Crinetics Pharmaceuticals

CRN04894: FIRST IN HUMAN SINGLE ASCENDING DOSE (SAD) PRELIMINARY RESULTS

August 10, 2021

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This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

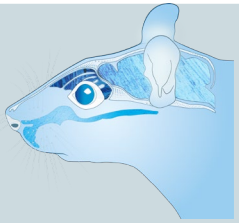
Phase 1 Pharmacologic Proof-of-Concept for CRN04894 in Healthy Volunteers

PK Results	• Orally bioavailable, dose proportional pharmacokinetics
Safety Results	• Well-tolerated • No Serious Adverse Events (SAEs) • All Adverse Events (AEs) considered mild
Pharmacology Results	• Dose-dependent reduction of basal cortisol levels • Dose-dependent suppression of cortisol following ACTH challenge • Evidence of clinically meaningful cortisol suppression
Next Steps	• Multiple Ascending Dose data expected in Q4

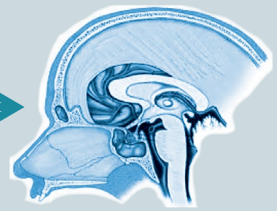
Crinetics' Endocrine Development Strategy: Hormone Levels from Preclinical to Approval

Preclinical POC

ΔHormones,
PK, Safety



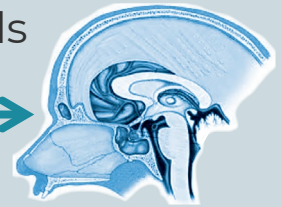
Phase 1 Healthy Volunteers



Phase 1 Healthy Volunteer Safety, Pharmacologic POC

ΔHormones,
PK, Safety

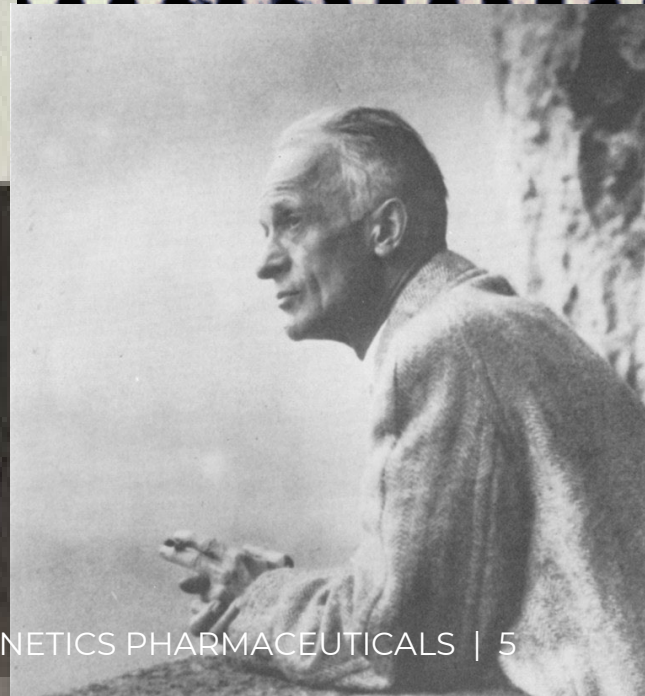
Phase 2/3 Trials (Patients)



