



CRN04894: PHASE 1 MULTIPLE ASCENDING DOSE (MAD) PRELIMINARY RESULTS

May 25, 2022

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CRN04894 MAD Results Support Moving to Patient Studies in Both CAH and Cushing's



Well tolerated at doses from 40 mg to 80 mg administered daily for 10 days

- No Serious Adverse Events; All Adverse Events considered mild/moderate
- MTD not reached: may allow further dose escalation in some patients if necessary



Favorable pharmacokinetics support goal of once daily dosing

- Excellent oral bioavailability with ~24-hour half life
- PK results and exposures consistent with expectations from SAD data



Confirmed pharmacologic POC & established starting dose range for patient studies

- Substantial and dose-dependent reductions in adrenal activity (cortisol)
- Clinically-meaningful adrenal suppression following disease relevant ACTH challenge



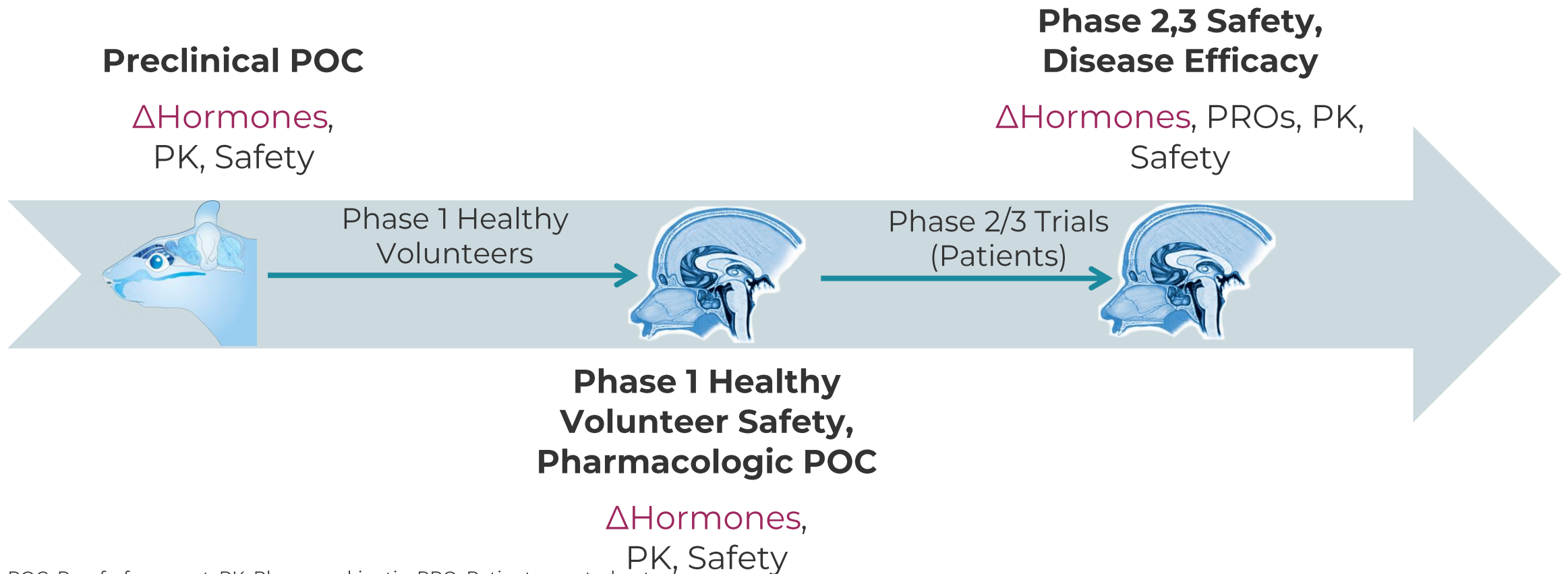
Next steps:

- Advance clinical programs in CAH and Cushing's patients with QD dosing
- Engage with regulators on design of clinical programs in patients

MAD: Multiple-ascending dose SAD: Single-ascending dose; MTD: Maximum tolerated dose; POC: Proof-of-concept; PK: Pharmacokinetic; CAH: Congenital adrenal hyperplasia

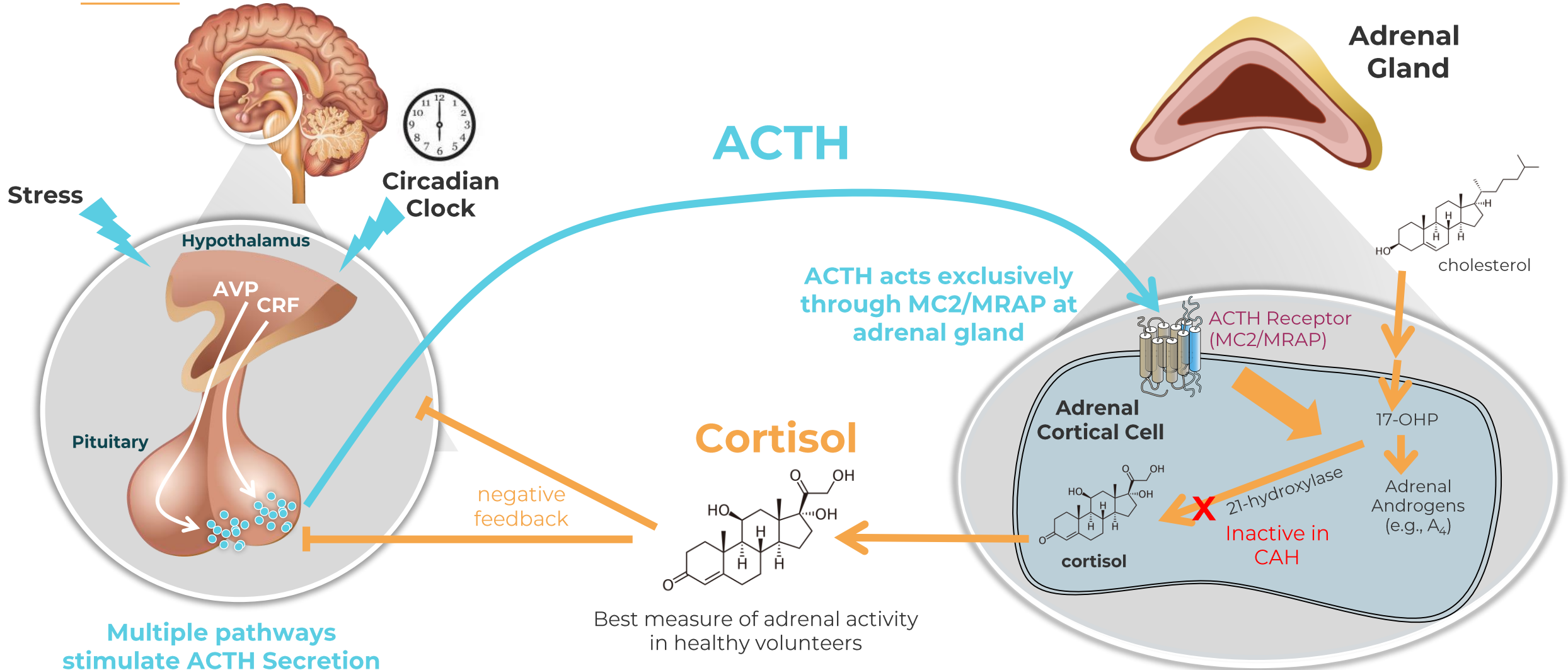
Crinetics' Endocrine Development Strategy: Hormone Levels from Preclinical to Approval

Leveraging Highly Conserved Biology and Purpose-Built Molecules to
Optimize Probability of Success in Diseases of High Unmet Need

