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

Presenter: Umasuthan Srirangalingam, MD, PhD, on behalf of the TouCAHn Study Group

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Author disclosures

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U Srirangalingam received consulting fees from Crinetics Pharmaceuticals, Diurnal Ltd, and H Lundbeck A/S.

D Bruera has nothing to disclose.

A Ayala, Y Wu, EDl Torre Ames, and A Krasner are employees of Crinetics Pharmaceuticals and own stocks and shares from Crinetics Pharmaceuticals.

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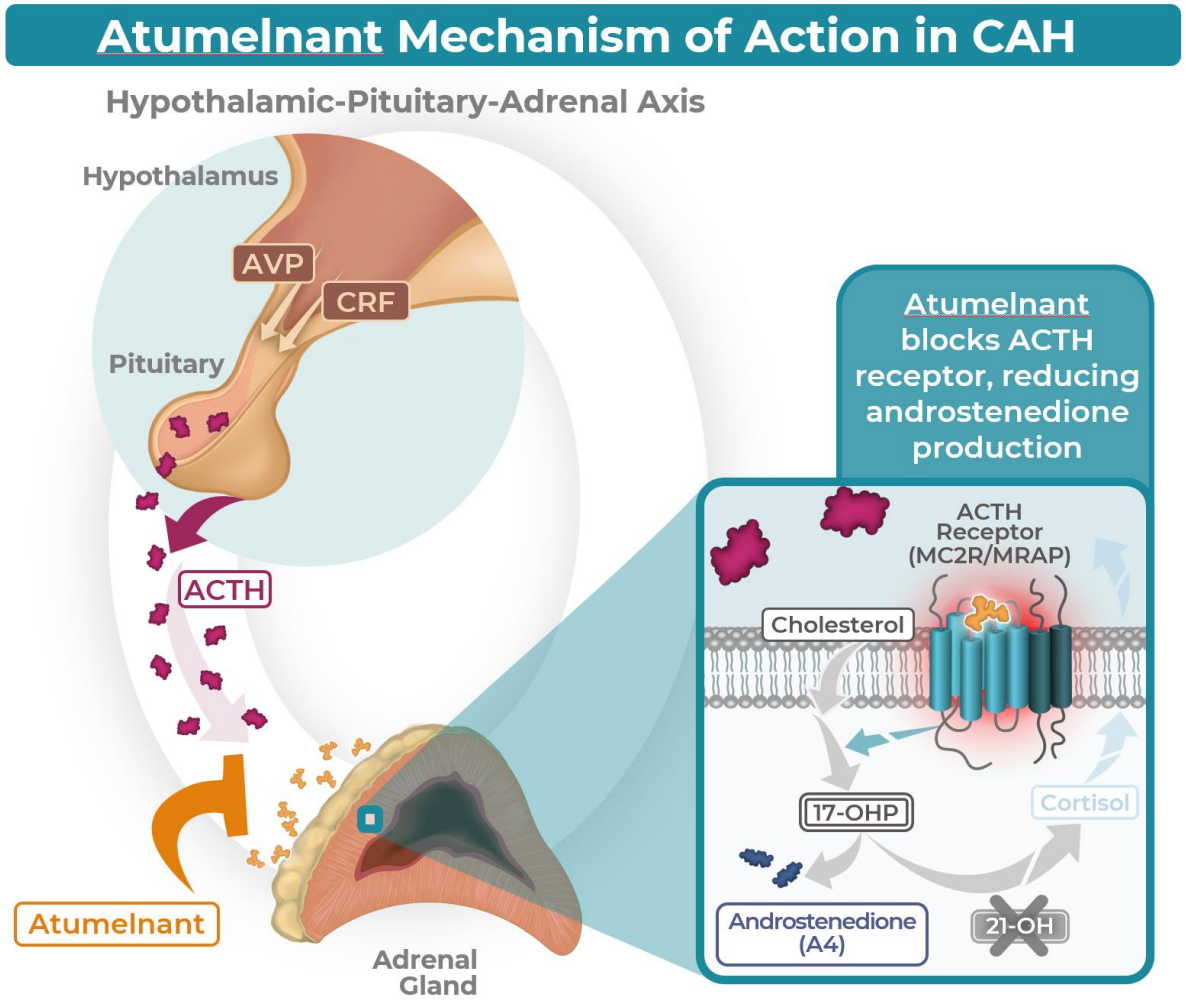
Background

- Atumelnant (CRN04894) is a first-in-class, once-daily, oral, nonpeptide, MC2R antagonist[1]
  - Selectively and specifically inhibits ACTH-mediated adrenal steroidogenesis[2]
  - Being developed for the treatment of CAH and ACTH-dependent Cushing's syndrome

Objective

- To present results from a Phase 2, open-label, dose-finding study of atumelnant in patients with classic CAH (TouCAHn study; NCT05907291)



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.