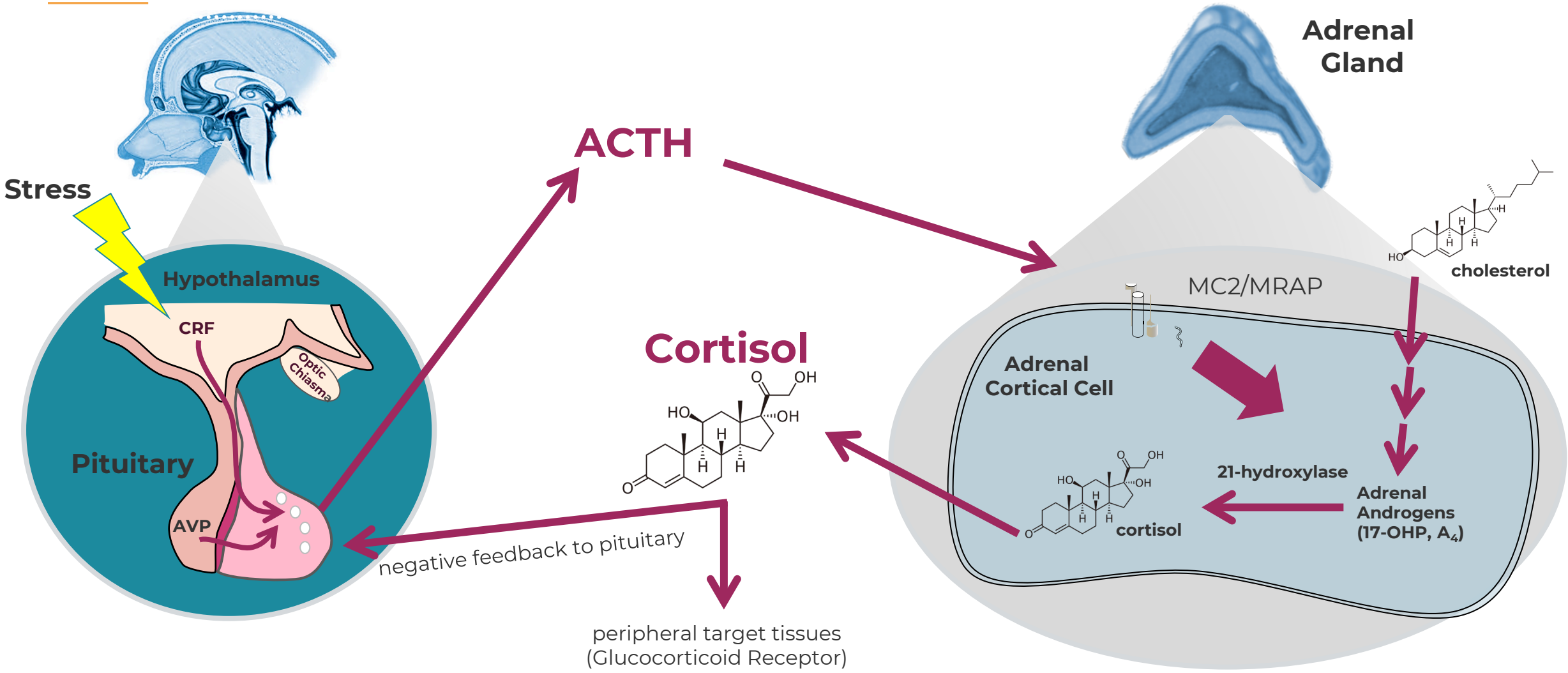
Phase 2,3 Safety, Disease Efficacy

ΔHormones, PROs,
PK, Safety

Harvey Cushing

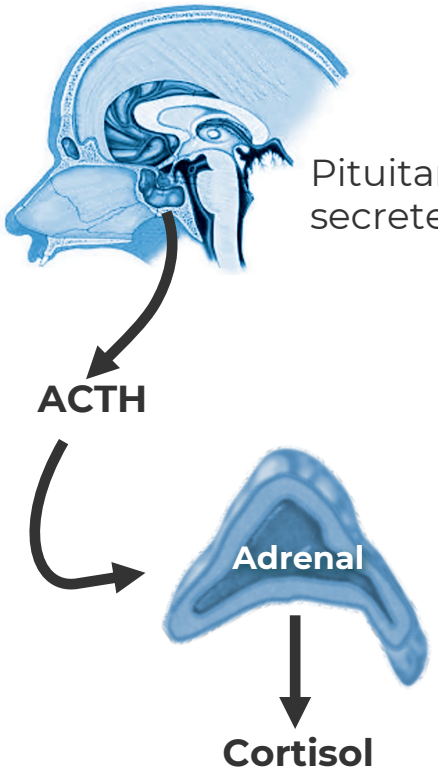


The Hypothalamic-Pituitary-Adrenal (HPA) Axis is the Body's Emergency Response System for Stress

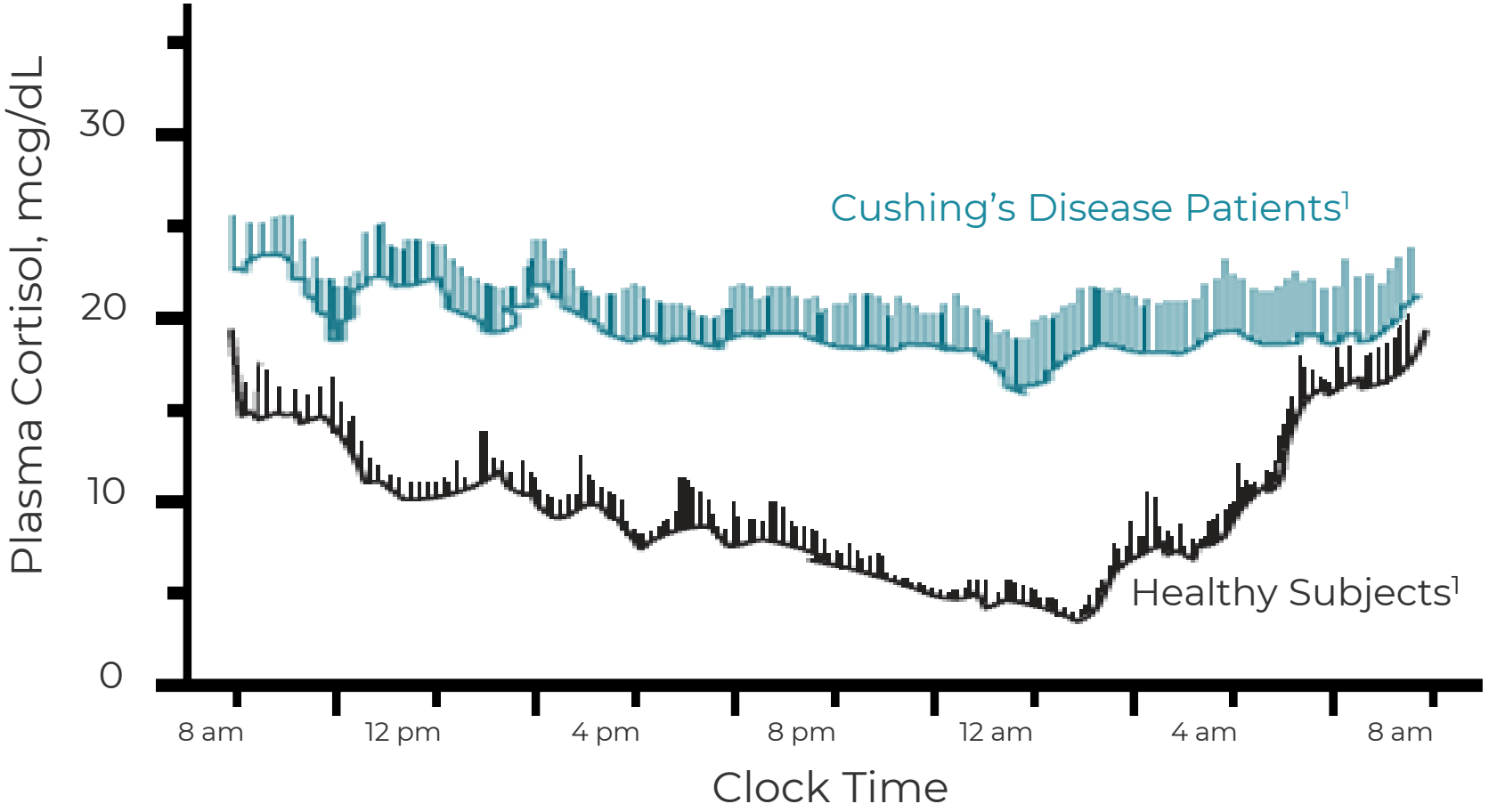


Hypothalamic-Pituitary-Adrenal (HPA) Axis: Cortisol Levels Rise and Fall in a Diurnal Rhythm

