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ADRENAL
(EXCLUDING MINERALOCORTICOIDS)

Model-Informed Atumelnant Dose Selection for a Phase 3 Study In Adult Patients With Classic Congenital Adrenal Hyperplasia

MON-494

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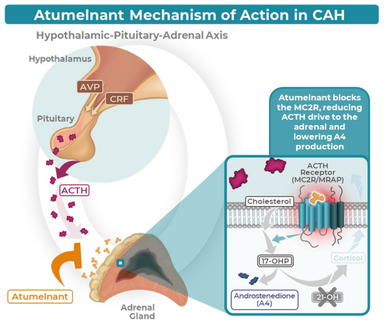
*Presenting author; †Employee of A2-Ai at the time of the analysis; Potential conflicts of interest may exist. Refer to the Meeting App.

BACKGROUND

- Atumelnant (CRN04894) is a first-in-class, once-daily, oral, selective melanocortin type 2 receptor (MC2R) antagonist currently in development for the treatment of diseases of ACTH excess, including CAH, with the goal of normalizing adrenal androgen levels while allowing for glucocorticoid (GC) use at physiologic doses[1-4]



17-OHP, 17-hydroxyprogesterone; 21-OH, 21-hydroxylase; ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; CRF, corticotropin-releasing factor; MRAP, melanocortin 2 receptor accessory protein.

- In a Phase 2, open-label study of adults with CAH (CRN04894-03; NCT05907291),[5] atumelnant induced rapid, substantial, and sustained reductions in pharmacodynamic (PD) biomarkers of efficacy, androstenedione (A4) and 17-hydroxyprogesterone (17-OHP)[3]
- Atumelnant was well tolerated with a consistent safety profile in both healthy volunteers and participants with CAH[3,6,7]

OBJECTIVES

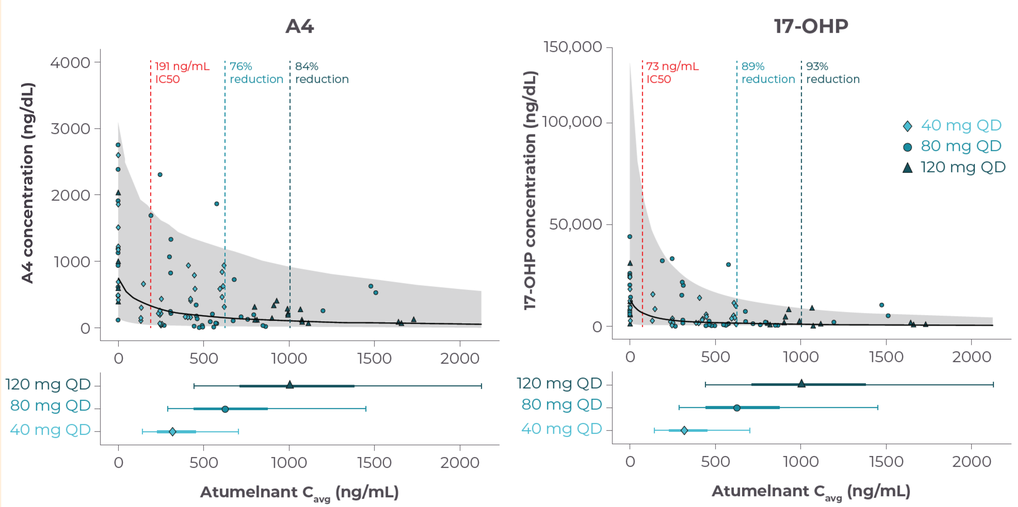
- Quantify the exposure-response (E-R) relationship between atumelnant exposure and serum A4 and 17-OHP concentrations
- Explore the E-R relationship between atumelnant and treatment-emergent adverse events (TEAEs)
- Identify the efficacious atumelnant dose range for a Phase 3 study in adult participants with CAH

STUDY DESIGN AND METHODS

- Participants in the Phase 2 CAH study (N=27; data cut 10 November 2024) received 40, 80, or 120 mg atumelnant once daily in the evening for 12 weeks while continuing stable supraphysiologic GC replacement (≥15 mg hydrocortisone equivalent) dosing throughout the study
- E-R models relating atumelnant exposure to pre-GC mean morning A4 and 17-OHP PD biomarker response data were developed to characterize the E-R relationship in participants with CAH over the studied dose range
- Model-predicted reduction from baseline in A4 and 17-OHP was summarized for atumelnant doses studied in the Phase 2 CAH study

