Rapid and Sustained Reduction of 11-Oxygenated Androgens in Adults With Classic Congenital Adrenal Hyperplasia Following Once-Daily Oral Atumelnant (CRN04894): Results From a 12-Week, Phase 2, Open-Label Study

SUN-438

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BACKGROUND

- A hallmark of classic congenital adrenal hyperplasia (CAH) is 21-hydroxylase deficiency (21-OHD), which disrupts normal steroidogenesis pathways, resulting in decreased cortisol and aldosterone levels and excess adrenal androgens[1,2]
 - Traditional biomarkers of disease activity include 17-hydroxyprogesterone (17-OHP) and androstenedione (A4);[3] however, traditional androgen markers may not fully reflect the total androgen burden in CAH
 - The adrenals produce 11β-hydroxyandrostenedione (11-OHA4), which is metabolized to the androgen 11-ketotestosterone (11-KT); 11-oxygenated androgens contribute substantially to the total androgen burden in patients with CAH[4]
 - Assessment of 11-oxygenated androgens may aid in quantification of total androgen load and treatment response
- Atumelnant (CRN04894), a first-in-class, once-daily, oral, nonpeptide, melanocortin 2 receptor antagonist[5,6] that selectively inhibits adrenocorticotropic hormone (ACTH)-mediated adrenal steroidogenesis, is currently under development for the treatment of CAH and ACTH-dependent Cushing's syndrome
 - Rapid and sustained reductions with atumelnant, including change from baseline in A4 of -96% at Week 12 with 80 mg treatment, have been previously reported[7]

OBJECTIVE

- To present results from 2 exploratory endpoints of the ongoing Phase 2 study: change from baseline in morning serum 11-OHA4 and 11-KT over time

STUDY DESIGN AND METHODS

Key Eligibility Criteria

- Male or female participants age ≥18 to 75 years (≥16 years in USA)
- Classic CAH (21-OHD)
- On ≥15 mg hydrocortisone equivalent daily dose
- Serum A4 >1.5 × ULN

Cohorts[a]

- 40 mg once daily (n=11)
- 80 mg once daily (n=11)
- 120 mg once daily (n=6)

Study Endpoints

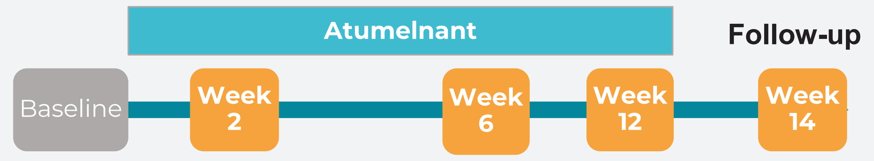
Primary: Change from baseline in serum A4

Secondary: Change from baseline in serum 17-OHP

Safety: Incidence of TEAEs

Exploratory: Change from baseline in serum steroid levels and PD biomarkers over time
- 11-OHA4
- 11-KT

Assessment Schedule


Atumelnant
Follow-up
Baseline
Week 2
Week 6
Week 12
Week 14

11-KT, 11-ketotestosterone; 11-OHA4, 11β-hydroxyandrostenedione; 17-OHP, 17-hydroxyprogesterone; 21-OHD, 21-hydroxylase deficiency; A4, androstenedione; CAH, congenital adrenal hyperplasia; PD, pharmacodynamics; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.
[a]Participants received fixed doses of oral atumelnant administered nightly for 12 weeks.