Normal Biology

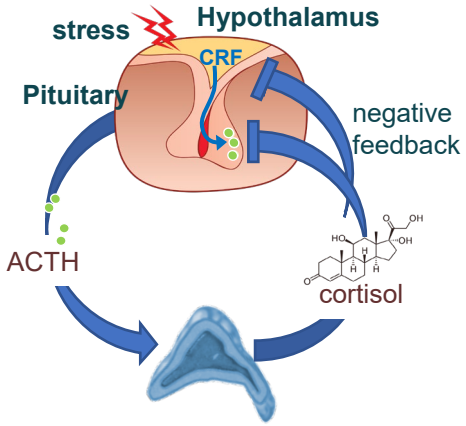
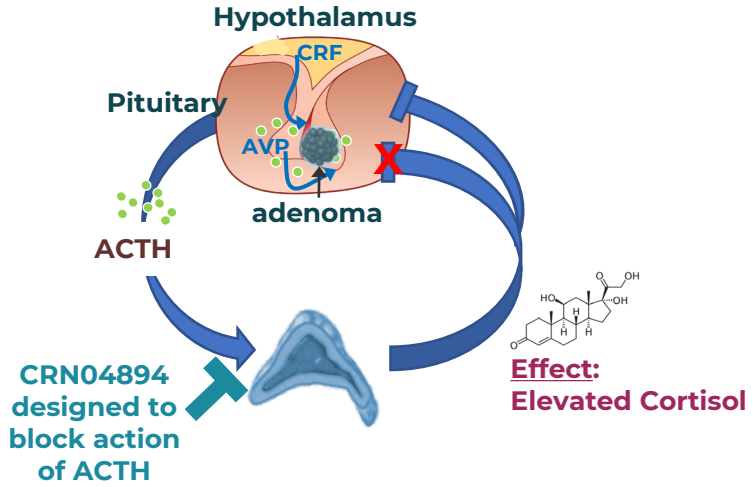
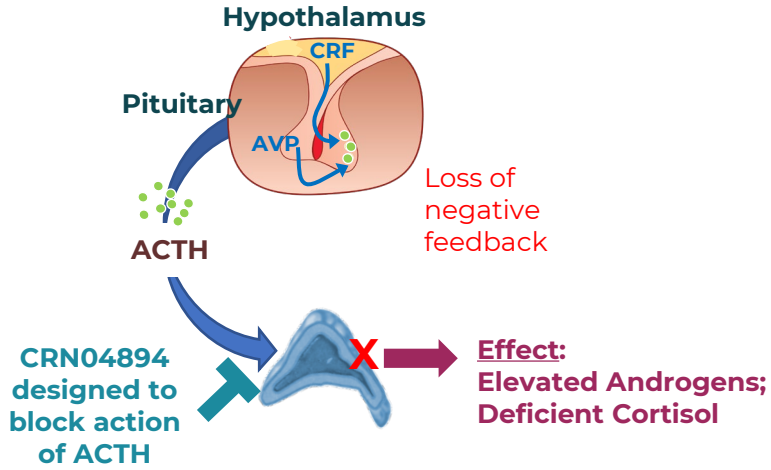


Time course of plasma cortisol levels over a diurnal cycle



[1] Data from Oster et al., Endocrine Reviews 2017 (data shown are mean ± SEM, N=8-10)

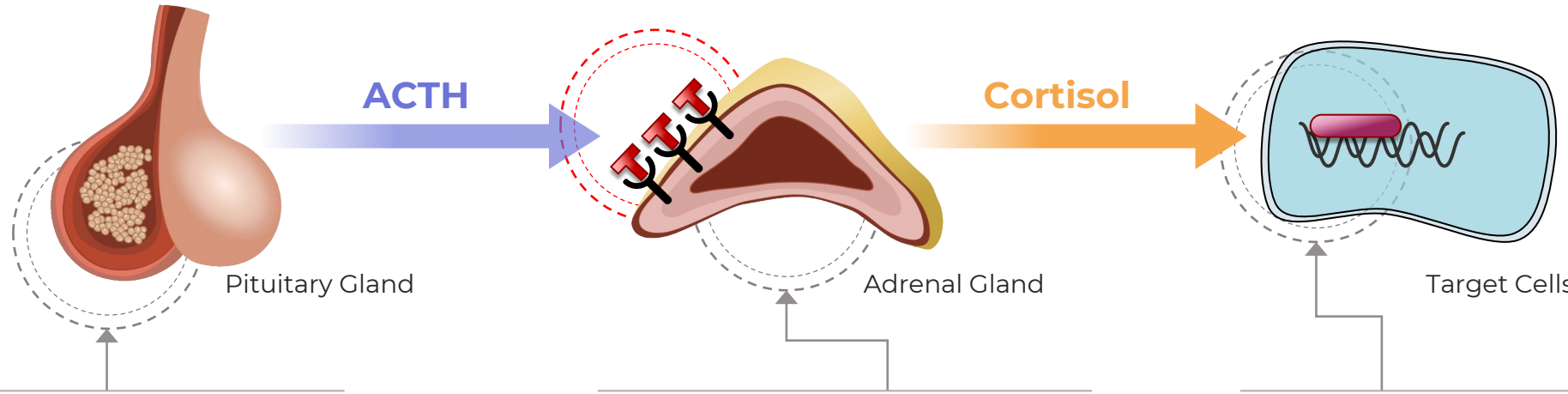
Hypothesis: An Oral, Selective ACTH Antagonist Will Have Utility in Treating Diseases of ACTH Excess

Normal	Cushing's Disease (CD)	Congenital Adrenal Hyperplasia (CAH)
 ACTH Range = 5 – 60 pg/mL [1, 4, 5]	 ACTH Range = 20-200 pg/mL [1]	 ACTH Range = 150-500 pg/mL [2, 3]
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

[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

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

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



Pituitary Directed Agents to Suppress ACTH Secretion

Available: glucocorticoids, pasireotide, cabergoline
- Limited efficacy
- Safety issues

In Development: CRF antagonists

Adrenal Steroidogenesis Inhibitors

Available: ketoconazole, metyrapone/osilodrostat
- Limited Efficacy
- Safety Issues
- Low Adherence

