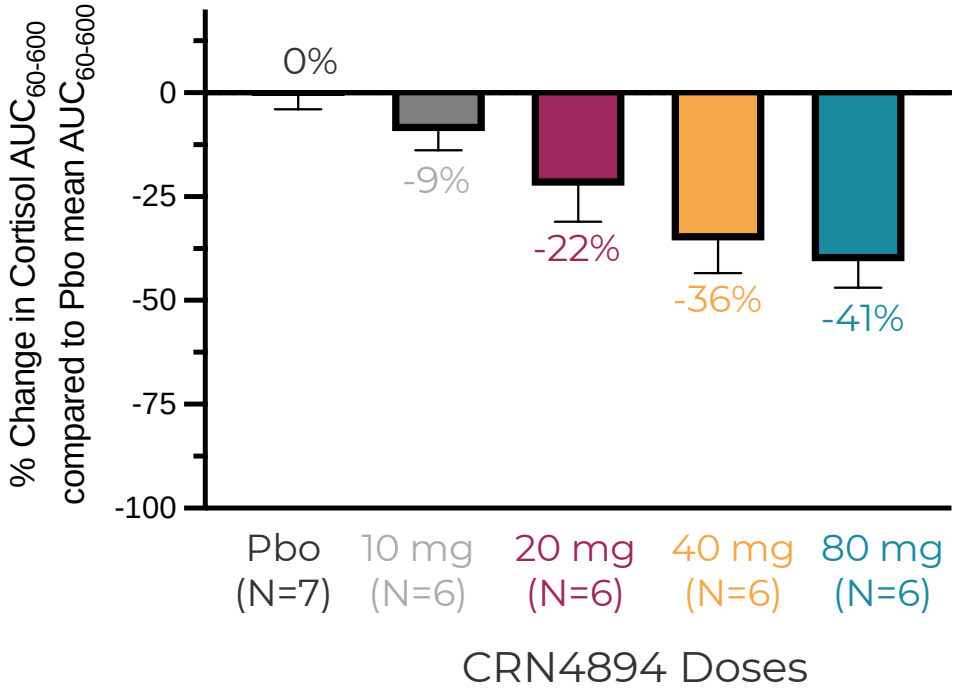


Data shown are mean ± SEM.

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) in Healthy Volunteers





Data shown are mean ± SEM.

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

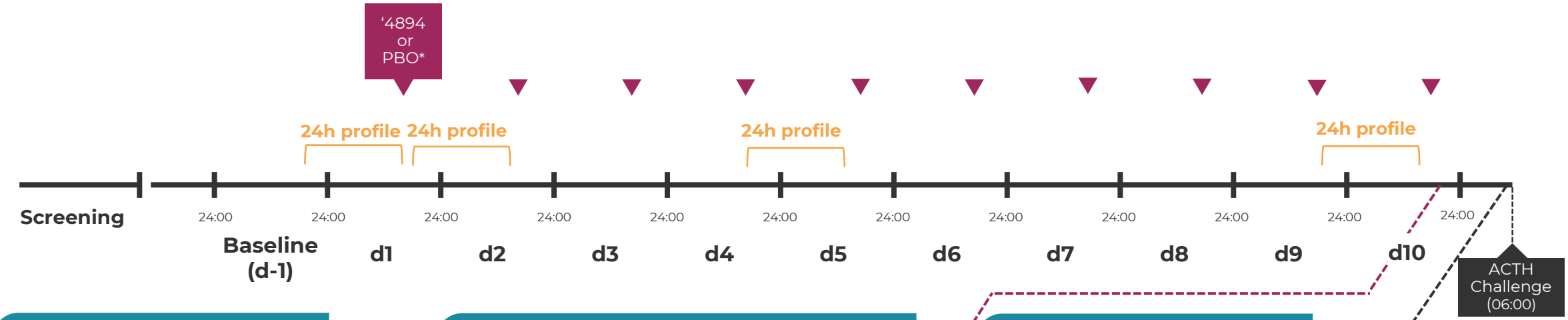
- Once daily 08:00 dosing: 40 mg
- **Once daily 22:00 dosing: 40, 60, & 80 mg**
- BID dosing: 40 mg (total of 80 mg daily)

Proof-of-Concept

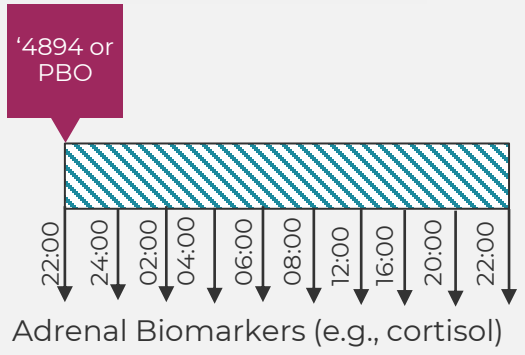
- Dose dependent suppression of basal and ACTH-induced adrenal activity (measured by cortisol) with CRN04894

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



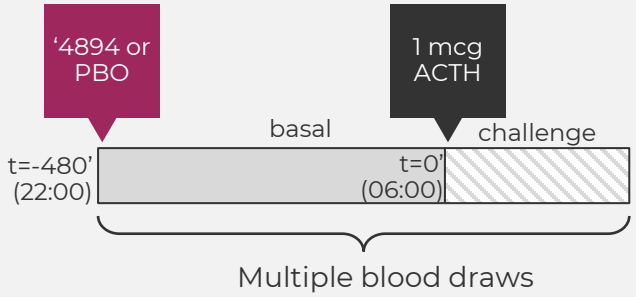
24h Profile



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).