Methods

Key Eligibility Criteria

- Male or female participants age ≥18 to 75 years (≥16 years in USA)
- Classic CAH (21-hydroxylase deficiency)
- On ≥15 mg hydrocortisone equivalent daily dose
- A4 >1.5×upper limit of normal

Treatment Arms:

- Completed cohorts, each 12 weeks (N=28)
- Atumelnant, administered once daily, at night

40 mg (n=11)

80 mg (n=11)

120 mg (n=6)

Endpoints

Primary: Change from baseline in pre-GC morning serum A4 at Week 12

Secondary: Change from baseline in pre-GC morning serum 17-OHP at Week 12

Exploratory: Change in serum A4:Testosterone in men; change in menstrual cycle in women[b]

Safety: Incidence of TEAEs throughout the study

Pre-study GC therapy (dose and regimen) maintained throughout the study

[a]Change in menstrual cycle was assessed via completion of at-home diary.

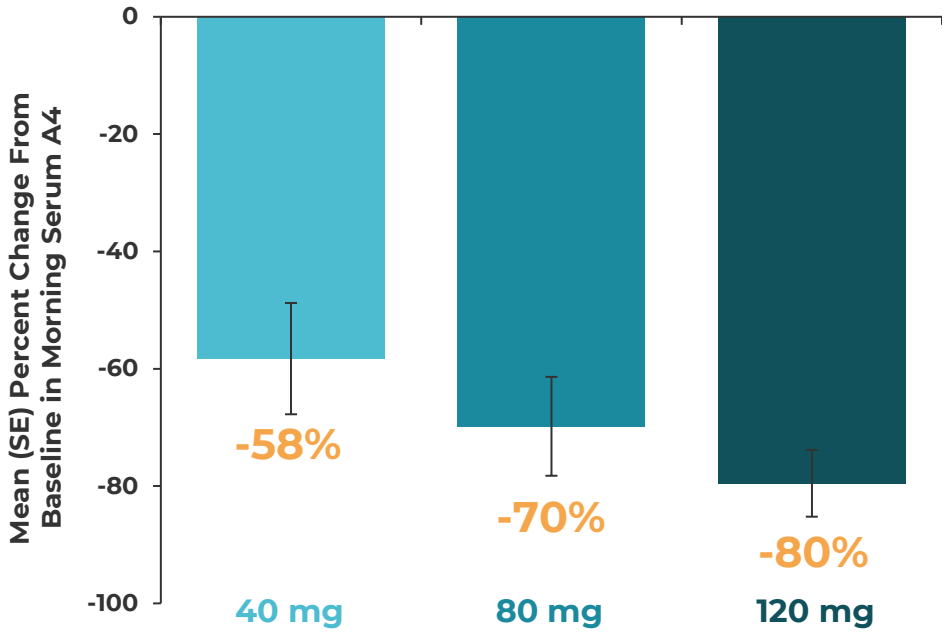
Demographics and Baseline Characteristics

Parameter			Atumelnant 40 mg (n=11)	Atumelnant 80 mg (n=11)	Atumelnant 120 mg (n=6)	All participants (N=28)
Age, years, mean (range)			28.0 (20-45)	33.0 (22-42)	34.0 (22-47)	31.3 (20-47)
Female, n (%)			4 (36.4)	8 (72.7)	3 (50.0)	15 (53.6)
Baseline biomarker levels, median (range)						
A4, ng/dL	Reference range		1180 (409-2600)	1125 (116-2755)	778 (383-2025)	1049 (116-2755)
	Women	30-200				
	Men	40-150				
17-OHP, ng/dL	Women	<80, follicular <285, luteal	13,300 (2720-24,250)	14,150 (4740-44,000)	10,310 (453-26,600)	12,750 (453-44,000)
	Men	<220				
Testosterone, ng/dL	Women	<48	92 (44-178)	211 (5-481)	387 (132-552)	178 (5-552)
A4:Testosterone	Men	<1	5.76 (0.51-10.35)	2.51 (0.30-6.39)	4.76 (0.57-5.33)	4.76 (0.30-10.35)
GC dose, mg/day, mean (range)[a]			30 (20-40)	31 (20-40)	23 (20-30)	29 (20-40)

[a]Glucocorticoid dose in hydrocortisone equivalents. Prednisone/prednisolone/methylprednisolone= 4.