In Development: levoketoconazole

Glucocorticoid Receptor Antagonist

Available: mifepristone
- Efficacy difficult to assess
- Safety issues

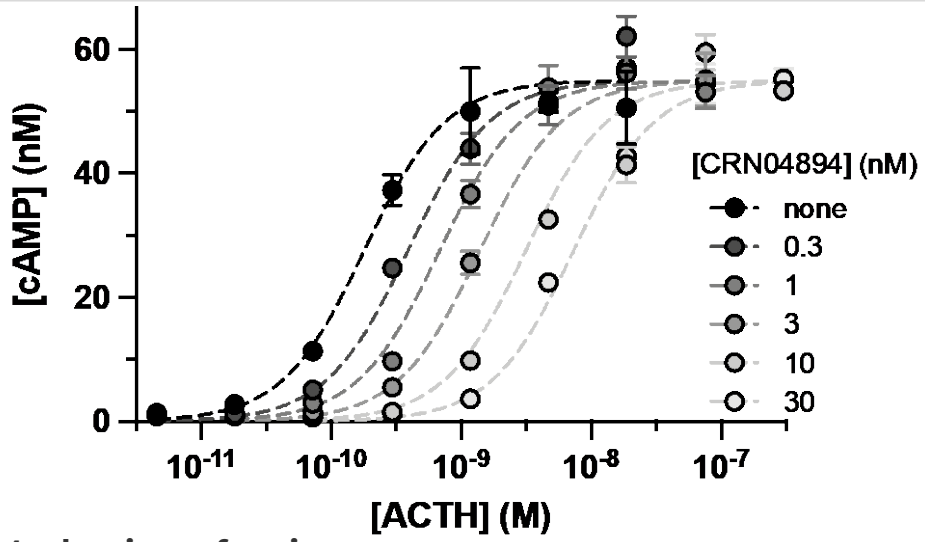
In Development: relacorilant

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

CRN04894 is the Only ACTH Antagonist in Clinical Development

CRN04894 was carefully crafted by Crinetics in-house discovery team

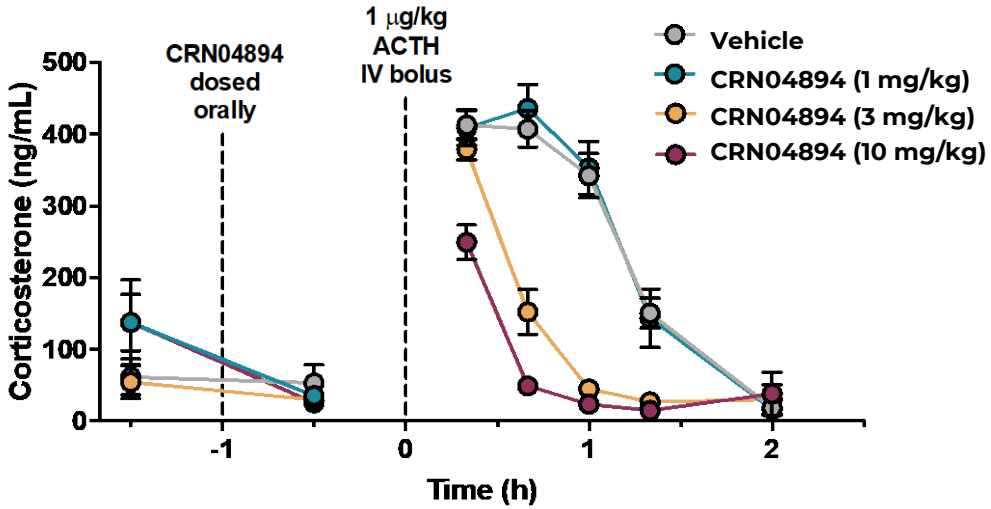
CRN04894 is a potent (K_b= 0.4 nM) competitive antagonist of ACTH signaling



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

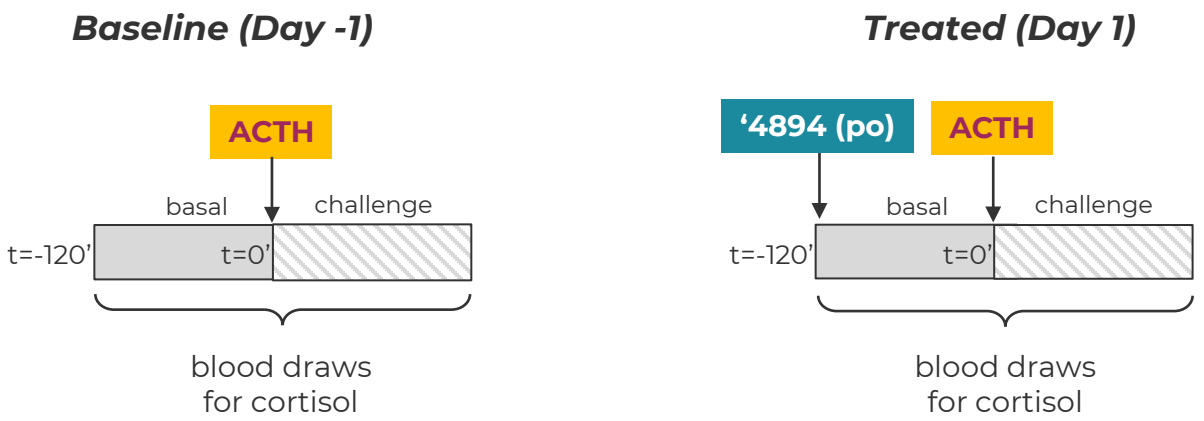
CRN04894 SAD Study Design to Establish Pharmacologic Proof-of-Concept

Follows Crinetics' core endocrine strategy of using hormonal biomarkers to drive development

Study Goals

- Evaluate safety [10-80 mg]
- Evaluate pharmacokinetics: oral absorption, dose-proportional exposure, half-life [10-80 mg]
- Evaluate dose-response & PK/PD on basal cortisol [10-80 mg]
- Evaluate dose-response & PK/PD using supra-pathophysiologic ACTH challenge (250 mcg) [10-80 mg]
- Evaluate cortisol suppression with selected dose in response to disease-relevant ACTH challenge (1 mcg) [80 mg only]