RESULTS

- As of January 14, 2025, a total of 28 participants (40 mg, n=11; 80 mg, n=11; 120 mg, n=6) completed treatment
- Baseline 11-OHA4 and 11-KT levels in participants with CAH were considerably higher than previously published ranges of circulating levels in healthy individuals[2]

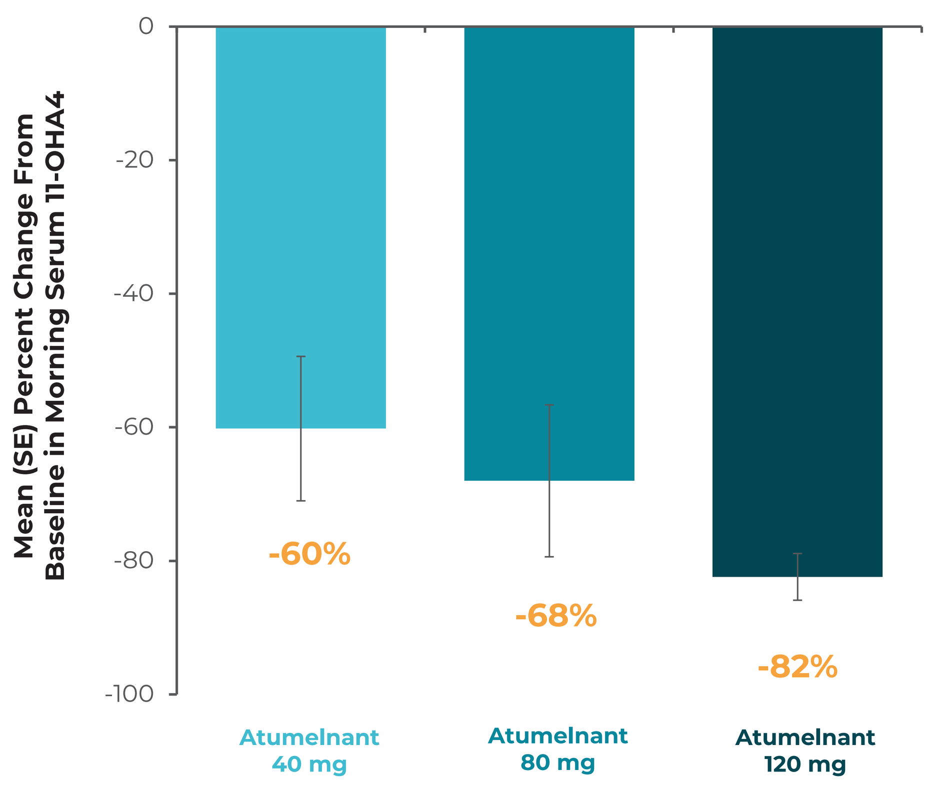
Participant Demographics and Baseline Characteristics

