Once-Daily Atumelnant (CRN04894) Enables Lowering of Glucocorticoid Doses With Sustained Androgen Reduction in Adults With Congenital Adrenal Hyperplasia

Presenter: Umasuthan Srirangalingam, MD, PhD
On behalf of the author group

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Author Disclosures

US received consulting fees from Crinetics Pharmaceuticals, Inc. (Crinetics) Diurnal Ltd, H Lundbeck A/S, and received consulting fees and research support from Neurocrine Biosciences.

AMR is a principal investigator for Crinetics and Spruce Biosciences and has received speaker fees from Merck Brasil Company.

AA, YW, EDITA, AK, and PJT are employee of Crinetics and own stocks and shares from Crinetics.

MRG has received speaker fees from Camarus, Crinetics, Novo Nordisk, and Recordati and has attended advisory boards for Crinetics, Novo Nordisk, and Recordati.

NR has received consulting fees from Crinetics, Diurnal Ltd, H Lundbeck A/S, Neurocrine Biosciences, Spruce Biosciences and received conference travel support from Recordati Rare Diseases.

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TASSB is a principal investigator for Crinetics and Spruce Biosciences and has received consulting fees from Novo Nordisk.

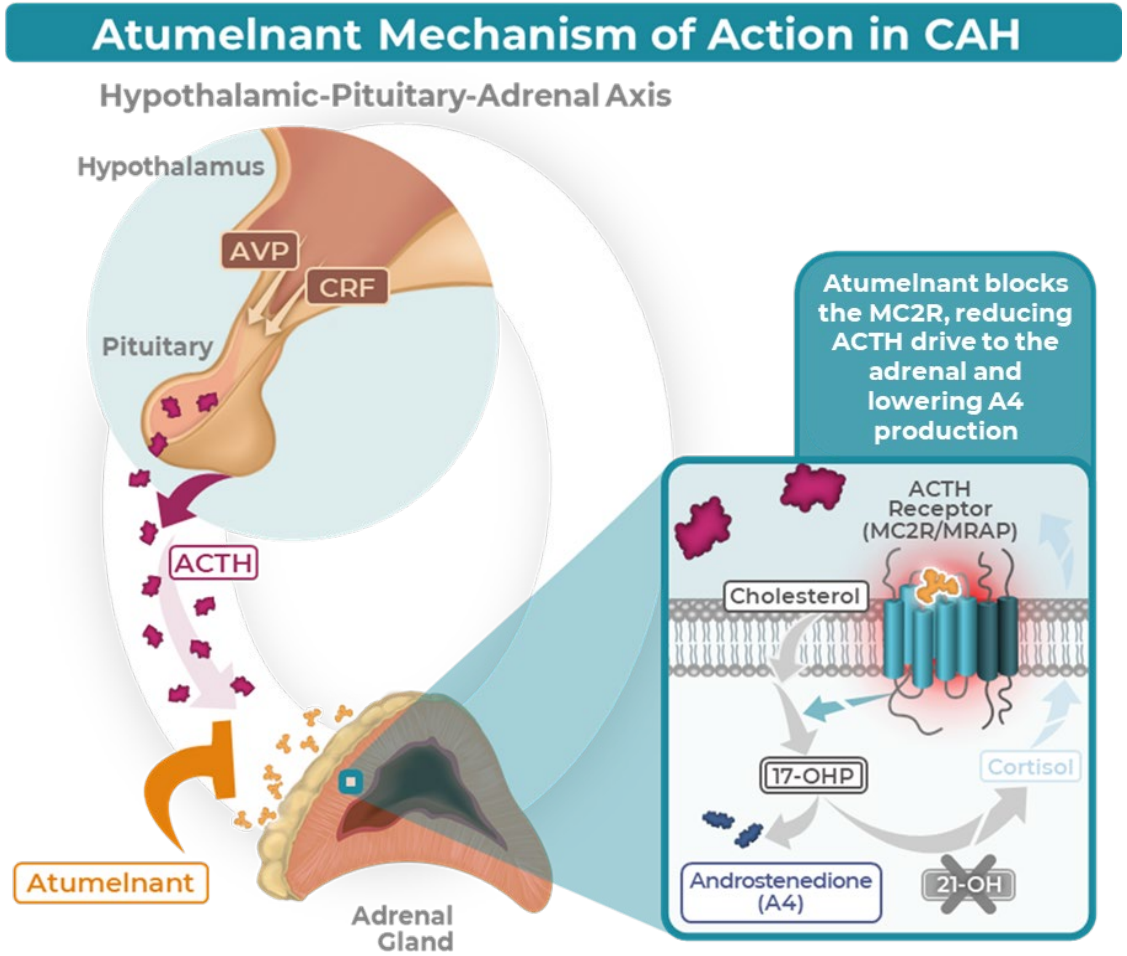
DB, FAC-B, and VdSN-N have nothing to disclose.

Background

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

Objective

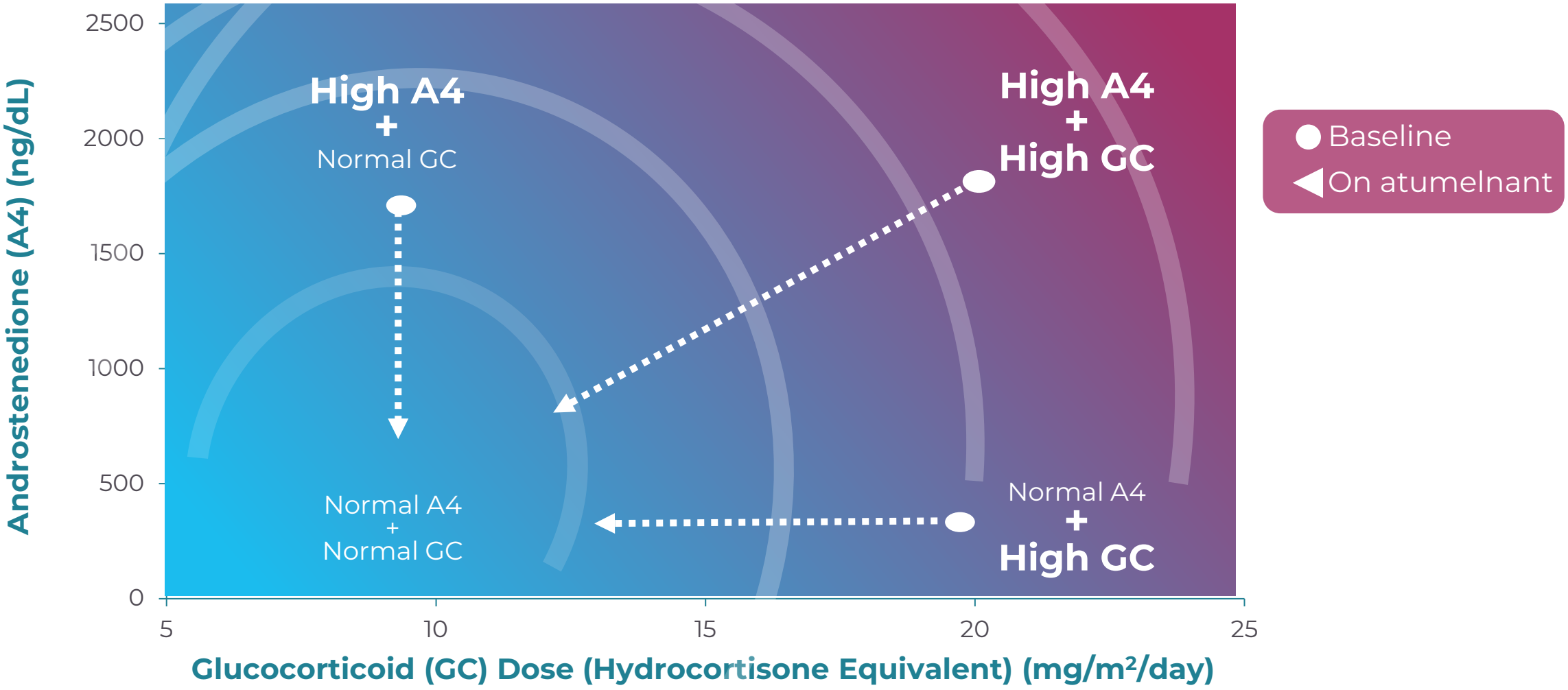
- To present results from a 12-week, Phase 2, open-label, dose-finding study conducted to evaluate the efficacy and safety of atumelnant in adult patients with classic CAH (TouCAHn study; NCT05907291)



AVP, arginine vasopressin; CRF, corticotropin-releasing factor; MC2R, melanocortin type 2 receptor; MRAP, melanocortin 2 receptor accessory protein.

1. Kim SH, et al. *ACS Med Chem Lett*. 2024;15(4):478-485. **2.** Kusnetzow AK, et al. J Endocr Soc. 2020;8(supplement_1):A133-A134.

