EFFECTS OF CRN04894, A NONPEPTIDE ORALLY BIOAVAILABLE ACTH ANTAGONIST, ON CORTICOSTERONE IN RODENT MODELS OF ACTH EXCESS

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Disclosures

Employed by and holds equity in Crinetics Pharmaceuticals, Inc
The Hypothalamic-Pituitary-Adrenal (HPA) axis is the body’s emergency response system for stress

**Adrenocorticotropic hormone (ACTH)**
- Secreted by pituitary and acts at MC2 receptor on the adrenal

**Cortisol**
- Secreted by the adrenal and
  - Provides negative feedback to the pituitary
  - Acts at peripheral target tissues via the Glucocorticoid Receptor

**Diseases of excess ACTH include:**

1. **Cushing’s disease and ectopic ACTH syndrome**
   - Hypercortisolemia
   - Central obesity and round face
   - Dorsal and supraclavicular fat pads
   - Hypertension, bone loss, hyperglycemia
   - Psychiatric disturbances

2. **Congenital adrenal hyperplasia**
   - Elevated adrenal androgens
   - Early puberty
   - Shorter final height
   - Masculine characteristics in females
CRN04894 is an oral ACTH antagonist for the treatment of diseases of excess ACTH

CRN04894 is an oral nonpeptide antagonist that blocks the action of ACTH on melanocortin 2 receptors (MC2R) on the adrenal gland

CRN04894 has the potential to:

- Reduce cortisol in Cushing’s disease and ectopic ACTH syndrome
- Reduce adrenal androgens in congenital adrenal hyperplasia
CRN04894 is an orally bioavailable small molecule that is potent and selective at MC2R

CRN04894 is a potent and selective antagonist of human and rat MC2R with desirable drug-like properties

<table>
<thead>
<tr>
<th>Property</th>
<th>CRN04894</th>
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<tbody>
<tr>
<td>MC2R potency (K_B, nM)_a</td>
<td>Human</td>
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<tr>
<td></td>
<td>Rat</td>
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<tr>
<td>Selectivity (IC_{50}, nM)_b</td>
<td>hMC1R</td>
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<td>hMC3R</td>
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<td></td>
<td>hMC4R</td>
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<td>hMC5R</td>
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<tr>
<td>Oral bioavailability (F, %)</td>
<td>Rat</td>
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<td>Dog</td>
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</table>

*a* equilibrium binding constant calculated from functional cell-based assays that measure the inhibition of ACTH-induced cellular cAMP levels

*b* half-maximal inhibitory concentration of compound required to block binding of the radiolabeled α-MSH to MCR-containing membranes
Continuous administration of ACTH causes hypercortisolemia and adrenal gland hypertrophy in a rat model of excess ACTH.

Subcutaneous administration of 100 μg/kg/day ACTH(1-24) via osmotic pumps for 7 days in male Sprague Dawley rats causes increased plasma corticosterone levels and adrenal gland hypertrophy.
Oral administration of CRN04894 suppressed corticosterone levels and reversed adrenal gland hypertrophy

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.

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Implantation of ACTH-secreting tumor cells in mice serves as a preclinical model of excess ACTH.

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 levels by 34 days post inoculation.

- **4-fold increase in ACTH**
- **2-fold increase in CORT**
Oral administration of CRN04894 suppressed corticosterone levels in AtT-20 tumor bearing mice

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

CRN04894 is an effective ACTH antagonist that suppresses corticosterone secretion in both rat and mouse preclinical models of excess ACTH.

CRN04894 has potential therapeutic utility as an oral medication for treating diseases of excess ACTH.

Phase 1, First in Human studies in healthy volunteers with CRN04894 designed to evaluate clinical proof of concept are ongoing.
Key references