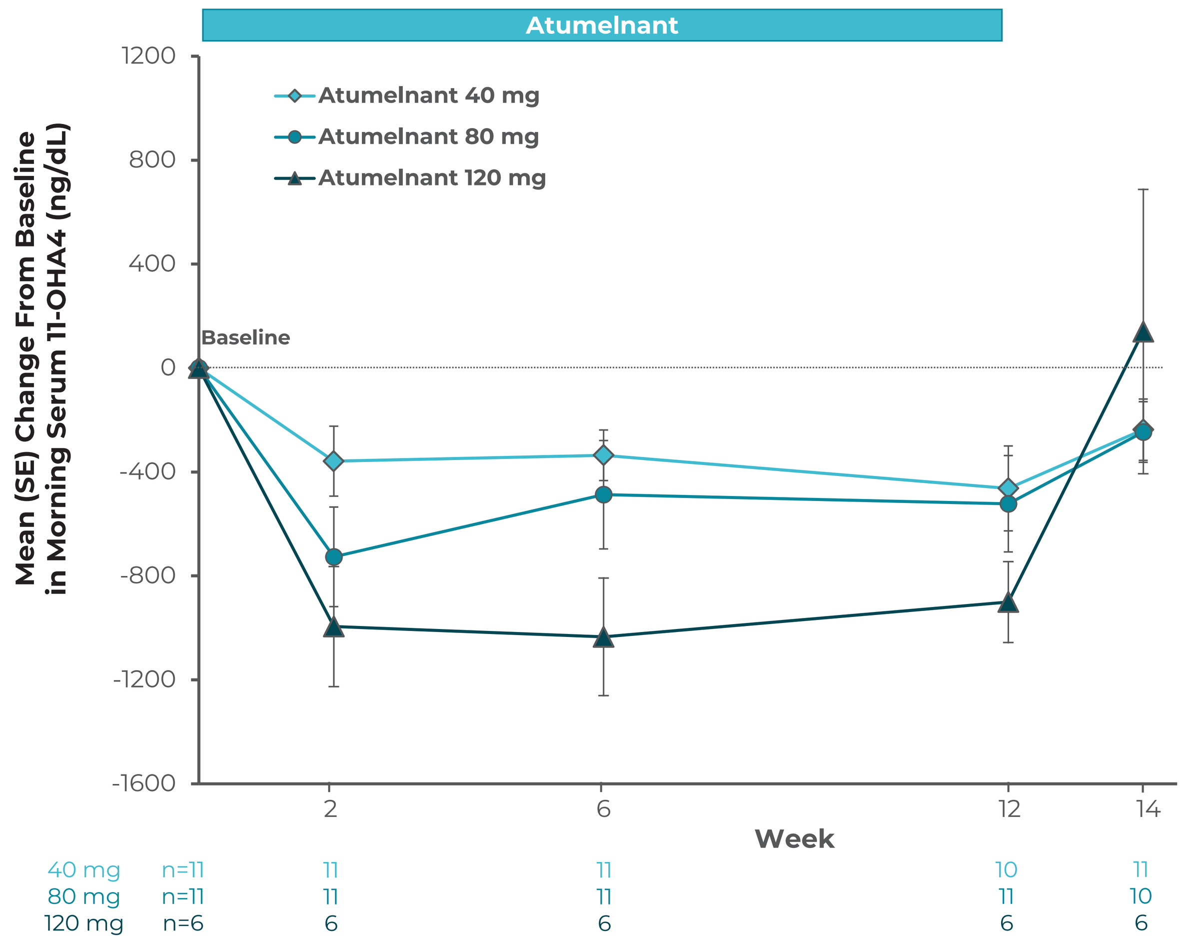
Parameters	Atumelnant 40 mg (n=11)	Atumelnant 80 mg (n=11)	Atumelnant 120 mg (n=6)	All participants (N=28)
Age, mean (range), y	28 (20-45)	33 (22-42)	34 (22-47)	31 (20-47)
Female, n (%)	4 (36)	8 (73)	3 (50)	15 (54)
Baseline biomarker levels, mean (range), ng/dL[a,b]				
11-OHA4	828 (142-2185)	1092 (171-3128)	1131 (350-1858)	997 (142-3128)
11-KT	298 (66-1292)	273 (54-680)	367 (141-547)	303 (54-1292)
GC dose, mean (range), mg/d[c]	30 (20-40)	31 (20-40)	23 (20-30)	29 (20-40)

11-KT, 11-ketotestosterone; 11-OHA4, 11β-hydroxyandrostenedione; GC, glucocorticoid.
[a]Reference range values for 11-OHA4 and 11-KT have not been established. Previous reports in healthy women suggest the following circulating levels: 11-OHA4, 121-272 ng/dL; 11-KT, 30 ng/dL.[2]
[b]The conversion factor from conventional units (ng/dL) to SI units (nmol/L) is 0.0331 for 11-OHA4 and 11-KT and 0.0347 for testosterone.
[c]GC dose in hydrocortisone equivalents.

