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Initial Phase 2 Results From Atumelnant* (CRN04894) in Congenital Adrenal Hyperplasia (CAH) and ACTH-dependent Cushing's Syndrome (ADCS)

June 3rd, 2024

* Proposed international nonproprietary name under review

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This presentation contains forward-looking statements. Crinetics Pharmaceuticals, Inc. ("Crinetics," the "company," "we," "us," or "our") cautions you that statements contained in this presentation regarding matters that are not historical facts are forward-looking statements. These statements are based on the company's current beliefs and expectations. Such forward-looking statements include, but are not limited to, statements regarding: the potential benefits of atumelnant (CRN04894) in patients with Congenital Adrenal Hyperplasia ("CAH") or ACTH-Dependent Cushing's syndrome ("ADCS"); the potential benefits of paltusotine for acromegaly patients and patients with carcinoid syndrome; the potential for the PATHFNDR program to support registration of paltusotine for all acromegaly patients who require pharmacotherapy; the expected plans and timing for data and data readouts from ongoing clinical studies; plans and timing for sharing the full results of the Phase 2 study of atumelnant with the FDA to align on one or more Phase 3 programs; the plans and timelines for the clinical development of atumelnant and paltusotine, including the therapeutic potential and clinical benefits or safety profile thereof as well as atumelnant's ability to revolutionize the treatment for CAH and ADCS or our ability to commercialize atumelnant globally; the expected timing of the submission of a new drug application for paltusotine for the treatment of acromegaly or for carcinoid syndrome and the plans and timelines for the commercial launch paltusotine if approved; the expected timing of initiation of a Phase 3 program in patients with carcinoid syndrome; our plans to identify and create new drug candidates for additional diseases or the potential for any such new drug candidates to show safety or efficacy and the expected plans and timing for candidate selection and clinical development of such candidates; our plans to identify and create new drug candidates for additional diseases; the direction or trajectory of the Company's potential future growth, the receipt of any revenues from product sales and the ability of such revenues to support continued growth, and our expected plans and timing for commercialization of paltusotine, altumenant and other product candidates pending regulatory approval. In some cases, you can identify forward-looking statements by terms such as "may," "believe," "anticipate," "could," "should," "estimate," "expect," "intend," "plan," "project," "will," "contemplate," "predict," "continue," "forecast," "aspire," "lead to," "designed to," "goal," "potential," "target," "our vision," "our mission" or the negative of or other similar terms.

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Crinetics' Vision for Atumelnant*

A single pill, taken once a day, that reliably enables people struggling with either CAH or ADCS to achieve **normal, healthy hormone levels** that will improve their daily lives.

OUR MISSION

To revolutionize the treatment paradigm for CAH and ADCS with an unprecedented, transformative therapy and bring this medicine to all people around the world.

*Atumelnant is a clinical stage investigational compound that has not yet been approved by any regulatory authority.

CAH: Congenital adrenal hyperplasia. ADCS: ACTH-dependent Cushing's syndrome.

Profound, Rapid and Sustained Reductions of A4 and 17-OHP in Congenital Adrenal Hyperplasia with Atumelnant

EFFICACY

- ☑ **100%** (n=6/6) of participants maintained androstenedione (A4) <ULN at all time points on atumelnant (80 mg)
  - *A4 and related androgens are key drivers of disease pathophysiology*
  - *A4 is a potential endpoint in registrational trials*

- ☑ **>90% reduction of A4** and **97% reduction of 17-OHP** on atumelnant (80 mg) beginning at 2 weeks and sustained through 12 weeks

- ☑ **Two female participants resumed regular menstrual cycles** on atumelnant (80 mg) who had not menstruated in > 2 years previously

SAFETY

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

More data from additional patients and dose levels expected in 2H 2024

ULN: Upper limit of normal. 17-OHP: 17-Hydroxyprogesterone. A4: Androstenedione.
Data presented represents data cut off date of May 21st, 2024. Available data: 80 mg: n=4 at 12 weeks; n=2 at 6 weeks; 40 mg: n=4 for 2 weeks.

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Profound, Rapid and Sustained Reduction of Excess Cortisol in ACTH-dependent Cushing's Syndrome with Atumelnant

EFFICACY

- ☑ **100%** (n=5/5) of participants achieved normal 24h Urinary Free Cortisol (UFC) on atumelnant (80 mg)
  - *UFC normalization has been recommended by FDA as a primary endpoint*
- ☑ **ALL** patients experienced improvements in 2 or more clinical symptoms

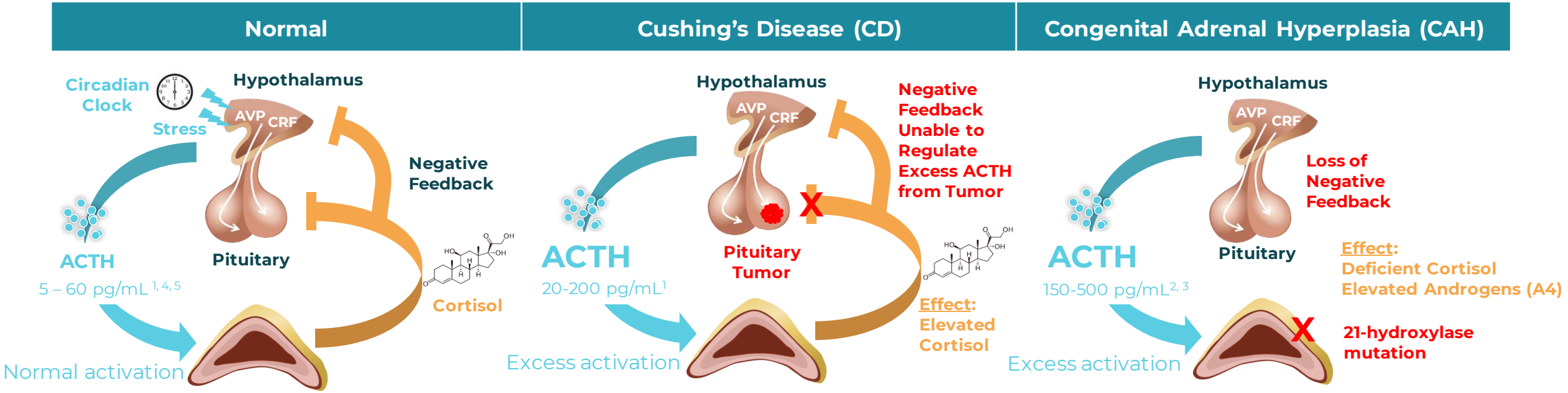
SAFETY

- ☑ Atumelnant was generally well-tolerated

More data from additional patients and dose levels expected in 2H 2024

ULN: Upper limit of normal. UFC: Urine free cortisol.

Disruptions in the HPA Axis Lead to Diseases of Excess ACTH and Excess Adrenal Activation



Cause	ACTH-secreting tumor	Inability to produce cortisol leads to loss of negative feedback & excess ACTH
U.S. Prevalence	11,200	27,000
Symptoms	Central obesity and round face; Dorsal and supraclavicular fat pads; Hypertension; Stretch marks; Bone loss; Hyperglycemia; Psychiatric disturbances	Adrenal insufficiency; Infertility; Hirsutism; Short stature; Precocious puberty; ambiguous genitalia at birth, Adrenal rest tumors

Raff et al. *Compr Physiol* 2015, Petersen *Acta Pediatr Scand* 1981, NBIX ENDO Online 2020 presentation, Oster et al., *Endocrine Reviews* 2017.
HPA: Hypothalamic-pituitary-adrenal. A4: Androstenedione; 17-OHP: 17-hydroxyprogesterone, ACTH: Adrenocorticotropic hormone.