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.

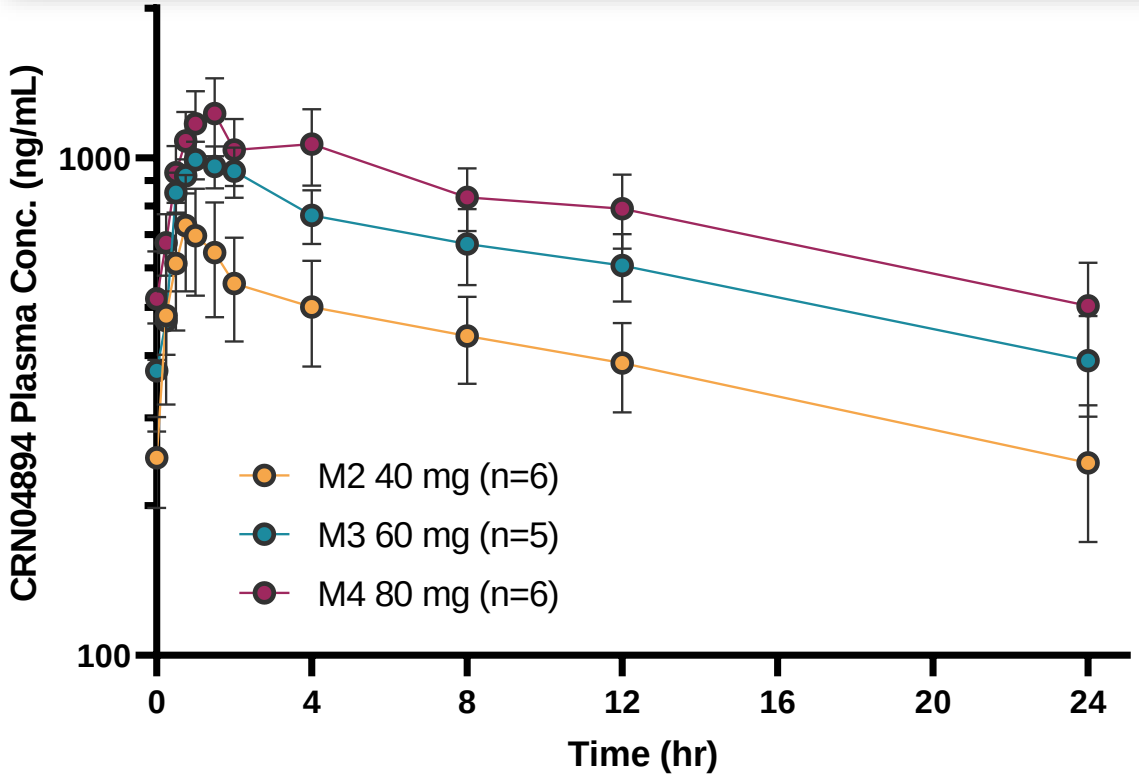
Pharmacokinetics of Night-Time (10 pm/2200) Dosing Cohorts in the MAD Portion of the Study

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

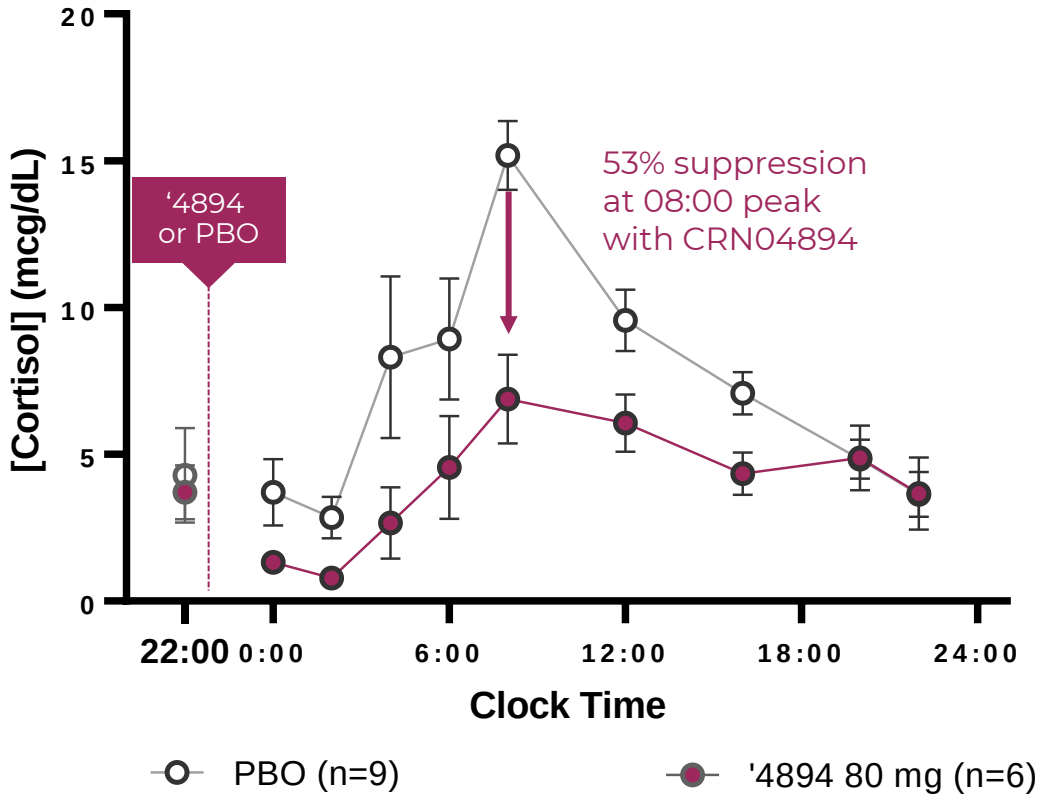
Concentration-Time Profile at Steady State (Day 10)



