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Reductions in Adrenal Volume in Patients With Congenital Adrenal Hyperplasia Receiving Once-Daily Oral Atumelnant (CRN04894): Interim Results From a 12-Week, Phase 2, Open-Label Study

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Abstract body

The enlargement of adrenal glands in patients with congenital adrenal hyperplasia (CAH) is due to excess stimulation by adrenocorticotropic hormone (ACTH) exerting a trophic effect over the lifetime of the individual. Atumelnant (CRN04894) is a potent, once-daily, orally bioavailable, nonpeptide, first-in-class, competitive and selective melanocortin type 2 receptor (MC2R or ACTH receptor) antagonist being developed for the treatment of CAH. In early results of the 12-week, Phase 2, open-label, dose-finding study of atumelnant (40 mg, 80 mg, or 120 mg) in adults with classic CAH (21-hydroxylase deficiency) (NCT05907291), treatment with atumelnant demonstrated rapid and profound reductions in morning androstenedione within 2 weeks of treatment that were maintained for the duration of treatment. Adrenal gland size and morphology of participants of the phase 2 trial were assessed via magnetic resonance imaging (MRI) following a standardized image acquisition protocol at baseline (during screening and prior to atumelnant dosing on day 1) and week 12. All MRI assessments were read by a single central radiologist. As of October 16, 2024, 12 patients (40 mg, n=2; 80 mg, n=7; 120 mg, n=3) had evaluable adrenal MRI data at baseline and week 12 and were included in this analysis. Included patients were a median (range) age 24 (22-42) years, 75% were women, and on a median (range) glucocorticoid dose of 30 (20-40) mg/day. Total adrenal volume (reference range 8-10 mL) was >10 mL in all 12 patients at baseline (median [range] 19.7 [10.2-943.6] mL). Following 12 weeks of atumelnant treatment, median (range) total adrenal volume changed by −4.3 (−77.5 to 9.1) mL, a median (range) change from baseline of −13.7% (−36% to 49%). Overall, 10/12 patients had a decline in volume in 1 or both adrenal glands. Adrenal masses suggestive of myelolipoma, which are commonly associated with CAH, were incidentally discovered in 3 of 12 patients, suggesting that the study population is representative of the real-world patient population. In conclusion, through potent blockade of the adrenal MC2R and reduction or

normalization of adrenal androgens, consistent reduction in adrenal size was demonstrated with 12 weeks of once-daily atumelnant. Furthermore, these results demonstrate the plasticity of hyperplastic adrenal tissue in adults with long-standing CAH and that ongoing adrenal hyperplasia is dependent on continued exposure to excess ACTH.

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