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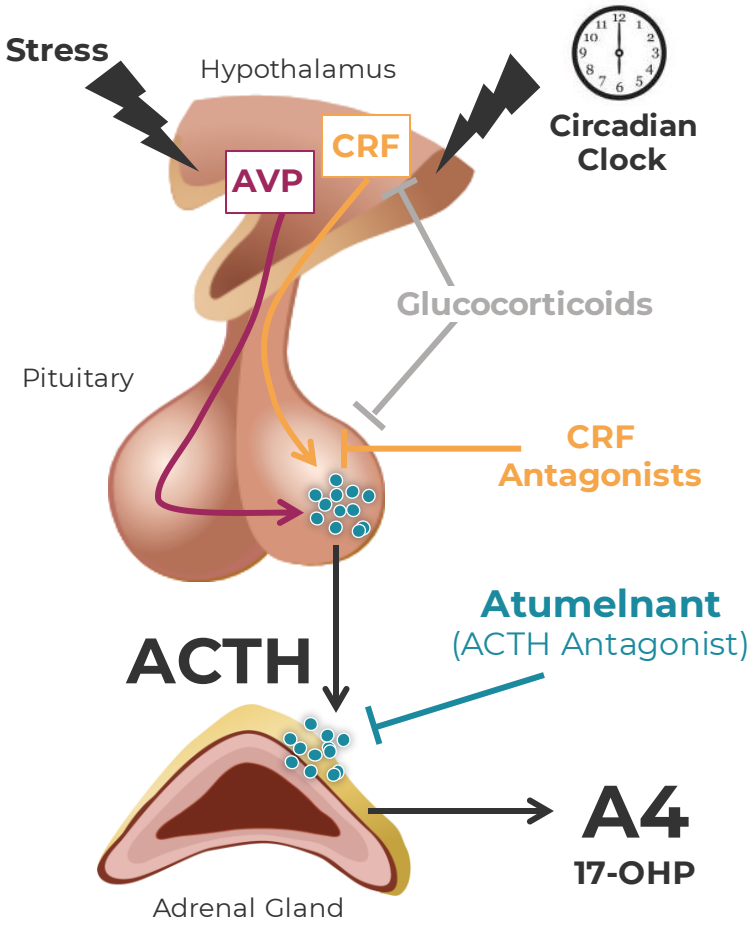
CONGENITAL ADRENAL HYPERPLASIA

Atumelnant: Second Clinical Asset in Late-Stage Development Skillfully Crafted to Help Subjects Reach Their Treatment Goals



Lead Indication: Congenital Adrenal Hyperplasia (CAH)

Estimated ~27,000 people in the US based on genetic prevalence

Treatment Goals

- Normalize/eliminate adrenal androgen production
- Restore normal menstrual cycles and fertility in women
- Shrink testicular adrenal rest tumors, alleviate pain, restore fertility in men
- Avoid complications of glucocorticoid excess (e.g weight gain, hypertension, bone disease) and enable physiologic replacement levels

AVP: arginine vasopressin, CRF: corticotropin releasing factor; A4: Androstenedione; 17-OHP: 17-hydroxyprogesterone, ACTH: Adrenocorticotropic hormone.

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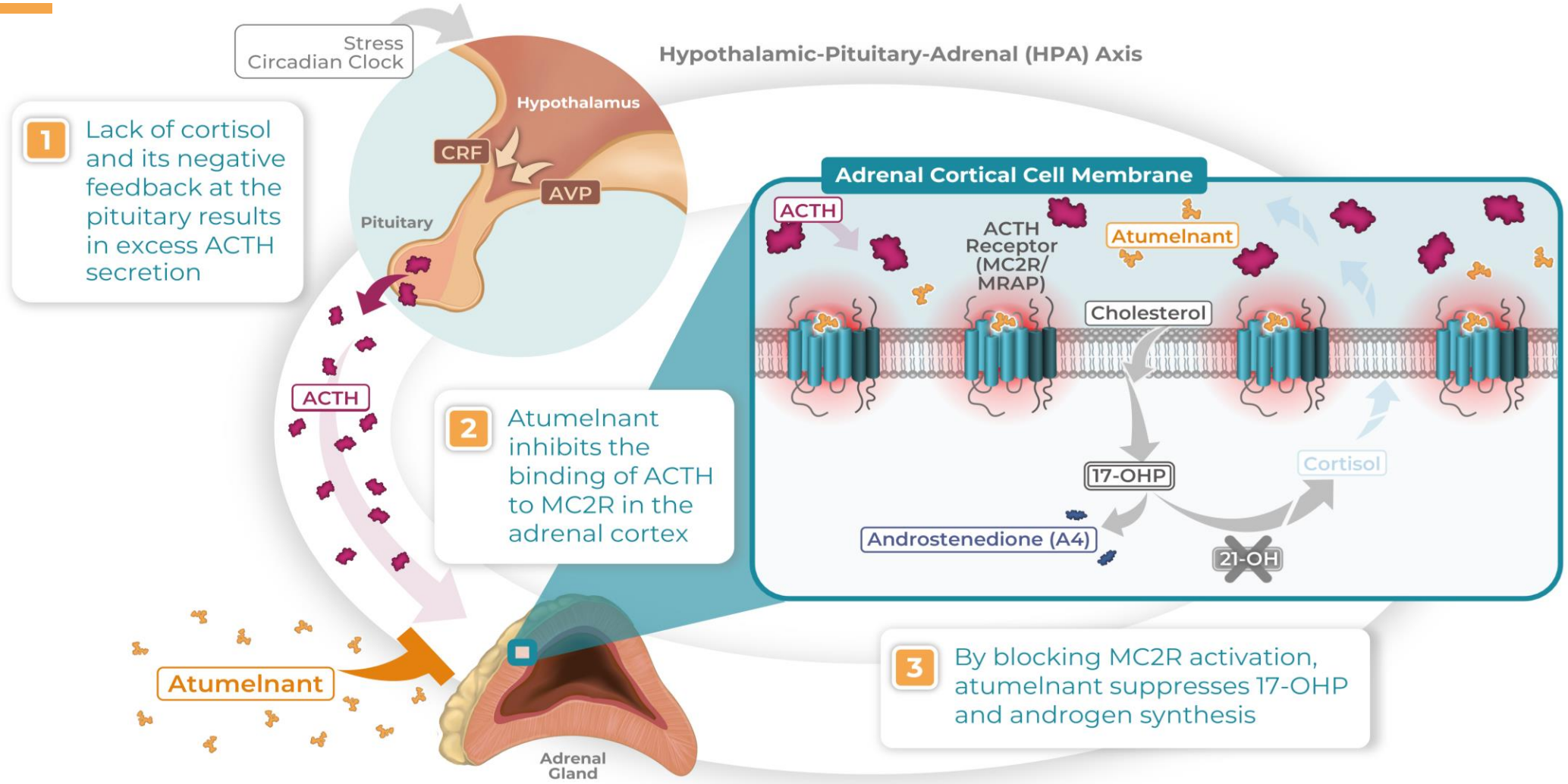
Atumelnant: The First Oral, Selective ACTH Antagonist



Atumelnant is an investigational drug being evaluated in clinical studies for CAH. Atumelnant has not yet been approved by any regulatory authority.
A4: Androstenedione; 17-OHP: 17-hydroxyprogesterone, ACTH: Adrenocorticotropic hormone. MC2R: Melanocortin receptor 2.