RESULTS

Figure 1. Model-Predicted and Observed A4 and 17-OHP Response to Atumelnant Exposure



C_{avg}, average concentration at steady state; IC50, concentration at which 50% of the maximum effect is achieved; I_{max}, maximal effect; QD, once daily.
Top panels: The data points represent observed data, colored by dose. The black lines represent the median, and the grey shaded region represents the 90% prediction intervals of the simulated values. Dashed vertical lines denote the IC50 and the model-predicted percent reduction from baseline at the median predicted C_{avg} for atumelnant doses of 80 or 120 mg QD. I_{max}=100%.
Bottom panels: The colored shapes represent medians, colored thick lines represent the IQR (25th to 75th), and thin lines represent the 5th and 95th percentiles of predicted atumelnant exposure at each dose level.

Exposure-Response Efficacy Model Development

- The E-R relationships for A4 and 17-OHP response to atumelnant exposure were best fit to proportional, inhibitory, maximal effect (I_{max}) models
- Atumelnant was ~2.6-fold more potent at suppressing 17-OHP (C_{avg} IC50=73.0 ng/mL) relative to A4 (C_{avg} IC50=191 ng/mL) (**Figure 1**)

Model Applications

- The model-predicted % reduction from baseline in A4 and 17-OHP increased with increasing atumelnant dose (**Figure 1, Table 1**)
- The predicted median % reduction from baseline in A4 increased from 76% with 80 mg once daily to 84% with 120 mg once daily, suggesting some patients would see further benefit from a 120 mg once daily dose

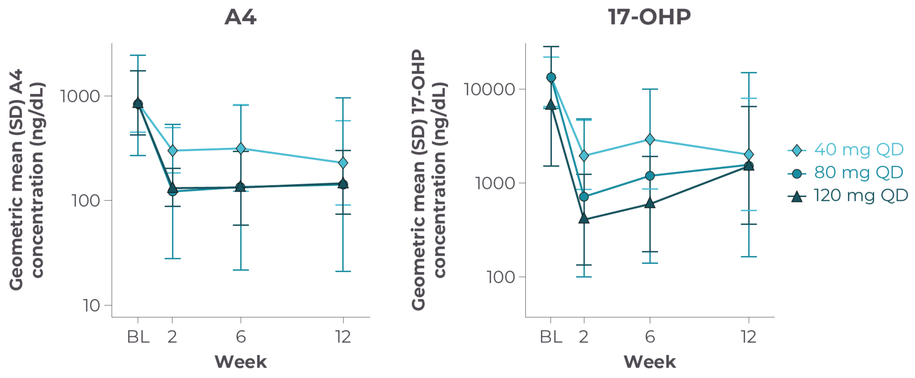
Table 1. Efficacy E-R Predictions at Steady-State by Atumelnant Daily Dose

Atumelnant Dose (Once Daily)	Model-Predicted % Reduction From Baseline Median (5th-95th Percentile)	
	A4	17-OHP
40 mg	62% (43-79%)	81% (66-91%)
80 mg	76% (60-88%)	89% (80-95%)
120 mg	84% (70-92%)	93% (86-97%)

Exploratory Data Analysis

- The E-R efficacy analysis set included 27 unique participants with CAH, contributing a total of 106 A4 and 106 17-OHP biomarker assessments
- Dose-dependent reductions in pre-GC morning A4 and 17-OHP corresponded to mean percent changes from baseline >75% at doses ≥80 mg once daily (**Figure 2**)

Figure 2. Observed A4 and 17-OHP Change From Baseline Over Time



Note: The data points represent the geometric mean of observed concentration of A4 or 17-OHP, colored by dosing regimens.

Exposure-Response Safety

- A total of 27 unique participants with CAH were included in the E-R TEAE safety analysis set
- There was no evidence of a relationship between atumelnant exposure and occurrence of commonly occurring TEAEs

CONCLUSIONS

- The impact of atumelnant exposure on reductions in mean morning serum A4 and 17-OHP were adequately described using direct maximal inhibitory effect E-R models
- The E-R model predicted percent reduction from baseline in A4 and 17-OHP increased with increasing atumelnant doses
- These data support further investigation of 80 mg and 120 mg once daily atumelnant in the CALM-CAH Phase 3 study of adults with CAH
- Future E-R analyses of efficacy and safety will be conducted based on final data from the Phase 3 study

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For author disclosures, acknowledgments, references, and supplemental information, please use the QR code.