ACTH Challenge Test

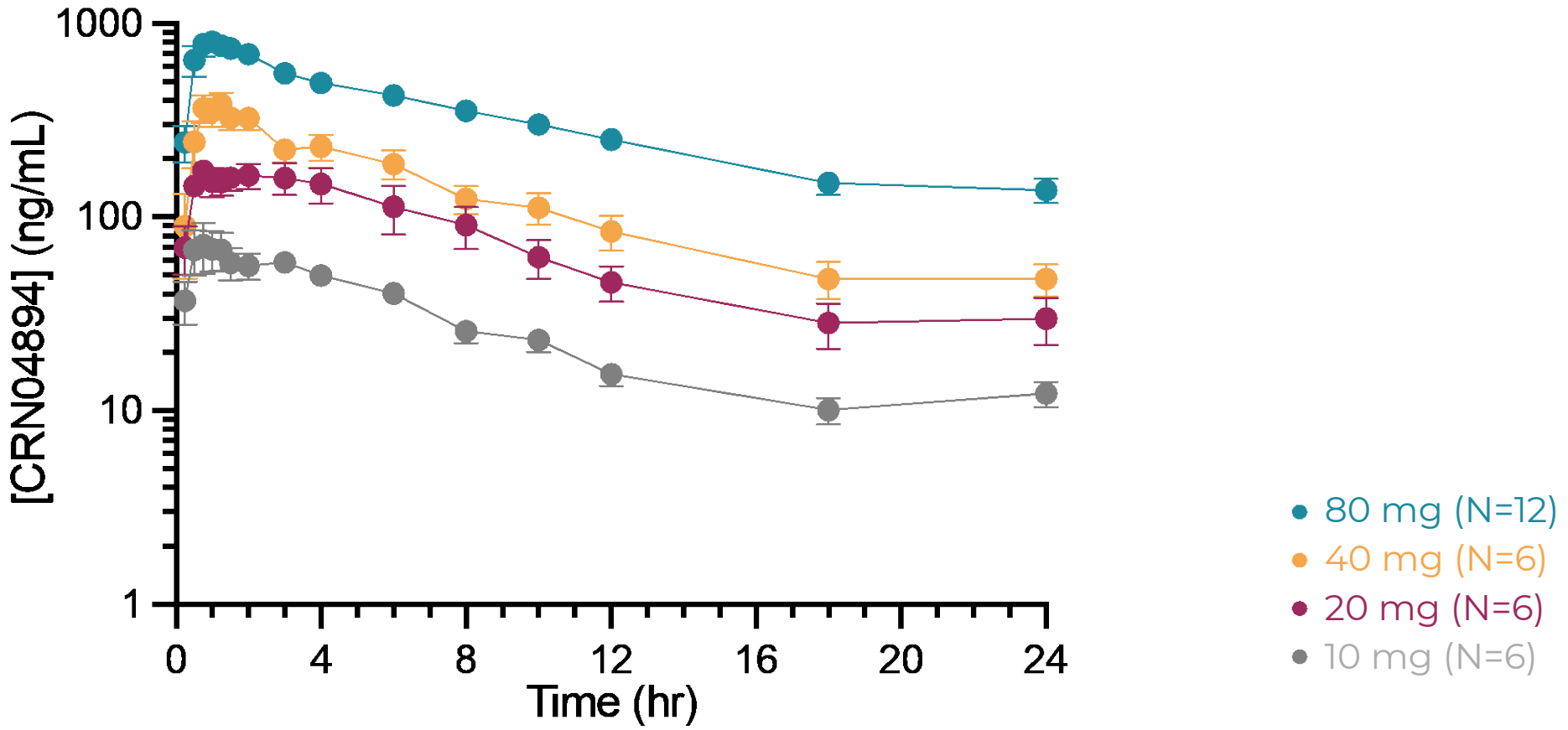


Healthy volunteers received single oral dose of CRN04894 (n=8, 6 active/2 Pbo in each cohort)

Proof of concept: dose dependent suppression of basal cortisol and ACTH-stimulated cortisol with CRN04894

