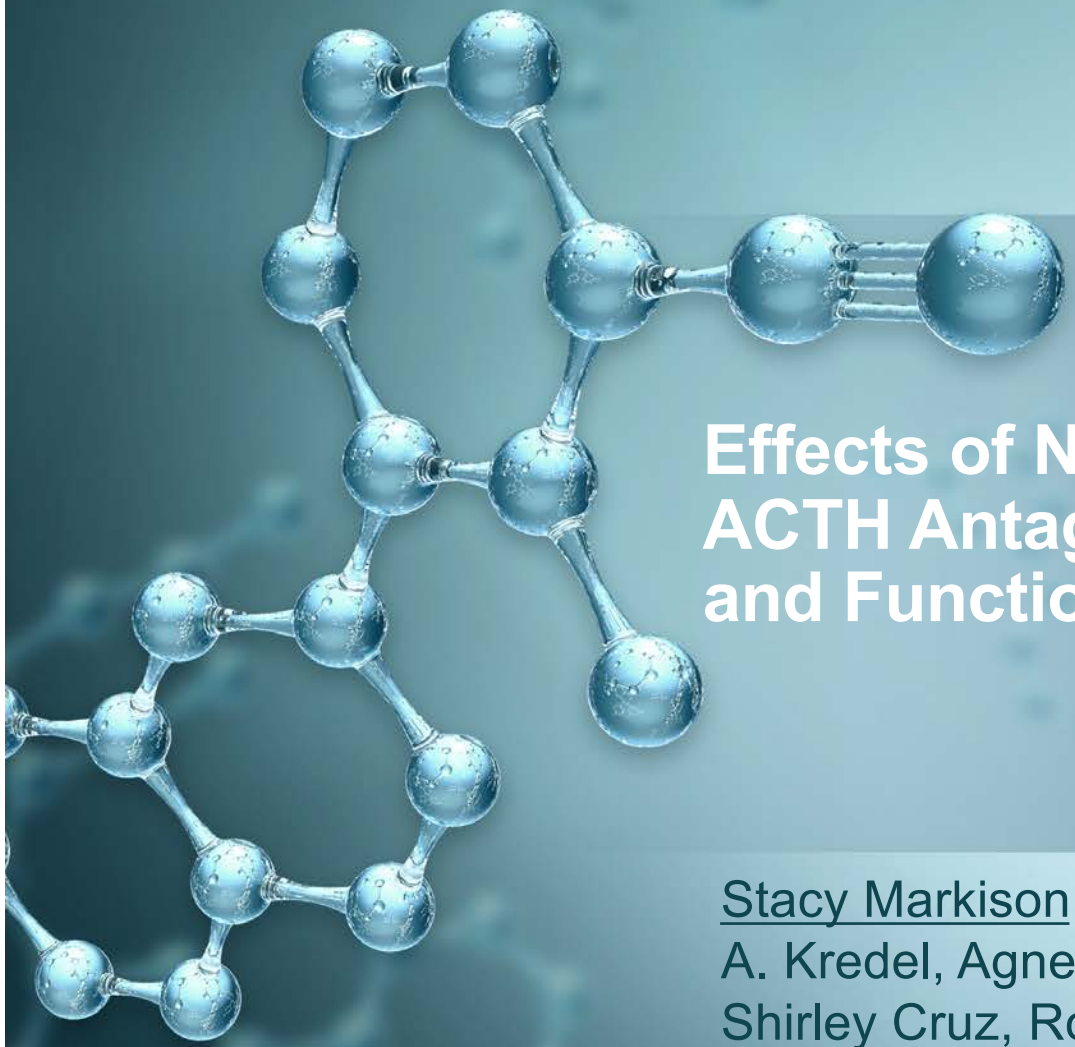
e-ECE 2020: OC6.1 Late-Breaking

Crinetics Pharmaceuticals



Effects of Nonpeptide Orally Bioavailable ACTH Antagonists on Adrenal Gland Size and Function in Rats

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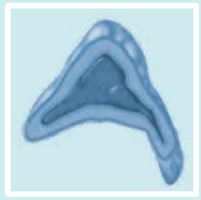
Disclosures

Employed by and holds equity in Crinetics Pharmaceuticals, Inc.