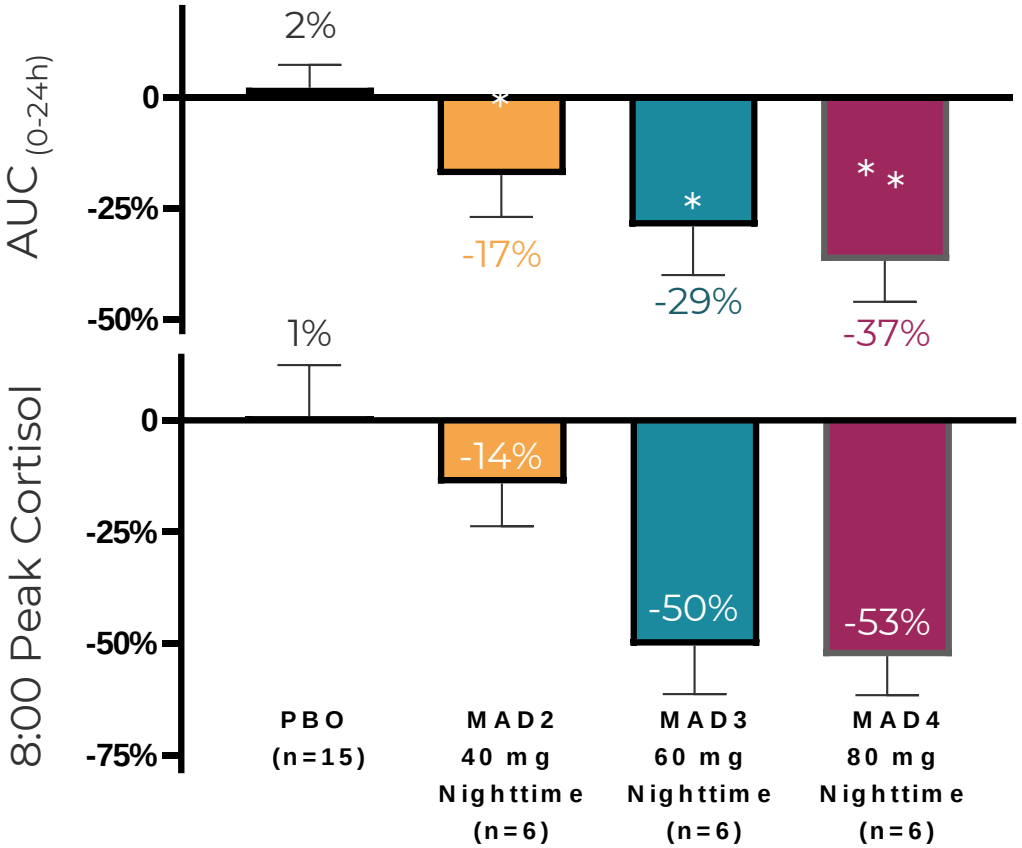
Data shown are mean ± SEM. N=1 subject was an outlier and excluded in 60 mg cohort; MAD: Multiple-ascending dose; SAD: Single-ascending dose; PK: Pharmacokinetics; BID: Twice daily.

