

Abstract citation ID: bvaf149.272

**Adrenal (Excluding Mineralocorticoids)
OR07-06*****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*****Umasuthan Srirangalingam, MD, PhD¹**, **Dario Bruera, MD²**, **Alejandro Ayala, MD³**, **Yang Wu, PhD³**, **Eduardo De La Torre Ames, MD³**, **Alan Krasner, MD³**, **Mônica R. Gadelha, MD, PhD⁴**, **Nicole Reisch, MD⁵**, **Flavia Amanda Costa-Barbosa, MD, PhD⁶**, **Vania dos Santos Nunes-Nogueira, MD⁷**, **Richard J. Auchus, MD, PhD⁸**, and **Tania A.S.S. Bachega, MD, PhD⁹**¹University College London Hospitals NHS Foundation Trust, Kent, United Kingdom; ²Hospital Misericordia, Córdoba, Argentina; ³Crinetics Pharmaceuticals, Inc., San Diego, CA, USA; ⁴Centro de Pesquisa Clínica, Instituto Estadual do Cérebro Paulo Niemeyer, Rio de Janeiro, Brazil; ⁵Klinikum der Universität München, LMU München, Munich, Germany; ⁶Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil; ⁷Department of Internal Medicine, São Paulo State University (UNESP), Medical School, Botucatu, São Paulo, Brazil; ⁸Division of Metabolism, Endocrinology, and Diabetes and the Departments of Internal Medicine and Pharmacology, University of Michigan, Ann Arbor, MI, USA; ⁹Laboratório de Hormônios e Genética Molecular-LIM 42, da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil**Disclosure:** **U. Srirangalingam:** Crinetics, Diurnal Ltd, H Lundbeck A/S. **D. Bruera:** None. **A. Ayala:** Crinetics. **Y. Wu:** Crinetics. **E. De La Torre Ames:** Crinetics. **A. Krasner:** Crinetics. **M.R. Gadelha:** Camarus, Ipsen, Novo Nordisk, Recordati, Crinetics. **N. Reisch:** Crinetics, Diurnal Ltd, Lundbeck A/S, Neurocrine Biosciences, Recordati Rare Diseases, Spruce Biosciences. **F. Costa-Barbosa:** None.**V. dos Santos Nunes-Nogueira:** None. **R.J. Auchus:** Neurocrine Biosciences, Diurnal Ltd, Corcept Therapeutics, Recordati Rare Diseases, Crinetics, Adrenas, Spruce Biosciences, Quest Diagnostics, Xeris Pharmaceuticals, Novo Nordisk, H Lundbeck A/S, Sparrow Pharmaceuticals. **T.A. Bachega:** Crinetics, Spruce Biosciences, Novo Nordisk.

Atumelnant (CRN04894) is a potent, once-daily, orally bioavailable, nonpeptide, first-in-class competitive and selective melanocortin type 2 receptor (MC2R, or adrenocorticotrophic 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.

Presentation: Saturday, July 12, 2025