Background



Crinetics is developing orally available, small molecule ACTH antagonists that suppress ACTH-induced secretion of glucocorticoids by inhibiting the melanocortin 2 receptor (MC2R)

ACTH antagonism may be a useful therapeutic approach for diseases of ACTH excess, such as Cushing's disease, ectopic ACTH syndrome, and congenital adrenal hyperplasia

Here we describe the effects of repeated administration of ACTH antagonists on adrenal gland size, morphology, and function in rat models

ACTH blockade via MC2R antagonism

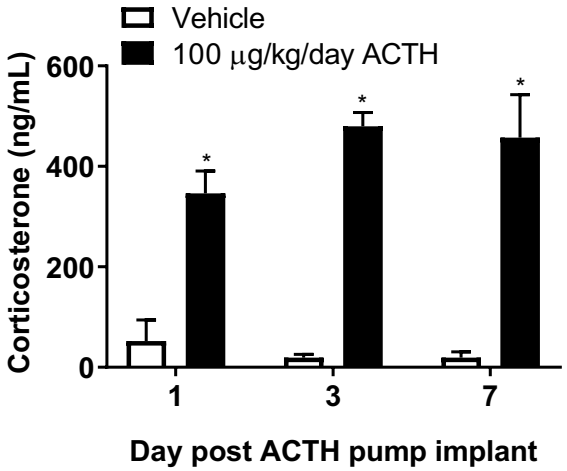
- Potent and selective ACTH antagonists were used to examine effects of sustained antagonism of MC2R on adrenal gland size and function
- ACTH antagonists used in studies described here are potent at rat and human MC2R, selective over other MCR subtypes, are stable, orally bioavailability, and appear to have a good safety profile in initial tests

Compound Characteristics	Value
MC2R rat potency (K_B)	≤ 1.2 nM
Selectivity for human MC2R (K_B) over other MCR	>2940-fold
Rat LM stability ($t_{1/2}$)	> 200 minutes
Rat oral bioavailability (F)	> 45%
Safety Screening Tests	**Value**
CYP450 inhibition	> 10 µM
hERG inhibition	> 10 µM

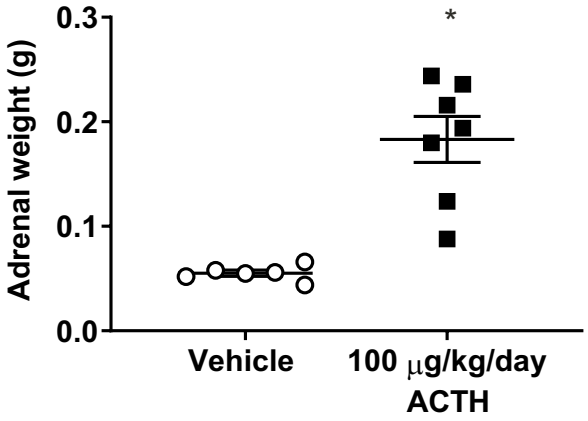
Disease Model of ACTH excess: Continuous ACTH administration causes hypercortisolemia and adrenal gland hypertrophy

Administration of 100 µg/kg/day ACTH(1-24) by subcutaneously implanted minipumps for 7 days in male Sprague Dawley rats induced elevated levels of corticosterone and adrenal gland hypertrophy