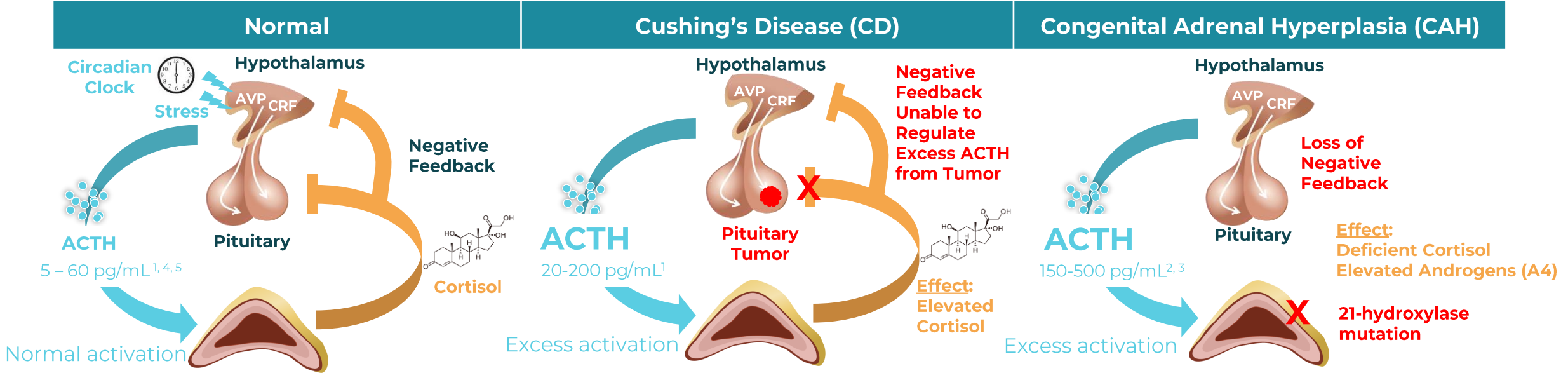


POC: Proof-of-concept; PK: Pharmacokinetic; PRO: Patient reported outcome

The Hypothalamic-Pituitary-Adrenal (HPA) Axis: The ACTH Receptor Is Key for Adrenal Activation

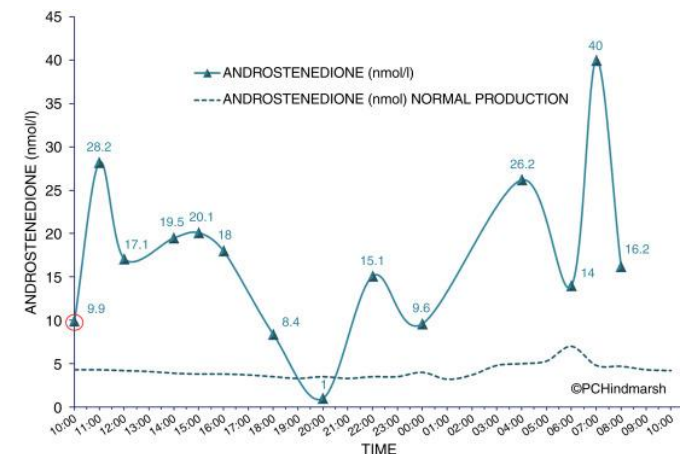
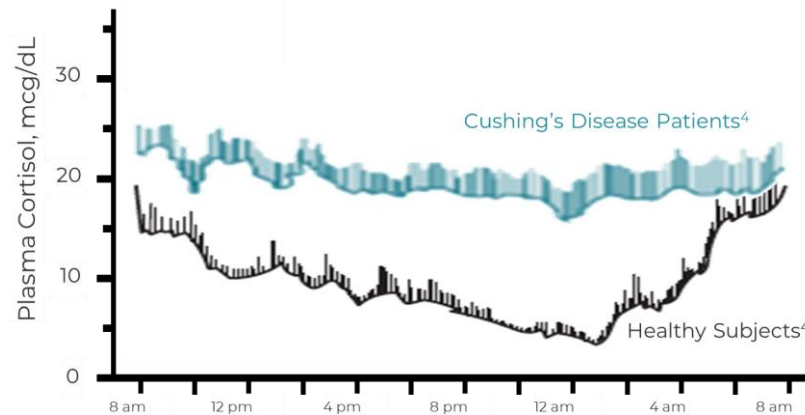
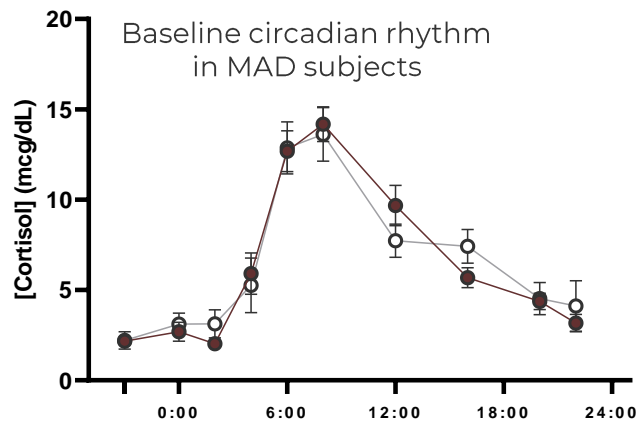
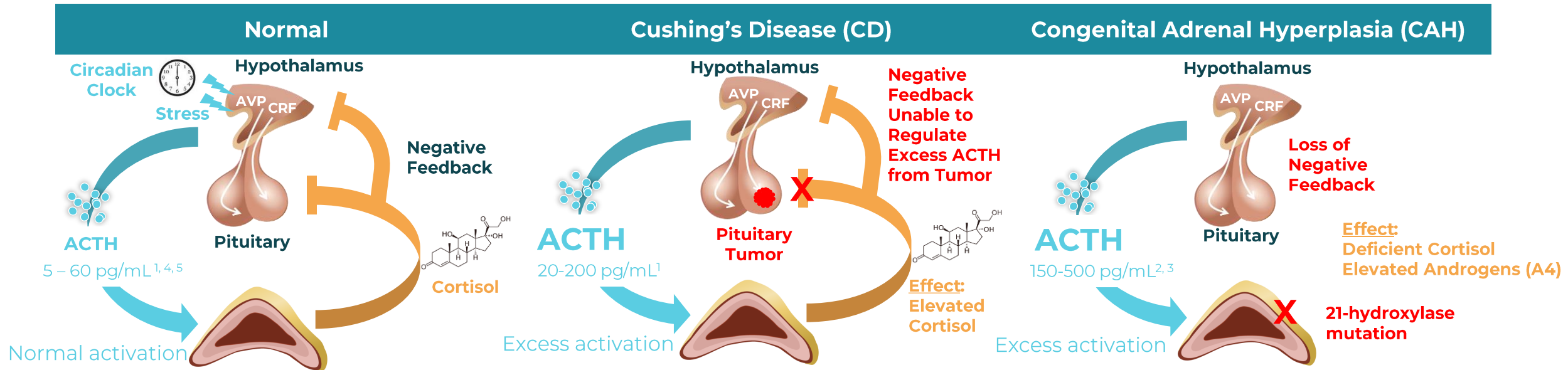


Disruptions in the HPA Axis Lead to Diseases of Excess ACTH and Excess Adrenal Activation



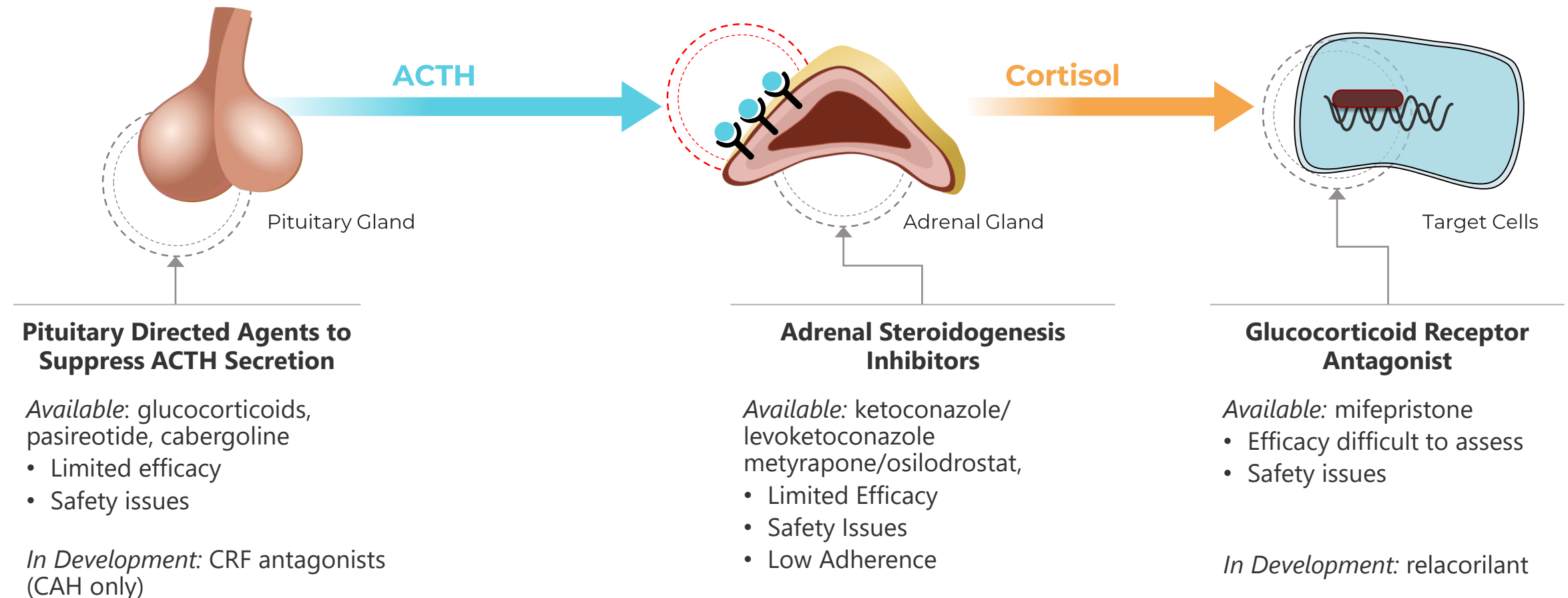
Cause	ACTH-secreting pituitary tumor	Inability to produce cortisol leads to loss of negative feedback & excess ACTH
US Prevalence (global incidence per 100,000)	10k (2.5-3.8)	27k (6.7-10.0)
Symptoms	Central obesity and round face; Dorsal and supraclavicular fat pads; Hypertension; Stretch marks; Bone 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



