Once Daily Oral Atumelnant (CRN04894) Induces Rapid and Profound Reductions of Androstenedione and 17-hydroxyprogesterone in Participants with Classical Congenital Adrenal Hyperplasia: Initial Results From a 12-Week, Phase 2, Open-Label Study

MON-677

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BACKGROUND

- Atumelnant (CRN04894): once-daily, orally bioavailable, nonpeptide, first-in-class ACTH receptor antagonist being developed for the treatment of congenital adrenal hyperplasia (CAH) and ACTH-dependent Cushing's syndrome[1]
  - Competitive and selective for adrenal cortex melanocortin type 2 receptor (MC2R)[1]
  - Selectively and specifically inhibits ACTH-mediated adrenal steroidogenesis[2]

OBJECTIVE

- To present initial results from a phase 2, open-label, dose-finding study in participants with classical CAH (TouCAHn study; NCT05907291)

METHODS

- Sequential cohorts received fixed doses of once-daily oral atumelnant administered nightly for 12 weeks

Key Eligibility Criteria

- Male or female participants age ≥18 to 75 years (≥16 years in USA)
- Classical CAH (21-hydroxylase deficiency)
- On ≥15mg hydrocortisone equivalent daily dose for ≥6 months (stable for duration of study)
- Androstenedione (A4) >1.5 × ULN

Cohorts

80 mg once daily (n=9)

40 mg once daily (n=9)

120* mg once daily (n=6)

Endpoints

Primary endpoint: change from baseline in morning serum A4 at Week 12

Secondary endpoint: change from baseline in morning serum 17-OHP at Week 12

Primary safety assessment: incidence of adverse events throughout the study

*Originally an optional cohort up to 160 mg.
17-OHP, 17-hydroxyprogesterone.

RESULTS

Baseline Characteristics

Parameters	Cohort 1 80 mg (n=6)	Cohort 2 40 mg (n=4)	All (n=10)
Age, years, mean (range)	35.2 (25-42)	24.3 (22-27)	30.8 (22-42)
Female, n (%)	5 (83.3)	0	5 (50.0)
Baseline biomarker levels, mean (range)			
A4, ng/dL	838 (116-2755)	1680 (1180-2465)	1175 (116-2755)
17-OHP, ng/dL	9880 (4740-24,300)	15,600 (12,150-22,800)	12,168 (4740-24,300)
ACTH, pg/mL	554 (155-1009)	658 (115-1082)	596 (115-1082)
GC dose, mg/day, mean (range)*	35 (25-40)	28 (20-40)	32 (20-40)

*Glucocorticoid dose in hydrocortisone equivalents.

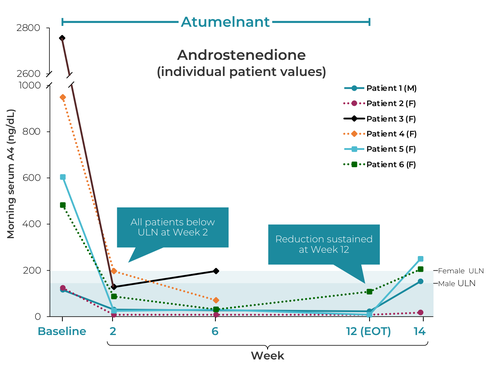
Treatment Status*

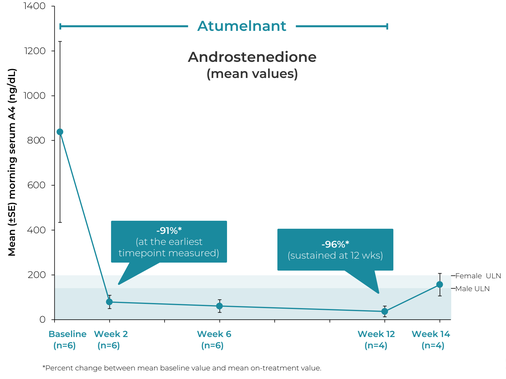
	Cohort 1 80 mg (n=6)	Cohort 2 40 mg (n=4)	All (n=10)
Treated	**6**	**4**	**10**
Completed 2 wks treatment	6	4	10
Completed 6 wks treatment	6	0	6
Completed 12 wks treatment	4	0	4
Completed study	4	0	4
Discontinued treatment	**0**	**0**	**0**

*As of this analysis.