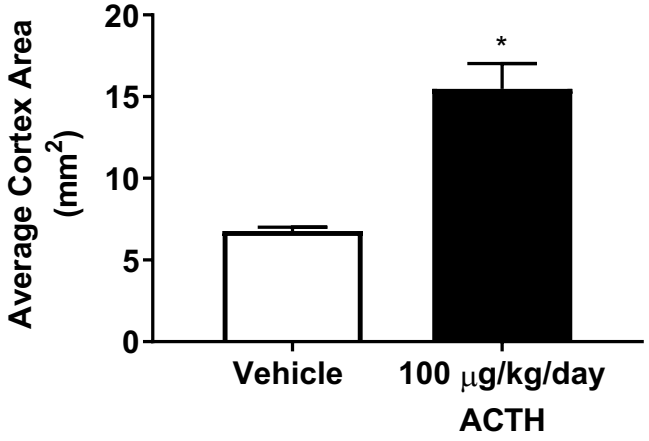
Increased Plasma Corticosterone

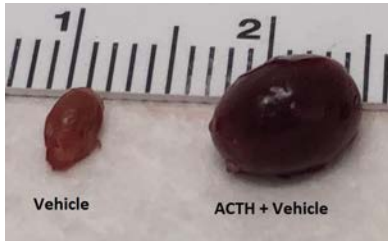


Increased Paired Adrenal Weight



Increased Adrenal Cortex Area

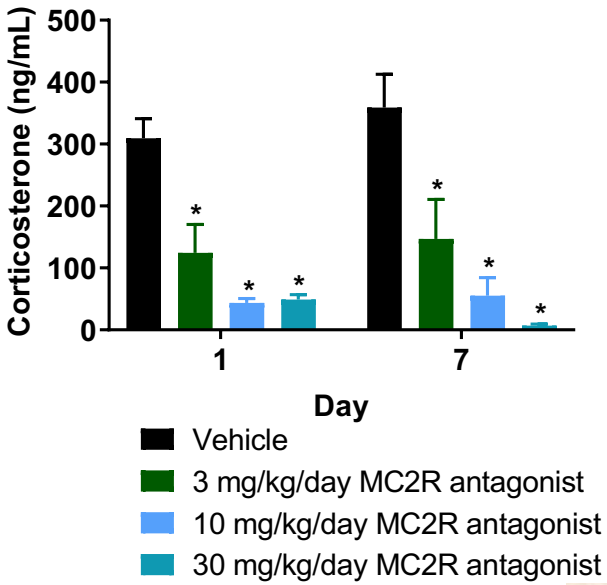




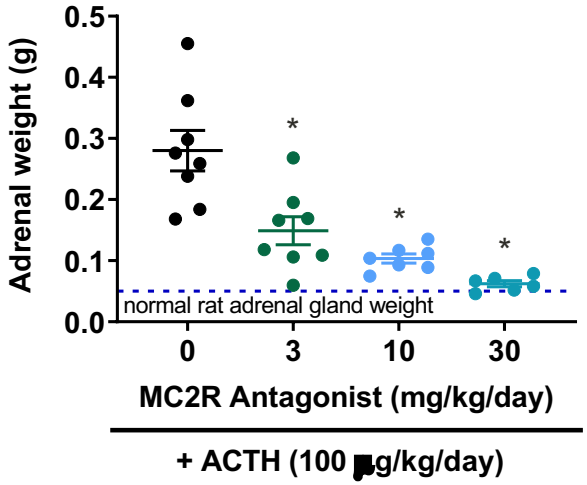
ACTH antagonists reverse the effects of ACTH excess

MC2R antagonist administration once daily for 7 days in rats with ACTH excess dose-dependently reduced corticosterone levels and prevented adrenal gland hypertrophy