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Updated Design and Status: Phase 2 Atumelnant in Congenital Adrenal Hyperplasia (CAH) (TouCAHn)

TOUCAHN

Key Eligibility Criteria

N=24

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

Treatment Arms:

- 3 cohorts, each 12 weeks (N=6-12)

80 mg Once Daily (n=9)

40 mg Once Daily (n=9)

120 mg Once Daily (n=6)

Pre-trial glucocorticoid therapy (dose and regimen) maintained throughout the trial

Objectives: Evaluate the Safety, Efficacy, and Pharmacokinetics of atumelnant

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 TEAEs throughout the study

A4: Androstenedione; ULN: Upper limit of normal; 17-OHP: 17 hydroxyprogesterone; TEAE: Treatment emergent adverse event.
Baseline is defined as the last morning window value (i.e. the average of any early morning samples on or after 06:00 but prior to 11:00) prior to the first dose of atumelnant.

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Demographics and Baseline Characteristics

	40 mg N=4	80 mg N=6	All Participants N=10
Age (yrs), mean (range)	24.3 (22-27)	35.2 (25-42)	30.8 (22-42)
Female, n (%)	0	5 (83%)	5 (50%)
BMI (kg/m²)*, mean (range)	26.5 (21.7-30.2)	30.9 (22.3-35.8)	29.0 (21.7-35.8)
Baseline Biomarker levels			
A4 (ng/dL), mean (range)	1,680 (1,180-2,465)	838** (116-2,755)	1,175 (116-2,755)
17-OHP (ng/dL), mean (range)	15,600 (12,150-22,800)	9,880 (4,740-24,300)	12,168 (4,740-24,300)
ACTH (pg/mL), mean (range)	658 (115-1,082)	554 (155-1,009)	596 (115-1,082)
Glucocorticoid dose* (mg/day), mean (range)**	28 (20-40)	35 (25-40)	32 (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. *** In hydrocortisone equivalents. Available data: 80 mg: n=4 for 12 weeks; n=6 for 6 weeks; 40 mg: n=4 for 2 weeks.

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No Significant Safety Signals Reported

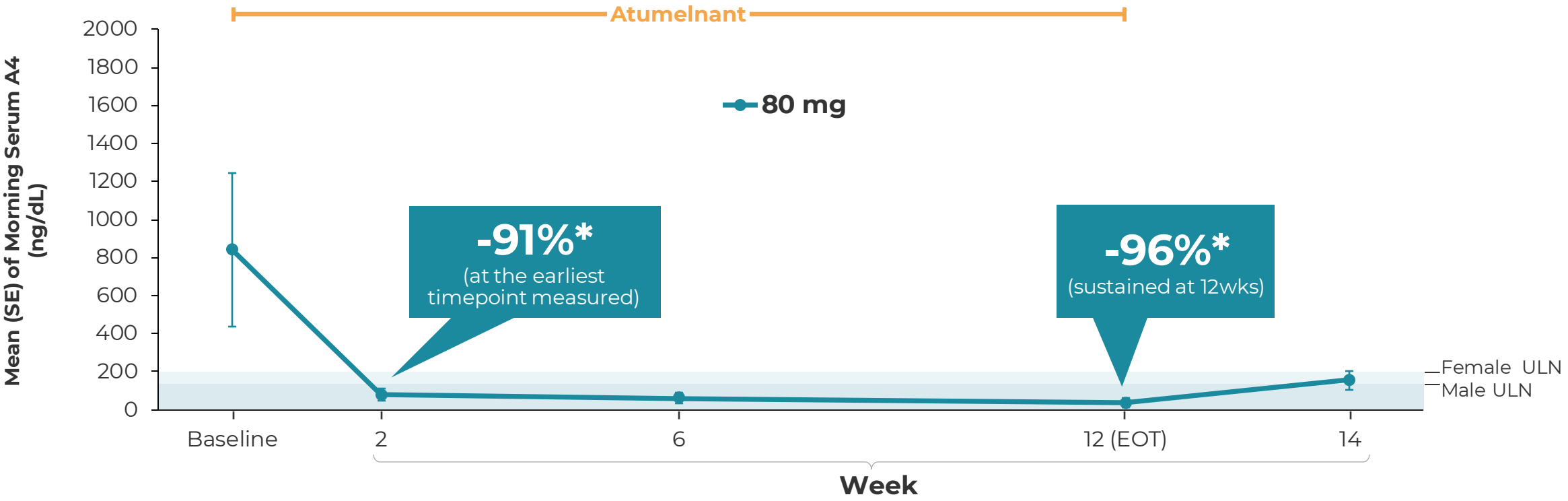
Summary of TEAEs by Preferred Term
(Reported by ≥2 of Total Participants)

Preferred Term	40 mg N=4 n (%)	80 mg N=6 n (%)	All N=10 n (%)
Participants with at least 1 TEAE	3 (75%)	4 (67%)	7 (70%)
Fatigue	2 (50%)	1 (17%)	3 (30%)
Headache	2 (50%)	0	2 (20%)
Upper respiratory tract infection	0	2 (33%)	2 (20%)

- No severe or serious adverse events and no discontinuations
- Both atumelnant 80 mg and 40 mg have been generally well tolerated
- All adverse events have been either mild or moderate and transient
- No significant changes in safety labs or electrocardiograms

Data presented represents data cut off date of May 21st, 2024. Available data: 80 mg: n=4 for 12 weeks; n=6 for 6 weeks; 40 mg: n=4 for 2 weeks.
TEAE = treatment emergent adverse event.

Atumelnant (80 mg) Profoundly and Rapidly Reduced Mean A4, Sustained at 12 Weeks



Number of Participants:

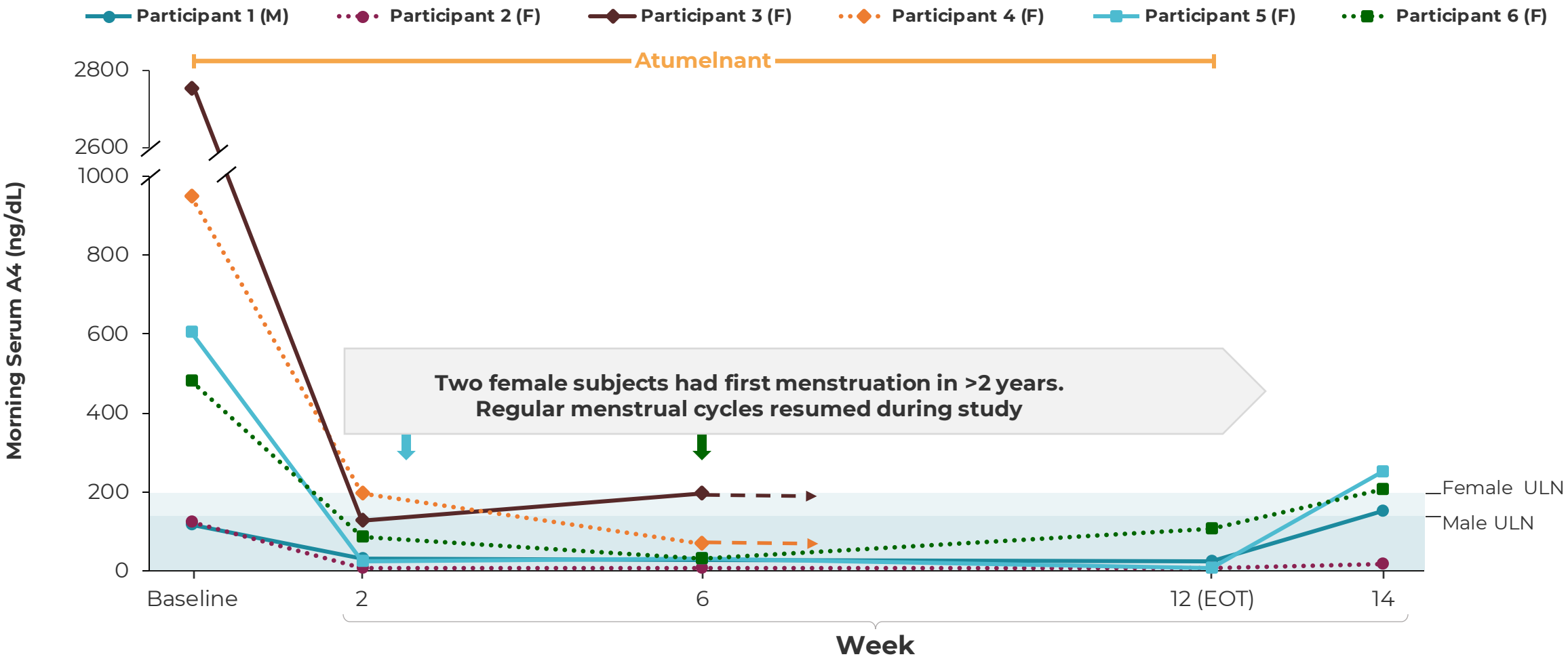
80 mg	**6**	**6**	**6**	**4**	**4**

* Percent change between mean baseline and mean post-baseline value.

