Topline Phase 2 Results from Atumelnant in Congenital Adrenal Hyperplasia (CAH)

January 10, 2025

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Atumelnant Positive Phase 2 Results: Demonstrated Strong Effect on Both Biomarkers and Clinical Outcomes in CAH

EFFICACY

- **Rapid, substantial, sustained statistically significant reduction of A4 in all dose groups:** Up to 80% mean reduction on atumelnant as soon as 2 weeks, sustained at 12 weeks
- **Dose response demonstrated**
- **Substantial reductions in 17-OHP across dose groups:** Up to 67% mean reduction at 12 weeks
- **Broad improvement in signs and symptoms:** Resumption of menses, resolution of androgen-mediated polycythemia and consistent reductions in total adrenal volume seen in many participants

SAFETY

- Atumelnant has been well-tolerated with **no treatment-related severe or serious adverse events**

Efficacy and safety support progressing to Phase 3

A4: Androstenedione; 17-OHP: 17-hydroxyprogesterone.
Atumelnant is an investigational drug. The safety and efficacy of atumelnant have not been established. In clinical studies, atumelnant was well-tolerated with no severe or serious adverse events.

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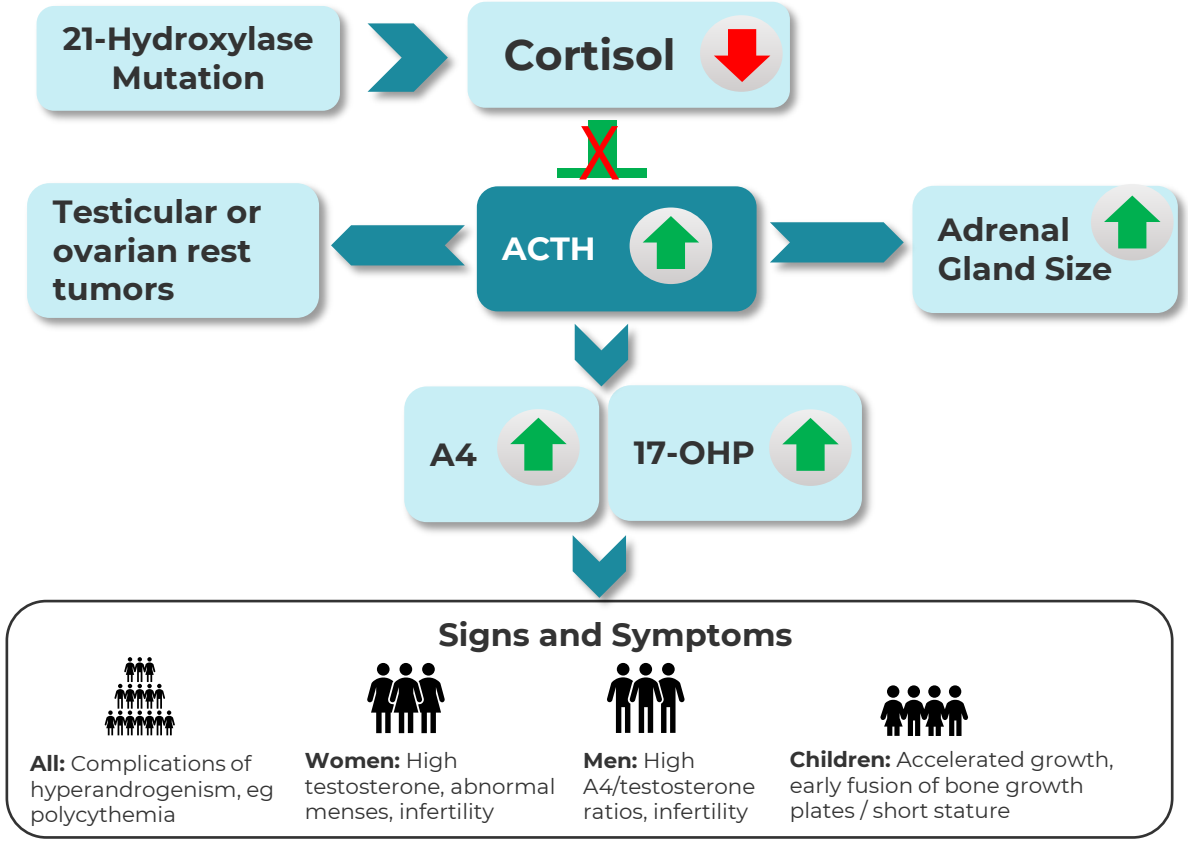
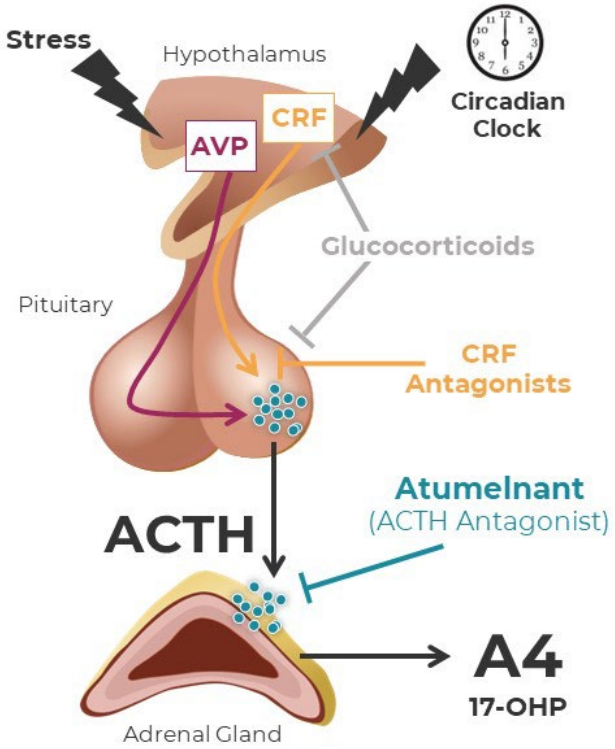
Atumelnant is the First and Only ACTH Antagonist in Clinical Development for Congenital Adrenal Hyperplasia