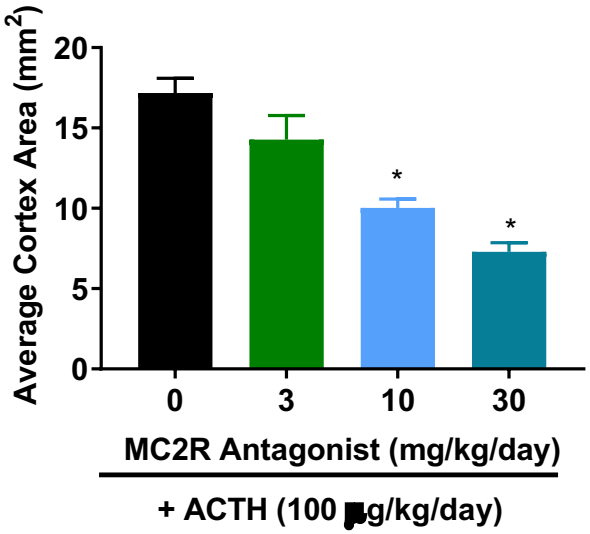
Decreased Plasma Corticosterone

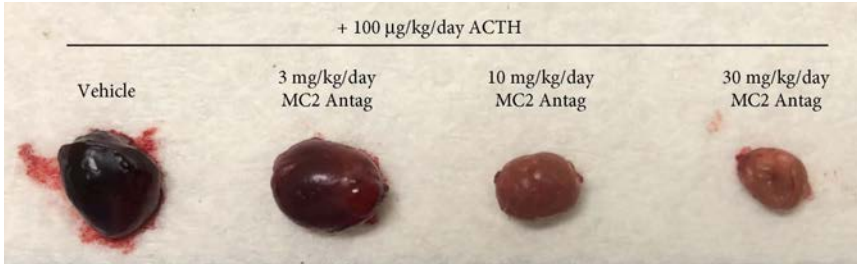


Decreased Paired Adrenal Weight



Decreased Adrenal Cortex Area

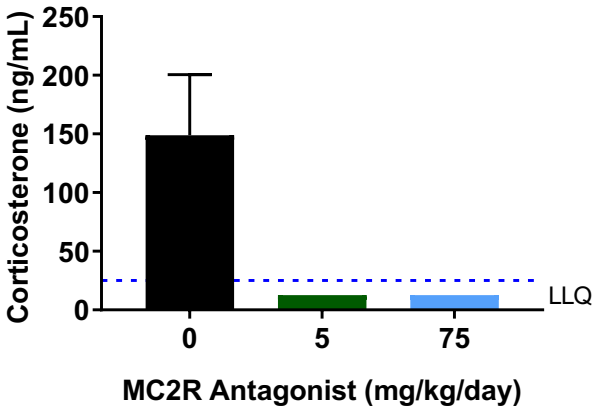




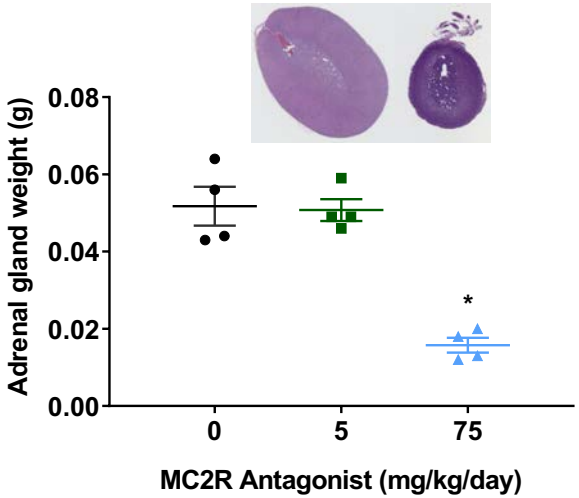
Differential dose dependent effects of repeated ACTH antagonist administration under basal ACTH conditions

Repeated oral administration of an MC2R antagonist over 14 days suppressed corticosterone but only caused adrenal gland atrophy at supra-pharmacological doses with greatest effects in ZF and ZR