PK Results: CRN04894 Showed Oral Bioavailability With Dose-Proportional Exposure

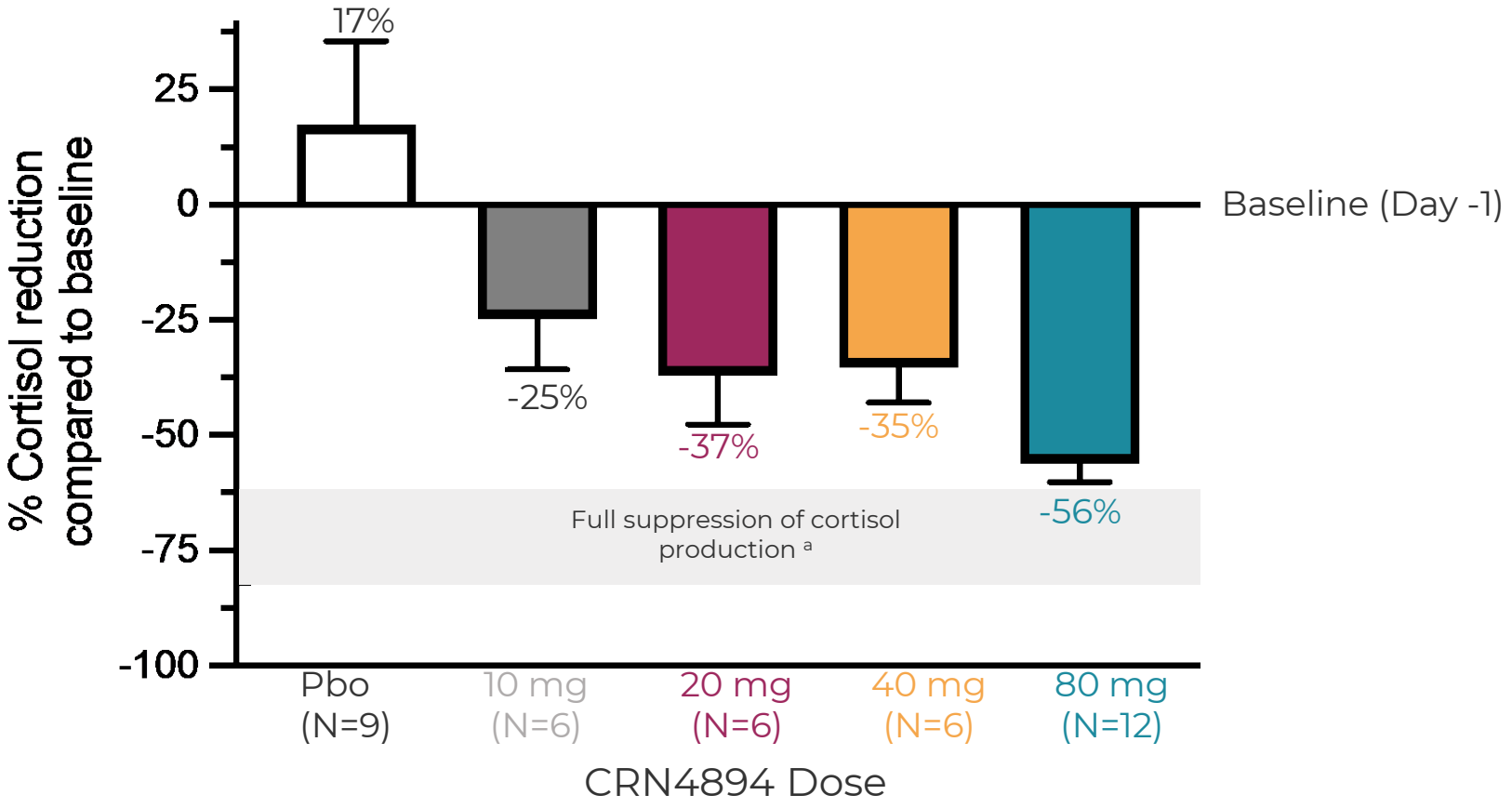
Half-life ~24 hour and t_{max} ~1 hour



Data shown are mean±SEM

CRN04894 Rapidly Reduced Basal Cortisol Output from Adrenal Glands

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

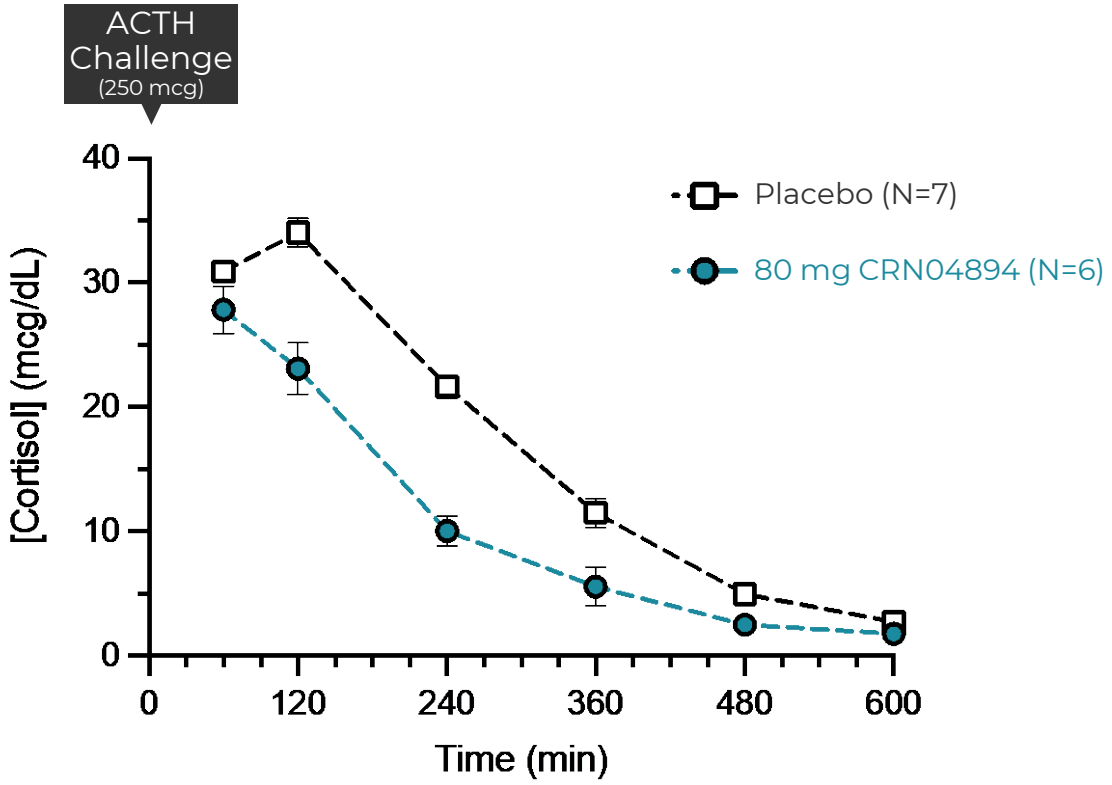


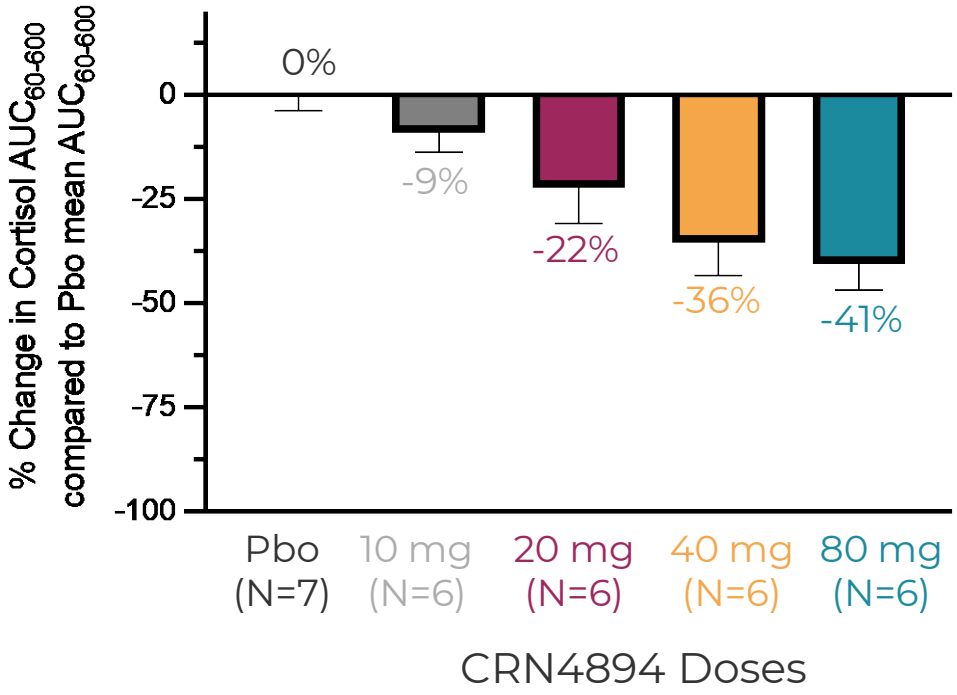
Data shown are mean±SEM

[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

Dose-Dependent Suppression of Cortisol Observed Following Supra-Pathophysiologic ACTH Challenge (250 mcg)