Dose-Dependent Suppression of Serum Cortisol Below Normal Levels

Day 9 Cortisol Profiles

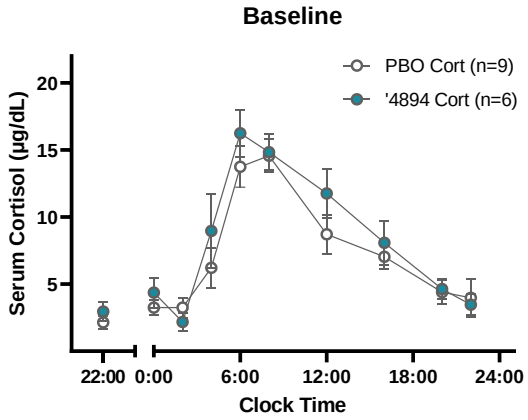


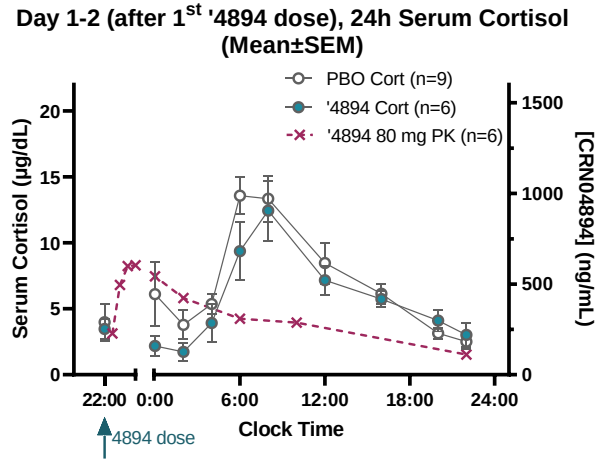
Change in Cortisol from Baseline

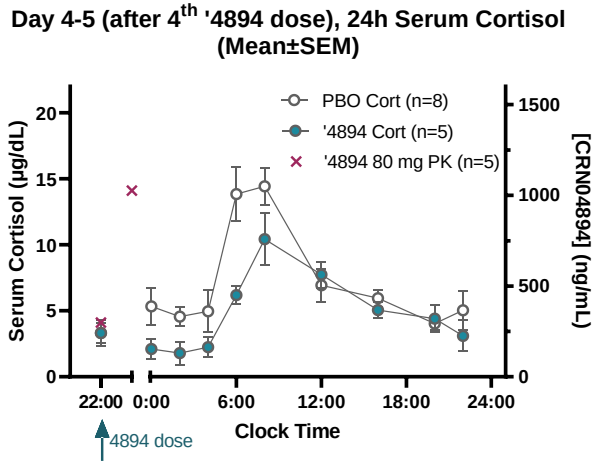


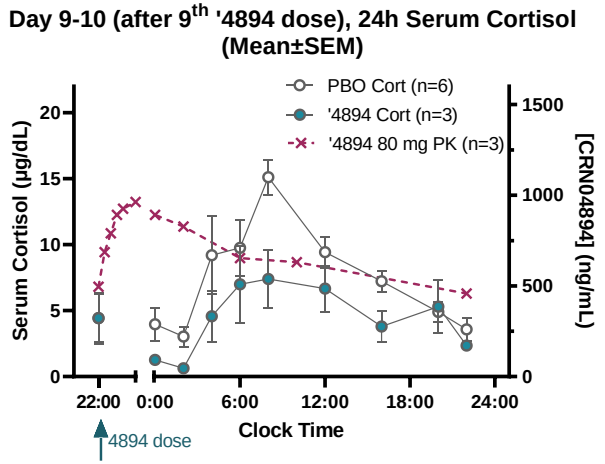
Data shown are mean ± SEM. White asterisks in graph on upper right represent values for subjects who received glucocorticoid rescue; since GC add-back last administered at 14:00 it is expected to not contribute to 08:00 plasma levels. PBO: Placebo; HV: Healthy volunteers.

24-hour Mean Serum Cortisol & PK Profiles with 80 mg once daily CRN04894 at 22.00