- Resumption of menstrual cycle (first time in >2 years) in two female patients receiving altumelnant 80 mg
  - Serum testosterone decreased from baseline (211 ng/dL and 125 ng/dL; ULN, 48 ng/dL) to Week 2 (5 ng/dL and 17 ng/dL) and remained below the ULN throughout treatment
- No observed effect of atumelnant 80 mg on ACTH (mean±SE of: 554±150 at baseline, 392±120 at Week 2, 552±99 at Week 6, and 379±232 at Week 12)
- For atumelnant 40 mg (4 patients treated for 2 weeks):
  - A4: mean value decreased by -53% (mean±SD at baseline, 1680±304 ng/dL; Week 2, 792±454 ng/dL)
  - 17-OHP: mean value decreased by -49% (baseline, 15600±2435 ng/dL; Week 2, 7918±4903 ng/dL)

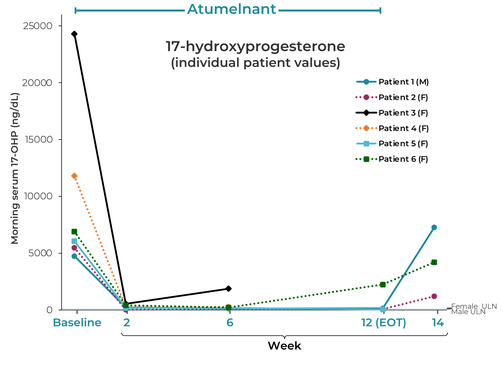
Rapid and Sustained Reduction in A4 with Atumelnant 80 mg

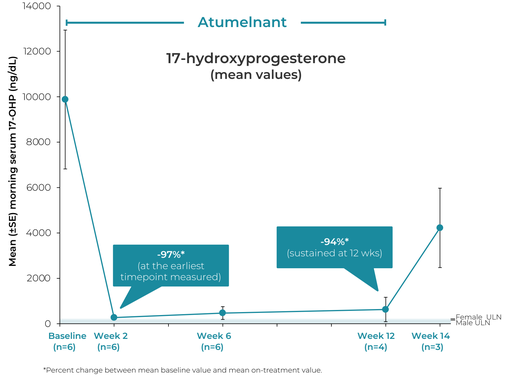




*Percent change between mean baseline value and mean on-treatment value.

Rapid and Sustained Reduction in 17-OHP with Atumelnant 80 mg





*Percent change between mean baseline value and mean on-treatment value.

CONCLUSIONS

- Once-daily, oral atumelnant showed profound, rapid, and sustained suppression of A4 (-96% at Week 12) and 17-OHP (-94% at Week 12) in patients with CAH
- Atumelnant resulted in A4 lowering and consistent levels below the upper limit of normal in 100% of patients evaluated to date
- No meaningful changes in ACTH were observed
- Atumelnant was well tolerated, with no severe or serious adverse events
- Initial data are supportive of continued clinical development of atumelnant

Summary of Adverse Events

Adverse Events, n (%)	Cohort 1 80 mg (n=6)	Cohort 2 40 mg (n=4)	All (n=10)
Any AE	4(66.7)	3 (75.0)	7 (70.0)
Severe or serious AEs*	0	0	0
Discontinuation due to AE	0	0	0
Most common AEs (≥2 patients overall)			
Fatigue	1 (16.7)	2 (50.0)	3 (30.0)
Headache	0	2 (50.0)	2 (20.0)
Upper respiratory tract infection	2 (33.3)	0	2 (20.0)

*All adverse events reported to date were mild or moderate and transient.

REFERENCES

1. Kim SH, et al. *ACS Med Chem Lett.* 2024;15(4):478-485. **2.** Kusnetzow AK, et al. Poster presented at ENDO Virtual Meeting; June 8-22, 2020.

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