CRN04894 resulted in strong cortisol suppression (41% @ 80 mg) despite anticipated ACTH exposure orders of magnitude higher than disease states

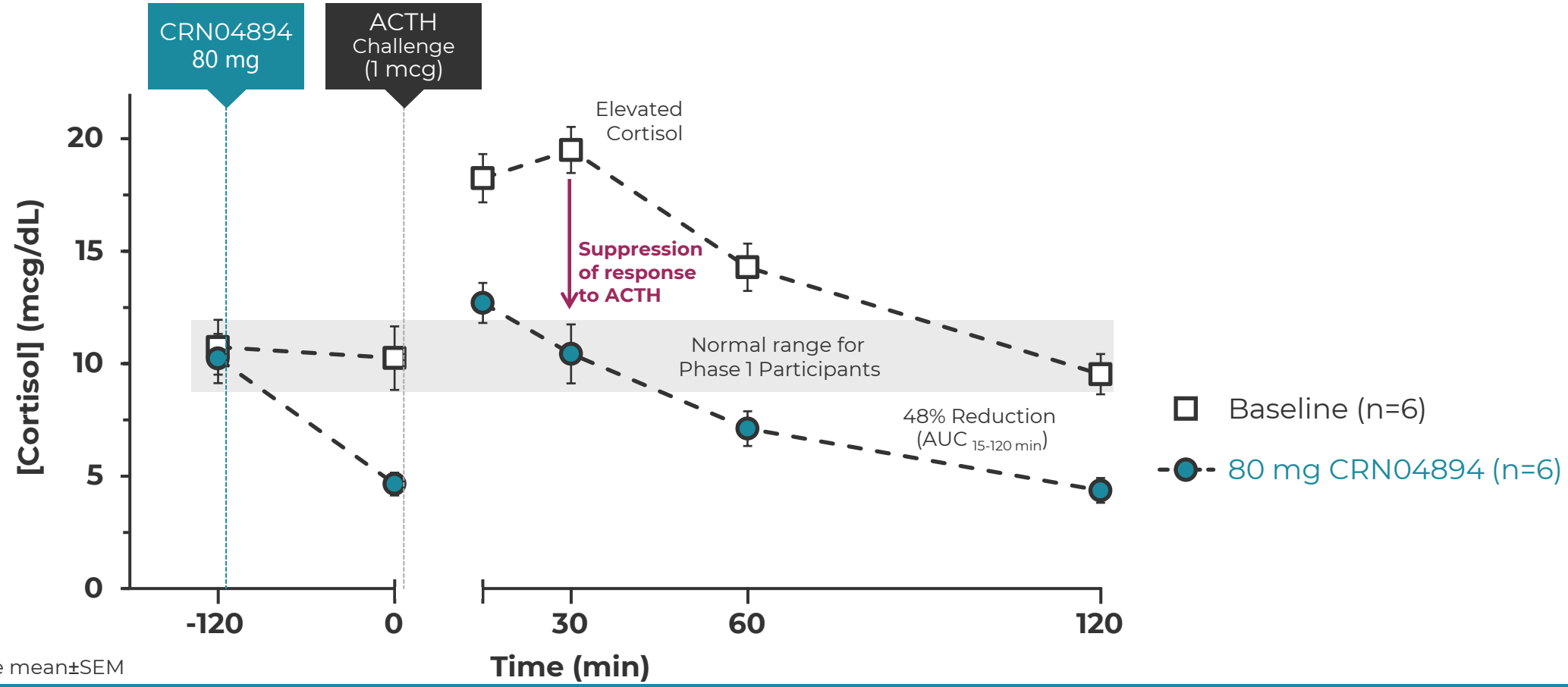




Data shown are mean±SEM

Clinically Meaningful Cortisol Suppression Observed in Response to Disease-relevant ACTH Challenge (1 mcg)

CRN04894 maintains normal cortisol levels for these subjects in face of disease-relevant ACTH (1 mcg) challenge



Data shown are mean±SEM

Conclusions from CRN04894 SAD Results

Objectives

- Safety and tolerability
- Drug-like Pharmacokinetics
- PK/PD for suppression of ACTH-induced adrenal activity