EXCESS ACTH IS THE FUNDAMENTAL DRIVER OF CAH SIGNS AND SYMPTOMS



ATUMELNANT MECHANISM OF ACTION

Hypothalamic-Pituitary-Adrenal (HPA) Axis in CAH



Reference: Kim SH, Han S, Zhao J, et al. Discovery of CRN04894: A novel potent selective MC2R antagonist. ACS Med Chem Lett. 2024;15(4):478-485.

Abbreviations: ACTH, adrenocorticotrophic hormone; AVP, arginine vasopressin; CRF, corticotropin-releasing factor; MC2R, melanocortin type 2 receptor; MRAP, melanocortin 2 receptor accessory protein; 17-OHP, 17-hydroxyprogesterone; 21-OH, 21-hydroxylase;

CAH Affects ~17,000 Addressable Adult and Pediatric Patients in the US

Treatment Goals in Adults with CAH

- Reduction of A4 and other androgens to address hyperandrogenism, which can manifest as excessive facial hair, acne and polycythemia
- Restore normal menstrual cycles and fertility in women
- Shrink testicular adrenal rest tumors, alleviate pain and restore fertility in men
- Eliminate excessive exposure to glucocorticoids to minimize steroid therapy related adverse effects including weight gain, cardiovascular issues, diabetes, and osteoporosis

Abram
Living with CAH

CAH Has a Range of Clinical Implications

"There's so many different facets of a person's life that it can affect. It can demoralize people. It takes a toll."

– Spouse of a CAH Patient

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Phase 2 Open-Label Study of Atumelnant in CAH Designed to Evaluate Safety, Efficacy and Pharmacokinetics

TOUCAHN

Key Eligibility Criteria

- Male or female participants ≥16 years (≥18 years ex-US) and ≤75 years
- Classic 21-hydroxylase deficiency
- On ≥15mg Hydrocortisone equivalent daily dose
- A4 >1.5xULN

Treatment Arms:

- Completed cohorts, each 12 weeks (n=28)

40 mg Once Daily (n=11)

80 mg Once Daily (n=11)

120 mg Once Daily (n=6)

Primary Endpoint: Change from baseline in pre-GC morning serum A4 at week 12
Secondary Endpoint: Change from baseline in pre-GC morning serum 17-OHP at week 12
Primary Safety Assessment: Incidence of TEAEs throughout the study
Pre-trial glucocorticoid therapy (dose and regimen) maintained throughout the trial

A4: Androstenedione; ULN: Upper limit of normal; 17-OHP: 17 hydroxyprogesterone; TEAE: Treatment emergent adverse event. PK: pharmacokinetics

Demographics and Baseline Characteristics

	40 mg N=11	80 mg N=11	120 mg N=6	All Participants N=28
Age (yrs), 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%)
BMI (kg/m²)*, mean (range)	29.7 (21.7-42.2)	31.7 (22.3-41.4)	25.3 (19.7-27.6)	29.5 (19.7-42.2)
Baseline Biomarker levels				
A4 (ng/dL), mean (range)**	1,213 (409-2,600)	1,231 (116-2,755)	1,064 (383-2,025)	1,188 (116-2,755)
17-OHP (ng/dL), mean (range)	14,371 (2,720-24,250)	16,876 (4,740-44,000)	11,630 (453-30,400)	14,767 (453-44,000)
ACTH (pg/mL), mean (range)	434 (36-1,082)	466 (155-1,009)	1216 (204-5,700)	614 (36-5,700)
Hydrocortisone equivalent (mg/day), mean (range)	28.8 (20-40)	30.8 (20-40)	23.3 (20-30)	28.4 (20-40)

Upper limit of normal (ULN):
- A4 (ng/dL) – Male: 150, Female: 200
- 17-OHP (ng/dL) – Male: 220, Female (luteal): 285
- ACTH (pg/mL): 63

* One participant in 80mg had no height assessment at baseline and was excluded in the summary. ** Central laboratory data reported. 2 participants entered the study based on elevated A4 levels measured locally that were >1.5 ULN.