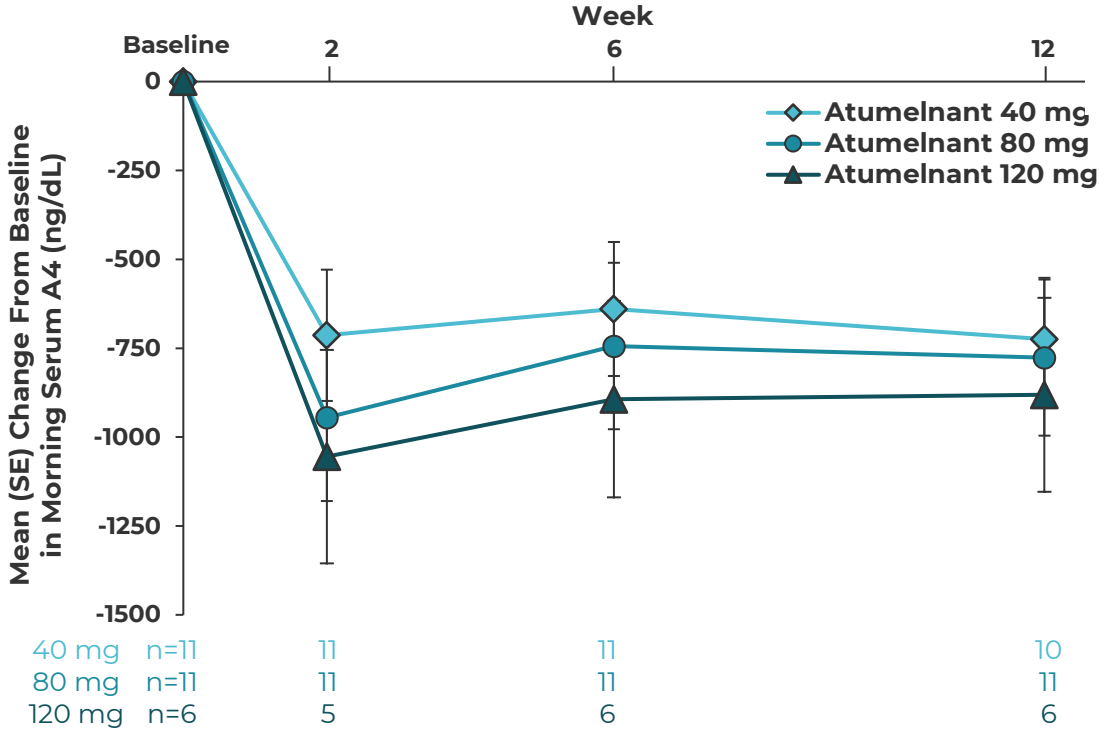
Rapid, Substantial, and Sustained Reduction in Pre-GC Morning Serum A4 With Atumelnant

Reduction in A4 From Baseline to Week 12



A4 (ng/dL) at Week 12	40 mg	80 mg	120 mg
LS mean[a], change from baseline	-601	-771	-953
P value	*P*=0.0003	*P*<0.0001	*P*<0.0001