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

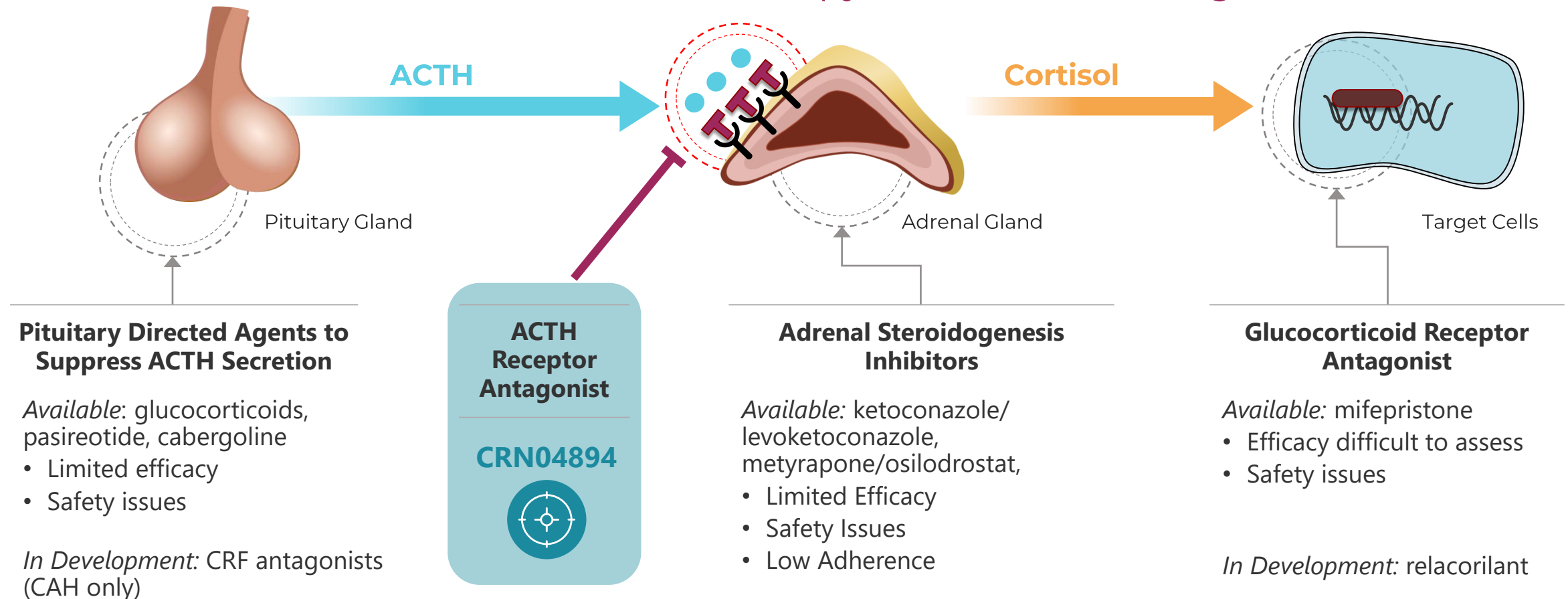
Current HPA Therapeutics Have Limited Efficacy and/or Safety Issues, Leaving High Unmet Need



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

CRN04894: The First-in-Class ACTH Antagonist for ACTH Driven Diseases

Targeting the ACTH receptor blocks the key chokepoint of HPA signaling, and could become cornerstone of therapy in CAH and Cushing's



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

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

- QD 08:00 (8 am) dosing: 40 mg
- **QD 22:00 (10 pm) dosing: 40, 60, & 80 mg**
- BID dosing: 40 mg (total of 80 mg daily)

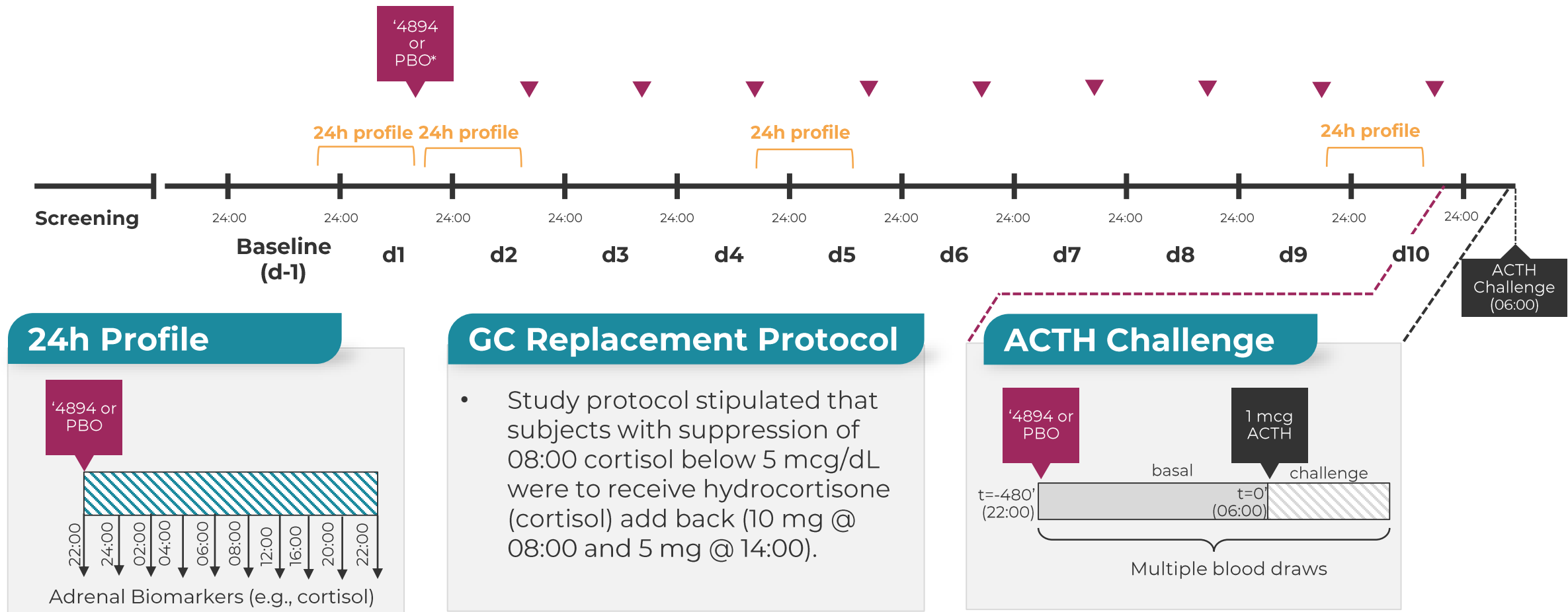
Proof-of-Concept

- 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



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).