12 Weeks of Treatment with Atumelnant Was Well Tolerated

- Once daily dosing of 40, 80 and 120 mg of atumelnant **generally well tolerated**
- **No severe or serious adverse events** observed to date
- TEAEs **mild to moderate in nature**, most were transient and did not require intervention
- No negative clinical trends relative to vital signs, physical examination or electrocardiograms (ECG)
- Clinical safety laboratory parameters did not reveal any consistent negative trends
  - 1 participant at 120 mg experienced AST/ALT increases without increases in bilirubin and with values reverting to baseline off study drug
- All participants completed 12 weeks of dosing and **no TEAEs required dose reduction** / cessation of treatment

Overview of Treatment-Emergent Adverse Events

	40 mg N=11 n (%)	80 mg N=11 n (%)	120 mg N=6 n (%)	All Participants N=28 n (%)
Any Treatment-Emergent Adverse Events (TEAE)	8 (72.7%)	7 (63.6%)	5 (83.3%)	20 (71.4%)
Mild	5 (45.5%)	4 (36.4%)	4 (66.7%)	13 (46.4%)
Moderate	3 (27.3%)	3 (27.3%)	1 (16.7%)	7 (25.0%)
Severe	0	0	0	0
Any Related TEAE	4 (36.4%)	3 (27.3%)	4 (66.7%)	11 (39.3%)
Any Serious TEAE	0	0	0	0
Any Serious Related TEAE	0	0	0	0
Any TEAE of Special Interest (adrenal insufficiency)	1 (9.1%)	1 (9.1%)	0	2 (7.1%)
Any TEAE Leading to Discontinuation of Study Drug	0	0	0	0
Any TEAE Leading to Discontinuation of Study	0	0	0	0
Any Fatal TEAE	0	0	0	0

No severe or serious TEAEs observed during Phase 2 study

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Atumelnant Was Well Tolerated

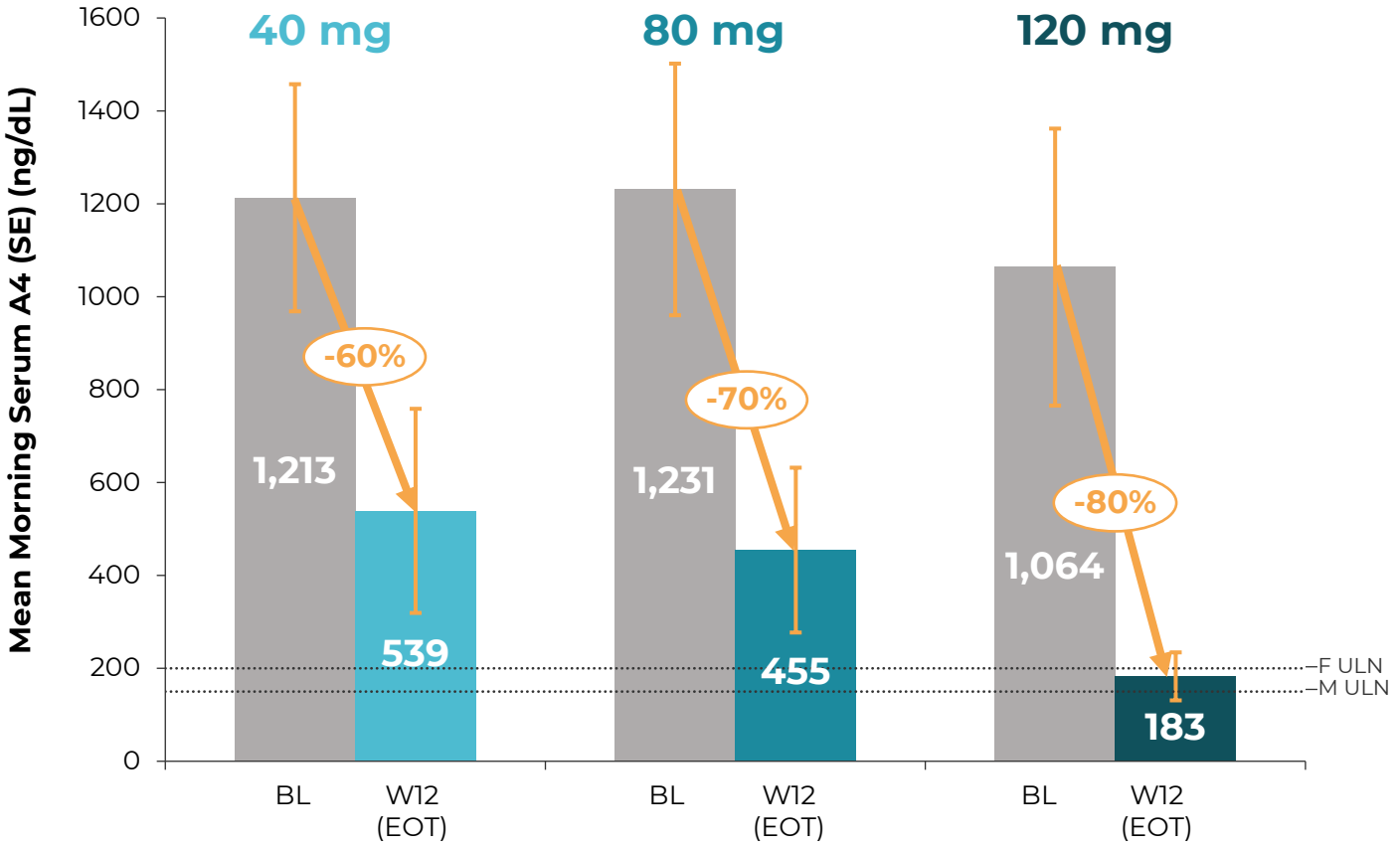
Summary of TEAEs by Preferred Term

(Reported by ≥2 of Total Participants)