Atumelnant Vision: Healthier Hormone Levels for People Living with CAH



Methods

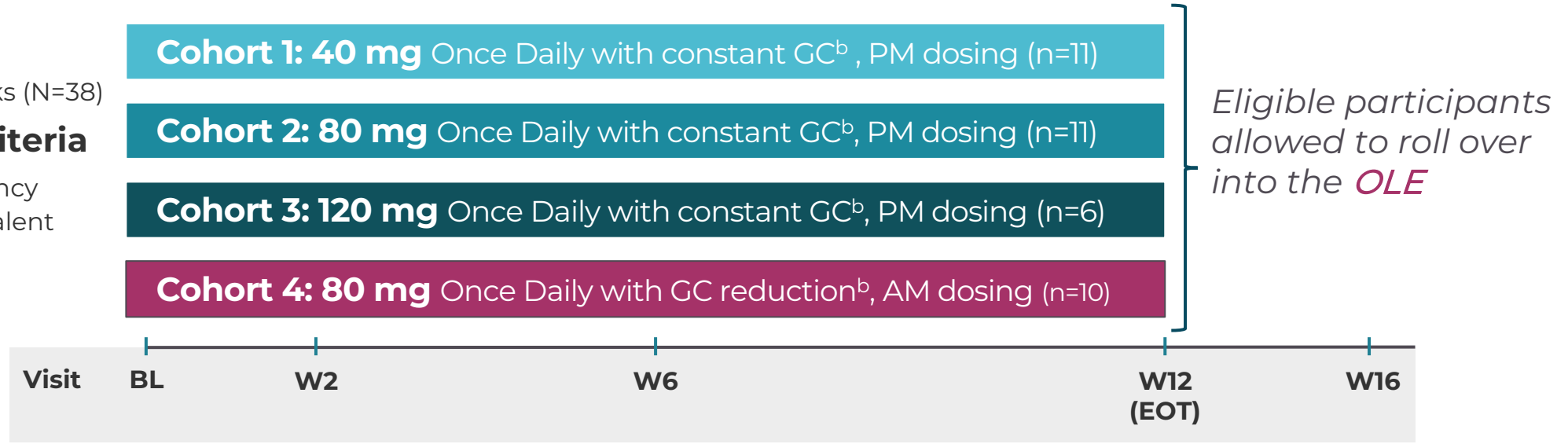
TOUCAHN

Study Size

4 cohorts, each 12 weeks (N=38)

Key Eligibility Criteria

- Classic 21-OH deficiency
- On ≥15 mg HC equivalent daily dose[a]
- A4 >1.5 × ULN



Primary Endpoints – All Cohorts

- Change from baseline (CFB) in pre-GC morning serum A4 at Week 12
- Incidence of TEAEs throughout the study

Secondary Endpoint – All Cohorts

- CFB in pre-GC morning serum 17-OHP at Week 12

Exploratory Endpoints – All Cohorts

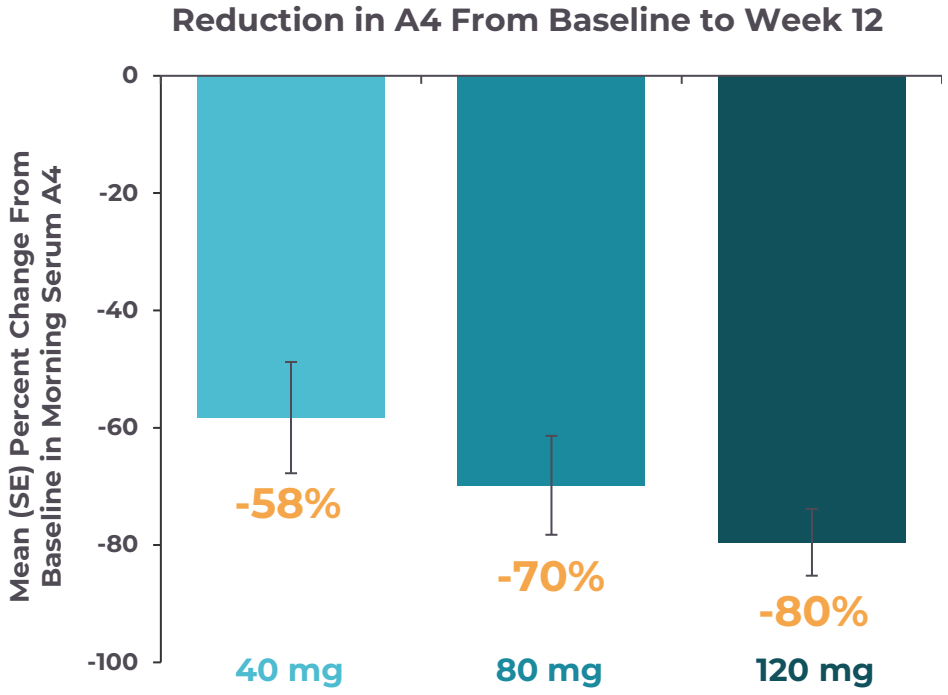
- Change in menstrual cycle in women[c]; change in serum A4:testosterone in men; change in serum 11-OHA4 and 11-KT; CFB in adrenal volume to Week 12[d]

Additional Objective – Cohort 4

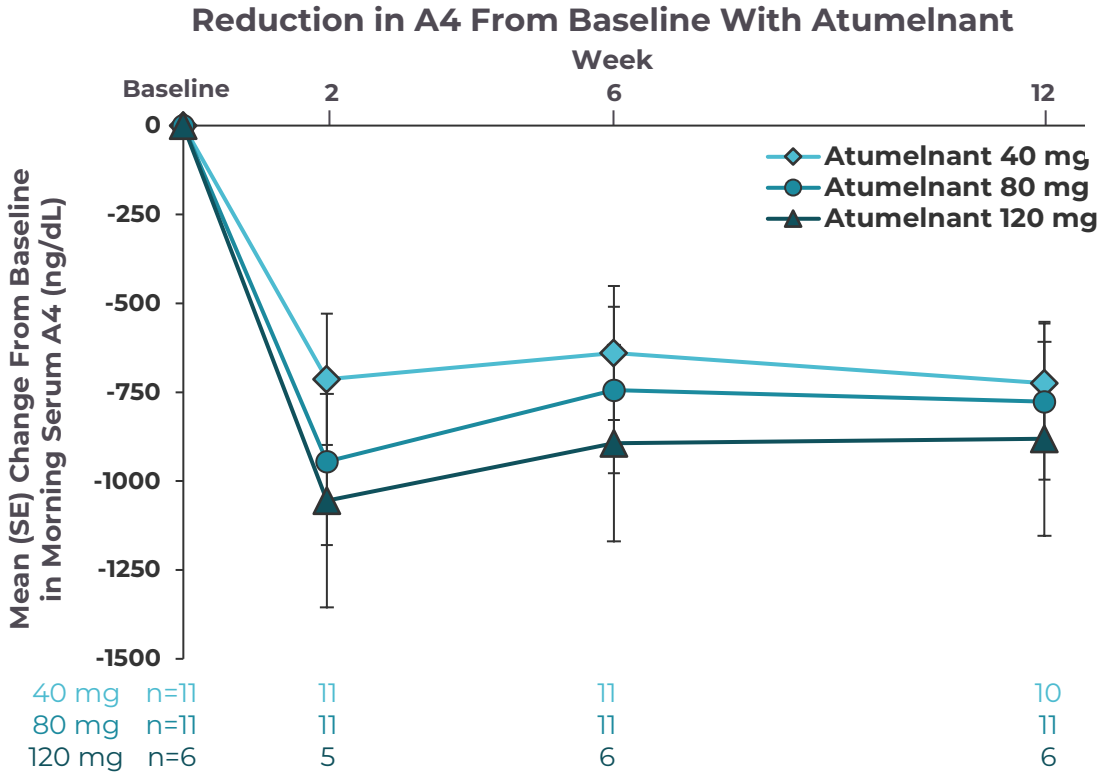
- Assess maintenance of lower A4 levels when GCs are reduced to physiologic doses
  - **GC dose reduced stepwise by 5-10 mg HC equivalents independent of A4 to target <11 mg/m²/d HC equivalents.**

[a]>11 mg/m²/day for Cohort 4. [b]Pre-trial glucocorticoid therapy (dose and regimen) maintained throughout trial (Cohorts 1-3 and first 2 weeks of Cohort 4). [c]Change in menstrual cycle was assessed via completion of at-home diary. [d]Adrenal gland size and morphology were assessed via magnetic resonance imaging (MRI) following a standardized image acquisition protocol at baseline and Week 12; all MRIs were ready by a single central radiologist.

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



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



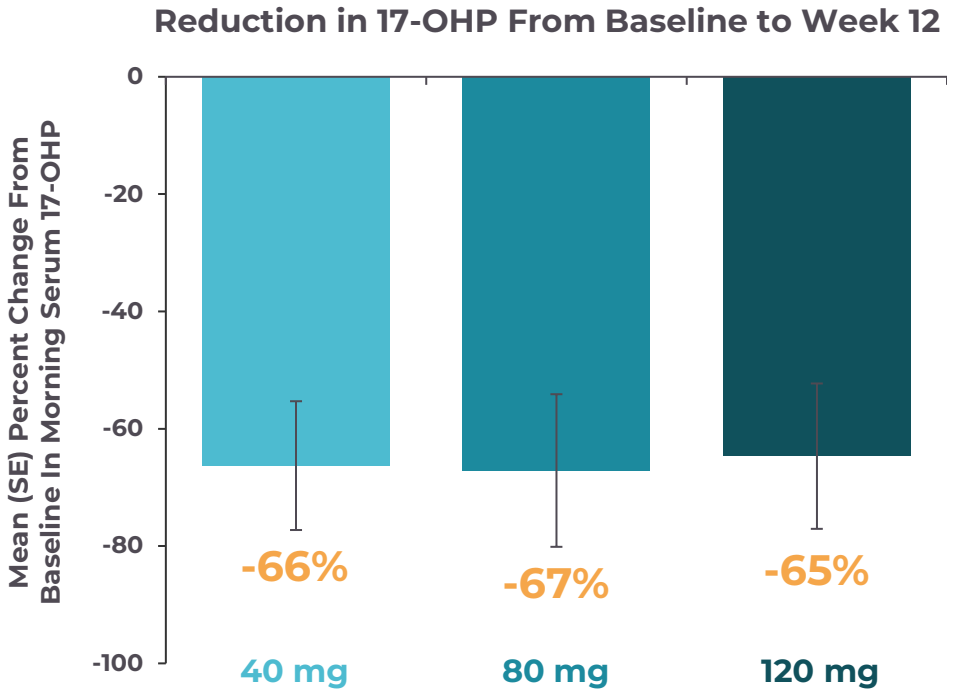
12/28 participants had A4 <ULN at Week 12