Reduction in A4 From Baseline With Atumelnant



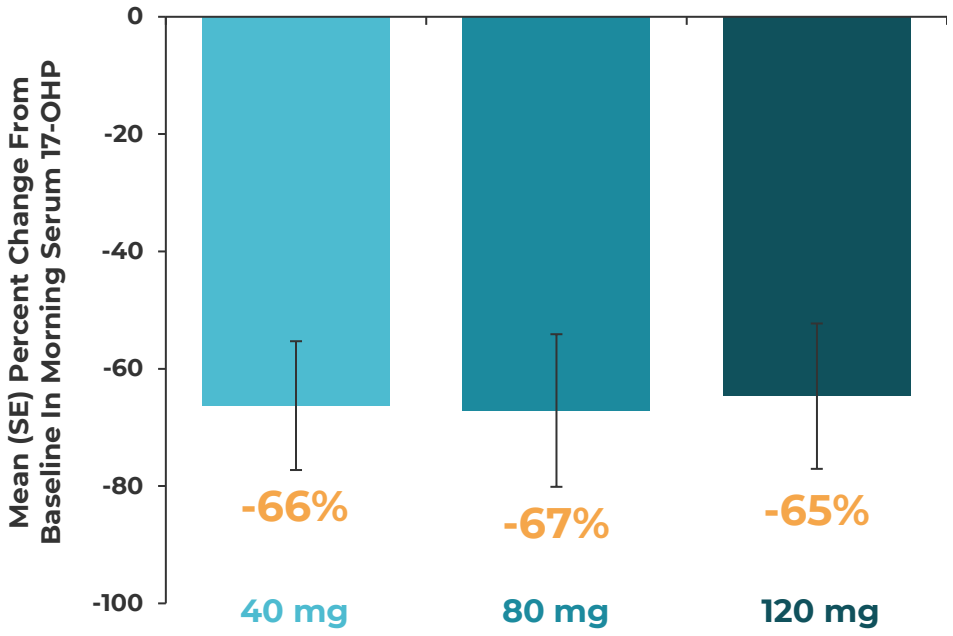
12/28 participants had A4 <ULN at Week 12

40 mg	80 mg	120 mg
3/11	6/11	3/6

[a]LS mean (SE) are from a by-visit analysis of covariance model with CFB as the dependent variable, sex and cohort as fixed effects, and baseline A4 as a covariate.

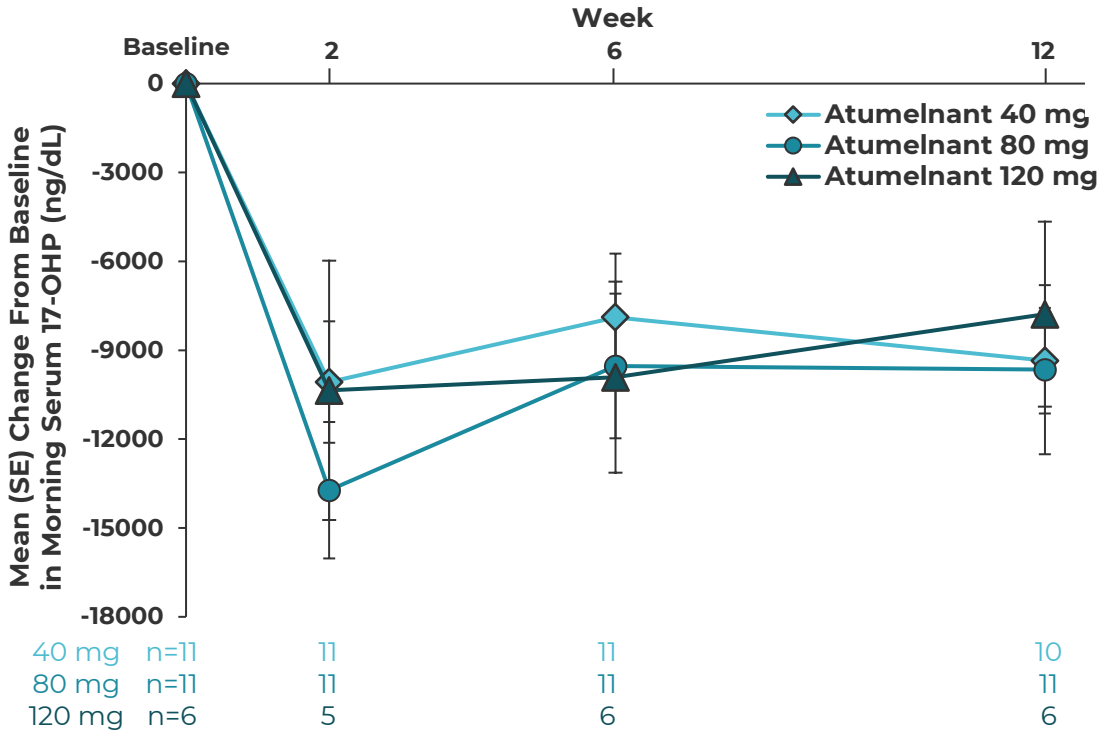
Rapid, Substantial, and Sustained Reduction in Pre-GC Morning Serum 17-OHP With Atumelnant