Preferred Term	40 mg N=11 n (%)	80 mg N=11 n (%)	120 mg N=6 n (%)	All Participants N=28 n (%)
Participants with at least 1 TEAE	8 (72.7%)	7 (63.6%)	5 (83.3%)	20 (71.4%)
Headache	2 (18.2%)	3 (27.3%)	2 (33.3%)	7 (25.0%)
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	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%)

Rapid, Substantial and Sustained A4 Reductions, the Key Biomarker for CAH Disease Control

- Across each cohort, baseline A4 levels were significantly elevated (>1,000 ng/dL)
- All dose cohorts saw substantial decreases vs. baseline, with the magnitude of response increasing with dose
- The 120 mg cohort experienced the largest A4 reduction, with a mean decline of 80% at Week 12



Primary Endpoint: CFB in pre-GC morning serum A4 at week 12			
A4 CFB (ng/dL) at week 12, LSM	-619	-774	-954
p-value	*p=0.0003*	*p<0.0001*	*p<0.0001*

Participants At Baseline: 40 mg N=11; 80 mg N=11; 120 mg N=6.
Participants At Week 12: 40 mg N=10; 80 mg N=11; 120 mg N=6.
CFB: change from baseline, LSM: Least-square-mean

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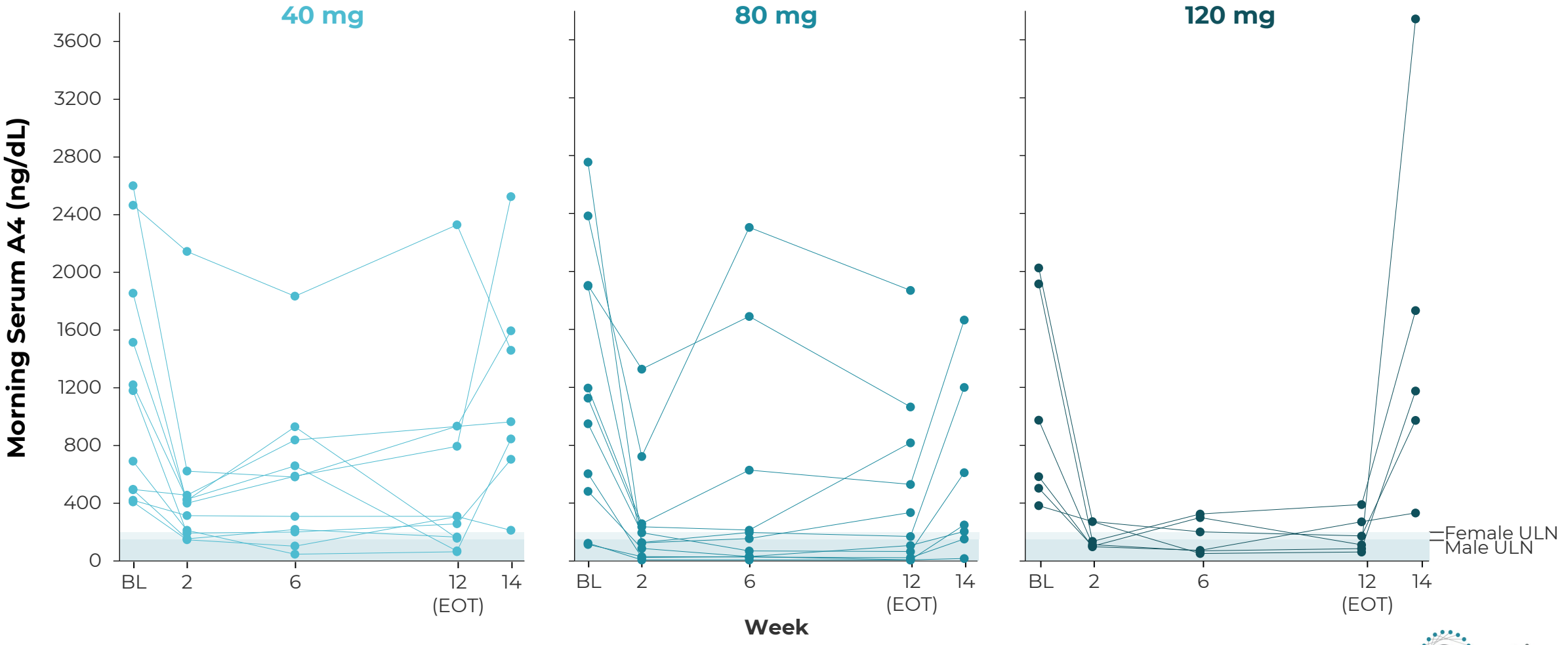
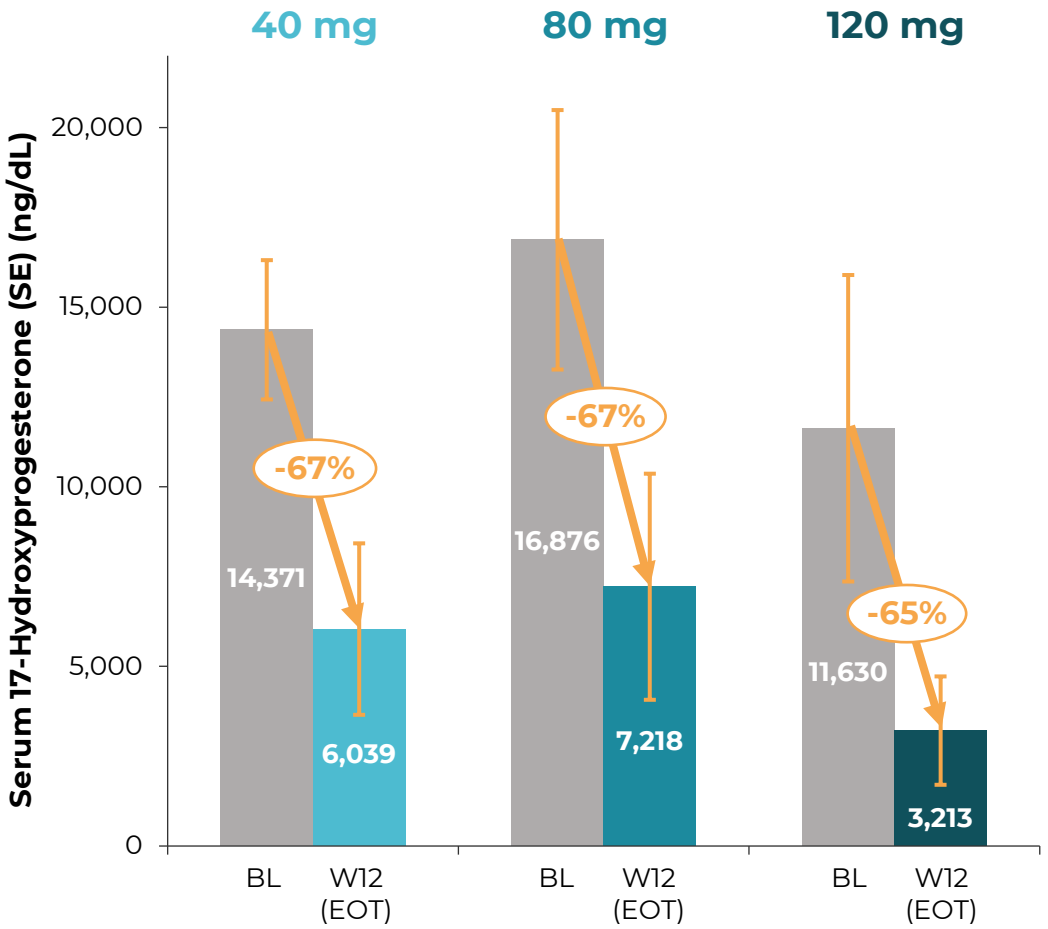
The Majority of Participants at 80mg and 120 mg* Achieved A4<ULN by Week 2