CRN04894 was Well Tolerated: No Study Drug Discontinuations due to Treatment Related AEs

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

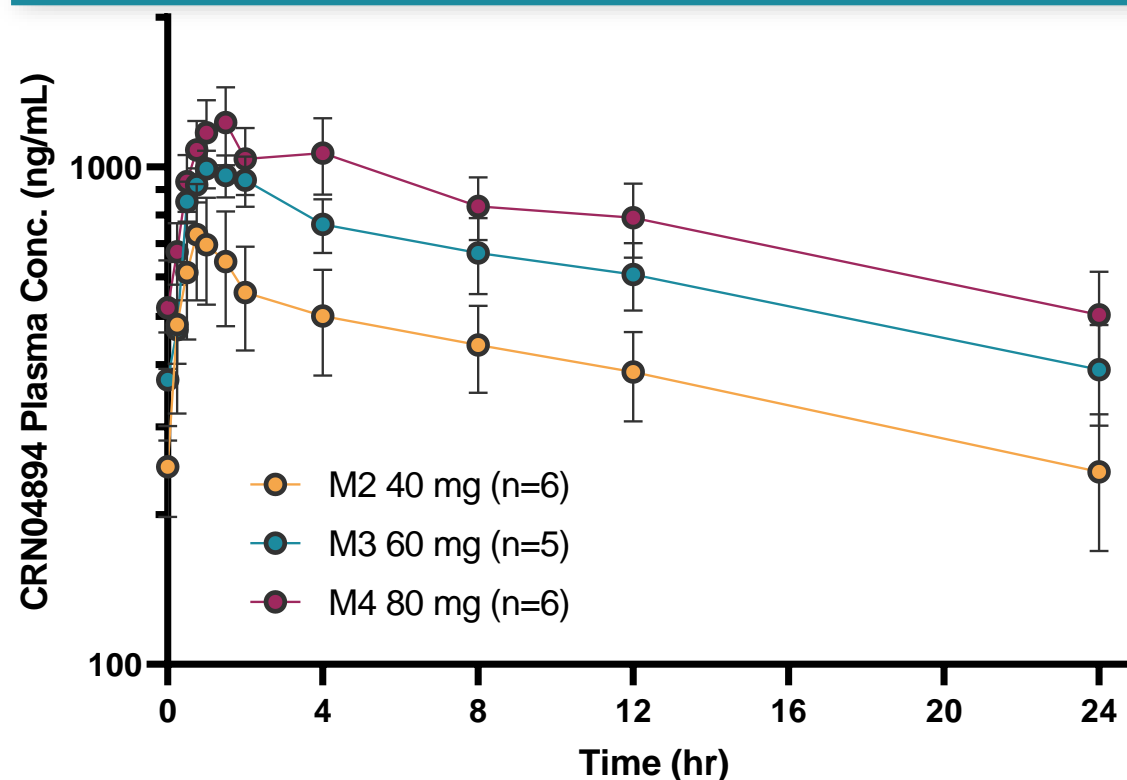
PK Supports Goal of Once Daily Oral Dosing

MAD PK Consistent with Expectations from SAD Data at the Same Doses

Steady State PK

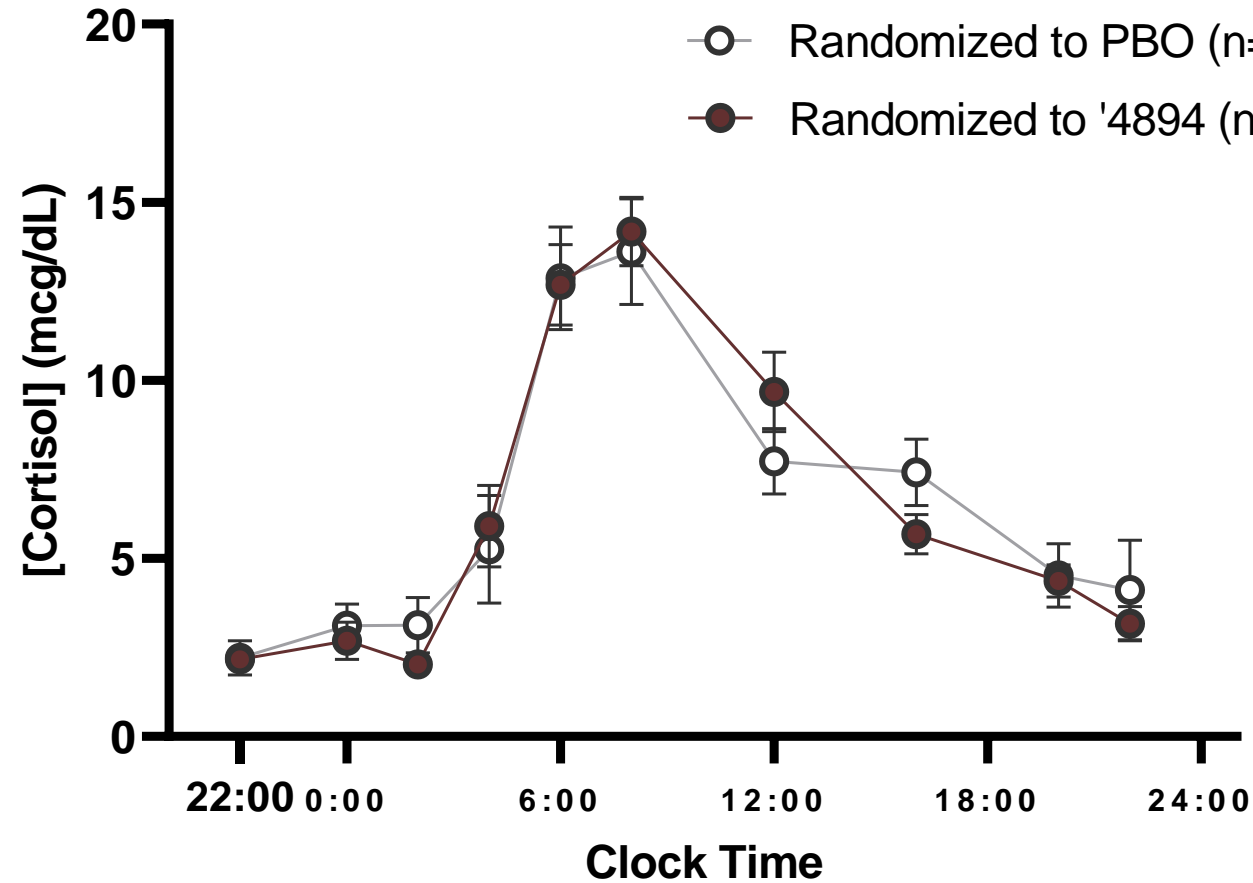
- Oral bioavailability
- Favorable half-life of ~24 hours
- Rapidly absorbed with a t_{\max} of ~1-2 hours
- Dose proportional exposure
- PK profile is consistent with morning, nighttime, or BID dosing

Concentration-Time Profile at Steady State (Day 10)



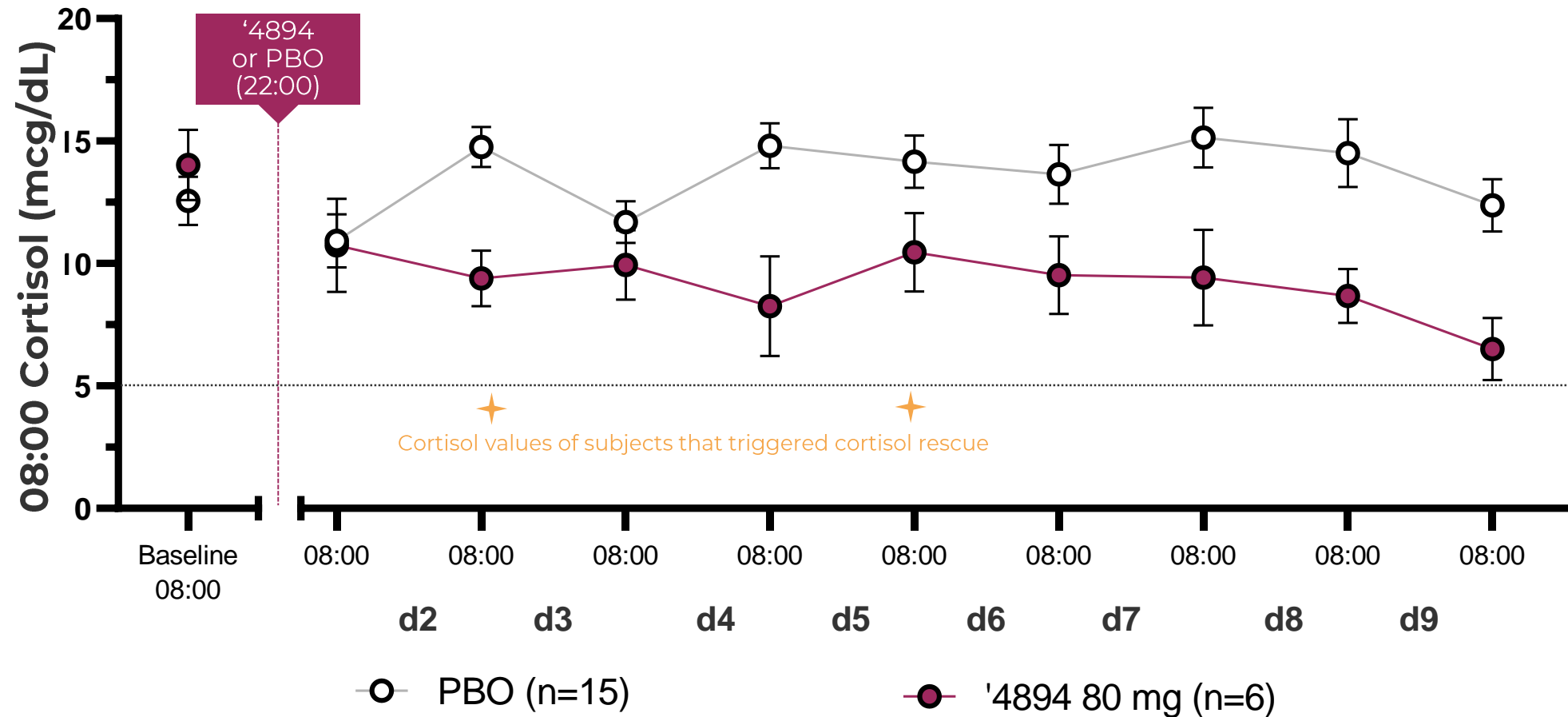
Data represent mean \pm SEM. N=1 subject was an outlier and excluded in 60 mg cohort; MAD: Multiple-ascending dose; SAD: Single-ascending dose; PK: Pharmacokinetics; BID: Twice daily