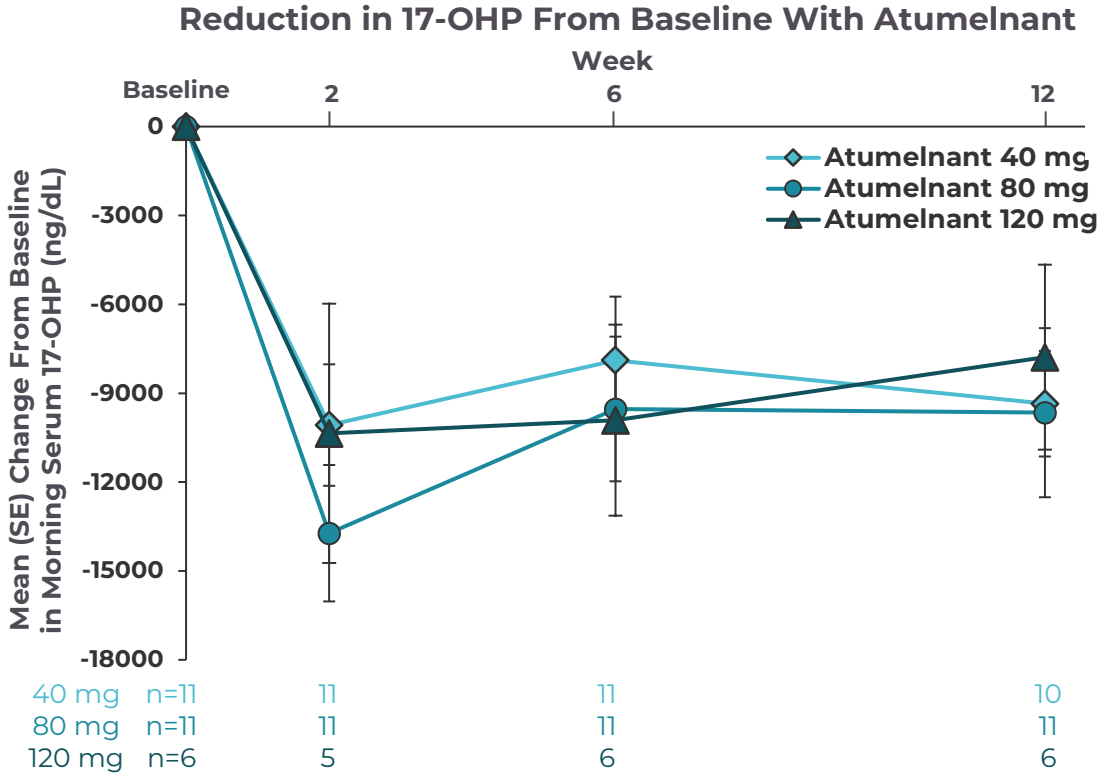
40 mg	80 mg	120 mg
3/11	6/11	3/6

[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.

Srirangalingam U. et al. *J Endocr Soc*. 2025;9(Supplement_1):A146.

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





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

[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.

Srirangalingam U. et al. *J Endocr Soc*. 2025;9(Supplement_1):A146.

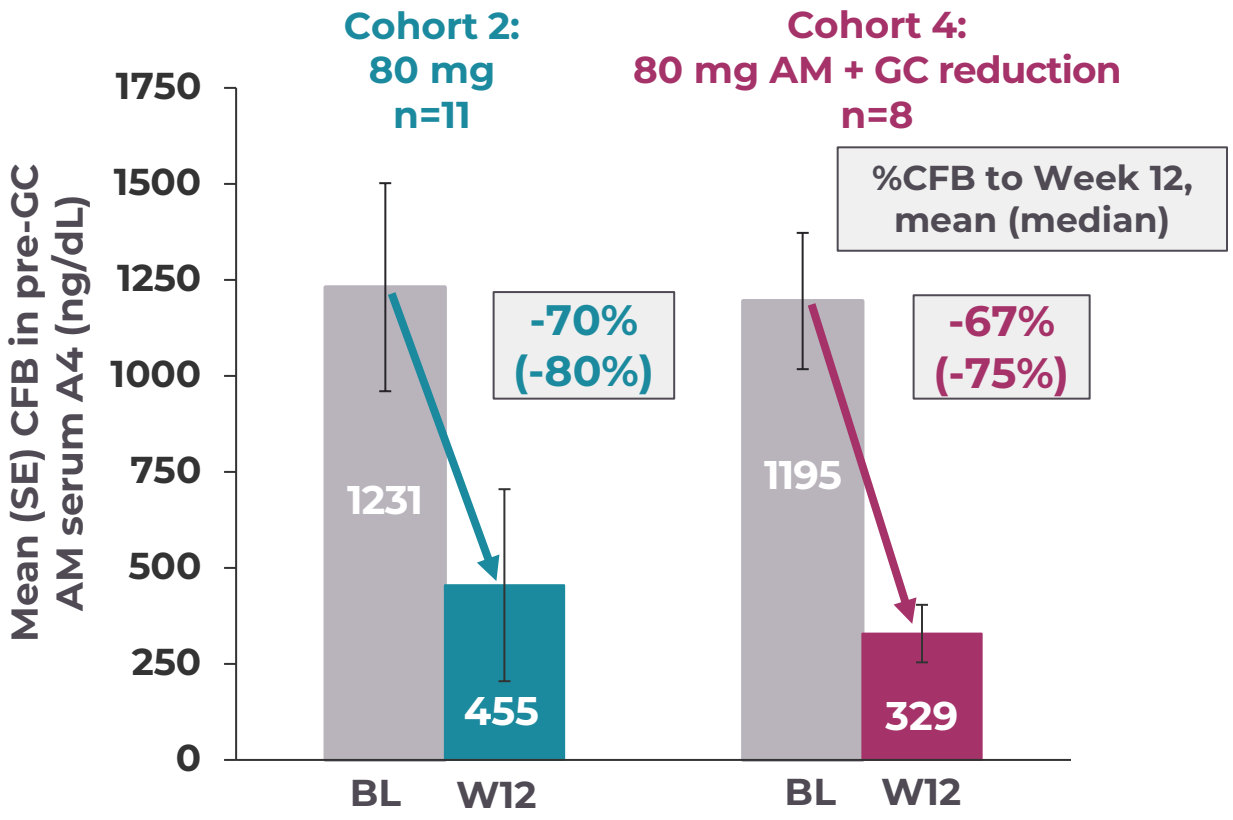
Demographics and Baseline Characteristics

Parameter			Cohort 2: Atumelnant 80 mg (n=11)	Cohort 4: Atumelnant 80 mg AM + GC dose reduction (n=10)
Age, years, mean (range)			33.0 (22-42)	38.6 (25-64)
Female, n (%)			8 (72.7)	6 (60.0)
Baseline biomarker levels, median (range)[a,b]				
A4, ng/dL	Reference range		1125 (116-2755)	981 (121-2210)
	Women	30-200		
	Men	40-150		
17-OHP, ng/dL	Women	<80, follicular <285, luteal	14,150 (4740-44,000)	10,890 (955-30,650)
	Men	<220		
Testosterone, ng/dL	Women	<48	211 (5-481)	195 (135-269)
A4:Testosterone	Men	<1	2.5 (0.30-6.38)	1.7 (0.3-3.2)
11-OHA4, ng/dL	N/A		674 (171-1310)	883 (158-1310)
11-KT, ng/dL	N/A		203 (54-680)	260 (42-969)
GC dose[c]	mg/m^2/d, mean (SE)		17.4 (10.5-25.0)[d]	13.1 (10.5-18.7)

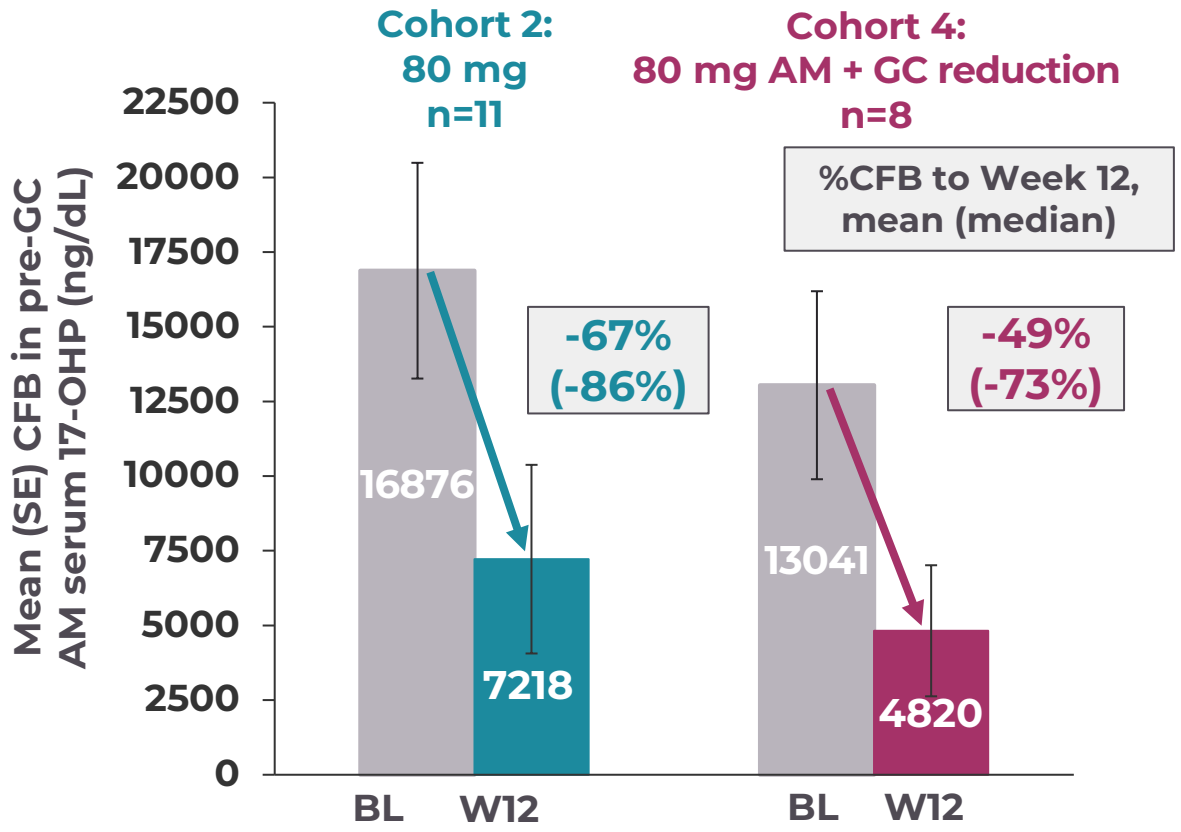
[a]Reference range values for 11-OHA4 and 11-KT have not been established. [b]The conversion factor from conventional units (ng/dL) to SI units (nmol/L) is 0.0349 for A4, 0.0303 for 17-OHP, 0.0331 for 11-OHA4 and 11-KT and 0.0347 for testosterone. [c]Glucocorticoid dose in HC equivalents. Prednisone / prednisolone / meprednisone = 4; methylprednisolone = 5. [d]n=10 for GC dose adjusted for body surface area; 1 participant did not have a recorded height.

