Atumelnant (CRN04894) Induces Rapid and Sustained Reductions in Serum and Urine Cortisol in Patients With ACTH-Dependent Cushing Syndrome During a Phase 1b/2a, Single Center, 10-Day, Inpatient, Open-Label Study

Henrik Elenius[1]; Raven McGlotten[1]; Casey Moore[1]; Alejandro Ayala[2]; Yang Wu[2]; Peter J. Trainer[2]; R. Scott Struthers[2]; Alan Krasner[2]; Stephen F. Betz[2]; Lynnette K. Nieman[1]

[1]Section on Translational Endocrinology, NIDDK, NIH, Bethesda, MD, USA; [2]Crinetics Pharmaceuticals, Inc., San Diego, CA, USA

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INTRODUCTION

- Available medical therapies for Cushing syndrome are not optimal, with variable efficacy, delays to target cortisol, and significant adverse reactions
- Atumelnant (CRN04894) is a potent, once-daily, oral, nonpeptide, first-in-class competitive and selective melanocortin type 2 receptor antagonist
  - Blocks ACTH-mediated G-protein activation and signaling at the adrenal cortex
  - Being developed for the treatment of ACTH-dependent Cushing syndrome (ADCS) and classic congenital adrenal hyperplasia
- We report preliminary data from the first-in-disease, dose-finding study of atumelnant in patients with ADCS (NCT05804669)

METHODS

- Inpatient participants with active ADCS: 24h urine free cortisol (UFC) >1.3× upper limit of normal (ULN), ACTH >10 pg/mL
- Atumelnant 80 mg administered orally, once daily at 08.00 for 10 days (D1-10) followed by a 4-day washout
- Efficacy endpoints included changes in UFC (ULN 45 µg/d), and pre-dose AM serum cortisol and AM plasma ACTH (ULN 46 pg/mL)
- Daily questionnaires assessed adverse events (AEs) and signs and symptoms of adrenal insufficiency (AI) and ADCS

RESULTS: PARTICIPANTS AND EFFICACY

- All 5 participants (4 men; 4 Cushing disease, 1 ectopic ACTH; median age, 47 years [range, 34-55]) completed the study

Outcome (median, range)	Day 1	Day 11
UFC (µg/d)	252 (99-293)	24 (3.9-51)
AM cortisol (µg/dL)	14 (10.7-18.1)	1.4 (1.0-4.7)
AM ACTH (pg/mL)	52.1 (33-1088)	78 (48.8-4045)

- Each participant developed biochemical evidence of AI (AM cortisol <5 µg/dL) after median 2 doses (range, 1-10), commenced physiologic hydrocortisone (HC) add-back, and completed 10 days of atumelnant
- All participants had biochemical disease control (normal UFC and AM cortisol <5 µg/dL) by day 11, while receiving HC replacement, despite increase in ACTH
- HC was stopped (median day 13; range, 12-18) when AM cortisol was ≥7 µg/dL