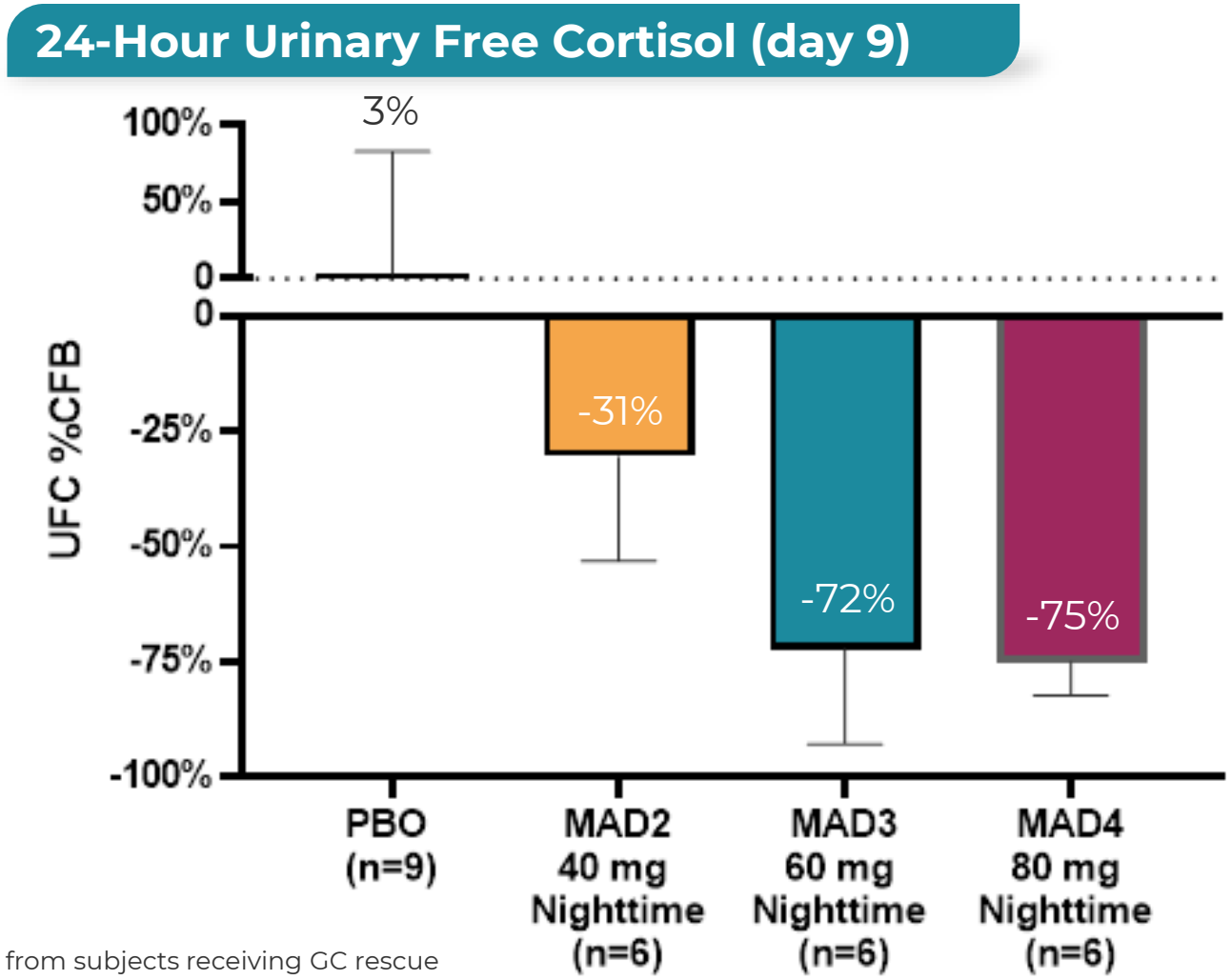






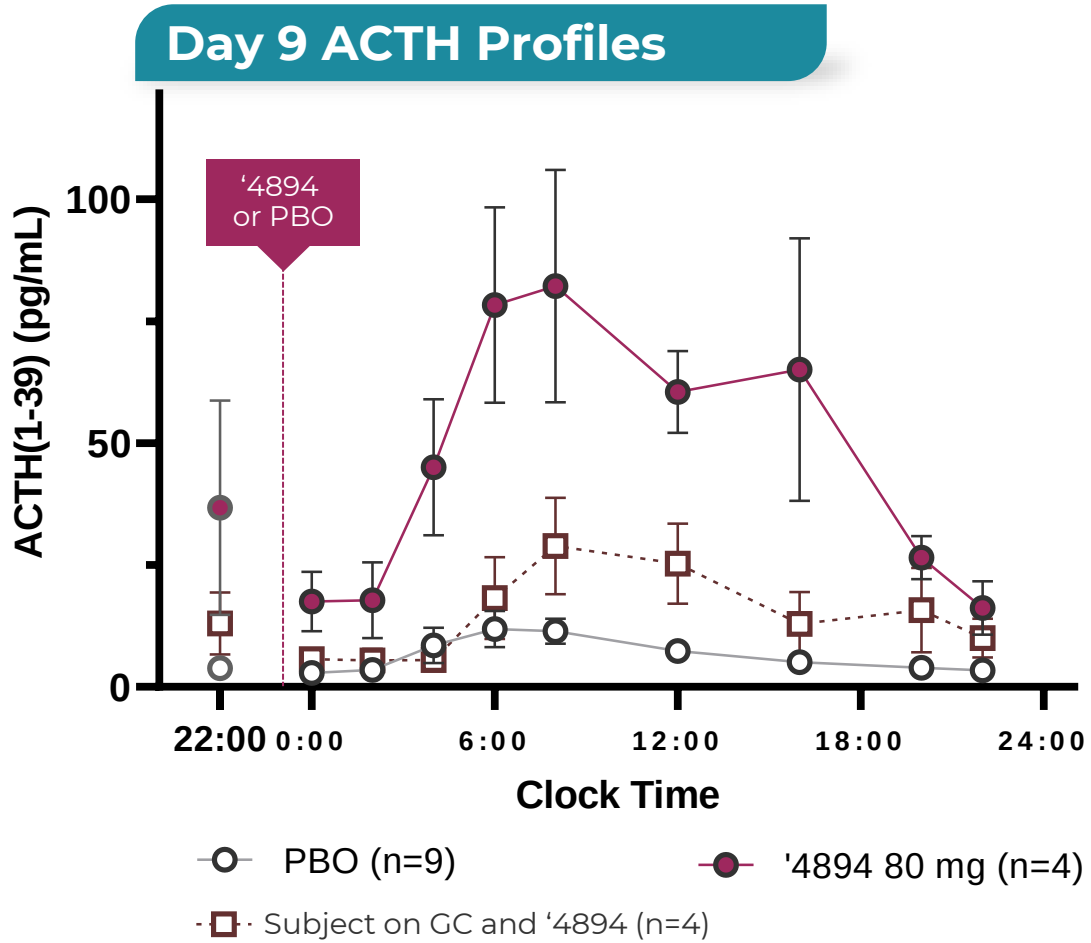
Data shown as mean±SEM;
MAD4 '4894 80 mg @22:00 data shown; placebo data were pooled (MAD2-4).