Reductions in Pre-GC Morning Serum A4 and 17-OHP Were Not Attenuated by GC Dose Reduction

Primary Endpoint – A4



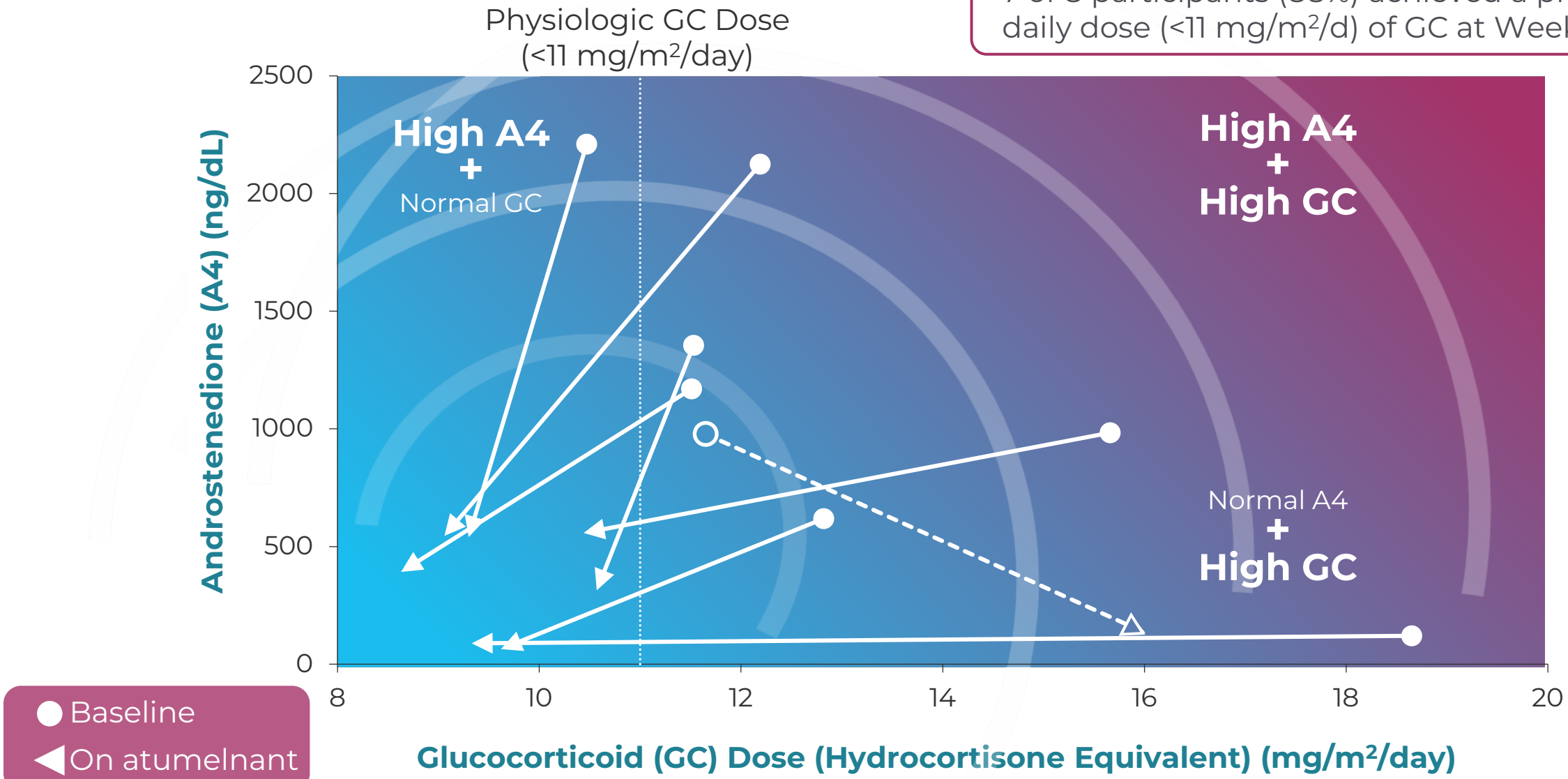
Secondary Endpoint – 17-OHP



Reduction in A4 and 17-OHP levels were similar regardless of GC reduction or timing of atumelnant dose

Cohort 4: Atumelnant Maintains Reductions in A4 Despite Lowering GC Daily Dose

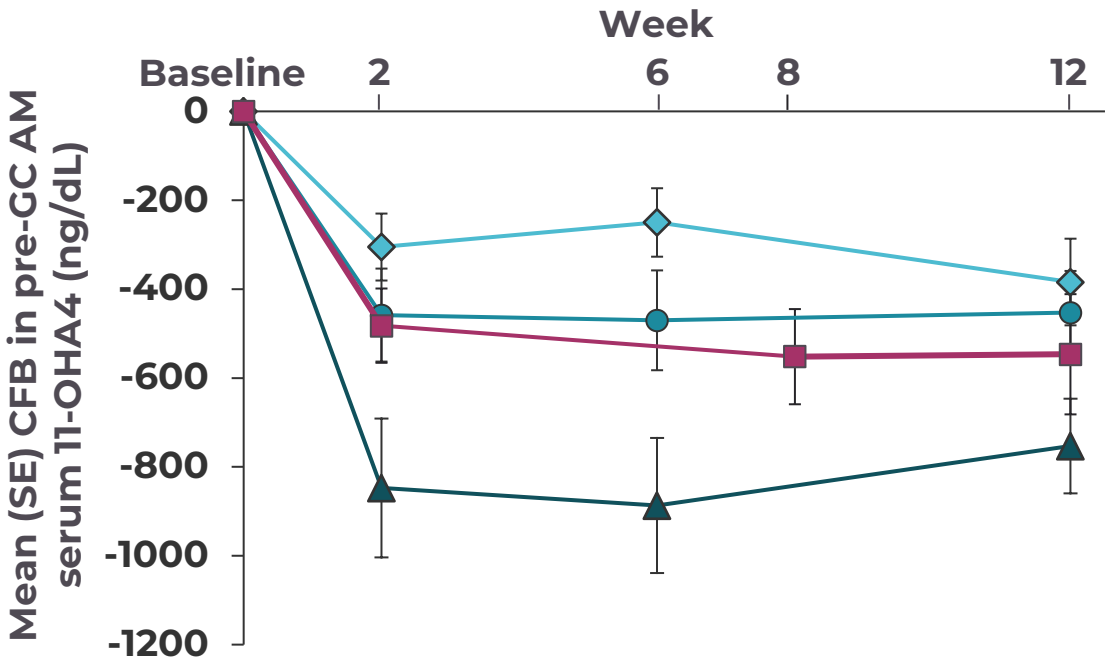
7 of 8 participants (88%) achieved a physiologic daily dose (<11 mg/m²/d) of GC at Week 12



Reductions in Pre-GC Serum 11-OHA4 and 11-KT Were Rapid and Sustained in All Atumelnant Dose Cohorts