Cortisol and ACTH Changes During Atumelnant Treatment

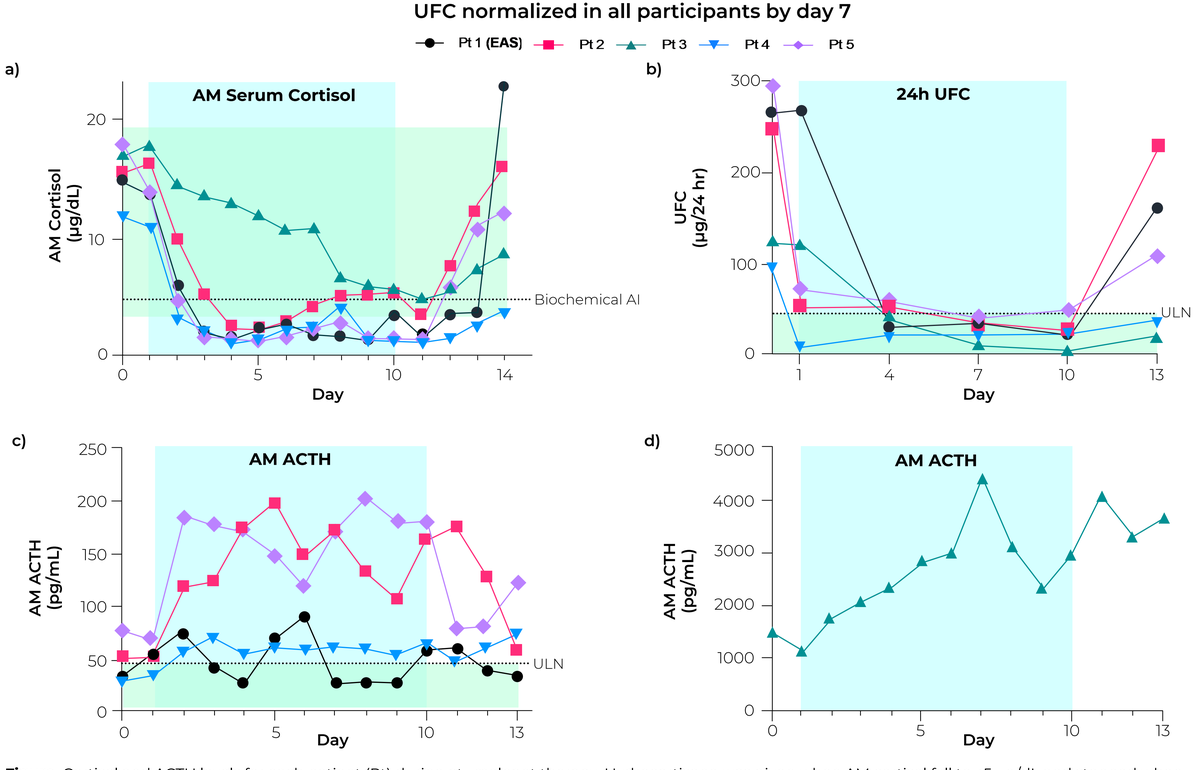

Figure. Cortisol and ACTH levels for each patient (Pt) during atumelnant therapy. Hydrocortisone was given when AM cortisol fell to <5 µg/dL and stopped when cortisol was ≥7 µg/dL. The dotted line represents adrenal insufficiency (cortisol <5 µg/dL) in a), and the ULN in b) and c). In b) day shown for UFC is start of 24h collection. Blue areas indicate treatment days, green areas mark the RR.

- Pt 3, with a slower reduction of serum cortisol, had a markedly higher baseline ACTH
- No loss of efficacy or clinical sequelae related to compensatory rises in ACTH caused by cortisol lowering. No change in ACTH seen in participant with ectopic ACTH syndrome

RESULTS: IMPROVEMENT IN CS SYMPTOMS

- Improvement in Cushing symptoms/signs: insomnia (4/4 pts), trouble concentrating (4/5), anxiety (3/4), tiredness (3/4), hypertension (3/5), brain fog (3/5), bloating (2/4)
- Resolution of neutrophilia (3/3), leukocytosis (2/2), low testosterone (3/4)

RESULTS: ADVERSE EVENTS

- New headache + anorexia and/or nausea (4/5 pts). Most side effects improved with HC add-back
- Serious adverse events included AI (expected and reported per protocol) and one non-treatment related transient GI bleed on day 29
- Two participants had transient, minor elevations in serum creatinine (<1.2 × ULN). Two participants had small increases in ALT (<1.5 × ULN). Notably both had preexisting steatosis

CONCLUSIONS

- The first 5 patients with ADCS to receive once-daily, oral atumelnant experienced rapid lowering of serum and urine cortisol, leading to adrenal insufficiency and improvement or resolution of some signs and symptoms of ADCS
- The observed compensatory increase in ACTH was not associated with loss of efficacy or clinical sequelae
- Atumelnant was generally well-tolerated
- This ongoing study will explore further the relationship between atumelnant dose, including lower doses, and therapeutic response

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