CRN04894 Potently Suppressed Adrenal Activity as Measured by Urinary Free Cortisol



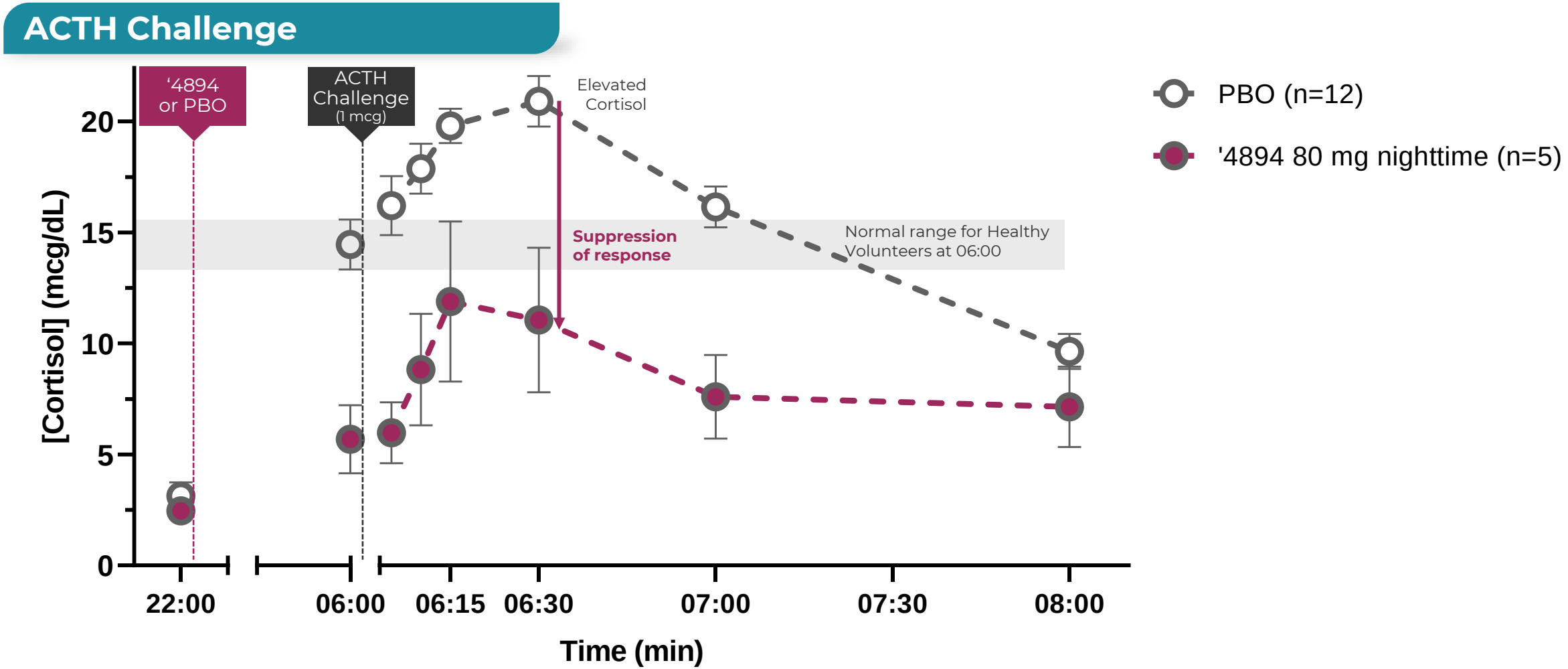
Data shown are median ± IQR. Includes data from subjects receiving GC rescue

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



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.

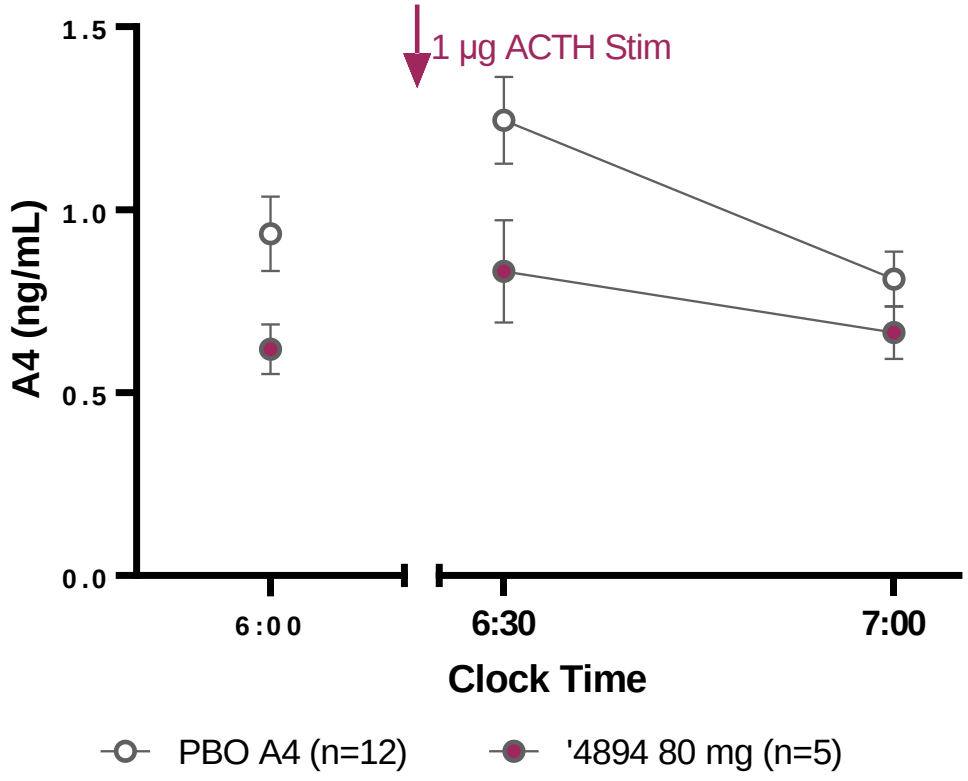
CRN04894 Maintained Cortisol Below Normal Levels After ACTH Challenge Test on Top of Sustained Elevated ACTH