ULN: Upper limit of normal. EOT: End of Treatment

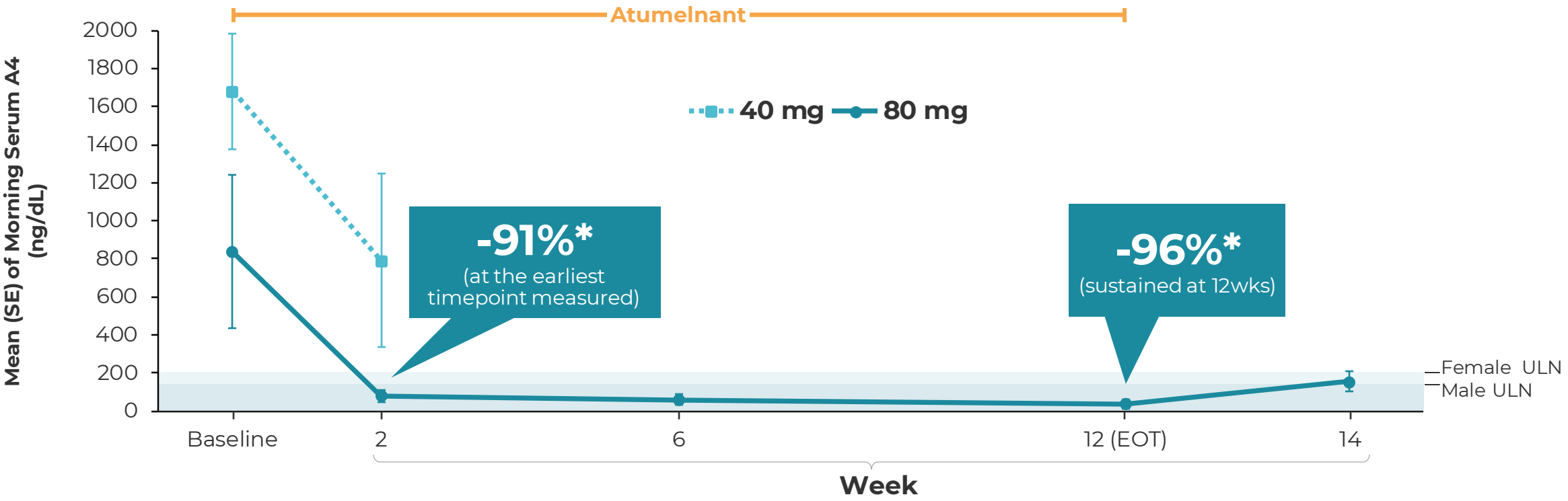
Available data: 80 mg: n=4 for 12 weeks; n=6 for 6 weeks.

Atumelnant (80 mg) Induced Rapid, Profound and Sustained Reduction of A4 in all Participants



M: Male; F: Female, EOT: End of Treatment. Participant 5 reported resumed menses on day 18, Participant 6 reported resumed menses on day 42. Captured as part of a menstrual cycle diary in the study. Available data: 80 mg: n=4 for 12 weeks; n=6 for 6 weeks.

Atumelnant (40 mg) Also Lowered A4 Levels



Number of Participants:

40 mg	**4**	**4**	**0**	**0**	**0**
80 mg	**6**	**6**	**6**	**4**	**4**

* Percent change between mean baseline and mean post-baseline value.

ULN: Upper limit of normal, EOT: End of Treatment.

Available data: 80 mg: n=4 for 12 weeks; n=6 for 6 weeks; 40 mg: n=4 for 2 weeks.

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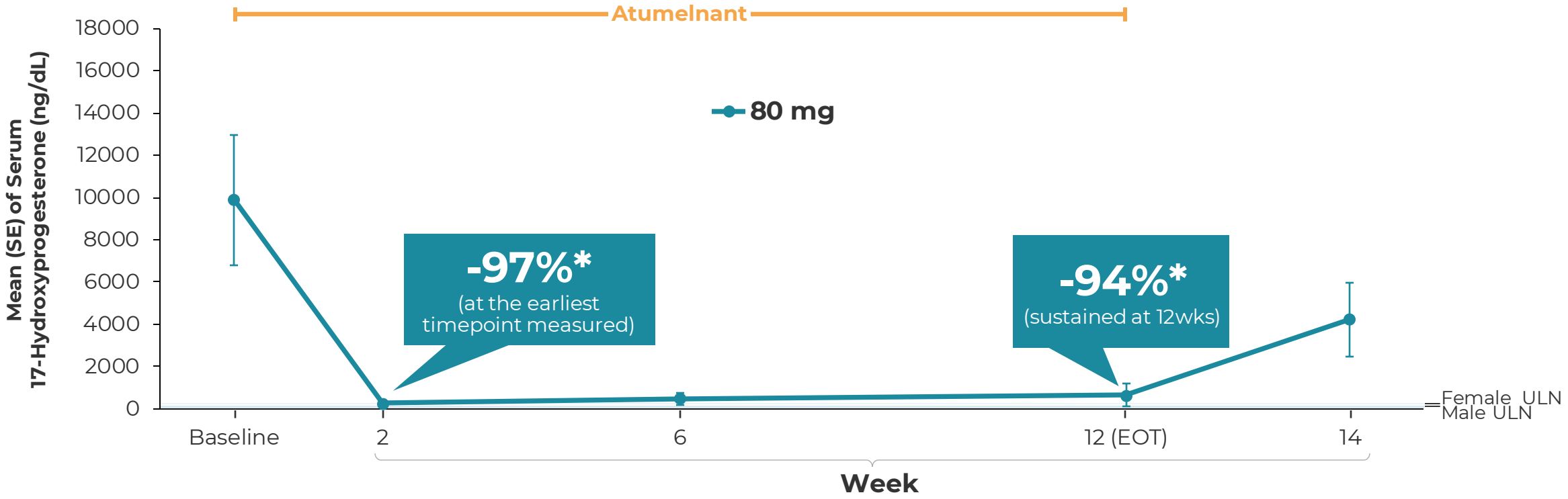
Atumelnant (80 mg) Profoundly and Rapidly Reduced Mean 17-OHP, Sustained at 12 Weeks

