CRN24ATU.2001 Phase 2 CAH abstract
Final Draft
January 30, 2025
ENDO 2025 July 12-15, 2025
Abstract Submission Deadline: Thursday, January 30, 2025

Once-Daily Oral Atumelnant (CRN04894) Induces Rapid, Substantial, and Sustained Reductions of Androstenedione and 17-Hydroxyprogesterone in Adults With Classical Congenital Adrenal Hyperplasia: Interim Results From a 12-Week, Phase 2, Open-Label Study

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Science type: Clinical Trial

Topic: Adrenal (Excluding Mineralocorticoids)

Subtopic: Adrenal Insufficiency and Congenital Adrenal Hyperplasia

Presentation type: Oral presentation

Keywords (limit, 3): Congenital adrenal hyperplasia (CAH), melanocortin type 2 receptor (MC2R), adrenocorticotropic hormone (ACTH)

Abstract maximum character count: 2500 (not including spaces); current count: 2498

Abstract body

Atumelnant (CRN04894) is a potent, once-daily, orally bioavailable, nonpeptide, first-in-class competitive and selective melanocortin type 2 receptor (MC2R, or adrenocorticotropic hormone receptor) antagonist being developed for the treatment of congenital adrenal hyperplasia (CAH). We report results from 3 of 4 cohorts of a 12-week, Phase 2, open-label, dose-finding study of atumelnant in patients with CAH (NCT05907291). Adults with classic CAH (21-hydroxylase deficiency) on a stable dose of glucocorticoid (GC) replacement (≥15 mg hydrocortisone equivalent) for ≥6 months and androstenedione (A4) level ≥1.5 times the upper limit of normal (ULN) were enrolled in 3 dose cohorts (40 mg, 80 mg, or 120 mg) and received oral atumelnant once daily for 12 weeks. The primary efficacy endpoint was change from baseline (CFB) to week 12 in early morning pre-GC serum A4. CFB in pre-GC serum 17-hydroxyprogesterone (17-OHP) levels and, in men, serum A4:testosterone were secondary and exploratory endpoints, respectively. Menstrual cycle diaries were completed by female patients throughout the study period. As of October 16, 2024, 28 patients (54% women; mean [range] age 31.3 [20-47] years; mean [range] GC dose 28.4 [20-40] mg/day [hydrocortisone equivalent]) had completed treatment (40 mg, n=11; 80 mg, n=11; 120 mg, n=6). Overall, baseline median (range) A4 was 1049 (116-2755) ng/dL (reference range [RR]; women 30-200 ng/dL; men 40-150 ng/dL) and baseline median (range) 17-OHP was 12,750 (453-44,000) ng/dL (RR: women <80 ng/dL [follicular], <285 ng/dL [luteal]; men, <220 ng/dL); there were no meaningful differences between groups in baseline values. At week 12, median (range) morning A4 was reduced from baseline by 65% (5.5%-94%), 80% (22%-99%), and 82% (54%-91%) and 17-OHP was reduced by 84% (1.8%-97%), 86% (21%-99%), and 70% (12%-95%) in the 40-, 80-, and 120-mg cohorts, respectively. At week 12, A4 was <ULN in 3/11, 6/11, and 3/6 patients, respectively,

and started as early as week 2 of treatment (earliest measure). Median (range) A4:testosterone (n=12) was reduced from 4.88 (0.51-10.35), 2.51 (0.30-6.39), and 4.76 (0.57-5.33) at baseline to 1.17 (0.47-7.09), 1.46 (0.07-1.69), and 0.52 (0.09-0.64) at week 12 in the 40-, 80-, and 120-mg cohorts, respectively (normal <1). Of 10 women with evaluable data, 6 of 10 with irregular menses (40 mg, n=2; 80 mg, n=3; 120 mg, n=1) had improvement in regularity of menstruation at the end of study. There were 11 patients with treatment-related adverse events (AEs), no serious AEs, and no AEs leading to discontinuation. Two patients had adrenal insufficiency (GC dose increased in 1 patient), and 2 had abnormal liver function tests. The most common treatment-emergent AEs were headache (n=7) and fatigue (n=5). Overall, rapid, substantial, and sustained reductions in A4 and 17-OHP were demonstrated with administration of atumelnant in adult patients with classical CAH.

Acknowledgments

Technical editorial and medical writing assistance were provided under the direction of the authors by Janetricks Okeyo, PhD, Crinetics Pharmaceuticals, and Joseph Kruempel, PhD, CMPP, from The Curry Rockefeller Group, LLC, a Citrus Health Group, Inc., company (Chicago, Illinois), and was funded by Crinetics Pharmaceuticals, Inc. (San Diego, California).

Funding

Crinetics Pharmaceuticals, Inc. (San Diego, California).

Disclosures

US received consulting fees from Crinetics Pharmaceuticals, Diurnal Ltd, and H Lundbeck A/S.

DB has nothing to disclose.

AA, YW, EDlTA, and AK are employees of Crinetics Pharmaceuticals and own stocks and shares from Crinetics Pharmaceuticals.

MRG has received speaker fees from Camarus, Ipsen, Novo Nordisk, and Recordati, and has attended advisory boards for Crinetics Pharmaceuticals, Novo Nordisk, and Recordati.

NR has nothing to disclose.

FACB has nothing to disclose.

VdSNN has nothing to disclose.

RJA contracted research support and consulting fees from Neurocrine Biosciences, Diurnal Ltd, Corcept Therapeutics, Recordati Rare Diseases, and Crinetics Pharmaceuticals; contracted research support from Adrenas Therapeutics and Spruce Biosciences; and received consulting fees from Quest Diagnostics, Xeris Pharmaceuticals, Novo Nordisk, H Lundbeck A/S, and Sparrow Pharmaceuticals.

TASSB is a principal investigator for Crinetics Pharmaceuticals and Spruce Biosciences, and has received consulting fees from Novo Nordisk.