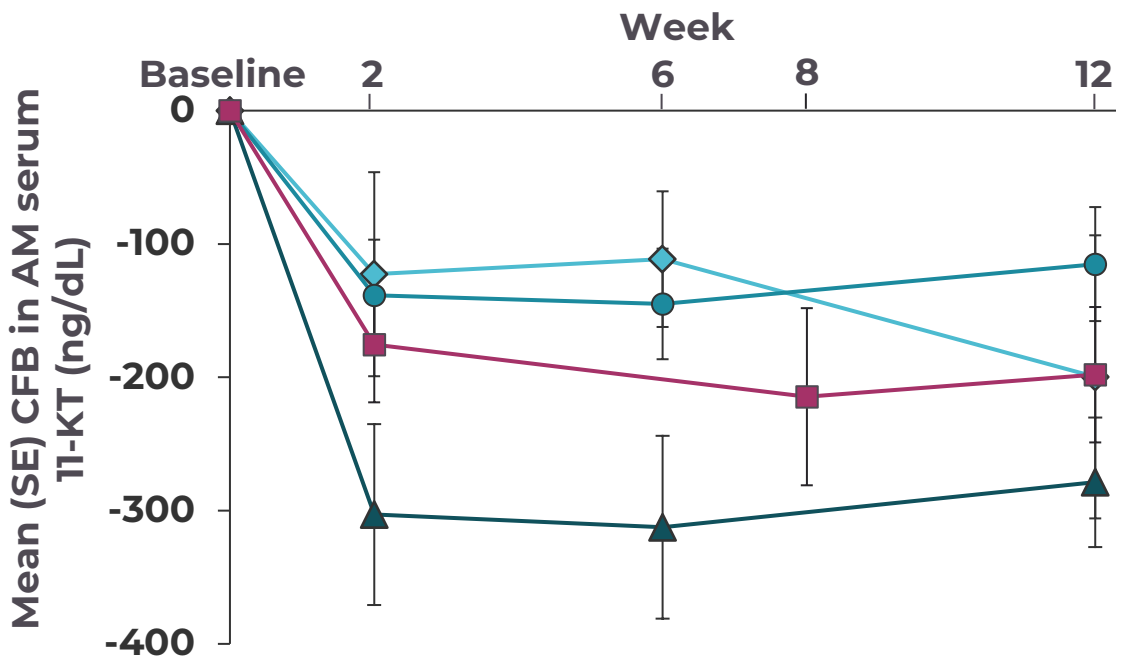
Exploratory Endpoints

Reduction in 11-OHA4 From Baseline With Atumelnant



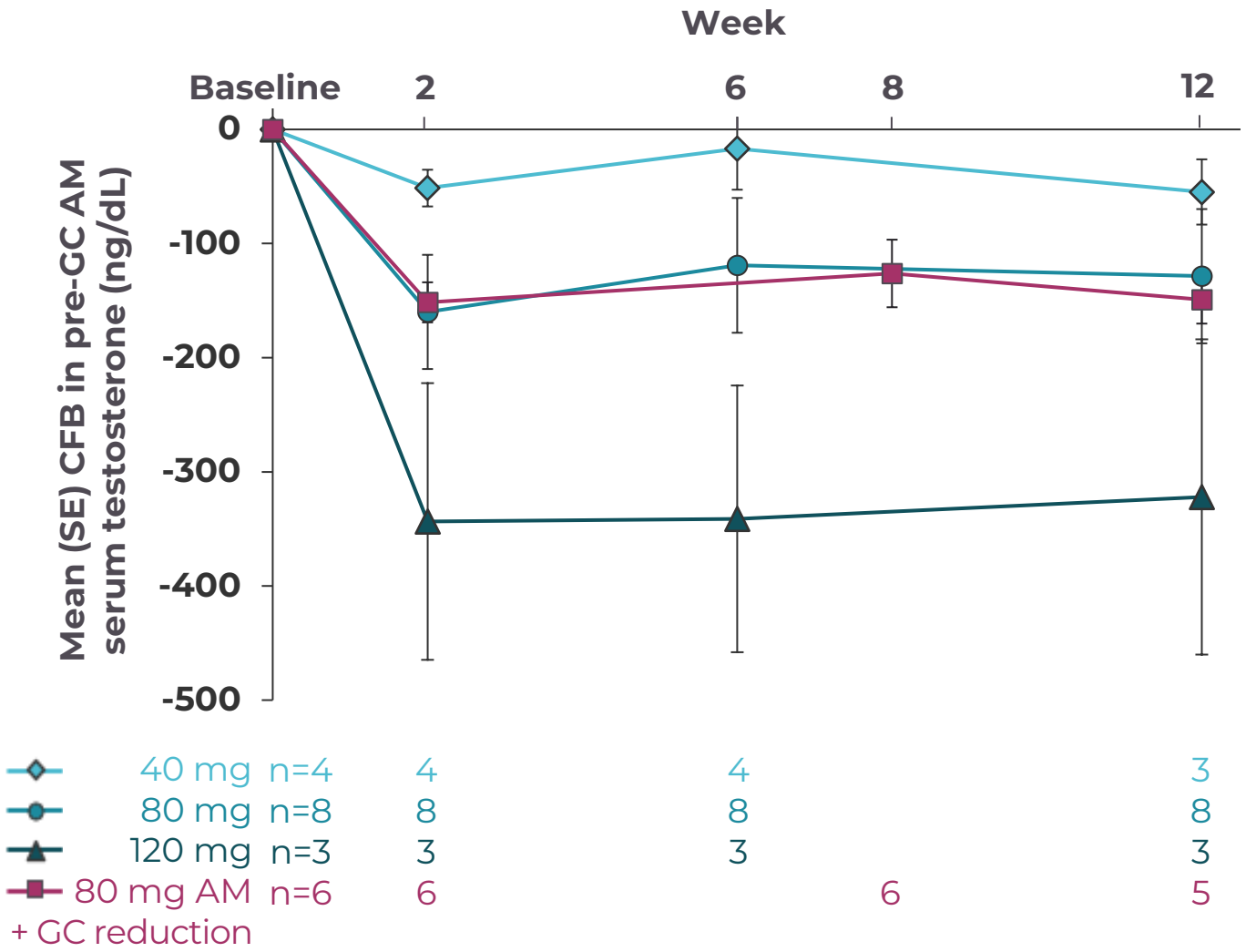
	Baseline	2	6	8	12
40 mg	n=11	11	11		10
80 mg	n=11	11	11		11
120 mg	n=6	6	6		6
80 mg AM +GC reduction	n=10	10		9	8

Reduction in 11-KT From Baseline With Atumelnant



	Baseline	2	6	8	12
40 mg	n=11	11	11		10
80 mg	n=11	11	11		11
120 mg	n=6	6	6		6
80 mg AM +GC reduction	n=10	10		9	8

Female Participants Experienced Improvements in Reproductive Function With Atumelnant



Exploratory Endpoints

- Regular menstruation was resumed by Week 12 in 6 of 12 participants[a]

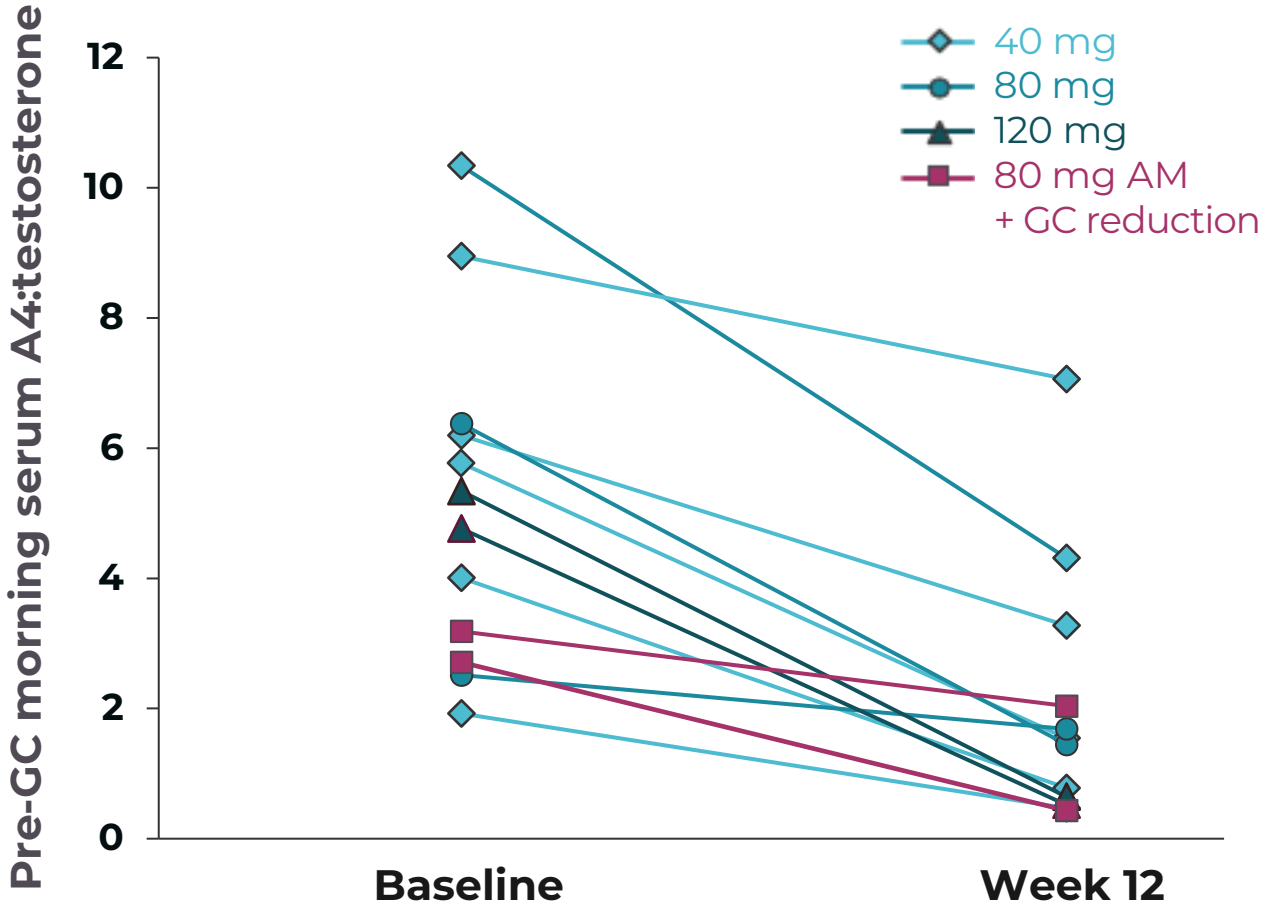
40 mg	80 mg	120 mg	80 mg AM
2/4	3/3	1/3	0/2

- 10 of 19 female participants with baseline testosterone > ULN achieved normal levels at Week 12

40 mg	80 mg	120 mg	80 mg AM
2/3	4/7	2/3	2/6

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

Atumelnant Reduced Pre-GC Serum A4:Testosterone and TART Volume in Male Participants