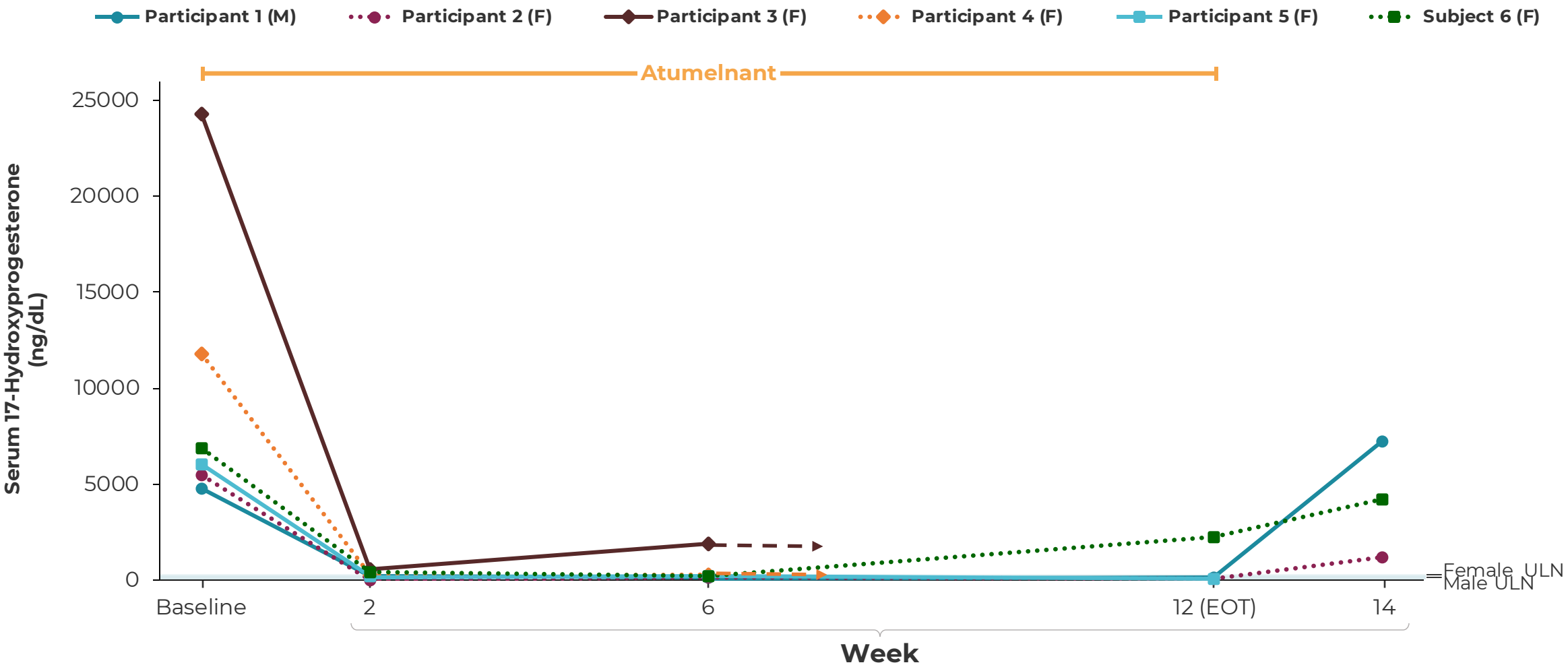


Number of Participants:

80 mg	6	6	6	4	3

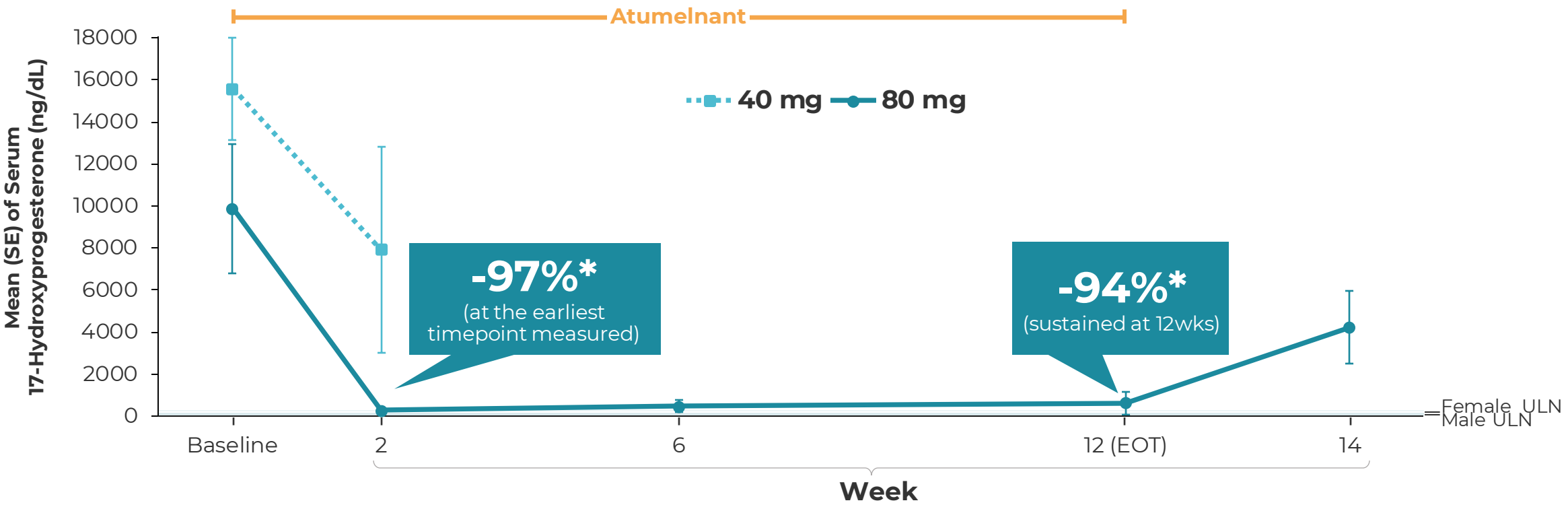
* Percent change between mean baseline and mean post-baseline value.
ULN: Upper limit of normal, EOT: End of Treatment.
Available data: 80 mg: n=4 for 12 weeks; n=6 for 6 weeks.

Atumelnant (80 mg) Induced Rapid, Profound and Sustained Reduction of 17-OHP in all Participants



EOT: End of Treatment.
Available data: 80 mg: n=4 for 12 weeks; n=6 for 6 weeks.

Atumelnant (40 mg) Also Lowered 17-OHP Levels



Number of Participants:

40 mg	**4**	**4**	**0**	**0**	**0**
80 mg	**6**	**6**	**6**	**4**	**3**

* Percent change between mean baseline and mean post-baseline value.
ULN: Upper limit of normal, EOT: End of Treatment.
Available data: 80 mg: n=4 for 12 weeks; n=6 for 6 weeks; 40 mg: n=4 for 2 weeks.