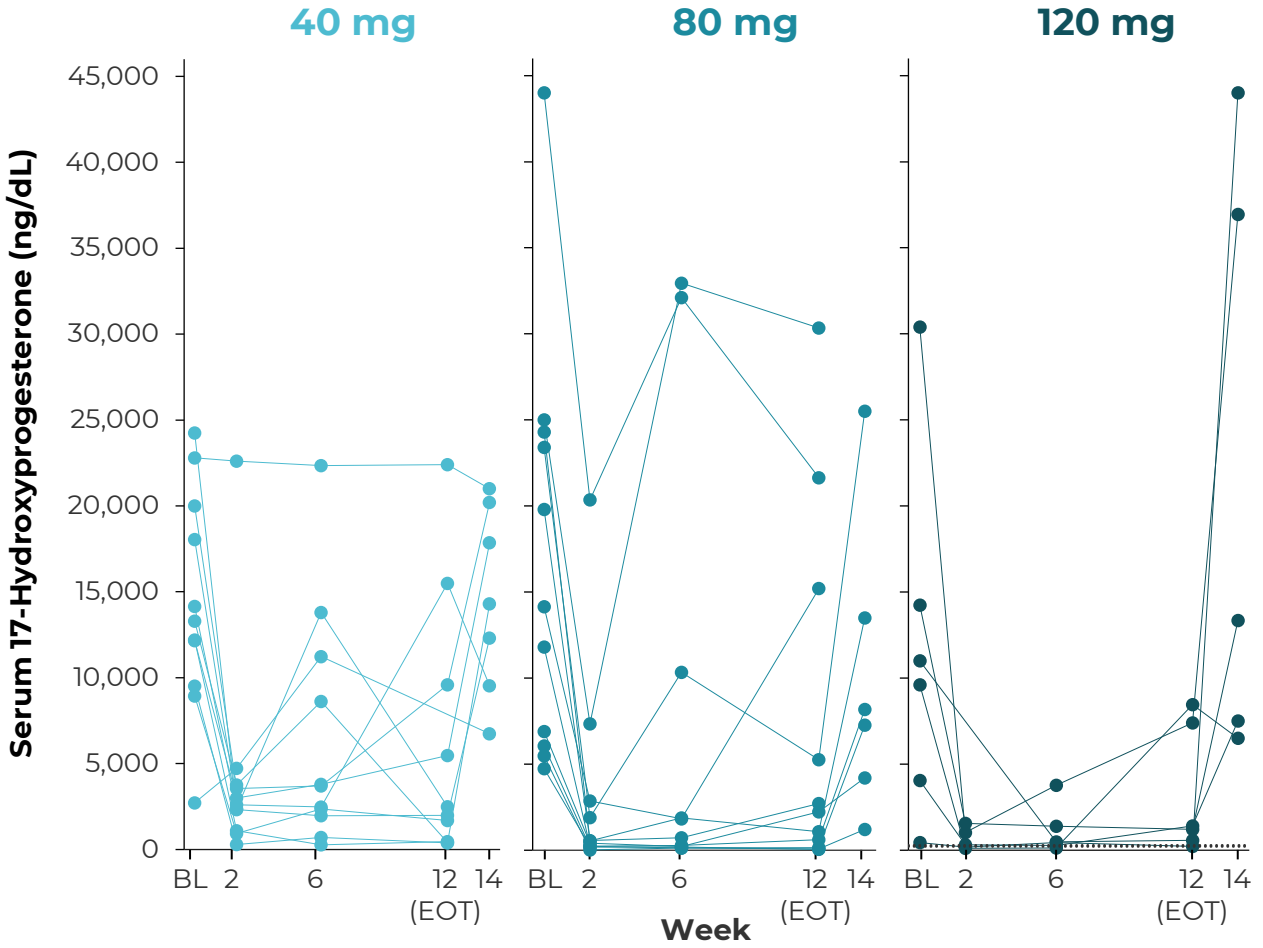
*7/11 participants at 80 mg and 4/6 at 120 mg achieved A4<ULN by week 2