Healthy Volunteers Have Expected Circadian Rhythm of Adrenal Activity (Cortisol) at Baseline



Data represent mean \pm SEM. Excluding subjects (n=1 in PBO, n=3 in active) with COVID-19 infection. PBO=placebo

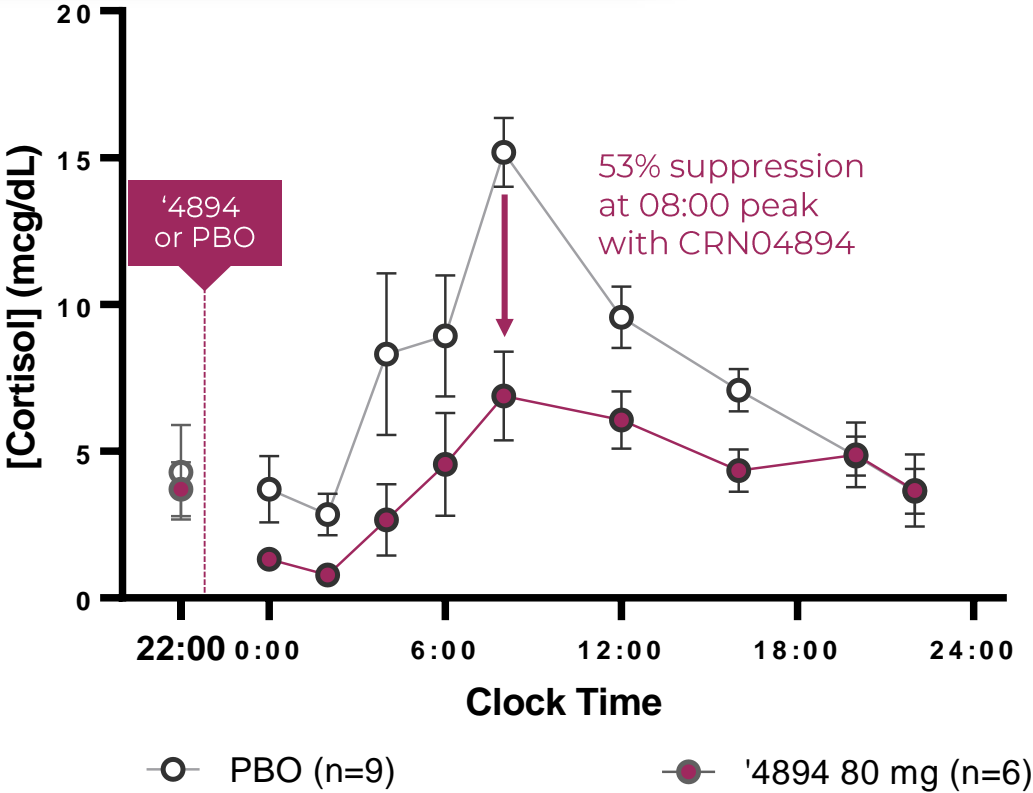
Administration of CRN04894 Suppressed Peak Adrenal Activity Below Normal Levels in HVs



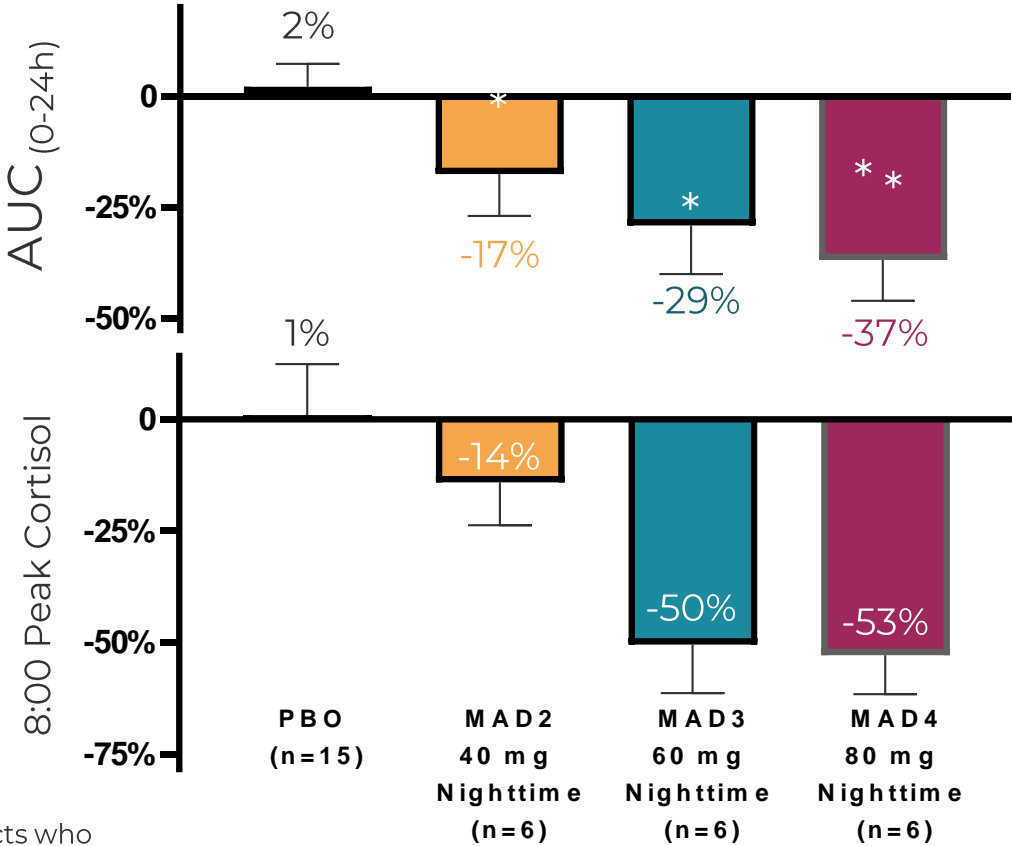
Data represent mean \pm SEM. Includes data from two subjects that required glucocorticoid replacement as per protocol (AM cortisol less than 5 mcg/dL) Cortisol (Hydrocortisone) (10 mg @ 08:00 and 5 mg @ 14:00) starting on day 2 for one subject and starting on day 5 for second subject; cortisol values measured before the morning dose of CC. HVs: Healthy volunteers; PBO: Placebo