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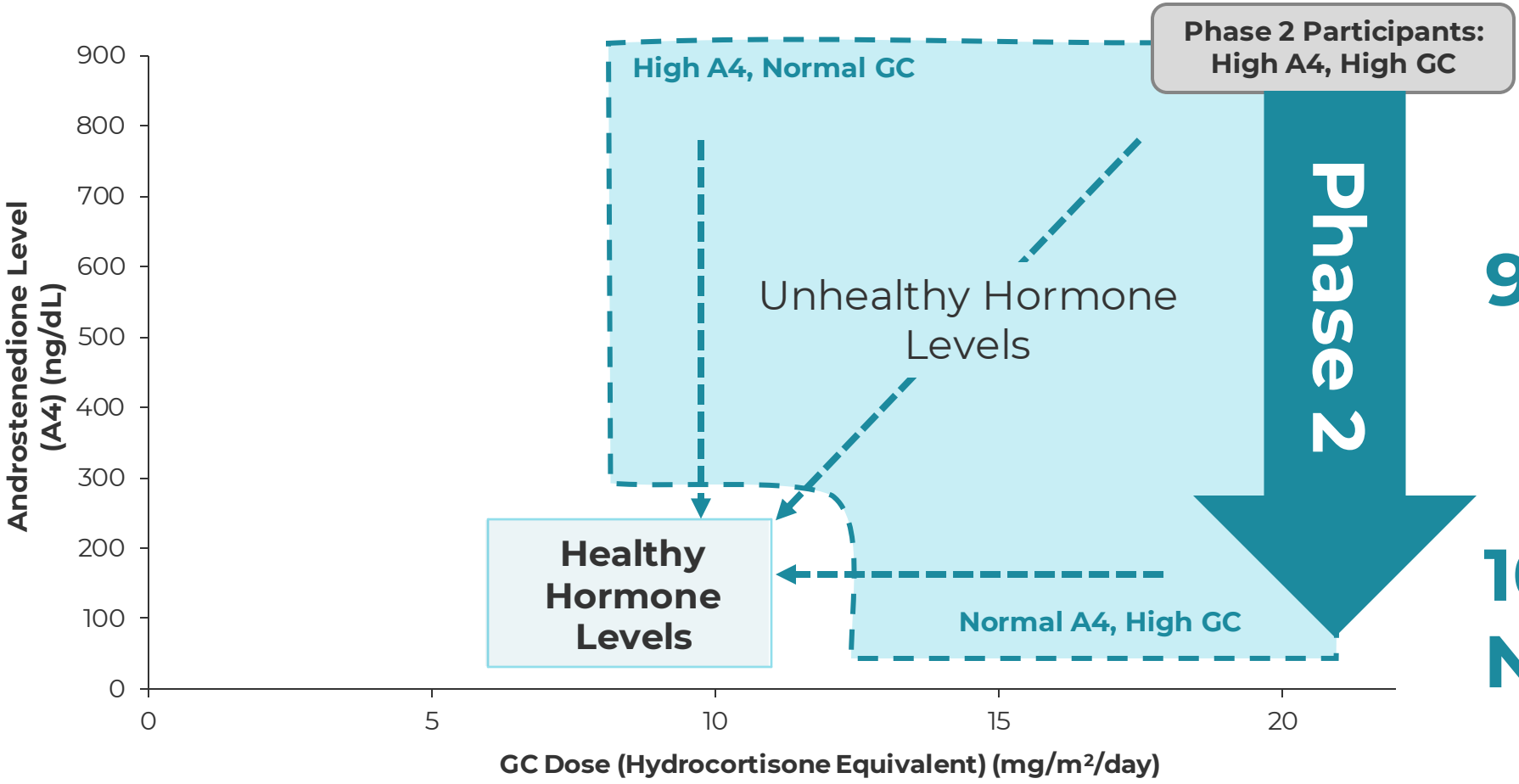
Goal: Achieving Healthy Hormone Levels with Atumelnant
Normalize A4 at Physiologic Glucocorticoid Replacement

Phase 3 study to be designed to benefit all patients with unhealthy hormone levels (A4 or GC)



91% A4*↓

100% A4 Normalization*

GC: glucocorticoid; A4: androstenedione. *Phase 2 results with 80 mg atumelnant at 2 weeks..

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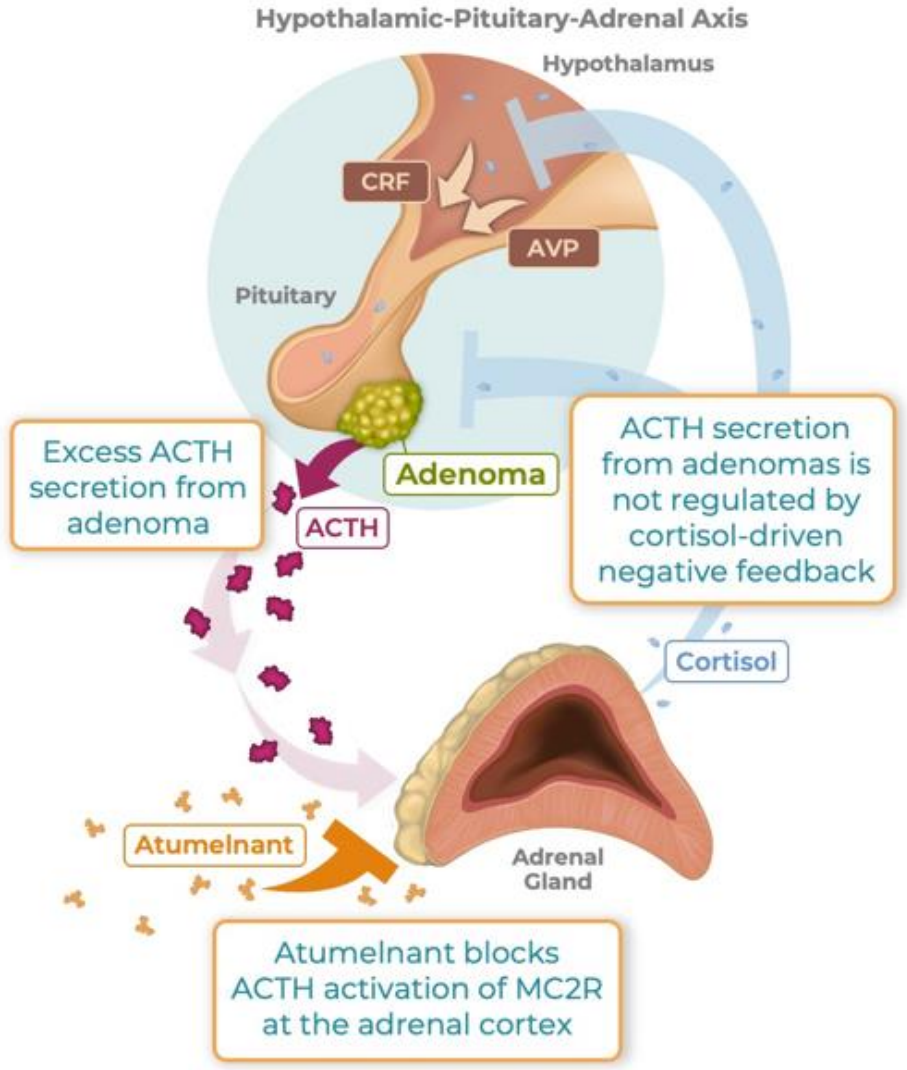
ACTH DEPENDENT CUSHING'S SYNDROME

Atumelnant in ACTH-dependent Cushing's Syndrome



ACTH-dependent Cushing's Syndrome (ADCS)

Treatment Goals

- Control cortisol levels and reduce associated complications (e.g., cardiovascular disease, infections, thromboembolism, diabetes, fractures)
- Correct ADCS symptoms and patient reported outcomes (weight gain, fatigue etc.)
- Lower systolic blood pressure and lower doses of BP meds
- Reduce androgens, restore menstruation, reduce hirsutism (women) and acne
- Improvement in glucose control

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.
ACTH: adrenocorticotrophic hormone; AVP: arginine vasopressin; CRF: corticotropin-releasing factor.

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Despite Recent Medical Advances, Optimal ADCS Medical Treatment Remains Elusive

Unpredictable outcomes with existing therapies

~50-80% efficacy but with unpredictable effects and lack of response in many patients

Therapies given multiple times daily

Unacceptable delay to cortisol normalization

Laborious Titration schedules (every 2+ weeks or longer)

"Change in treatment should be considered if cortisol levels are persistently elevated after 2–3 months on max tolerated doses" [1]

Multiple Limiting Adverse events

- Hepatotoxicity
- Hypokalemia
- Hypertension
- Hyperandrogenism
- Hypogonadism
- QT prolongation

1. Fleseriu, Maria, et al. "Consensus on diagnosis and management of Cushing's disease: a guideline update." *The Lancet Diabetes & Endocrinology* 9:847-875, 2021.
ADCS: ACTH-dependent Cushing's syndrome.