Rapid, Substantial and Sustained Reductions in 17-OHP, a Confirmatory Secondary Biomarker of Disease Control

Mean 17-OHP at Baseline and Week 12



Individual 17-OHP by Study Week



Participants At Baseline: 40 mg N=11; 80 mg N=11; 120 mg N=6.
Participants At Week 12: 40 mg N=10; 80 mg N=11; 120 mg N=6.
CFB: change from baseline, LSM: Least-square-mean

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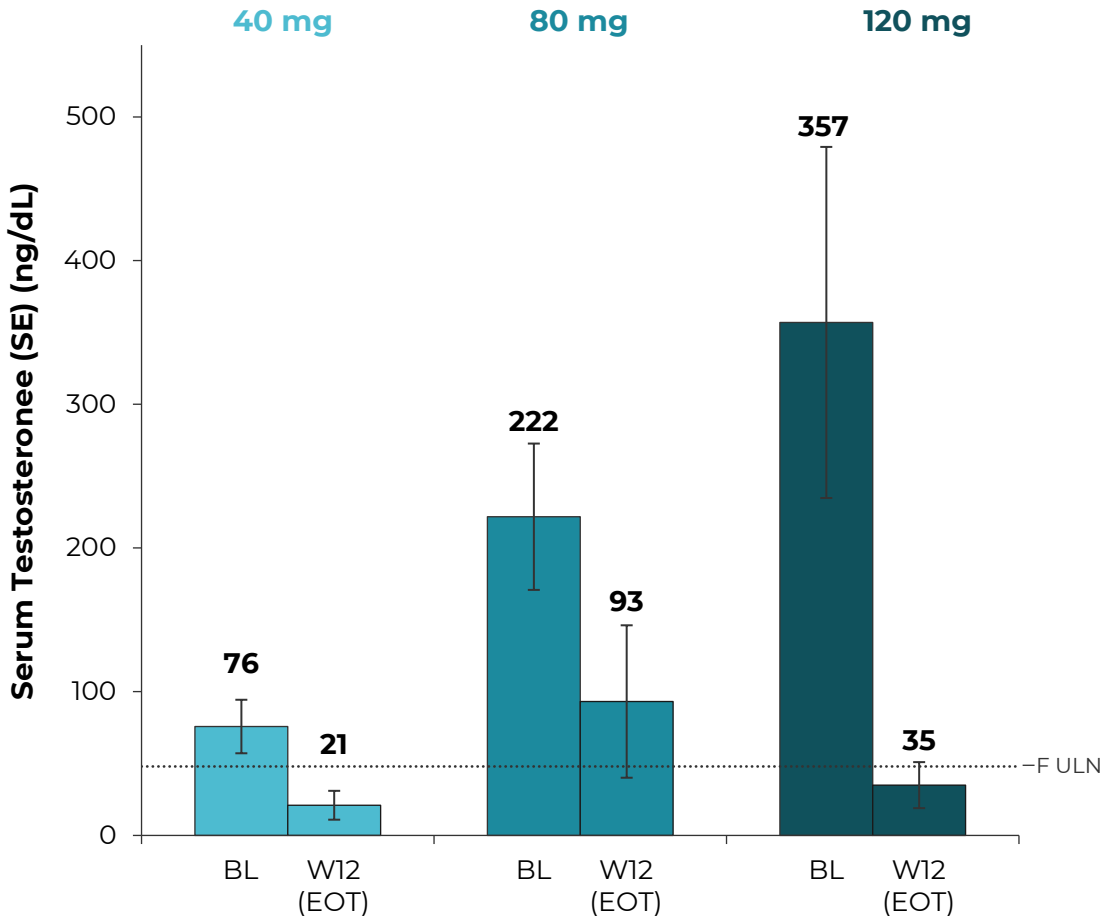
Female Participants Experienced Improvements in Reproductive Health