Reduction in 17-OHP From Baseline to Week 12



17-OHP (ng/dL) at Week 12	40 mg	80 mg	120 mg
LS mean[a], change from baseline	-7715	-8774	-9611
P value	*P*=0.0017	*P*=0.0009	*P*=0.0034

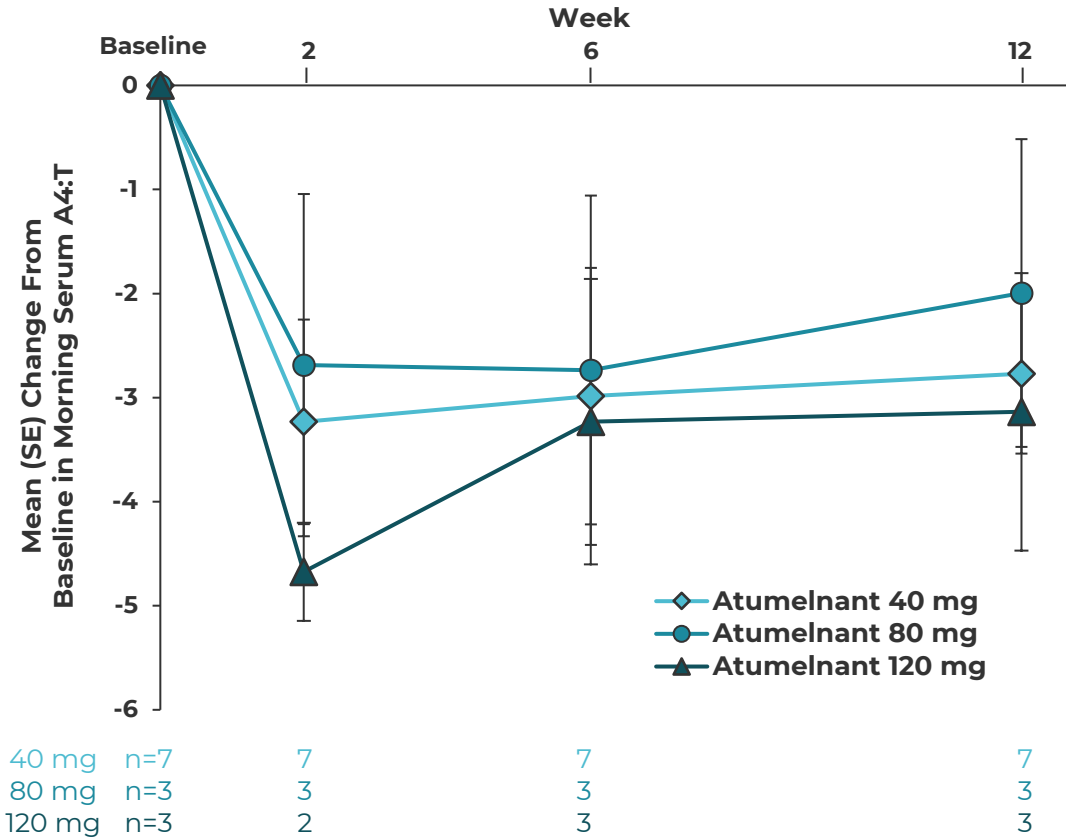
Reduction in 17-OHP From Baseline With Atumelnant



[a]LS mean (SE) are from a by-visit analysis of covariance model with CFB as the dependent variable, sex and cohort as fixed effects, and baseline 17-OHP as a covariate.