Open-Label Trial of Atumelnant in ACTH-dependent Cushing's Syndrome (ADCS)

Sequential Multiple Ascending Dose Cohorts

Key Eligibility Criteria

N=18

- Male or female, aged 18-75 years
- ADCS or Ectopic ACTH syndrome

Treatment Arms:

- 3 cohorts, 10 days treatment

80 mg Once Daily (n=6)

120 mg Once Daily (n=6)

TBD (n=6)

Objectives: Evaluate the Safety and PK of Atumelnant for the Treatment of Cushing's Syndrome

Primary Endpoints: Safety, tolerability and pharmacokinetics assessments

Secondary Endpoints:

- Change from baseline in early morning serum cortisol at Day 11

Exploratory Endpoints:

- To demonstrate the lowering of 24-hour urinary free cortisol
- Proportion of participants who normalize UFC at Day 10

Dose in third cohort of study will be determined after review of results from first two cohorts at 80 mg and 120 mg

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Demographics and Baseline Characteristics

	80 mg N=5
Age (yrs), median (range)	47 (34-55)
Male, n (%)	4 (80%)
BMI (kg/m^2), median, (range)	36 (24-43)
24h mUFC (ug/24h), median (range)	252 (99-293)
ACTH (pg/mL), median (range)	49 (26-1,504)

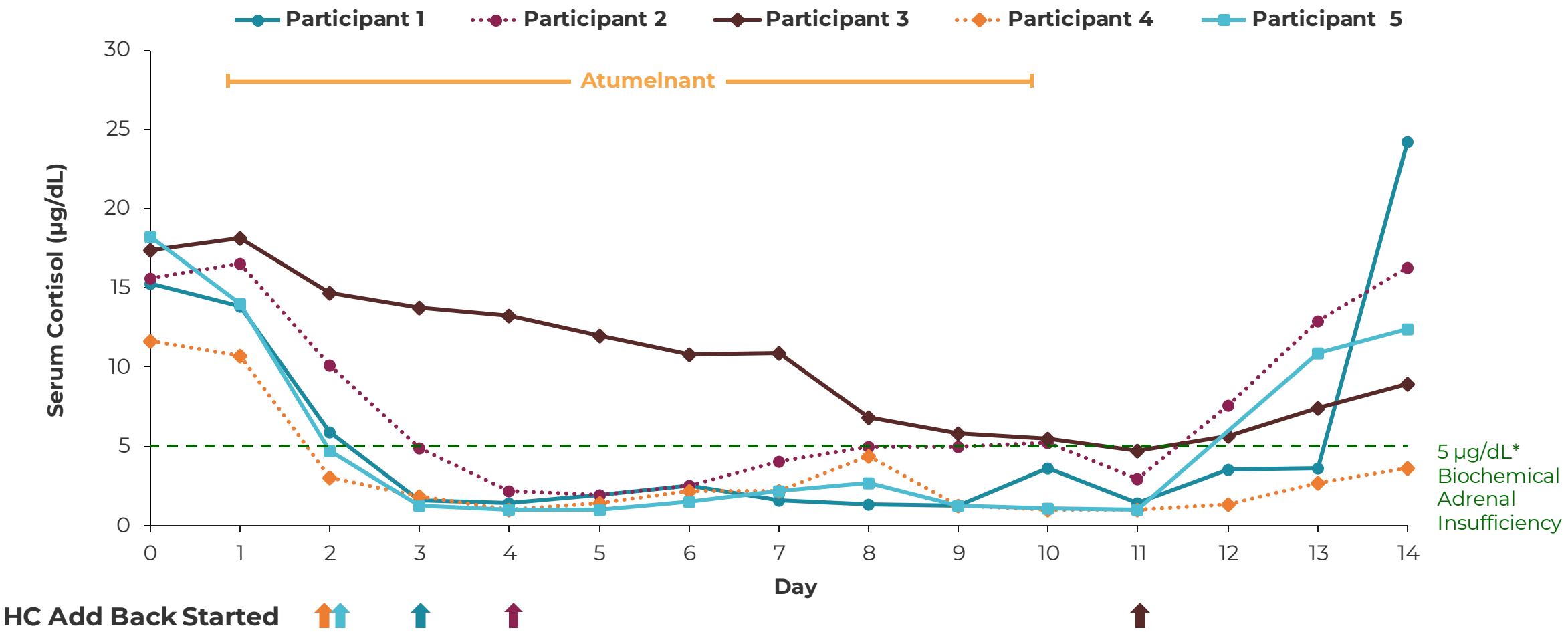
Reference range (RR): <45 ug/24h for mUFC and 5-46 pg/mL for ACTH.
BMI: Body mass index. UFC: Urine free cortisol. ACTH: Adrenocorticotropic hormone.

Safety and Tolerability

- Atumelnant 80 mg was generally well tolerated in this study
- Predefined biochemical adrenal insufficiency (serum cortisol <5 µg/dL) observed in all patients treated to date. Consistent with the known mechanism and pharmacology
- Two participants with pre-existing steatosis had small increases in ALT (<1.5x ULN)
  - No changes in bilirubin or AST
- Other AEs reported were mild to moderate:
  - Headache (4/5) and anorexia/nausea (4/5) coincided with AM cortisol <5 mcg/dL; most symptoms improved with HC add-back
  - Fatigue, malaise, itching, edema, sinus congestion each once

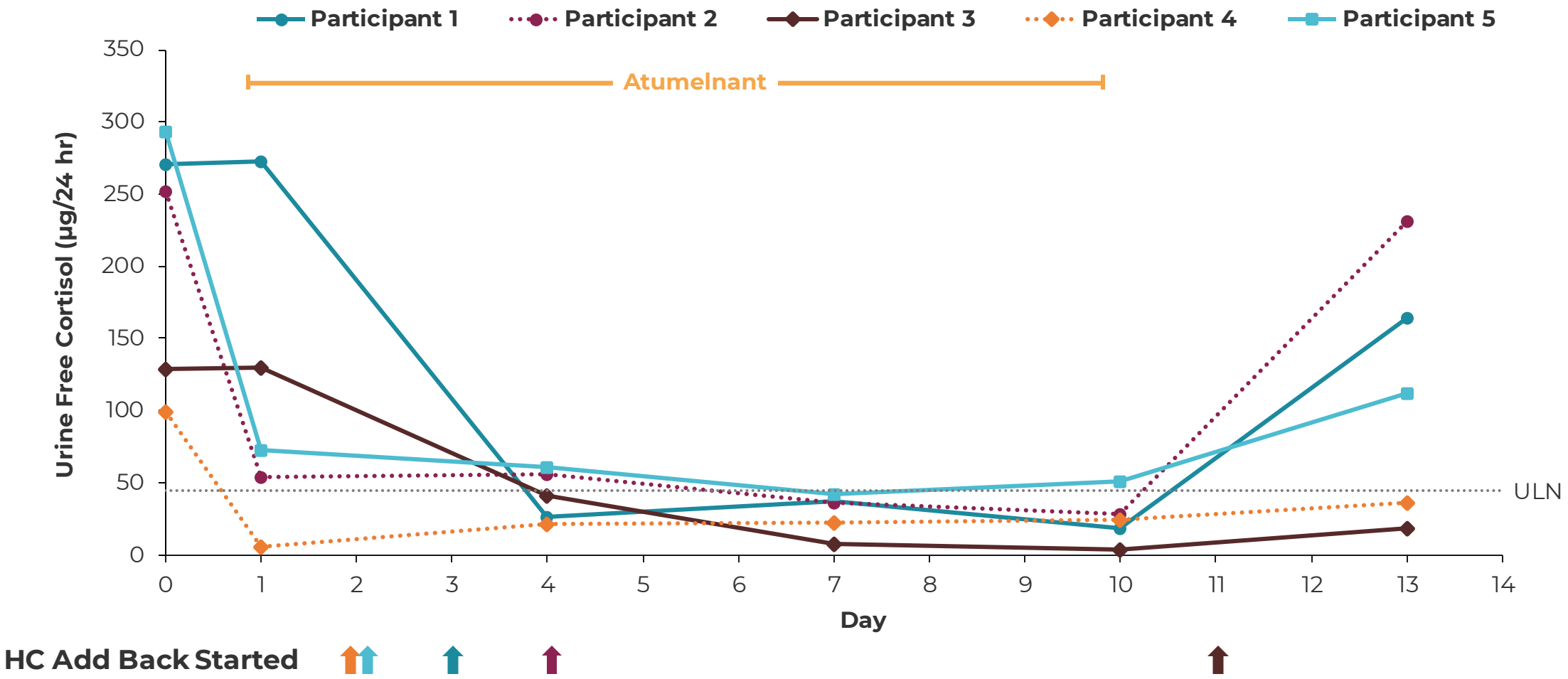
ALT: Alanine Transaminase. ULN: Upper limit of normal. AST: Aspartate Aminotransferase. AE: Adverse event.