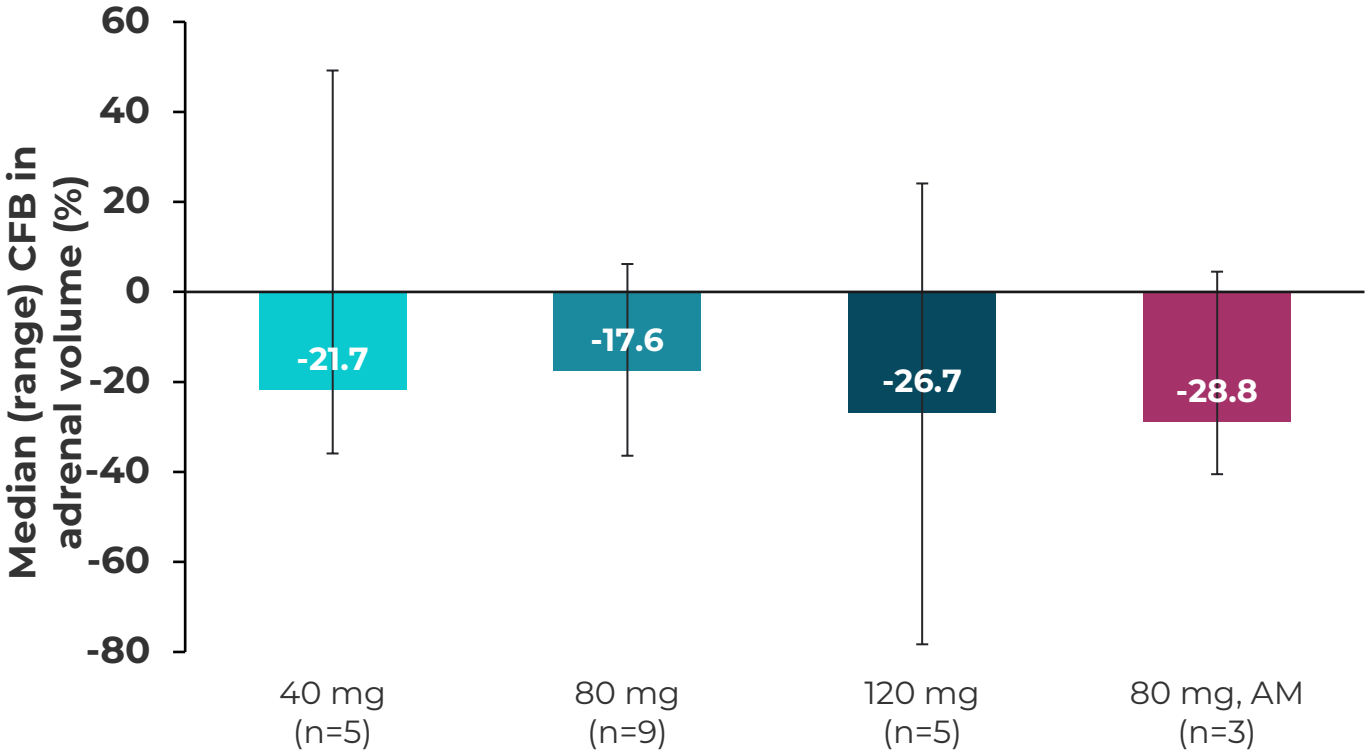
Exploratory Endpoints

- 5/12 males had normalized A4:T ratios at Week 12, including both participants in the 120 mg cohort (among all male participants with baseline A4:T>1.0)
- Among male participants with TARTs at baseline and evaluable images (n=2), total TART volume was reduced at Week 12 by
  - –25% (80 mg PM)
  - –17% (80 mg AM + GC reduction)

TART, testicular adrenal rest tumor.

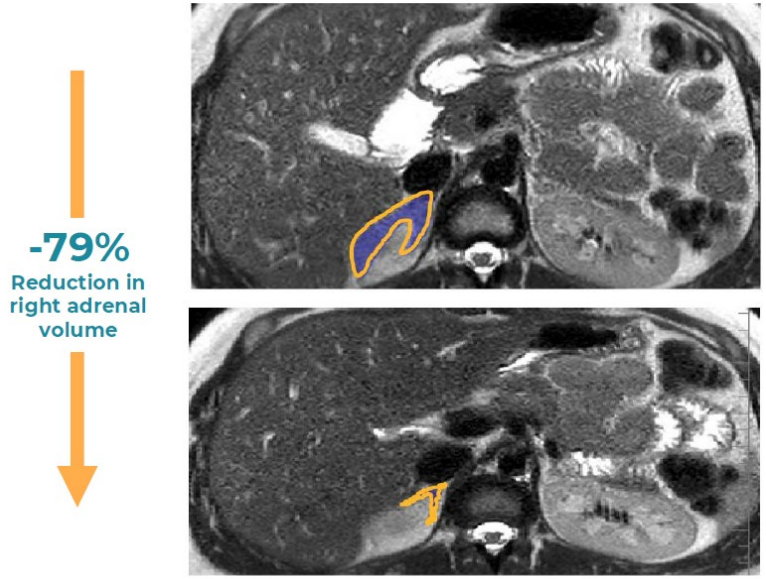
Atumelnant Treatment Reduced Adrenal Size by Week 12

Exploratory Endpoint



17 of 22 participants had a decrease in total adrenal volume[a]

40 mg	80 mg	120 mg	80 mg AM
4/5	7/9	4/5	2/3



- Male participant treated with 120 mg atumelnant and hydrocortisone 30 mg daily
- Baseline: volume 11.7 mL, A4 2025 ng/dL
- Week 12: volume 2.4 mL, A4 173.5 ng/dL
- Left adrenal volume findings were similar

MRI, magnetic resonance imaging. [a]Based on evaluable images. Total volume was derived as the sum of the left and right adrenal gland volumes; if only 1 side had evaluable volume, then that was set to the total volume.

Summary of Treatment-Emergent Adverse Events

Participants with TEAE, n (%)	40 mg (n=11)	80 mg (n=11)	120 mg (n=6)	80 mg + GC dose reduction (n=10)	All participants (N=38)
Any TEAE	8 (72.7)	8 (72.7)	5 (83.3)	10 (100)	31 (81.6)
TEAEs occurring in ≥2 total participants					
Headache	2 (18.2)	4 (36.4)	2 (33.3)	5 (50.0)	13 (34.2)
Fatigue	3 (27.3)	1 (9.1)	1 (16.7)	1 (10.0)	6 (15.8)
Diarrhea	1 (9.1)	1 (9.1)	0	2 (20.0)	4 (10.5)
Adrenal insufficiency[a]	1 (9.1)	1 (9.1)	0	1 (10.0)	3 (7.9)
Influenza	1 (9.1)	1 (9.1)	0	1 (10.0)	3 (7.9)
Nausea	1 (9.1)	0	1 (16.7)	1 (10.0)	3 (7.9)
Breast pain	0	1 (9.1)	1 (16.7)	1 (10.0)	3 (7.9)
Decreased appetite	2 (18.2)	0	0	0	2 (5.3)
Anxiety	1 (9.1)	1 (9.1)	0	0	2 (5.3)
Activated partial thromboplastin time prolonged	1 (9.1)	0	1 (16.7)	0	2 (5.3)
Urinary tract infection	1 (9.1)	0	0	1 (10.0)	2 (5.3)
Upper respiratory tract infection	0	2 (18.2)	0	0	2 (5.3)
Transaminases increased[b]	0	1 (9.1)	1 (16.7)	0	2 (5.3)
Abdominal pain	0	0	1 (16.7)	1 (10.0)	2 (5.3)
Glucocorticoid deficiency	0	0	0	2 (20.0)	2 (5.3)

- No severe or serious TEAEs
- No TEAEs led to study discontinuation

[a]Glucocorticoid dose increased. [b]Elevations were transient. Was not considered treatment related in the participant who received 80 mg atumelnant. Elevations in participant who received 120 mg returned to baseline following end of treatment.

Conclusions

Once-daily, oral atumelnant enables lowering of glucocorticoid doses with sustained androgen reduction

- In all cohorts, once-daily oral atumelnant resulted in:
  - rapid, substantial, and sustained suppression of pre-GC morning A4 and 17-OHP
  - reduced testosterone levels in hyperandrogenemic female participants
  - majority of oligomenorrheic females of childbearing potential resumed regular menses
  - reduced A4:testosterone and TART volume in male participants
  - reduced 11-oxygenated androgen levels
  - reduction in adrenal size in most participants
- In Cohort 4 (atumelnant 80 mg + GC dose reduction)
  - A4 was substantially reduced at Week 12 despite GC dose reduction
  - 88% of participants achieved a physiologic daily dose (<11 mg/m^2/d) of GC by Week 12
- Atumelnant was well tolerated at all doses, with no severe or serious TEAEs, and none that led to treatment discontinuation

Acknowledgments

Thank you to the study patients, nurses, and investigators who made this study possible.

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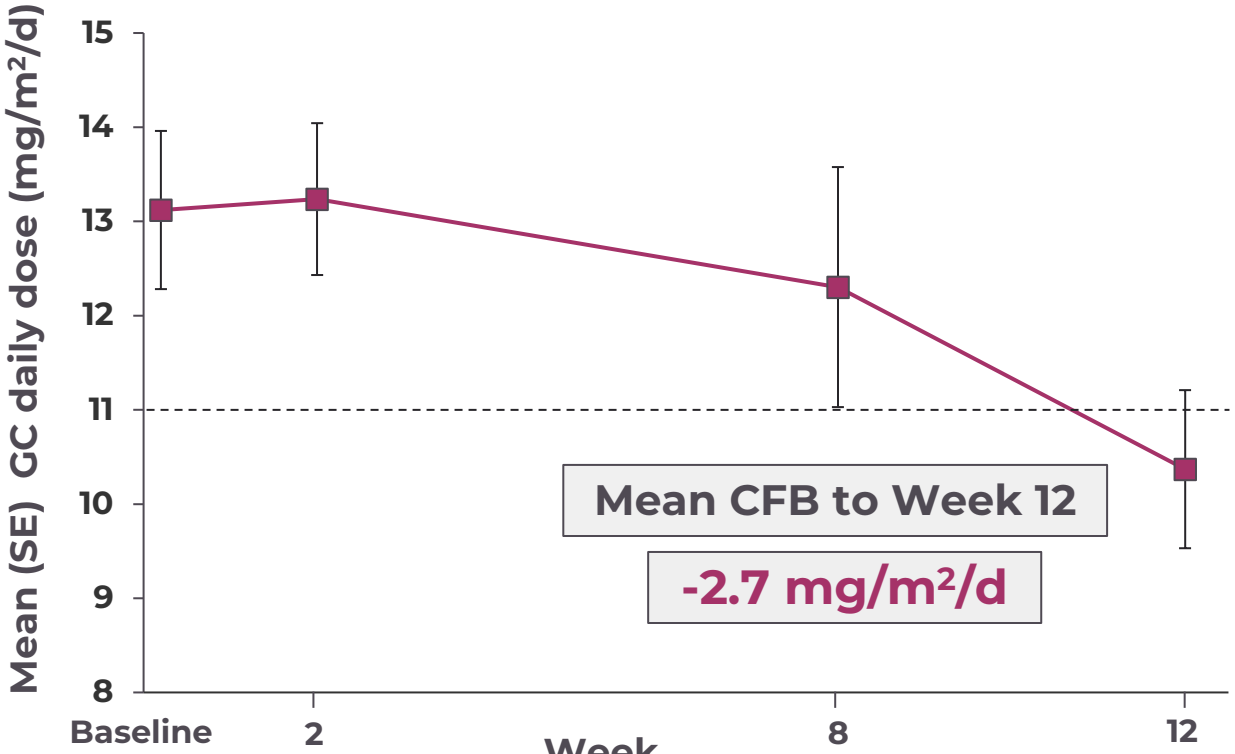
Thank You