RESULTS

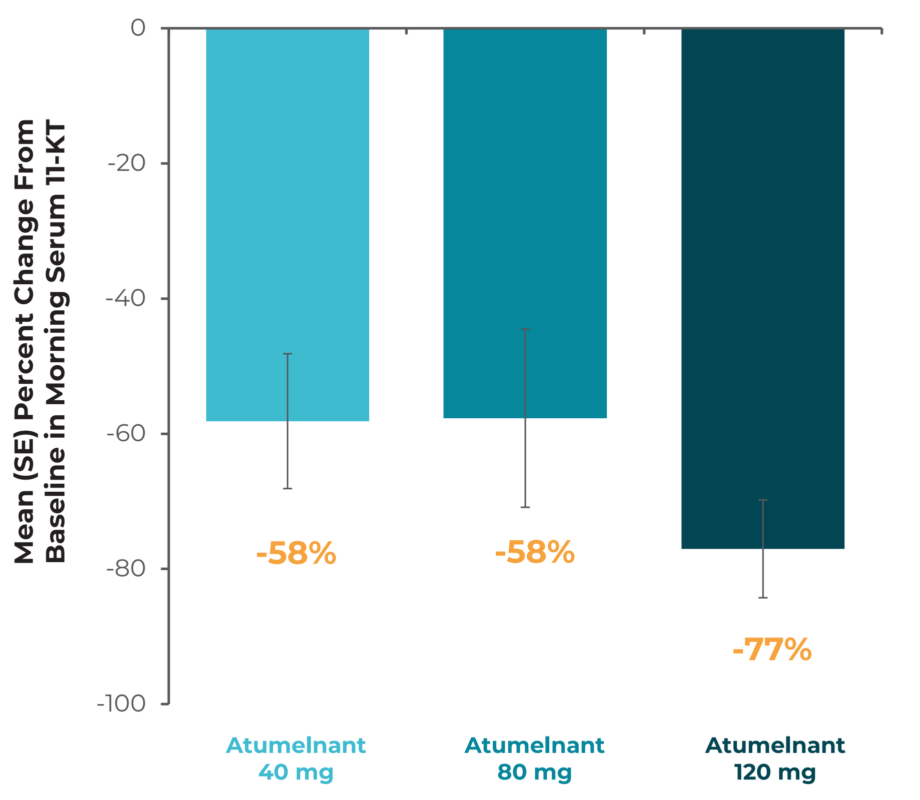
Substantial Reduction in Pre-GC Serum 11-OHA4 Was Rapid and Sustained Through Week 12 in All Atumelnant Dose Cohorts