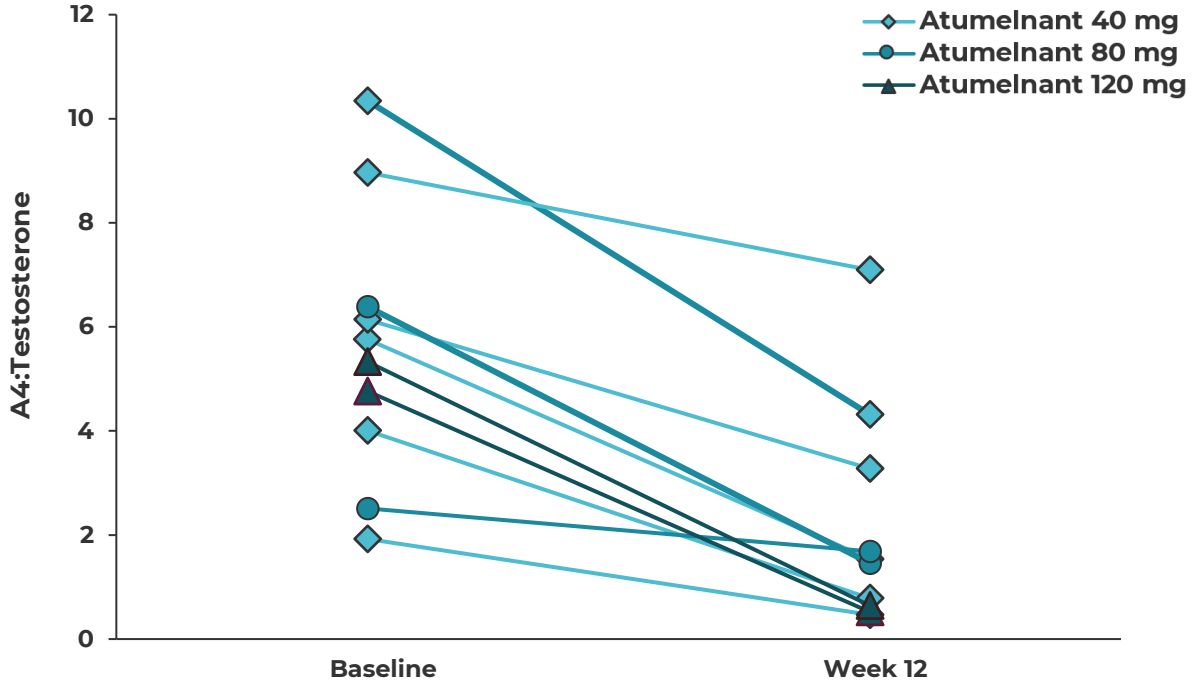
Pre-GC Serum A4:Testosterone Was Reduced in Male Participants in All Atumelnant Dose Cohorts

Reduction in A4:Testosterone From Baseline With Atumelnant



40 mg	n=7	7	7	7
80 mg	n=3	3	3	3
120 mg	n=3	2	3	3

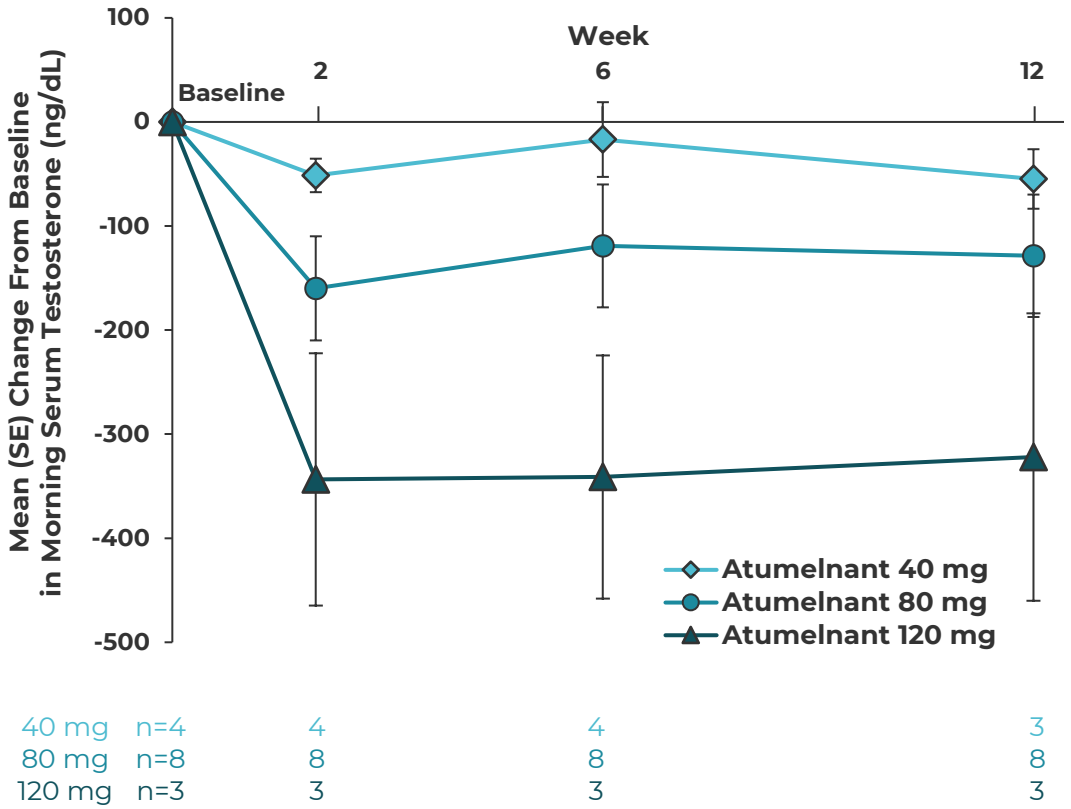
Change in A4:Testosterone From Baseline to Week 12 for Individual Participants[a]