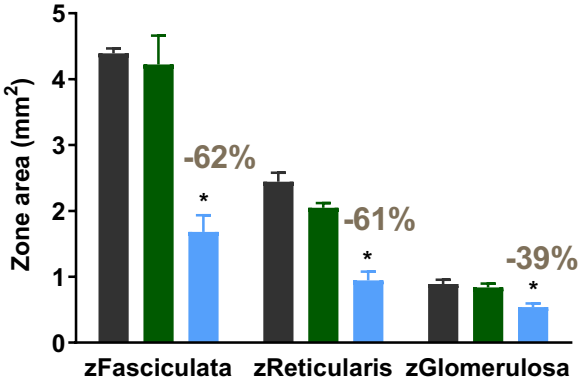
Decreased Plasma Corticosterone

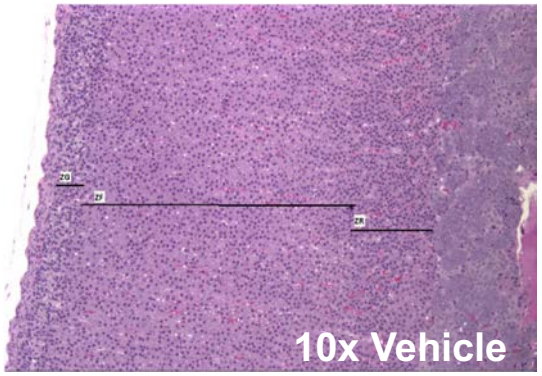


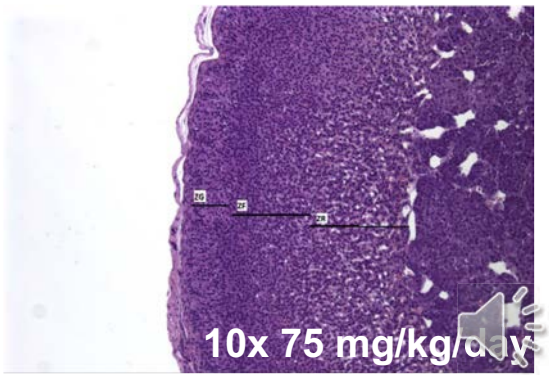
Paired Adrenal Weight



Adrenal Zone Area



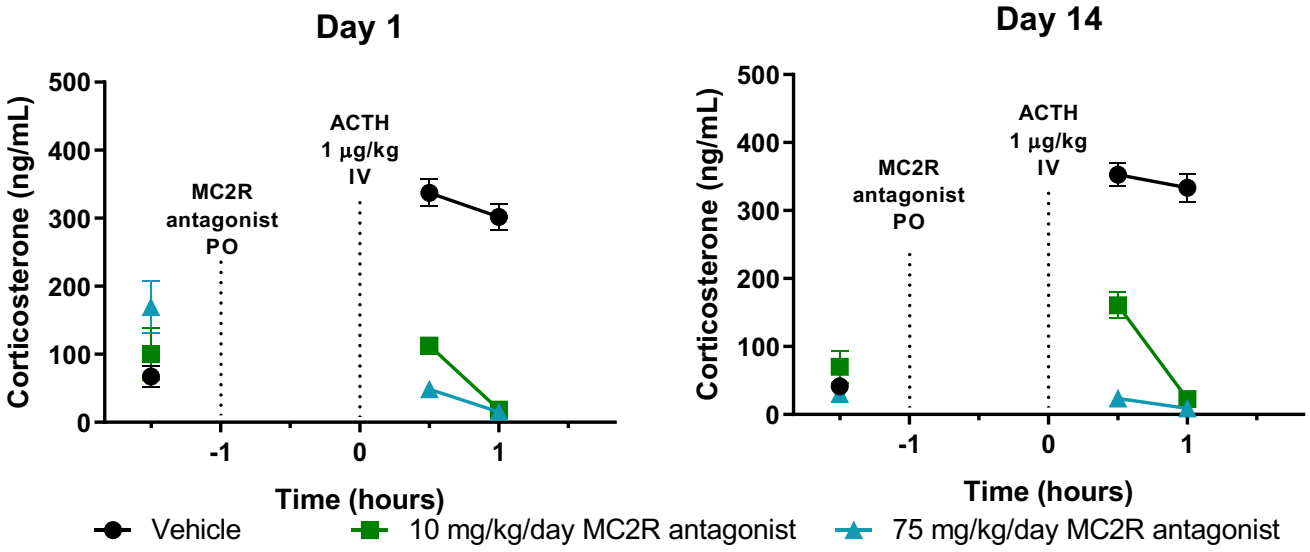




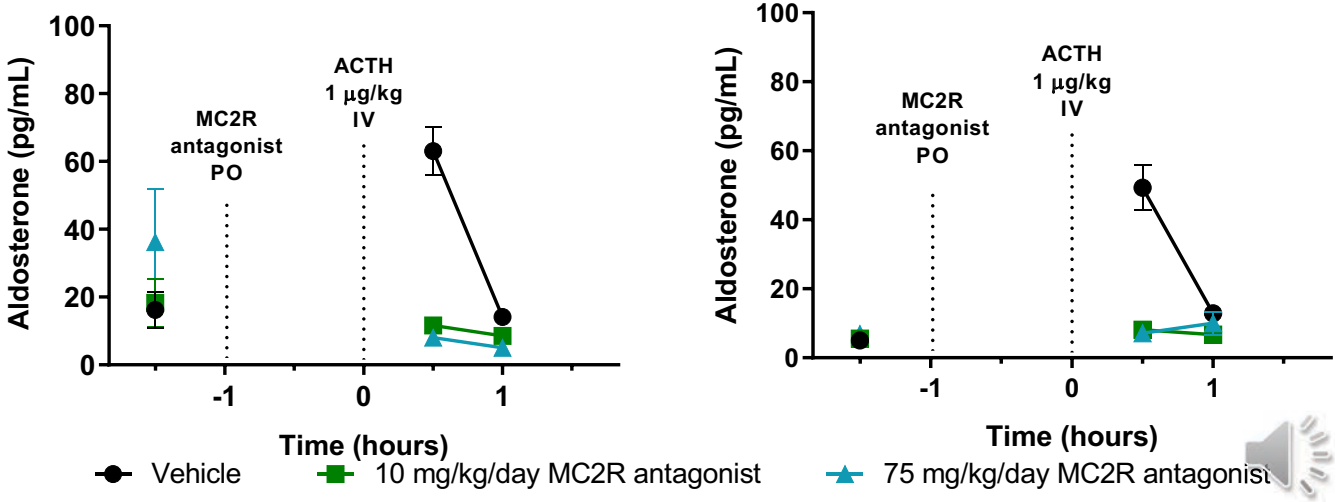
Adrenal function effects with repeated ACTH antagonist administration in conditions of basal ACTH