Many Participants Resumed Menses While Enrolled in the Study

- **6/11** female participants (not on hormonal contraceptives with intact uterus) resumed menses during the study
  - Includes 3 previously amenorrheic female participants, and 3 participants with previous irregular menses
- **8/13** female participants with baseline testosterone >ULN achieved normal testosterone levels at Week 12

Substantial Reduction in Testosterone in All Female Participants (N=14)



14 Number of female participants at each dose level with evaluable testosterone: 40 mg N=3; 80 mg N=8; 120 mg N=3.

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Case Study: Lifelong Adrenal Enlargement Improved on Atumelnant within 12 weeks

Consistent Decrease in Adrenal Volume Across Dose Cohorts

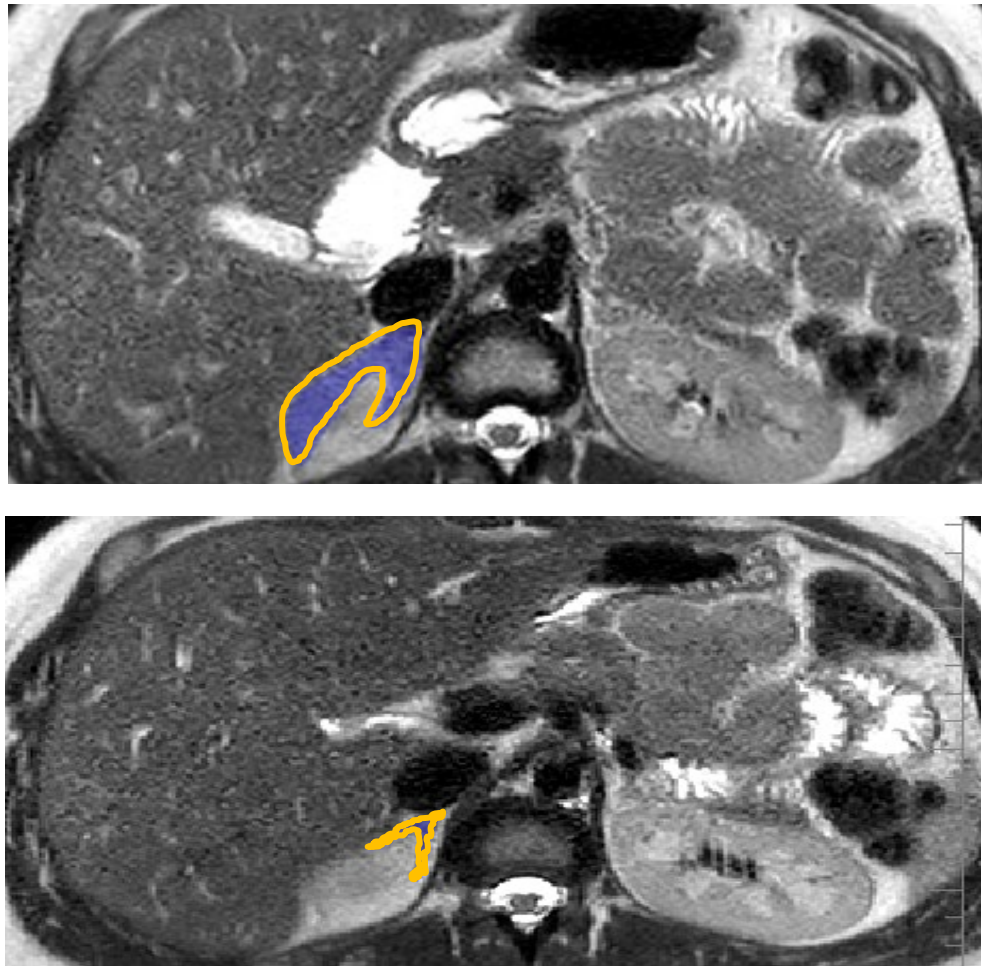
- Normal total adrenal gland volume of 8-10 mL
- Study median baseline total volume of 19.7 mL*
- 1.6-5.2 mL mean reductions in total adrenal volume observed across dose groups

Example 120mg Participant

- Male CAH trial participant taking 30 mg daily hydrocortisone
- Substantial adrenal size reduction** observed in 12 weeks
- Clinically important reductions at 12 weeks relative to baseline in:
  - A4 (**-91%**)
  - 17-OHP (**-91%**)
  - A4/Testosterone ratio (**-89%**)
  - Exploratory marker 21-Deoxycortisol (**-96%**)

-79%
Reduction

Example 120mg Participant



* In patients with evaluable MRIs at baseline and at 12 Weeks.
**77% reduction observed in the left adrenal (not shown).