SUPPLEMENTAL SLIDES

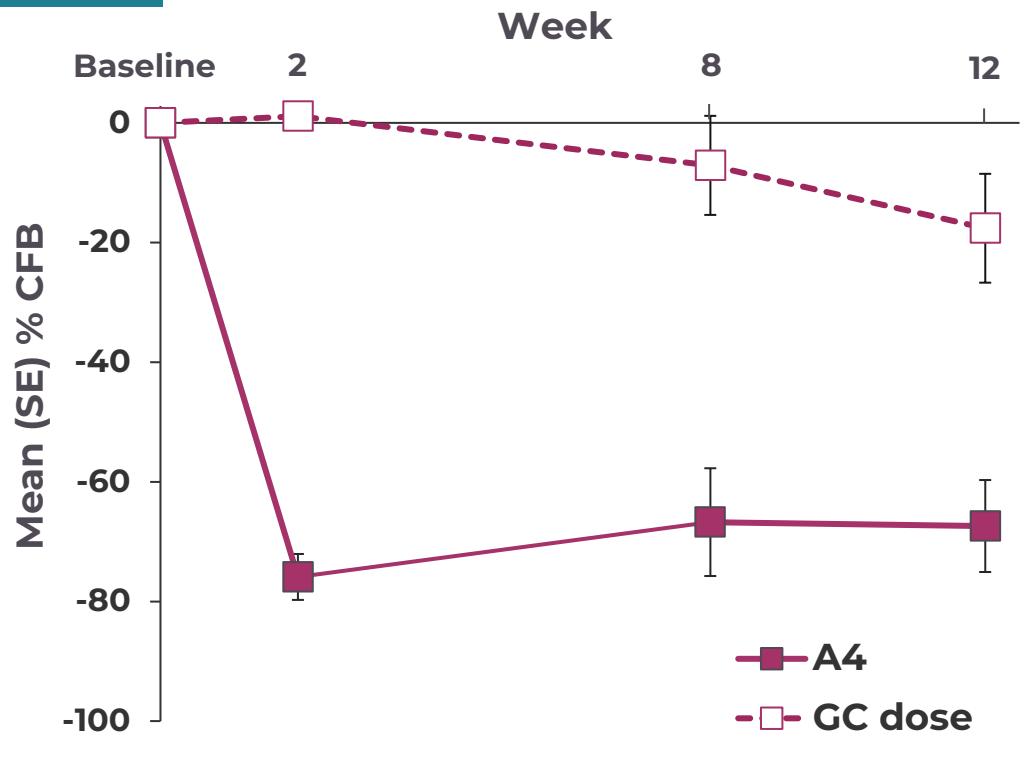
Most Cohort 4 Participants Achieved GC Daily Dose Reduction to Physiologic Levels

Exploratory Endpoint



80 mg AM + GC reduction

	Baseline	2	8	12
n=	10	10	9	8



	Baseline	2	8	12
n=	10	10	9	8

7 of 8 participants (88%) achieved a physiologic daily dose (<11 mg/m²/d) of GC at Week 12

Atumelnant maintains reductions in A4 despite lowering GC daily dose

Demographics and Baseline Characteristics (1 of 2)

Parameter			Atumelnant 40 mg (n=11)	Atumelnant 80 mg (n=11)	Atumelnant 120 mg (n=6)	Atumelnant 80 mg AM + GC dose reduction (n=10)	All participants (N=38)
Age, y, mean (range)			28.0 (20-45)	33.0 (22-42)	34.0 (22-47)	38.6 (25-64)	33.2 (20-64)
Sex, female, n (%)			4 (36.4)	8 (72.7)	3 (50.0)	6 (60.0)	21 (55.3)
Baseline biomarker levels, median (range)[a]							
A4, ng/dL	Reference range		1180 (409-2600)	1125 (116-2755)	778 (383-2025)	981 (121-2210)	981 (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)	10,890 (955-30,650)	12,175 (453-44,000)
	Men	<220					
GC dose[b], mg/m^2/d, mean (range)			15.5 (10.5-22.8)	17.4 (10.5-25.0)	13.7 (10.5-18.7)	13.1 (10.5-18.7)	15.1 (10.5-25.0)[c]

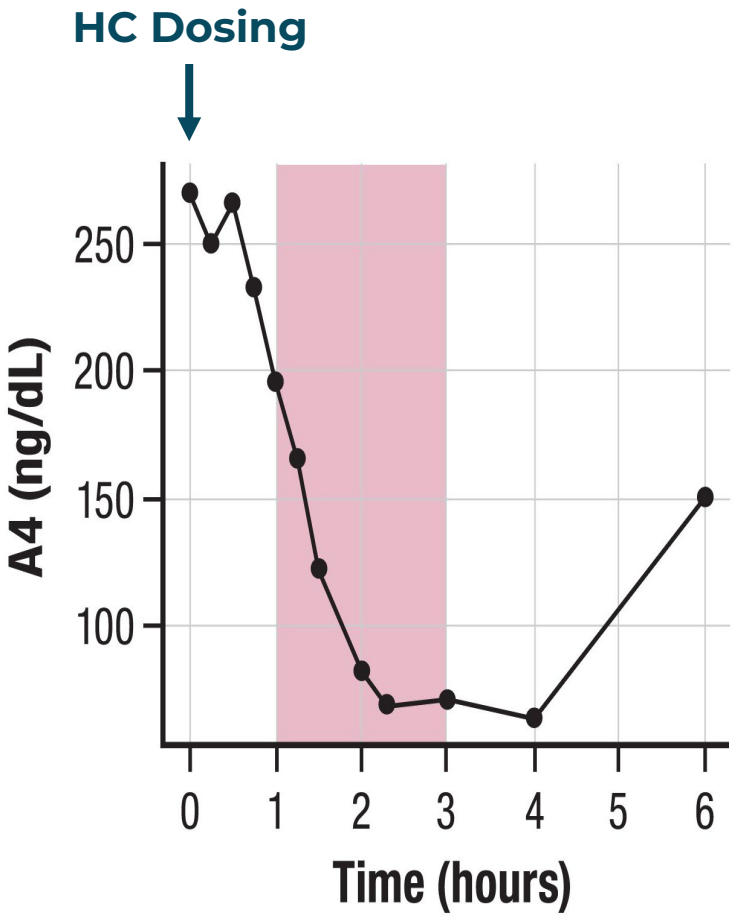
[a]The conversion factor from conventional units (ng/dL) to SI units (nmol/L) is 0.0349 for A4 and 0.0303 for 17-OHP. [b]Glucocorticoid dose in HC equivalents. Prednisone / prednisolone / meprednisone = 4; methylprednisolone = 5. [c]n=37 for GC dose adjusted for body surface area; 1 participant did not have a recorded height.

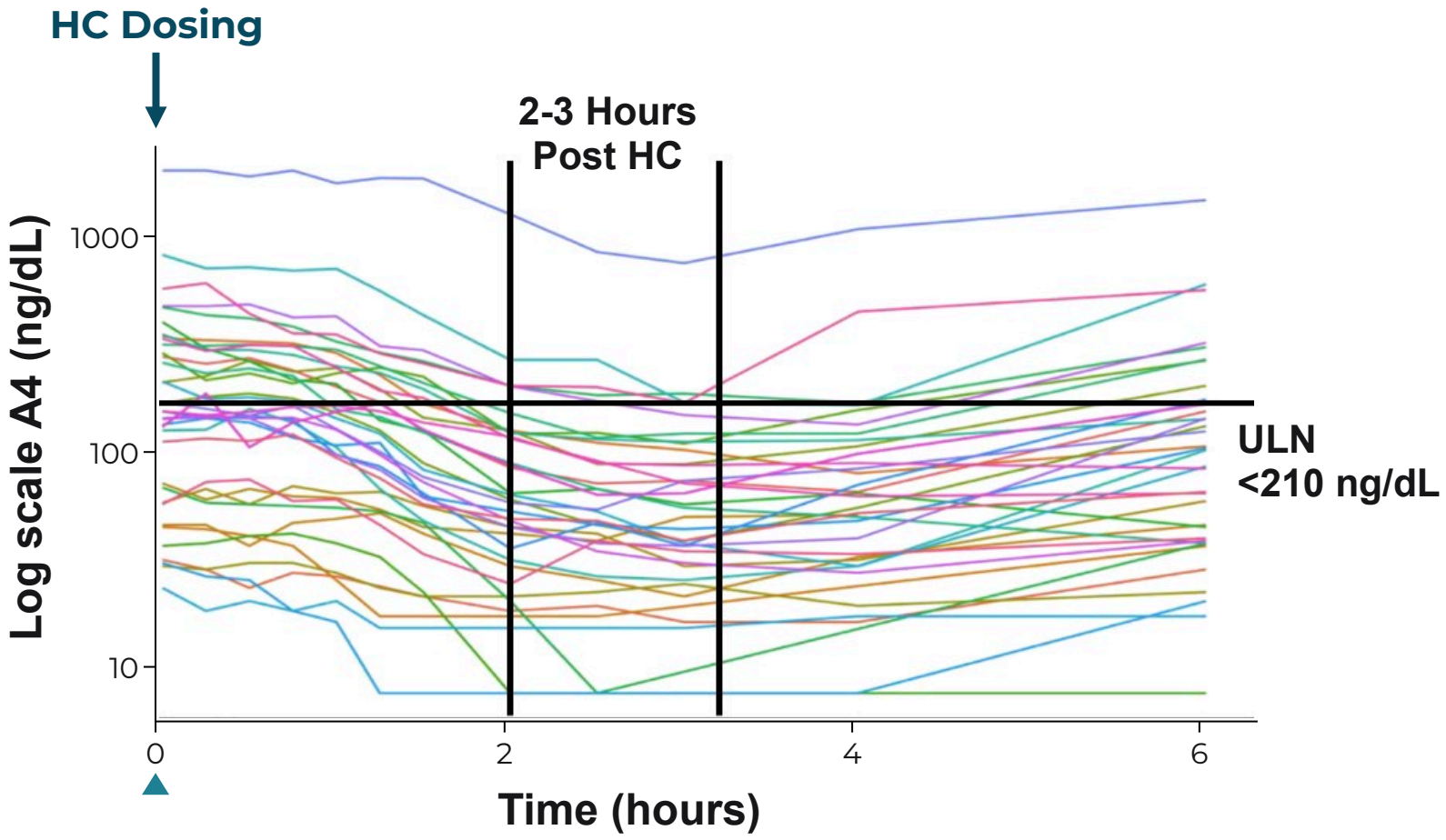
Demographics and Baseline Characteristics (2 of 2)