[a]Includes all male participants with baseline A4:Testosterone>1.0; all participants (2/2) in the 120 mg cohort had normalized ratio at Week 12.

Female Participants Experienced Improvements in Reproductive Health With Atumelnant

Reduction in Testosterone From Baseline With Atumelnant



- Regular menstruation was resumed by Week 12 in **6/10** participants[a]

40 mg	80 mg	120 mg
2/4	3/3	1/3

- **8/13** female participants with baseline testosterone > upper limit of normal achieved normal levels at Week 12

40 mg	80 mg	120 mg
2/3	4/7	2/3

[a]Includes all oligomenorrheic female participants of childbearing potential (ie, not on hormonal/intrauterine contraception who had irregular menses at baseline).

Summary of TEAEs

Participants with TEAE, n (%)	Atumelnant 40 mg (n=11)	Atumelnant 80 mg (n=11)	Atumelnant 120 mg (n=6)	All participants (N=28)
≥1 TEAE	8 (72.7)	8 (72.7)	5 (83.3)	21 (75.0)
TEAEs occurring in ≥2 total participants				
Headache	2 (18.2)	4 (36.4)	2 (33.3)	8 (28.6)
Fatigue	3 (27.3)	1 (9.1)	1 (16.7)	5 (17.9)
Decreased appetite	2 (18.2)	0	0	2 (7.1)
Adrenal insufficiency[a]	1 (9.1)	1 (9.1)	0	2 (7.1)
Anxiety	1 (9.1)	1 (9.1)	0	2 (7.1)
Diarrhea	1 (9.1)	1 (9.1)	0	2 (7.1)
Influenza	1 (9.1)	1 (9.1)	0	2 (7.1)
Activated partial thromboplastin time prolonged	1 (9.1)	0	1 (16.7)	2 (7.1)
Nausea	1 (9.1)	0	1 (16.7)	2 (7.1)
Upper respiratory tract infection	0	2 (18.2)	0	2 (7.1)
Breast pain	0	1 (9.1)	1 (16.7)	2 (7.1)
Transaminases increased[b]	0	1 (9.1)	1 (16.7)	2 (7.1)

[a]Glucocorticoid dose increased. [b]Was not considered treatment related in the participant who received 80 mg atumelnant.

- No severe or serious TEAEs were observed
- No TEAEs led to discontinuation of study
- Reversible elevations in AST/ALT considered potentially treatment related in 1 participant
  - No elevation in bilirubin
  - No clinical sequelae

Conclusions

- Once-daily, oral atumelnant showed profound, rapid, and sustained suppression of A4 and 17-OHP in participants with CAH, with clinical activity observed across all doses
  - Reductions of 80% and 65% in A4 and 17-OHP, respectively, were achieved in the 120-mg cohort
  - Atumelnant resulted in dose-dependent A4 lowering, with ≥50% of participants achieving normalization in the 80-mg and 120-mg cohorts
- Atumelnant treatment reduced A4:Testosterone in male participants
- The majority of oligomenorrheic females of childbearing potential resumed regular menses; testosterone levels were substantially reduced in hyperandrogenemic female participants
- Atumelnant was well tolerated at all doses, with no severe or serious TEAEs

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THANK YOU

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