Abstract citation ID: bvac150.1281

Pediatric Endocrinology

OR18-4

Crinecerfont (NBI-74788), a Novel CRF1 Receptor Antagonist, Lowers Adrenal Androgens and Precursors in Adolescents with Classic Congenital Adrenal Hyperplasia

Richard Auchus, Jean Chan, Robert Farber, Patricia Fechner, Nagdeep Giri, Natalie Nokoff, Eiry Roberts, Kyriakie Sarafoglou, Julia Sturgeon, Maria Vogiatzi, and Ron Newfield

Introduction: Classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is a rare autosomal recessive disease characterized by deficiency of cortisol and oftentimes aldosterone, with elevated adrenocorticotropic hormone (ACTH) and steroid precursors that are then shunted toward excess androgen production. A phase 2 study of adults with classic 21OHD demonstrated that crinecerfont—an oral, non-steroidal, selective corticotropin-releasing factor type 1 (CRF_1) receptor antagonist—substantially reduced elevated hormone markers after 14 days of treatment [1]. The current study evaluated the effect of crinecerfont in adolescents with classic 21OHD, who may be especially challenging to manage for multiple reasons including the hormonal changes associated with puberty [2].

Methods: Eligible adolescents (14—17 years of age) with classic 21OHD received open-label crinecerfont (50 mg BID) for 14 days. ACTH, 17-hydroxyprogesterone (17OHP), androstenedione, and testosterone were assessed over 24 hours prior to (baseline) and after 14 days of crinecerfont treatment. Morning window values were defined as the average of samples collected at 0700h and 1000h, before the morning glucocorticoid dose. The participants' glucocorticoid and fludrocortisone regimens were maintained stable during crinecerfont treatment.

Results: In 8 participants (3 males, 5 females, ages 14-16 years), baseline median hormone concentrations (based on morning window) were as follows: plasma ACTH, 226.2 pg/mL; serum 17OHP, 7703.7 ng/dL; serum androstenedione, 367.9 ng/dL; and in females, serum testosterone, 63.5 ng/dL. After 14 days of crinecerfont treatment, median percent reductions from baseline were: ACTH, -57.1%; 17OHP, -69.5%; androstenedione, -58.3%; and in females, testosterone, -76.2%. A ≥50% reduction from baseline to Day 14 in ACTH, 17OHP, and androstenedione was observed in 62.5%, 75.0%, and 50.0% of participants, respectively. Furthermore, 60% (3/5) of females had ≥50% reduction from baseline in testosterone. Thirteen treatment-emergent adverse events (TEAEs) were reported; all but 1 (bruising) were assessed as mild. The majority of TEAEs were assessed as unrelated by the investigator, with the most common being headache (n=2). There were no serious AEs, discontinuations due to AEs, or safety concerns related to routine laboratory tests, vital signs, or electrocardiograms.

Conclusions: In adolescents with classic 21OHD, substantial median reductions (57-76%) in adrenal androgens and androgen precursors were observed after 14 days of crinecerfont treatment, consistent with reported results from a similar study of adults with classic 21OHD. Further studies are warranted to evaluate whether longer-term treatment with crinecerfont can allow for lower, more physiologic glucocorticoid dosing by directly reducing adrenal androgens, and thereby improving clinical outcomes (weight, metabolic risk, growth/development, fertility, etc.), via antagonism of the CRF_1 receptor.

References: [1] Auchus RJ et al. J Clin Endocrinol Metab 2021;dgab749.

[2] Merke DP and Poppas DP. Lancet Diabetes Endocrinol 2013;341-52.

Presentation: Monday, June 13, 2022 11:45 a.m. - 12:00 p.m.