MC2R antagonist was orally administered once daily for 14 days and ACTH-stimulation test was used to evaluate adrenal function

MC2R antagonist dose-dependently suppressed corticosterone stimulated by ACTH



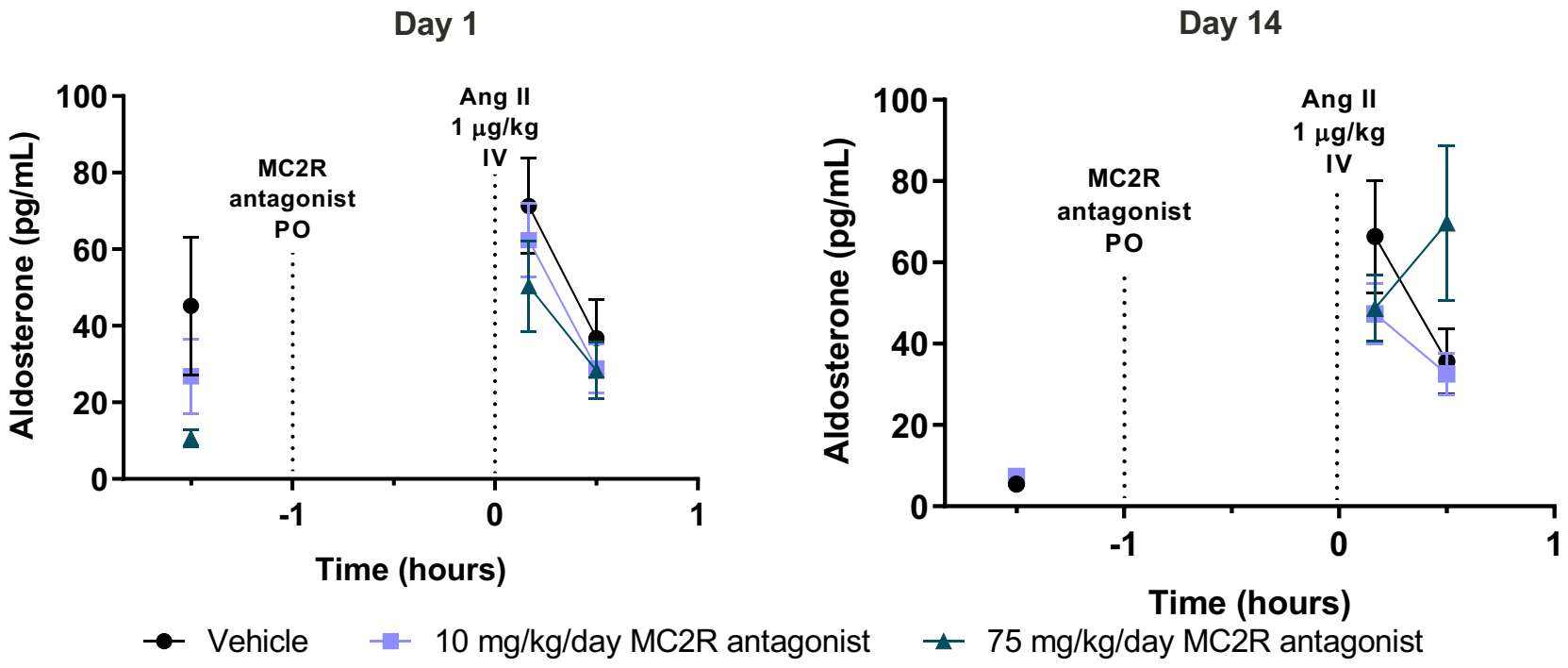
MC2R antagonist suppressed aldosterone stimulated by ACTH



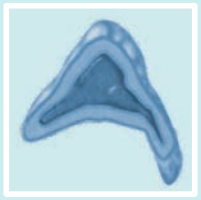
Repeated ACTH antagonist did not suppress aldosterone stimulated by Angiotensin II

To specifically investigate the effects of ACTH antagonism on the renin-angiotensin system, rats were treated with the MC2R antagonist over 14 days and Angiotensin II-stimulated aldosterone was evaluated