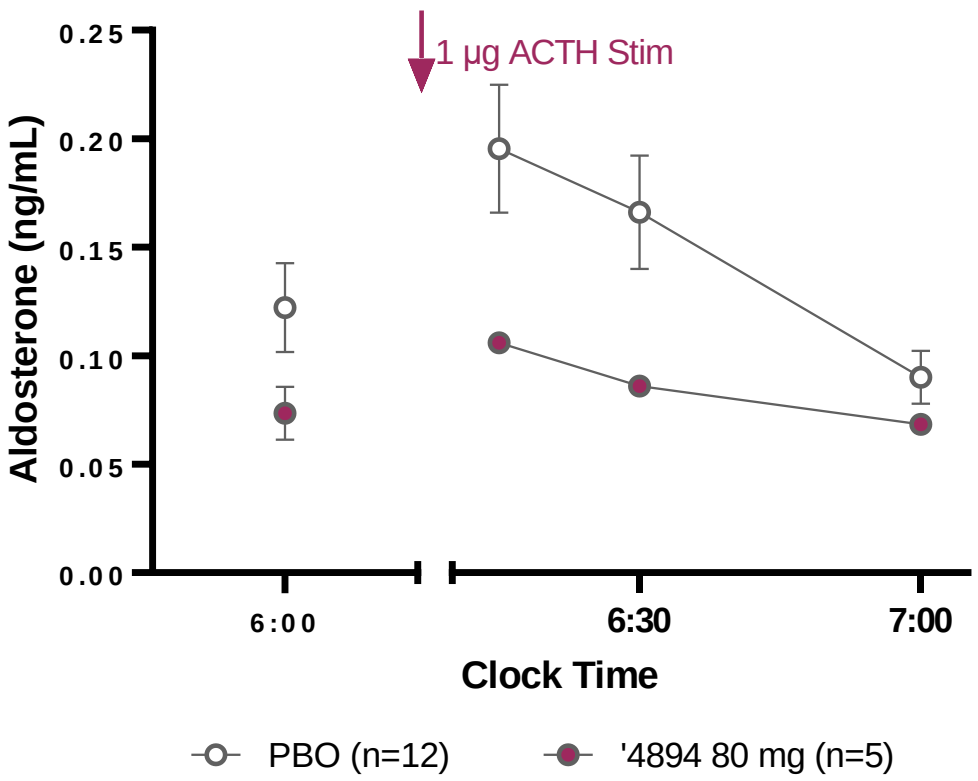
Data shown are mean ± SEM; one subject in 80 mg MAD arm did not receive ACTH challenge.

Suppression of Basal and ACTH Stimulated Androstenedione and Aldosterone

Androstenedione (A4)



Aldosterone

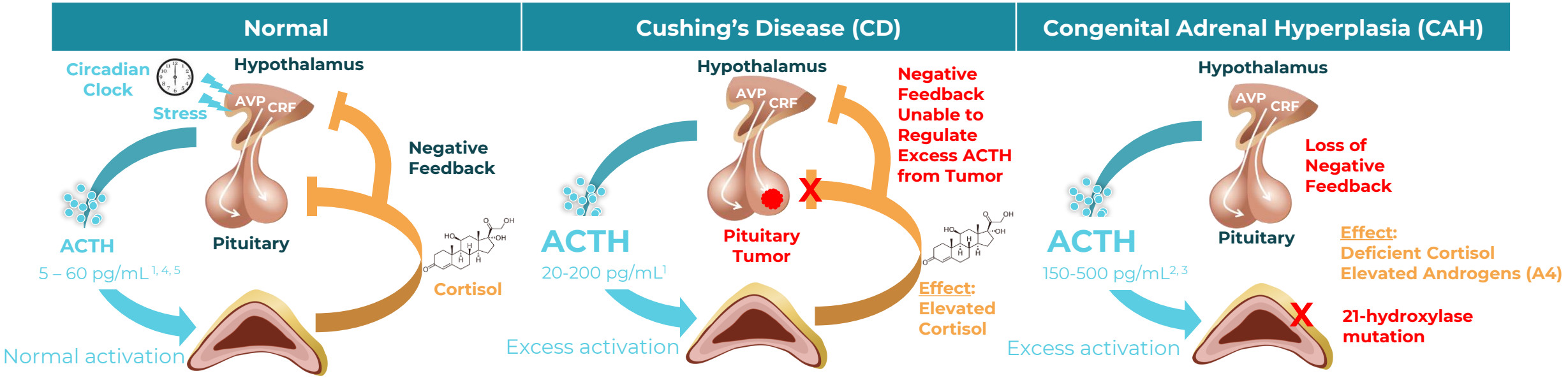


Data shown are mean ± SEM. One subject in 80 mg MAD arm did not receive an ACTH challenge at end of study.