Generally safe and well tolerated at single doses from 10 to 80 mg

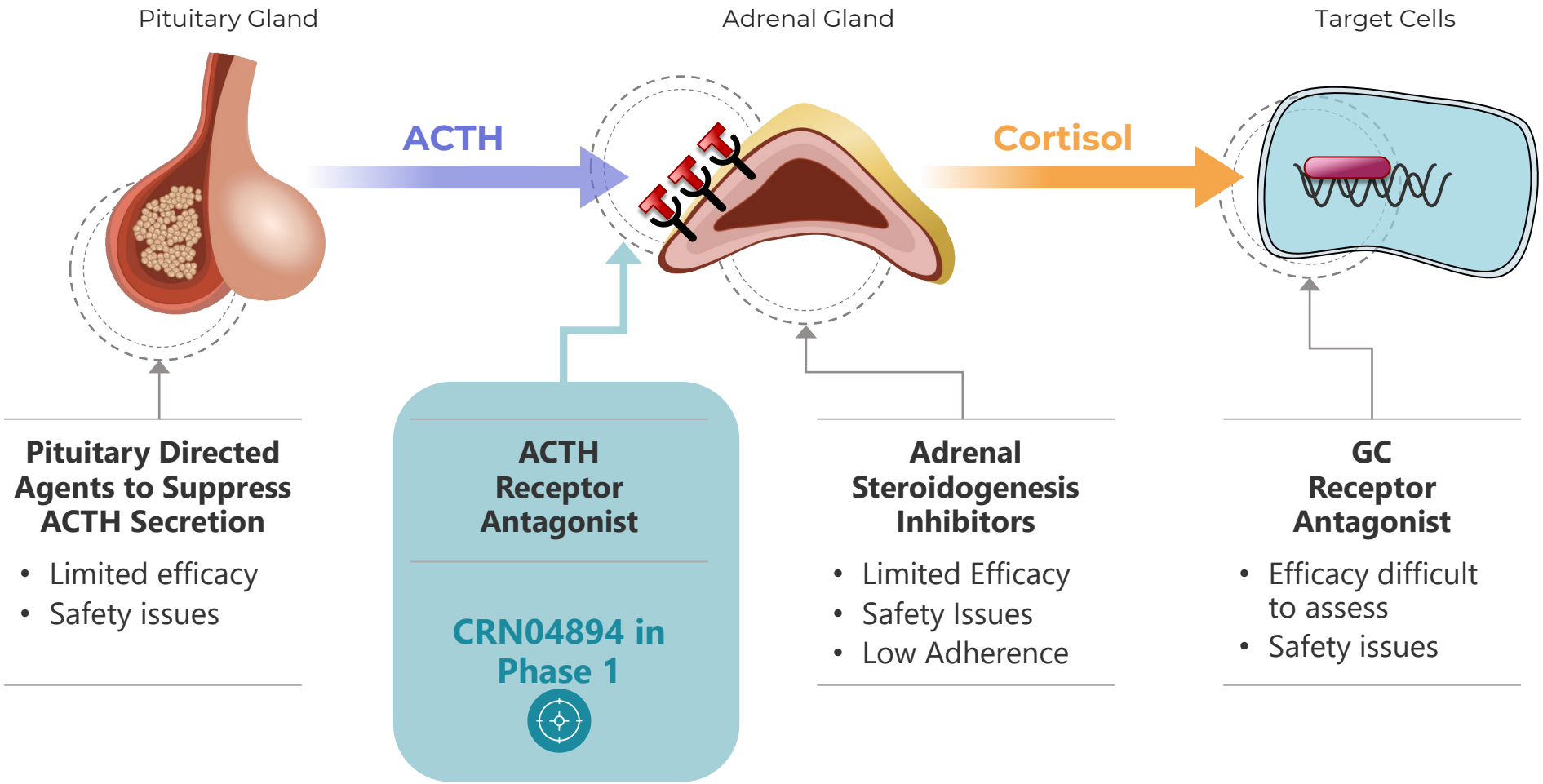
Achieved targeted pharmacokinetic profile

- **Rapidly absorbed after oral administration (tmax ~1 hr)**
- **Dose proportional exposure from 10 to 80 mg**
- **Favorable half-life of ~24 hours**

Demonstrated pharmacologic proof-of-concept for ACTH antagonism

- **Strong suppression of basal cortisol (56%)**
- **Dose-dependent, strong cortisol suppression (41%) following supra-pathophysiologic ACTH (250 mcg) challenge**
- **Maintains normal cortisol levels for the Phase 1 participants in face of disease-relevant ACTH (1 mcg) challenge**

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



Pipeline With Two Candidates Beyond Pharmacologic Proof-of-Concept

PROGRAM	Development Stage	Registrational Endpoint	Prevalence	
	Preclin / Phase 1 / Phase 2 / Phase 3		US Total	Global Range per 100,000
Paltusotine (SST2 agonist)	Pharmacologic POC			
Acromegaly		IGF-1 Levels	26K	2.8 – 13.0
Carcinoid Syndrome		Diarrhea & Flushing	33K	3.7 – 9.7
Nonfunctional NETs		Anti-tumor activity	138K	17 – 46
CRN04894 (ACTH antagonist)				
Cushing's Disease		Cortisol Levels	10K	2.5 – 3.8
Congenital Adrenal Hyperplasia (CAH)		Adrenal Androgens/ Glucocorticoid use	27K	6.7 – 10.0
CRN04777 (SST5 agonist)				
Congenital Hyperinsulinism (CHI)		Glucose Levels	2-4K	0.64 – 1.3
US TOTAL			**~236K**	

On Track to Achieve 2021 Goal of Three Programs with Proof-of-Concept Demonstrated in the Clinic

	Q1	Q2	Q3	Q4
Paltusotine SST2 Agonist for Acromegaly & NETs **POC Achieved**		Initiate PATHFNDR-1 ✓	Initiate PATHFNDR-2	
			Initiate Phase 2 NETs Trial in Carcinoid Syndrome	
CRN04894 ACTH Antagonist for Cushing's Disease & CAH **POC Achieved**	Initiate Phase 1 ✓		Phase 1 SAD Data ✓	
				Phase 1 MAD Data
CRN04777 SST5 Agonist for Congenital HI **Phase 1 Underway**	Initiate Phase 1 ✓		Phase 1 SAD Data (Sep)	
			Phase 1 MAD Data	

'4777 program follows development strategy validated by paltusotine and '4894