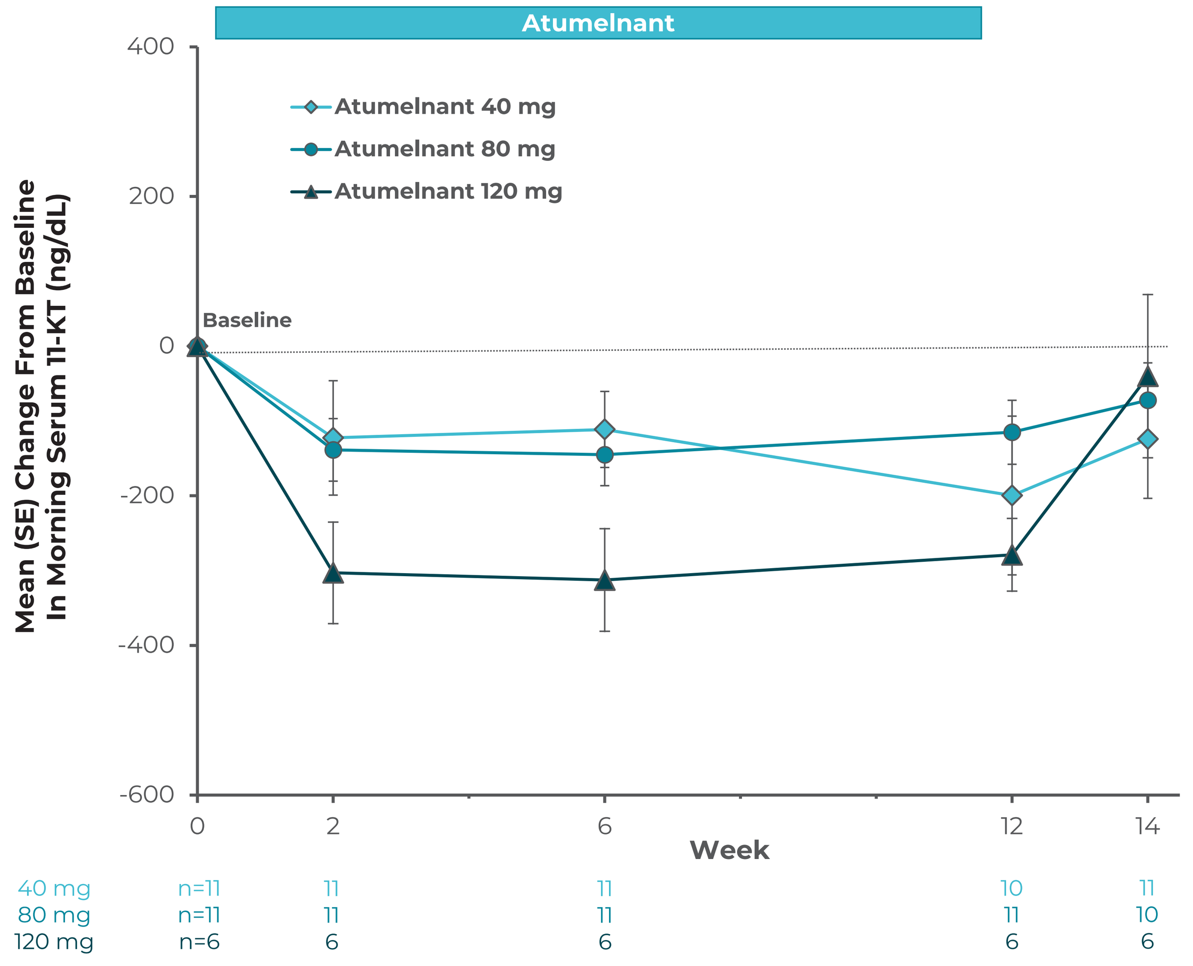

Mean (SE) Percent Change From Baseline in Morning Serum 11-OHA4
0
-20
-40
-60
-80
-100
-60%
-68%
-82%
Atumelnant 40 mg
Atumelnant 80 mg
Atumelnant 120 mg


Atumelnant
Atumelnant 40 mg
Atumelnant 80 mg
Atumelnant 120 mg
Baseline
Mean (SE) Change From Baseline in Morning Serum 11-OHA4 (ng/dL)
1200
800
400
0
-400
-800
-1200
-1600
2
6
12
14
Week
40 mg n=11 11 11 10 11
80 mg n=11 11 11 11 10
120 mg n=6 6 6 6 6

11-OHA4, 11β-hydroxyandrostenedione; GC, glucocorticoid.

Substantial Reduction in Pre-GC Serum 11-KT Was Rapid and Sustained Through Week 12 in All Atumelnant Dose Cohorts


Mean (SE) Percent Change From Baseline in Morning Serum 11-KT
0
-20
-40
-60
-80
-100
-58%
-58%
-77%
Atumelnant 40 mg
Atumelnant 80 mg
Atumelnant 120 mg


Atumelnant
Atumelnant 40 mg
Atumelnant 80 mg
Atumelnant 120 mg
Baseline
Mean (SE) Change From Baseline In Morning Serum 11-KT (ng/dL)
400
200
0
-200
-400
-600
0
2
6
12
14
Week
40 mg n=11 11 11 10 11
80 mg n=11 11 11 11 10
120 mg n=6 6 6 6 6

11-KT, 11-ketotestosterone; GC, glucocorticoid.

CONCLUSIONS

- Once-daily, oral atumelnant results in rapid and substantial reductions of 11-oxygenated androgens
- Atumelnant treatment for 12 weeks reduced 11-oxygenated androgen levels to circulating levels seen in healthy individuals[2]
- These results are in addition to the reductions in the traditional biomarkers A4 and 17-OHP in participants with classic CAH, with clinical activity observed across all doses[7]
- This reduction in total androgen burden may be linked to improvements in clinical outcomes previously reported within the 12-week time frame of this study, and lends support for assessing 11-oxygenated androgens to accurately quantify total androgen load and consequent treatment response in these patients

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