Conclusions of P1

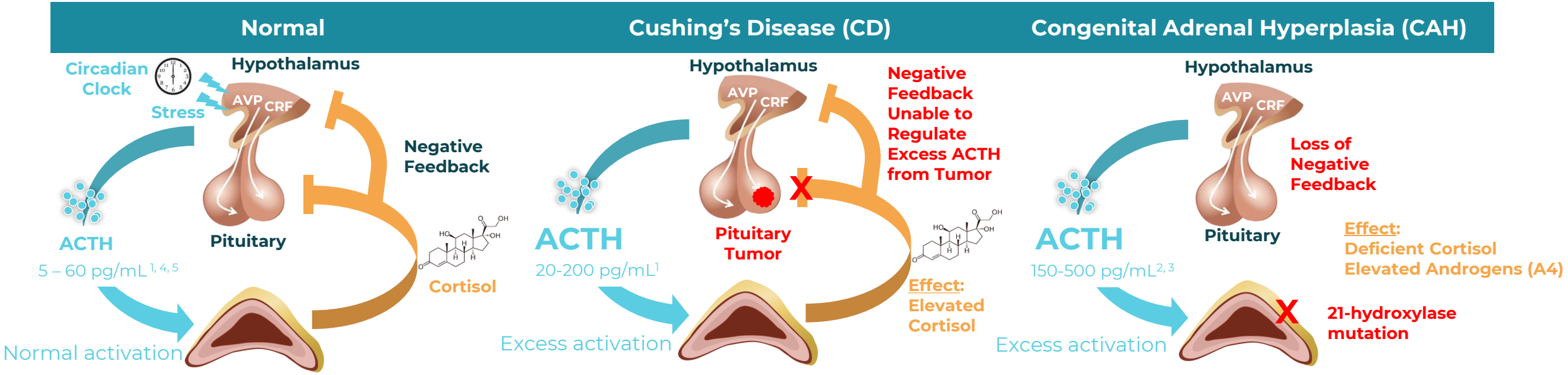
- Safety:
  - CRN04894 was well tolerated in healthy volunteers
- Pharmacokinetic profile:
  - Rapidly absorbed after oral administration (t_{max} ~1-2 hrs)
  - Dose proportional increases in exposure from 10 to 80 mg
  - Half-life of ~24 hours, expected to be suitable for once daily dosing
- Pharmacodynamics:
  - 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

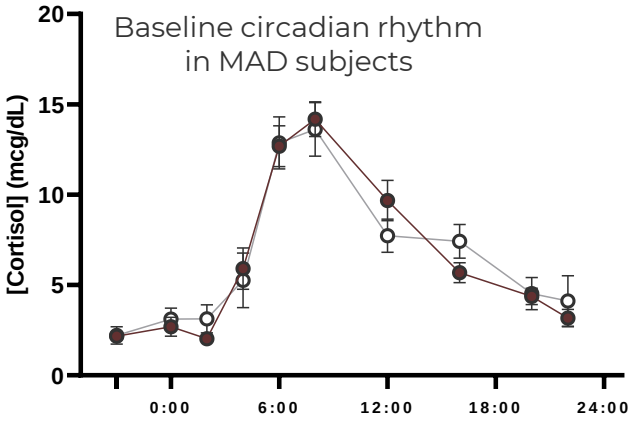
Disruptions in the HPA Axis Lead to Diseases of Excess ACTH and Excess Adrenal Activation

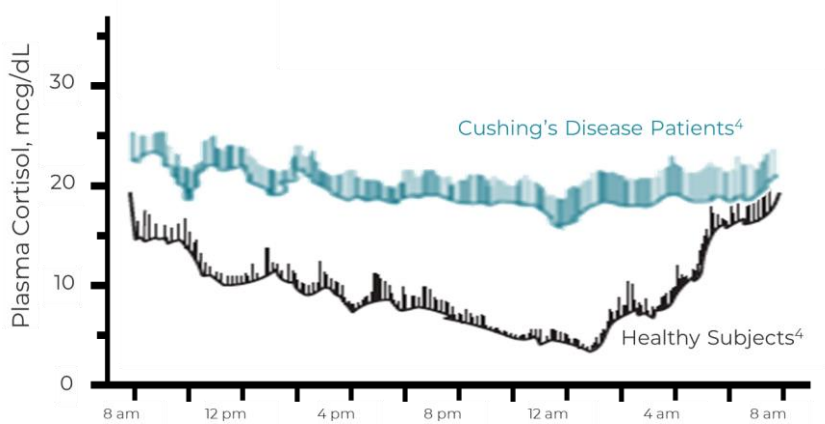


Cause	ACTH-secreting pituitary tumor	Inability to produce cortisol leads to loss of negative feedback & excess ACTH
US Prevalence	10k	27k
Symptoms	Central obesity and round face; Dorsal and supraclavicular fat pads; Hypertension; Stretch marks; Bone loss; Hyperglycemia; Psychiatric disturbances	Adrenal 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







Patients on life-long glucocorticoid replacement therapy
i.e. no change in glucocorticoid status with CRN04894

[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

Acknowledgements

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