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Crinecerfont and Mechanism of Action

Thank you for contacting Neurocrine Biosciences with your unsolicited medical information request regarding the mechanism of action of crinecerfont. Crinecerfont is currently not approved by the US Food and Drug Administration or another regulatory body for the treatment of any indication.

Congenital Adrenal Hyperplasia (CAH) Disease Background

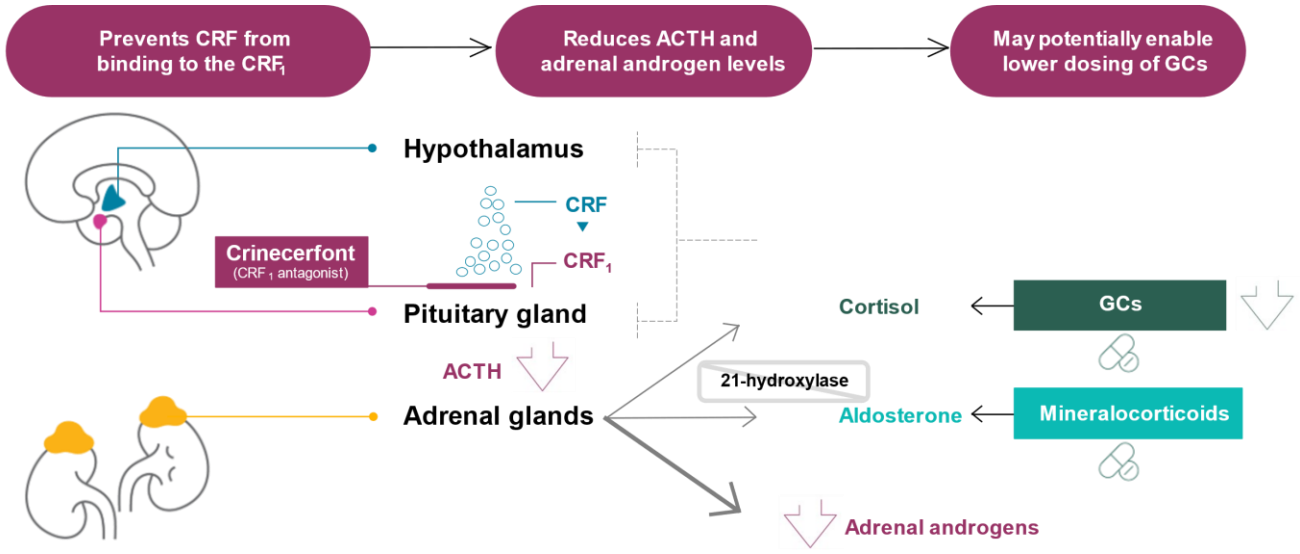
The hypothalamic-pituitary-adrenal (HPA) axis is a signaling cascade in which the hypothalamus produces corticotropin-releasing factor (CRF), a regulator of pituitary adrenocorticotropic hormone (ACTH) synthesis and secretion. CRF acts on the corticotropin-releasing factor type 1 (CRF_1) receptor in the anterior pituitary to signal the release of ACTH, which stimulates the adrenal glands to produce hormones, such as cortisol, aldosterone, and adrenal androgens.[1] 21-hydroxylase is a key enzyme in the production of cortisol and aldosterone.[2]

Patients with CAH have a deficiency in 21-hydroxylase, resulting in impaired synthesis of cortisol and often aldosterone.[1,3] Impaired cortisol synthesis attenuates the negative feedback on the HPA axis, leading to increased CRF and ACTH secretion, overstimulation of the adrenal cortex, and excess production of adrenal androgens.[2-5] Currently, glucocorticoids (GCs) are required to replace deficient endogenous cortisol, while greater than normal doses of GCs (supraphysiologic) are usually needed to reduce excess ACTH and adrenal androgens via negative feedback.[2]

Crinecerfont Putative Mechanism of Action

Crinecerfont is an investigational, oral, selective CRF_1 antagonist being developed to reduce and control excess ACTH and adrenal androgens through a GC-independent mechanism for the treatment of CAH. Antagonism of the CRF_1 receptor in the anterior pituitary has been shown to decrease ACTH levels, which in turn decreases the production of adrenal androgens and potentially the symptoms associated with CAH.[6-9] Crinecerfont's potential to lower adrenal androgen levels may allow for more physiologic GC dosing to manage androgen excess and may potentially reduce complications associated with supraphysiologic GC doses in patients with CAH.[8,9]

Figure 1. Crinecerfont Mechanism of Action[6-9]



Based on preclinical data, crinecerfont is thought to have limited brain penetration and is unlikely to have central effects in the brain. Rather, crinecerfont is believed to act primarily on the anterior pituitary, which sits outside the blood–brain barrier.[7]

ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; CRF_1, corticotropin-releasing factor type 1 receptor; GC, glucocorticoid; HPA, hypothalamic-pituitary-adrenal.

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This letter and the enclosed material are provided in response to your unsolicited medical information inquiry. Please feel free to contact Neurocrine Medical Information at (877) 641-3461 or medinfo@neurocrine.com if you would like to request additional information.

References:

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