MC2R antagonist had minor effects on aldosterone stimulated by Angiotensin II



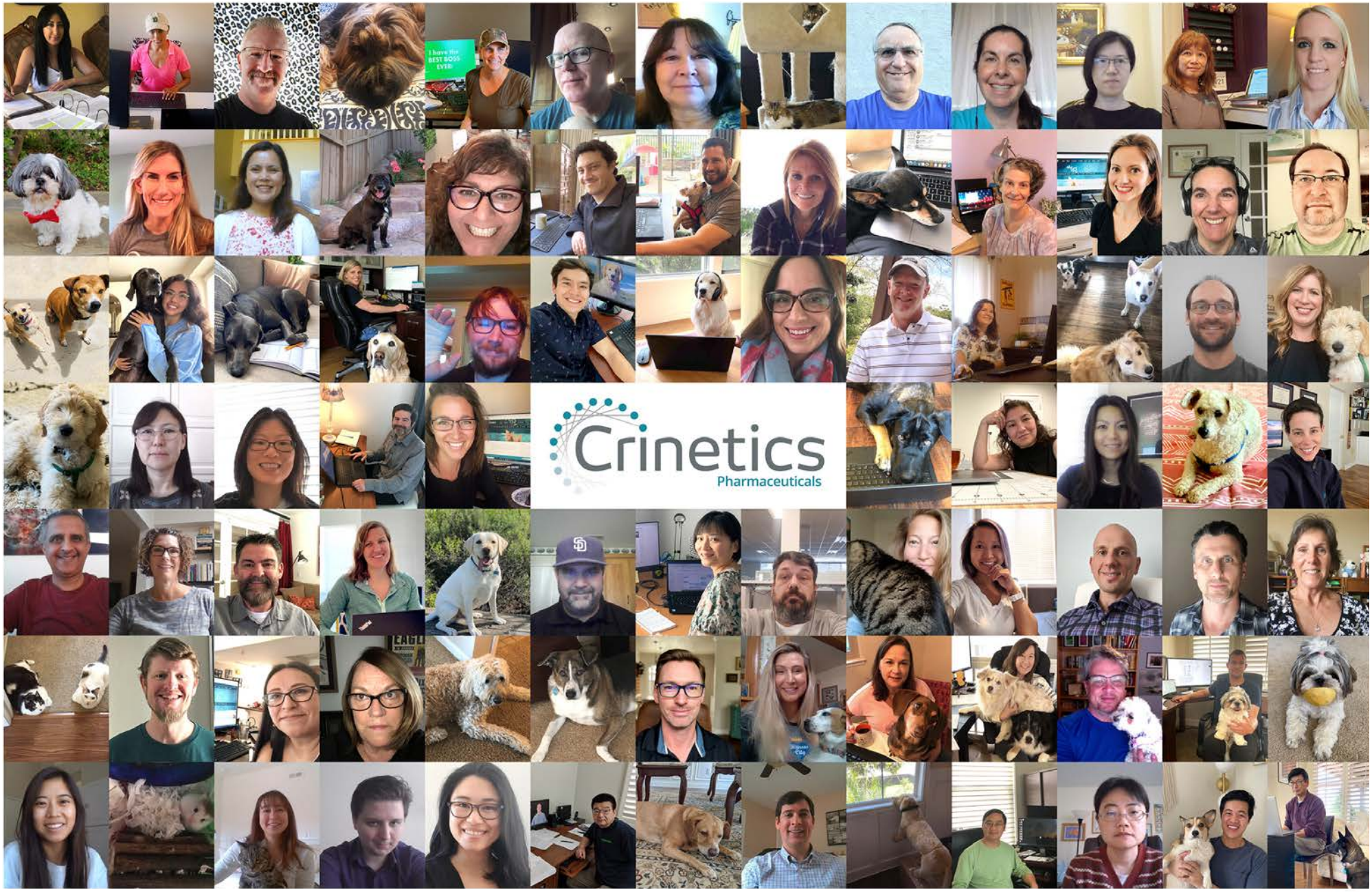
Conclusions



ACTH antagonists effectively suppress corticosterone and mitigate adrenal hypertrophy in a rat model of ACTH excess

These findings suggest that inhibitors of MC2R act as functional ACTH antagonists in vivo and may have therapeutic utility for diseases of ACTH excess

Under basal ACTH conditions, ACTH antagonists suppress corticosterone and aldosterone stimulated by ACTH but not aldosterone stimulated by Angiotensin II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