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AUTHOR DISCLOSURES

LC, XW, AA, and CL are employees of Crinetics Pharmaceuticals and own stocks and shares from Crinetics Pharmaceuticals.
AW was an employee of A2-Ai at the time of the analysis.
DR, and RLC are employees of A2-Ai, which has received research funding from Crinetics Pharmaceuticals.

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SUPPLEMENTAL METHODS

Analysis Sets

- Interim data were provided from ongoing study CRN04894-03 (data cut 10 November 2024), which included data from all participants in the first 3 cohorts from baseline through Week 12/end of treatment
- PK analysis set: healthy individuals (from CRN04894-01) and participants with CAH (from CRN04894-03 cohorts 1-3) who received ≥1 dose of atumelnant and had ≥1 quantifiable atumelnant plasma concentration
- E-R efficacy analysis sets: study participants with CAH from the PK analysis set with an average value of pre-GC morning A4 and/or 17-OHP in ≥1 post-baseline visit
- E-R TEAE safety analysis set: study participants with CAH included in the PK analysis set

Software

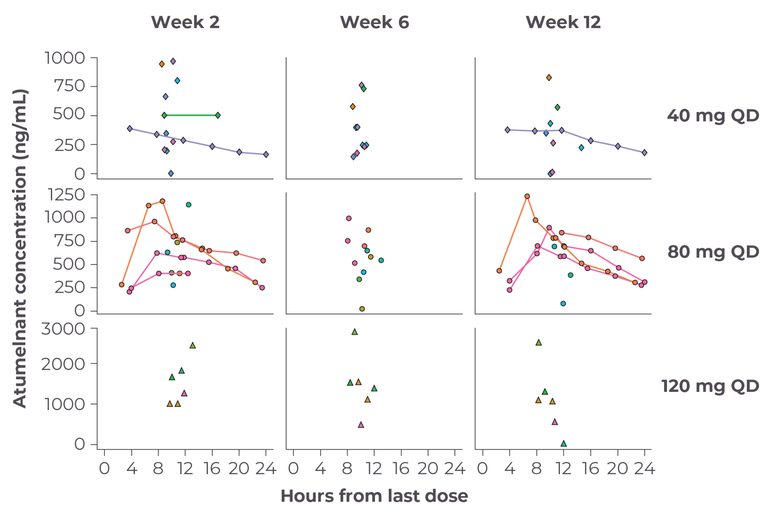
- Modeling was performed using nonlinear mixed-effects methodology implemented in NONMEM software
- The first-order conditional estimation with interaction method was used for all model runs
- Data processing and graphical analyses, and simulations were performed using NONMEM and R

Model Applications

- Model-predicted atumelnant exposure (C_{avg}) on A4 and 17-OHP biomarker responses were summarized for doses under consideration for the Phase 3 study in adults with CAH
- Exposure metrics: derived over a 24-hour period at steady-state from a simulated population 500 patients with CAH receiving atumelnant 40 mg, 80 mg, or 120 mg once daily
- Exposure distributions: plotted with the continuous E-R relationships for A4 and 17-OHP to assess dose-exposure-efficacy biomarker response relationship

SUPPLEMENTAL RESULTS

Supplemental Figure 1. Concentration-Time Profiles of Atumelnant



Note: Some participants had samples collected at multiple timepoints (ie, circadian PK assessment), denoted by solid line connecting data points.

Supplemental Table 1. Summary of Study Design and Participant Characteristics

Parameter	Study/Phase CRN04894-03 / Phase 2[a]
Participant population	Men and women with CAH ≥18 to 75 years of age
Atumelnant dose levels	40 mg, 80 mg, 120 mg once daily for 12 weeks
E-R analysis set	
Participants, n/N (%)	27/28 (96.4%)
Quantifiable atumelnant concentrations, n/N (%)	149/159 (93.7%)
Quantifiable efficacy biomarker concentrations, n	
A4	106
17-OHP	106
Body weight, mean (SD) [range] kg	74.7 (15.9) [51.4-129.0]

[a]Participants in Cohorts 1-3 of the Phase 2 study received atumelnant between 22:00-24:00 once daily before sleep; participants continued stable GC replacement dosing regimens throughout the study.