Dose-Dependent Suppression of Serum Cortisol Below Normal Levels

Day 9 Cortisol Profiles



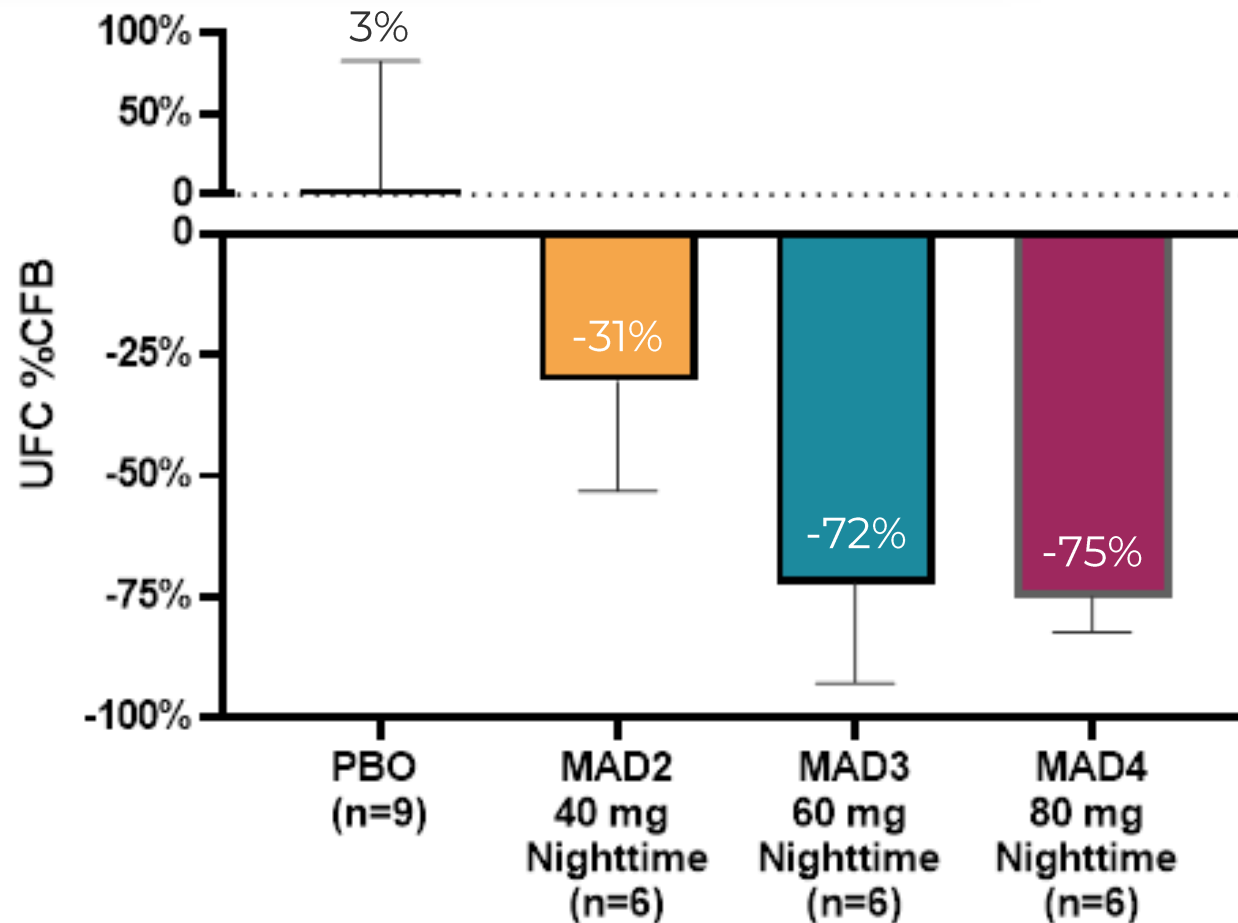
Change in Cortisol from Baseline



Data represent 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)

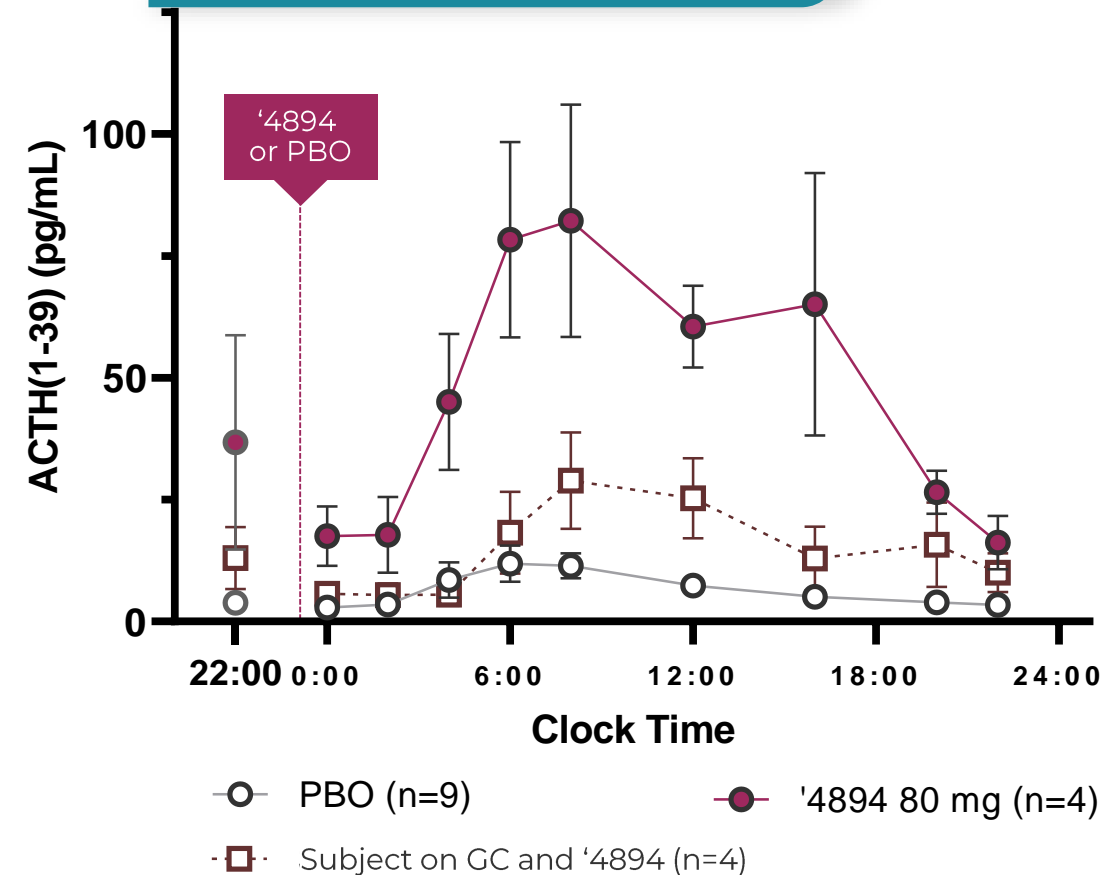


Normalization of 24-hour urinary free cortisol has been the registrational endpoint for previously approved Cushing's disease drugs

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

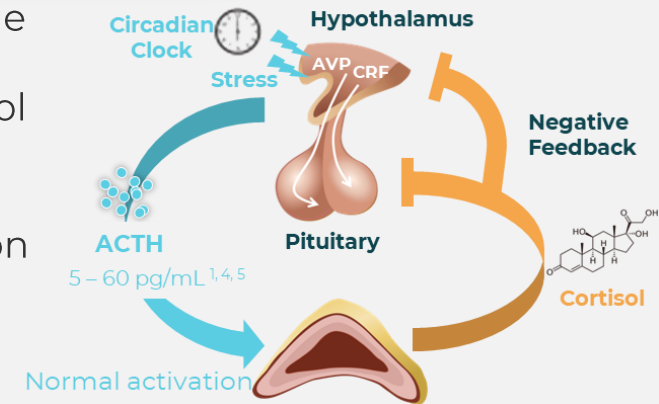
Loss of Cortisol Negative Feedback Resulted in HV ACTH Comparable to That Seen in Disease States

Day 9 ACTH Profiles



Healthy Volunteer HPA Axis

- Expected rise in ACTH was due to reduction of negative feedback with reduced cortisol levels
- Continued cortisol suppression in face of elevated ACTH demonstrated CRN04894's pharmacologic activity



