Rapid and Sustained Reduction of 11-Oxygenated Androgens in Adults With Classic Congenital Adrenal Hyperplasia Following Once-Daily Oral Atumelnant (CRN04894): Results From a 12-Week, Phase 2, Open-Label Study

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Abstract body

In classic congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency (21-OHD), normal steroidogenesis pathways are disrupted, leading to a decrease in cortisol and aldosterone levels and virilization due to excess adrenal androgens. Traditional biomarkers of disease activity include 17-hydroxyprogesterone (17-OHP) and androstenedione (A4). The adrenals produce 11β-hydroxyandrostenedione (11-OHA4), which is metabolized to the potent androgen 11-ketotestosterone (11-KT); these 11-oxygenated androgens substantially contribute to the total androgen burden in patients with CAH. Atumelnant, a first-in-class competitive and selective melanocortin type 2 receptor (adrenocorticotropic hormone receptor) antagonist, was assessed in a Phase 2, open-label, dose-finding study. Adults age ≥18-75 years with classic CAH taking stable doses of glucocorticoid (GC) replacement therapy (≥15 mg daily dose hydrocortisone equivalent) for ≥6 months and morning serum A4 level ≥1.5 times the upper limit of normal were enrolled in 3 dose cohorts of oral atumelnant, 40 mg, 80 mg, 120 mg once daily for 12 weeks. A total of 28 patients (40 mg, n=11; 80 mg, n=11; 120 mg, n=6) completed treatment; 54% were women; mean (range) age 31.3 (20-47) years; and mean (range) GC dose 28.9 (20-40) mg/day hydrocortisone equivalent. Baseline 11-OHA4 was mean (range) 997 (142-3128) ng/dL, and baseline 11-KT was mean (range) 303 (54-1292) ng/dL. At week 2, the mean (SE) percent change from baseline (CFB) in morning 11-OHA4 for the 40-, 80-, and 120-mg cohorts was −49% (9.8), −74% (6.9), and −85% (4.6), respectively; at week 12, CFB was −60% (10.8), −68% (11.4), and −82% (3.5), respectively. The mean (SE) percent CFB in morning 11-KT for the 40-, 80-, and 120-mg cohorts at week 2 was −40% (11.1), −56% (13.0), and −79% (7.3), respectively; at week 12, CFB was −58% (10.0), −58% (13.2), and −77% (7.2), respectively. In conclusion, atumelnant results in rapid and substantial reductions of 11-oxygenated androgens and the traditional biomarkers A4 and 17-OHP in patients with classic

CAH. The reduction in total androgen burden may explain previously reported improvements in clinical outcomes within the 12-week time frame of this study.

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