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Significant Clinical Improvements Achieved with Atumelnant Treatment

CAH Manifestations	Achieved following 12 weeks of treatment with atumelnant
Overproduction of androgens, and androgen precursors	Normalization of A4 in many participants and substantial reduction in 17-OHP levels (across dose groups)
Females: • **Elevated testosterone levels** • **Absent/irregular menses**	Testosterone substantially reduced/normalized in the majority of participants; 6/11 participants resumed menses
Males: Elevated A4/testosterone ratio	Clinically relevant reductions in many participants
Adrenal gland hyperplasia	Consistent reductions in adrenal volume
Androgen mediated polycythemia (linked to increased cardiovascular risks)	Resolution in 5/6 participants with polycythemia
Hirsutism and acne	Improvements reported, longer treatment likely needed for full effects

Summary of Results and Next Steps

Summary: Successful Phase 2 Results

- Rapid and sustained treatment effect, including in participants with high baseline A4
- Clinical activity observed across all doses (once daily 40, 80 and 120 mg)
  - Dose response demonstrated
  - 80 mg and 120 mg as the likely therapeutic doses of choice
- Evidence of meaningful improvement in multiple clinical signs and symptoms
- No serious adverse events and no severe related adverse events
- All participants completed 12 weeks of treatment

Next Steps

- Initiate Phase 3 pivotal trial in adult CAH population in 1H25
- Start Phase 2/3 pivotal trial in pediatric CAH population

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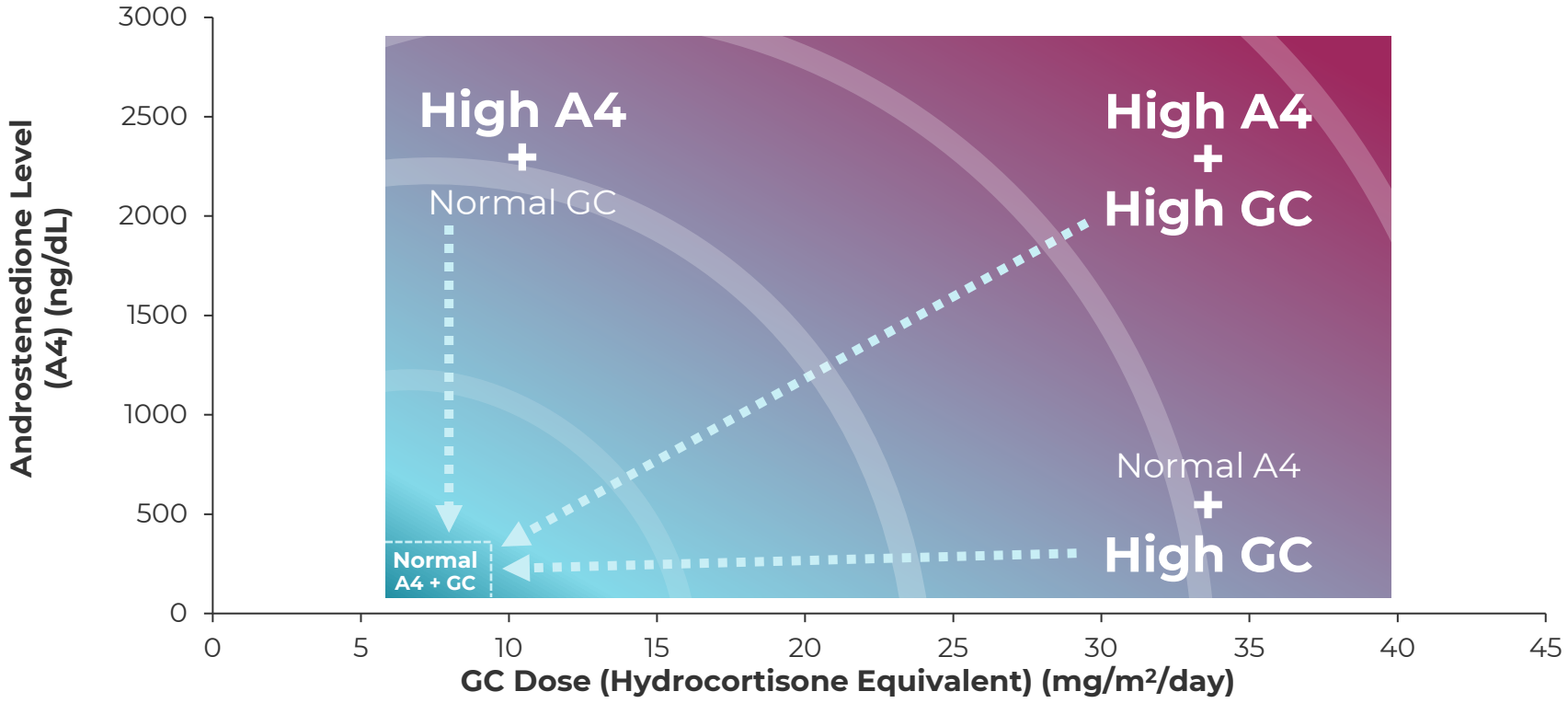
Atumelnant Vision: Healthier Hormone Levels for People Living with CAH



A single pill taken once a day, that eliminates excess ACTH driven adrenal activation *and its clinical sequalae* for people struggling with Congenital Adrenal Hyperplasia

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Q&A

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Founder and Chief Executive Officer

Dana Pizzuti, M.D.
Chief Medical & Development Officer

Alan Krasner, M.D.
Chief Endocrinologist

Marc Wilson
Chief Financial Officer

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Abbreviations

17-OHP	17-hydroxyprogesterone
A4	Androstenedione
ACTH	Adrenocorticotrophic hormone
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AVP	Arginine Vasopressin
BL	Baseline
BMI	Body Mass Index
CAH	Congenital adrenal hyperplasia
CRF	Corticotropin releasing factor
EOT	End of treatment
GC	Glucocorticoid
TEAE	Treatment emergent adverse event
TART	Testicular adrenal rests tumors
ULN	Upper limit of normal