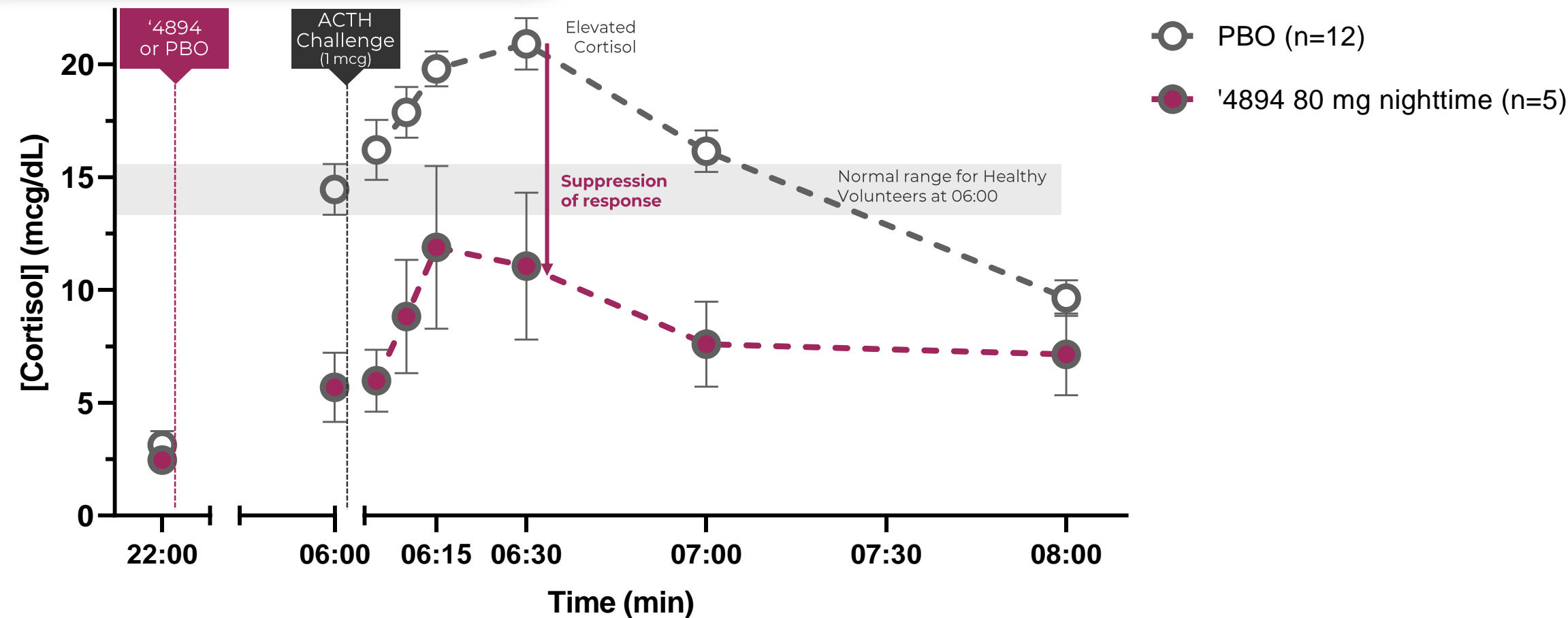
Disease-like ACTH Levels

- ACTH levels at 60 and 80 mg were in the disease-relevant range in CAH and Cushing's disease patients¹⁻³
- Cortisol (hydrocortisone) replacement reduced ACTH levels

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 Paediatr Scand 1981, 3. NBIX ENDO Online 2020 presentation; HV: Healthy volunteer PBO: Placebo; GC: glucocorticoid

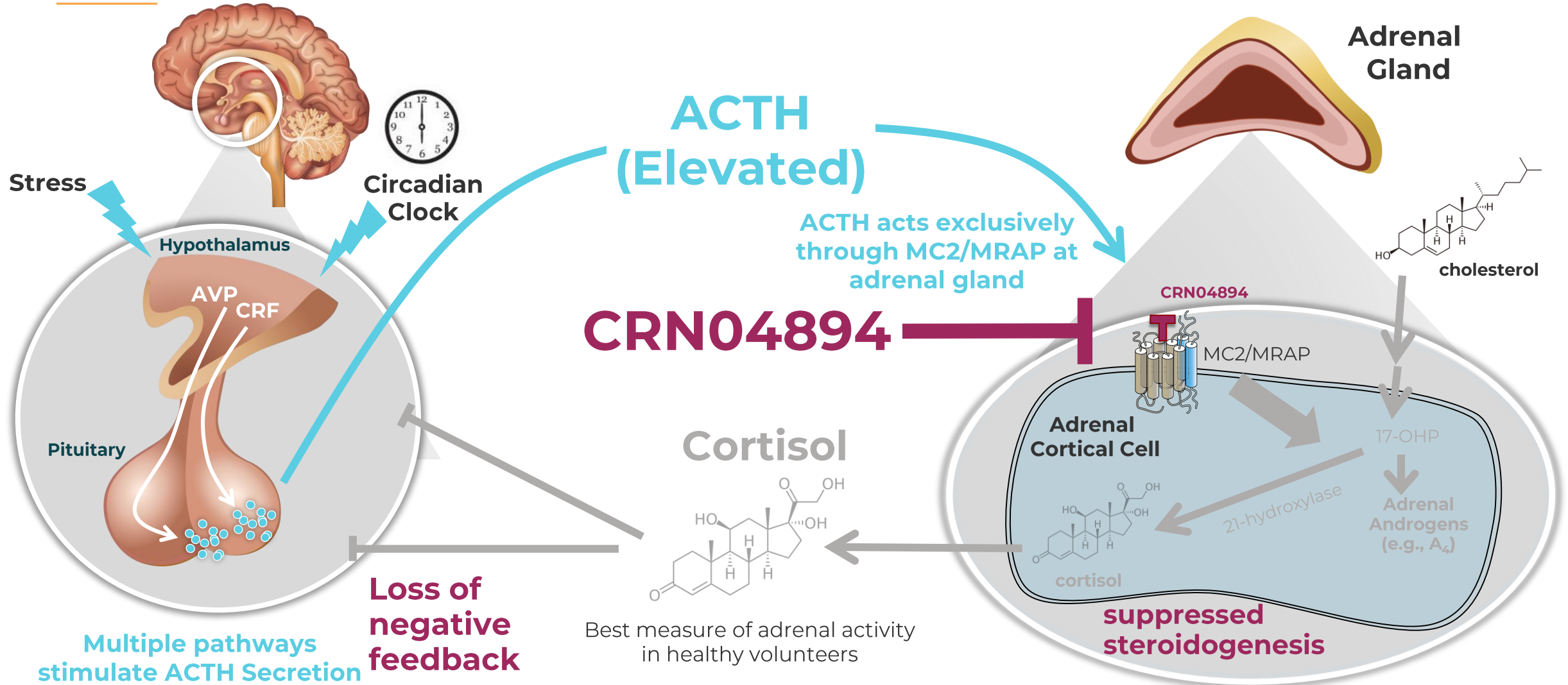
CRN04894 Maintained Cortisol Below Normal Levels After ACTH Challenge Test on Top of Sustained Elevated ACTH

ACTH Challenge



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

CRN04894 Suppressed Adrenal Activity in Presence of Sustained, Disease-like ACTH Levels



Results from Completed CRN04894 Phase 1 Program (SAD & MAD Cohorts)

Objectives

- Evaluate safety and tolerability
- Evaluate drug-like Pharmacokinetics
- Evaluate PK/PD for suppression of ACTH-induced adrenal activity
- Enable patient clinical studies

CRN04894 was well tolerated in the Phase 1 program



Achieved targeted pharmacokinetic profile

- Rapidly absorbed after oral administration (t_{\max} ~1-2 hrs)
- Dose proportional exposure from 10 to 80 mg
- Favorable half-life of ~24 hours



Confirmed pharmacologic POC & established starting dose range for patient studies (40 to >80 mg QD)

- Strong and dose-dependent suppression of basal adrenal function
- Clinically-meaningful suppression of cortisol following disease relevant ACTH challenge



PK: Pharmacokinetics; PD: Pharmacodynamics; POC: Proof-of-concept

Key Treatment Goal for Cushing's Disease Patients

Goal: prevent complications of excessive cortisol secretion

CD Treatment Objective

Inhibit excessive cortisol secretion, which is associated with serious complications such as:

- Weight gain, obesity
- Insulin resistance, diabetes mellitus
- Hypertension
- Muscle weakness
- Neuropsychiatric disorders
- Impaired reproductive health
- Estimated 5-year survival of 50% if untreated