Parameter			Atumelnant 40 mg (n=11)	Atumelnant 80 mg (n=11)	Atumelnant 120 mg (n=6)	Atumelnant 80 mg AM + GC dose reduction (n=10)	All participants (N=38)
Additional baseline biomarker levels, median (range)[a,b]							
	Reference range						
Testosterone, ng/dL	Women	<48	92 (44-178)	211 (5-481)	387 (132-552)	195 (135-269)	185 (5-552)
A4 : testosterone	Men	<1	5.8 (0.51-10.34)	2.5 (0.30-6.38)	4.8 (0.6-5.3)	1.7 (0.3-3.2)	3.2 (0.3-10.3)
11-OHA4, ng/dL	N/A		667 (142-1310)	674 (171-1310)	1081 (350-1310)	883 (158-1310)	778 (142-1310)
11-KT, ng/dL	N/A		190 (66-1293)	203 (54-680)	364 (141-547)	260 (42-969)	228 (42-1293)

[a]Reference range values for 11-OHA4 and 11-KT have not been established. [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.

Serum morning A4 pre- & post-hydrocortisone (HC)





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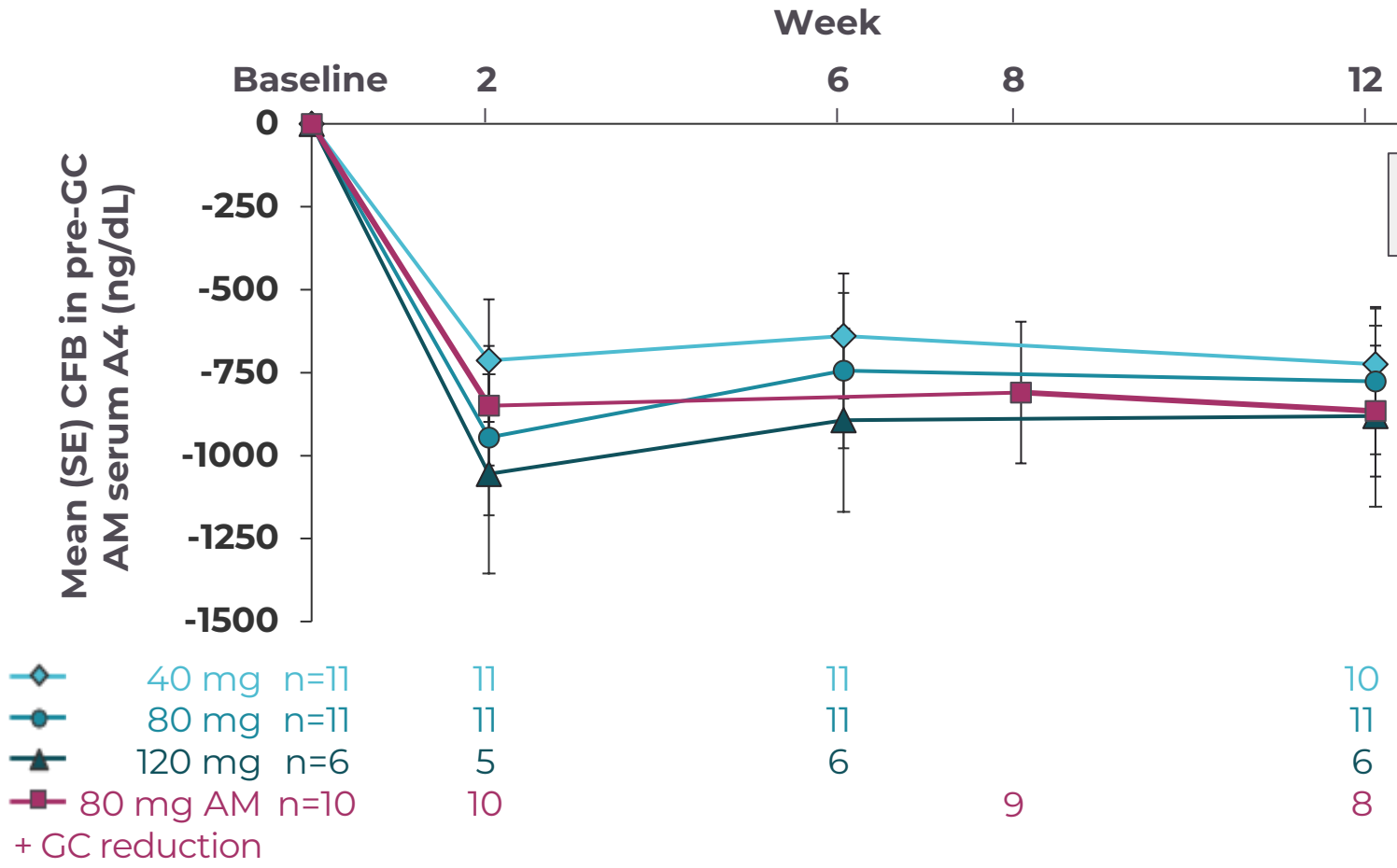
Al-Kofahi M, et al. *Br J Clin Pharmacol*. 2021;87(3):1098-1110.

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



Primary Endpoint

%Change from baseline to Week 12, mean (median)

- **-58% (-65%)**
- **-70% (-80%)**
- **-80% (-82%)**

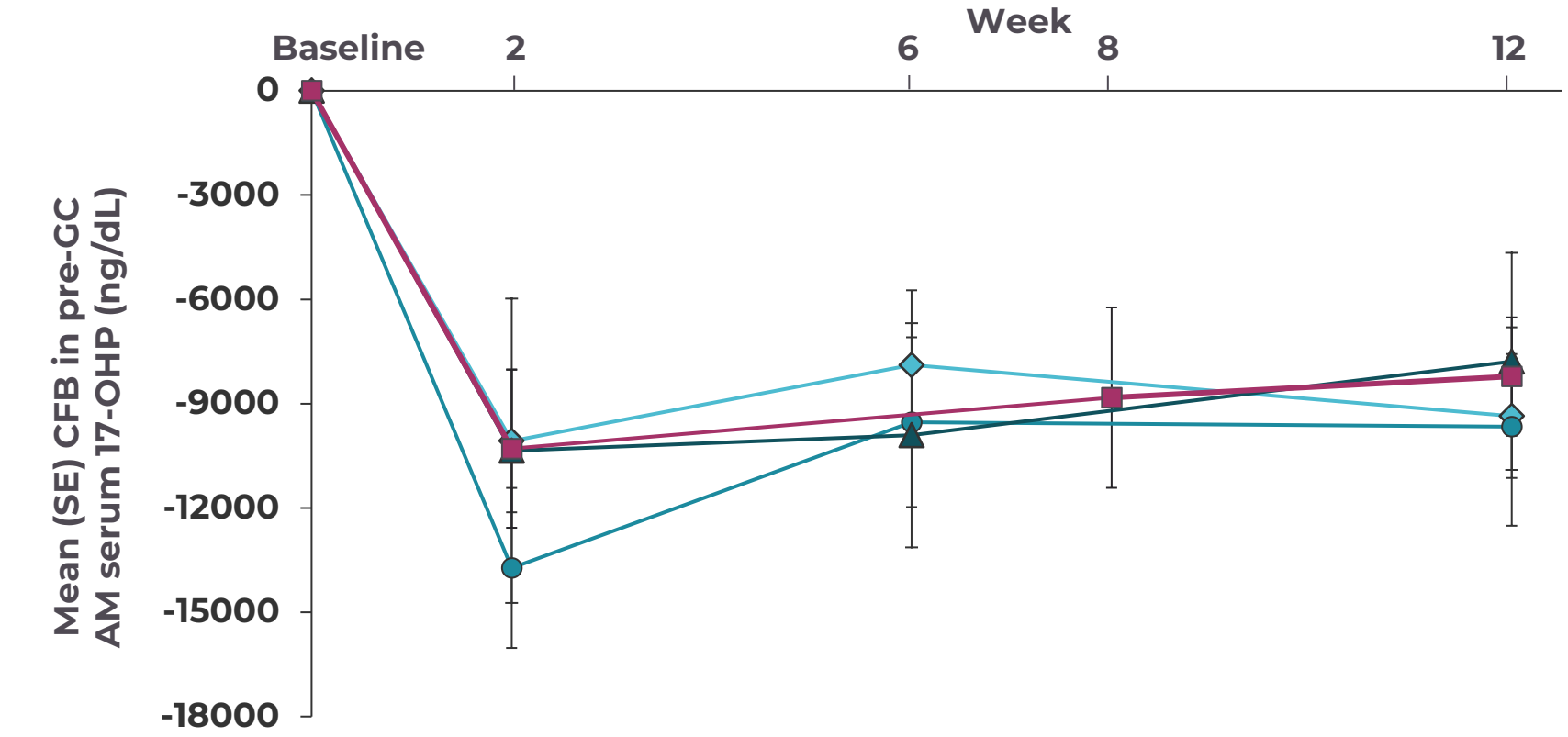
Fixed GC dosing

- **-67% (-75%)** **GC dose reduction**

15 of 38 participants had A4 ≤ ULN at week 12

40 mg	80 mg	120 mg	80 mg AM
3/11	6/11	3/6	3/10

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



	Baseline	2	6	8	12
40 mg n=11		11	11		10
80 mg n=11		11	11		11
120 mg n=6		5	6		6
80 mg AM n=10		10		9	8

+ GC reduction

Secondary Endpoint

%Change from baseline to Week 12, mean (median)

- **-66% (-82%)**
- **-67% (-86%)**
- **-65% (-69%)**
- **-49% (-73%)**