Registrational endpoint: Twenty-four-hour urinary free cortisol

Select Comorbidities Associated with CD

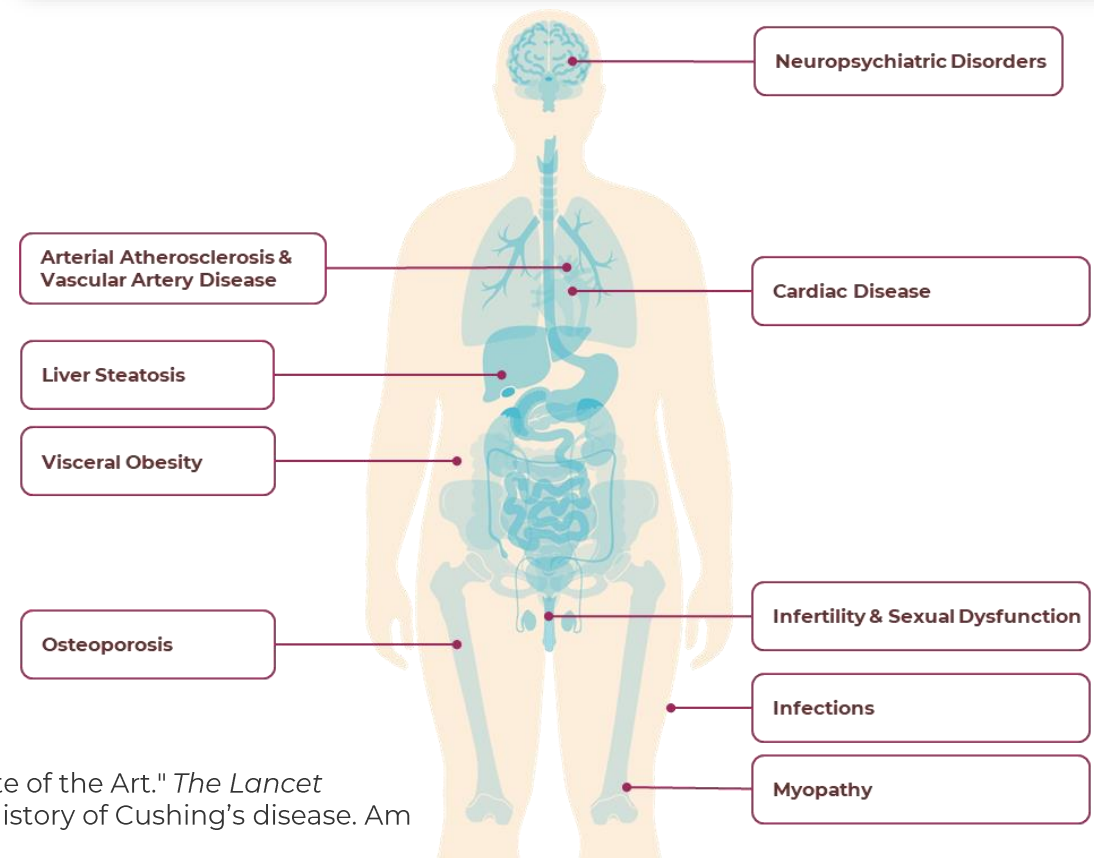


Figure adapted from: Pivonello, Rosario, et al. "Complications of Cushing's Syndrome: State of the Art." *The Lancet Diabetes & Endocrinology* 4.7 (2016): 611-629. Plotz D, Knowlton AI, Ragan C: The natural history of Cushing's disease. *Am J Med* 1952;13:597-614. CD: Cushing's Disease

Key Treatment Goals for CAH Patients

Goal: reduce symptoms of androgen excess and excess glucocorticoid treatment-related complications

CAH Treatment Objectives

- Normalization of adrenal androgens (e.g., androstenedione (A_4))
- Reduce dose of glucocorticoids needed for disease control
- Achieving both of these may improve signs and symptoms of adrenal hyperandrogenism (e.g., hirsutism, menstrual disorders, adrenal rest tumors) and of glucocorticoid overexposure (e.g., central weight gain, hyperglycemia, osteoporosis).
- **Expected registrational endpoints:**
Glucocorticoid sparing; A_4 reduction

CAH Symptoms/Complications

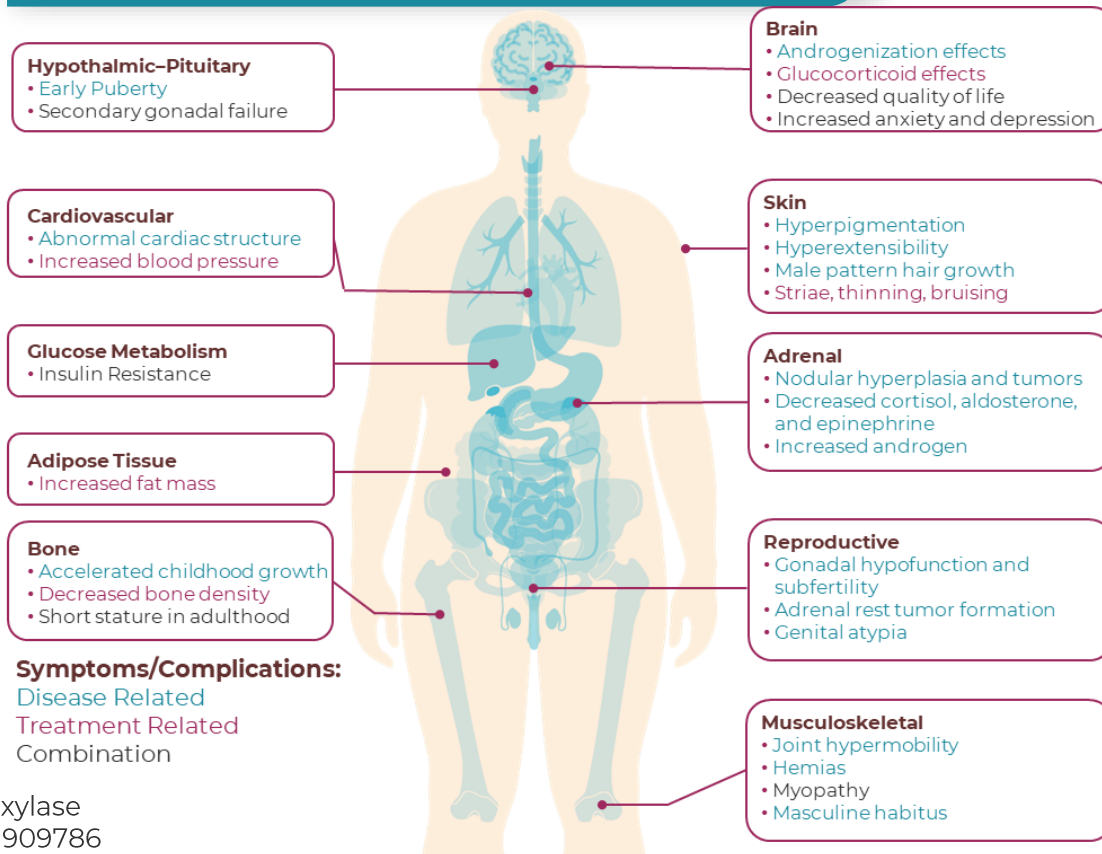


Figure adapted from: Merke D, Auchus R. Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency. New England Journal of Medicine. 2020;383(13):1248-1261.DOI: 10.1056 / NEJMr1909786

Phase I Data Supports Advancing to Studies in Both CAH and Cushing's Disease Patients

Next Steps

1

Review '4894 data package and discuss patient program with global regulators

- Seek confirmation of proposed dose range (40 to >80mg QD)
- Feedback on P2 trial designs
- Seek guidance on registration requirements

2

Initiate clinical program in patients (anticipated 2H22)

- CAH: Targeting single efficacious QD dose
- Cushing's Disease: Targeting patient specific QD dose range

Pipeline Targets Multi-Billion \$ Total Addressable Market with Internally Discovered Drug Candidates

NCE patent portfolio expected to provide protection into the 2040s

PROGRAM	Development Stage (Potential Registrational Endpoints)				Prevalence	
	Preclin	Phase 1	Phase 2	Phase 3	US Total	Global Range per 100,000
Paltusotine (SST2 agonist)	Pharmacologic POC					
Acromegaly	IGF-1 normalization				26K	2.8 - 13
Carcinoid Syndrome	Diarrhea & Flushing				33K	3.7 – 9.7
Nonfunctional NETs	Anti-tumor activity				138K	17 – 46
CRN04777 (SST5 agonist)						
Congenital Hyperinsulinism	Hypoglycemia/GIR				1.5 – 2K	0.64 – 1.3
Syndromic Hyperinsulinism	Hypoglycemia/GIR				2K	Variable
CRN04894 (ACTH antagonist)						
Congenital Adrenal Hyperplasia	A4, GC use				27K	6.7 – 10
Cushing's Disease	Cortisol				10K	2.5 – 3.8
PTH antagonist						
Hyperparathyroidism, HHM	Ca ⁺⁺				1 ^o HPT: 480k 2 ^o HPT: 13.2M HHM: 50-200k/yr.	



Spin-out company advancing nonpeptide precision radiotherapeutics targeting oncology indications.

2021 Accomplishments and Anticipated 2022 Milestones

2021 Accomplishments

- ✓ Initiated Ph 3 PATHFINDER program of paltusotine in acromegaly
- ✓ Phase 1 POC data for CRN04894
- ✓ Phase 1 POC data for CRN04777
- ✓ Launched Radionetics Oncology spinout
- ✓ Strengthened balance sheet
- ✓ Identified potential development candidate PTHR1 antagonists for hyperparathyroidism and HHM

2022 Accomplishments & Anticipated Milestones

- ✓ Strategic partnership for paltusotine in Japan
- ✓ CRN04777 MAD data in 1Q22
- ✓ CRN04894 MAD data in 2Q22
- ✓ Strengthened balance sheet
- CRN04777 patient program initiation in 2H22
- CRN04894 patient program initiation in 2H22
- Initiate IND enabling studies for PTHR1 antagonist

POC: Proof-of-concept; HHM: Humoral hypercalcemia of malignancy; MAD: Multiple-ascending dose