Morning Serum Cortisol: All Participants Rapidly Achieved Serum Cortisol Levels <5 µg/dL



HC: Hydrocortisone.

24h Urine Free Cortisol: Sustained at or Below the ULN and Maintained Control with Hydrocortisone (HC) Add Back



27 ULN: Upper limit of normal.

Every Participant Experienced Improvement in Multiple Clinical and/or Cushing's Lab Features

		Participant					Total
		1	2	3	4	5	
Clinical Features	Insomnia	●	●	-	●	●	4/4
	Irritability	-	●	-	●	●	3/3
	Malaise	-	-	-	-	●	1/1
	Poor concentration	●	●	●	○	●	4/5
	Anxiety/depression	-	●	●	○	●	3/4
	Fatigue	●	-	-	○	●	2/3
	Low Libido	●	○	-	-	●	2/3
	Brain Fog	●	○	●	○	●	3/5
	Hypertension	○	●	●	○	●	3/5
	Swelling/bloating	○	-	●	○	●	2/4
Laboratory Features of ADCS	Normalization of neutrophilia	●	-	●	●	-	3/3
	Normalization of leukocytosis	-	-	●	●	-	2/2
	Normalization of low testosterone	●	●	○	●	-	3/4

● Reported and improved ○ Reported but not improved - Not reported as bothersome or abnormal at entry

ADCS: ACTH-dependent Cushing's syndrome.

Atumelnant Program: Summary of Results and Next Steps

Summary: Phase 2 Data Exceeded Expectations with Unprecedented Effects

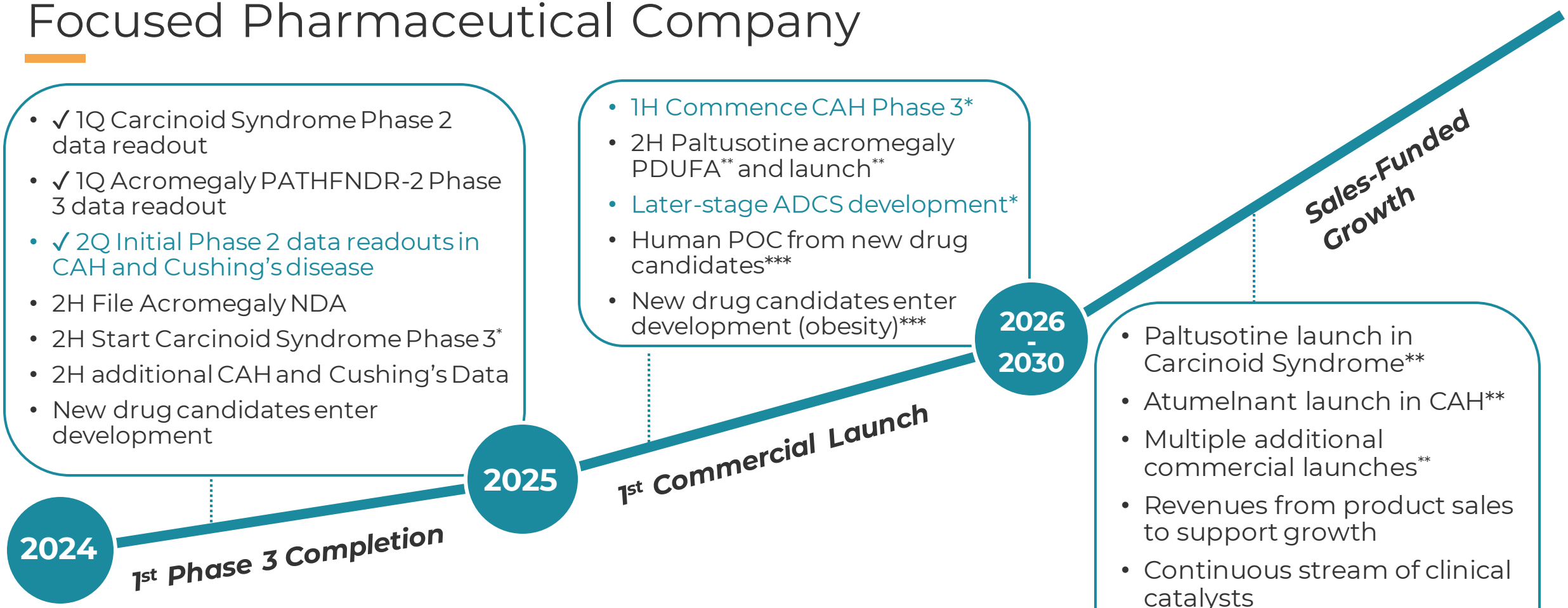
- Profound, rapid and sustained biomarker reduction in *both* CAH and ADCS
- Generally safe and well-tolerated
- Early signs of clinical symptom improvement in both CAH and ADCS
- Initial data support advancing towards Phase 3 in CAH
- Initial data support advancing towards later stage development in ADCS

Immediate Next Steps

- Complete the Phase 2 study in CAH (TouCAHn) and report top-line data in 2H 2024
- Complete the Phase 1b/2a study in ADCS and report additional data 2H 2024
- Design Phase 3 trial for CAH and align with regulators
- Design ADCS later stage development plan and align with regulators

CAH: Congenital adrenal hyperplasia. ADCS: ACTH-dependent Cushing's syndrome.

Crinetics is Building the Premier Fully Integrated Endocrine-Focused Pharmaceutical Company



- ✓ 1Q Carcinoid Syndrome Phase 2 data readout
- ✓ 1Q Acromegaly PATHFNDR-2 Phase 3 data readout
- ✓ 2Q Initial Phase 2 data readouts in CAH and Cushing's disease
- 2H File Acromegaly NDA
- 2H Start Carcinoid Syndrome Phase 3*
- 2H additional CAH and Cushing's Data
- New drug candidates enter development

- 1H Commence CAH Phase 3*
- 2H Paltusotine acromegaly PDUFA** and launch**
- Later-stage ADCS development*
- Human POC from new drug candidates***
- New drug candidates enter development (obesity)***

- Paltusotine launch in Carcinoid Syndrome**
- Atumelnant launch in CAH**
- Multiple additional commercial launches**
- Revenues from product sales to support growth
- Continuous stream of clinical catalysts
- New assets emerging from discovery into development

Strategic Approach to **Growing Long-term Value**

*Pending alignment with FDA **Pending NDA submission, acceptance and regulatory approval
***Pending clinical development of new drug candidates for additional diseases

NDA: New drug application. CAH: Congenital adrenal hyperplasia; PDUFA: Prescription Drug User Fee Act. ADCS: ACTH-dependent Cushing's syndrome. POC: Proof of concept.

Crinetics Pharmaceuticals

Q&A

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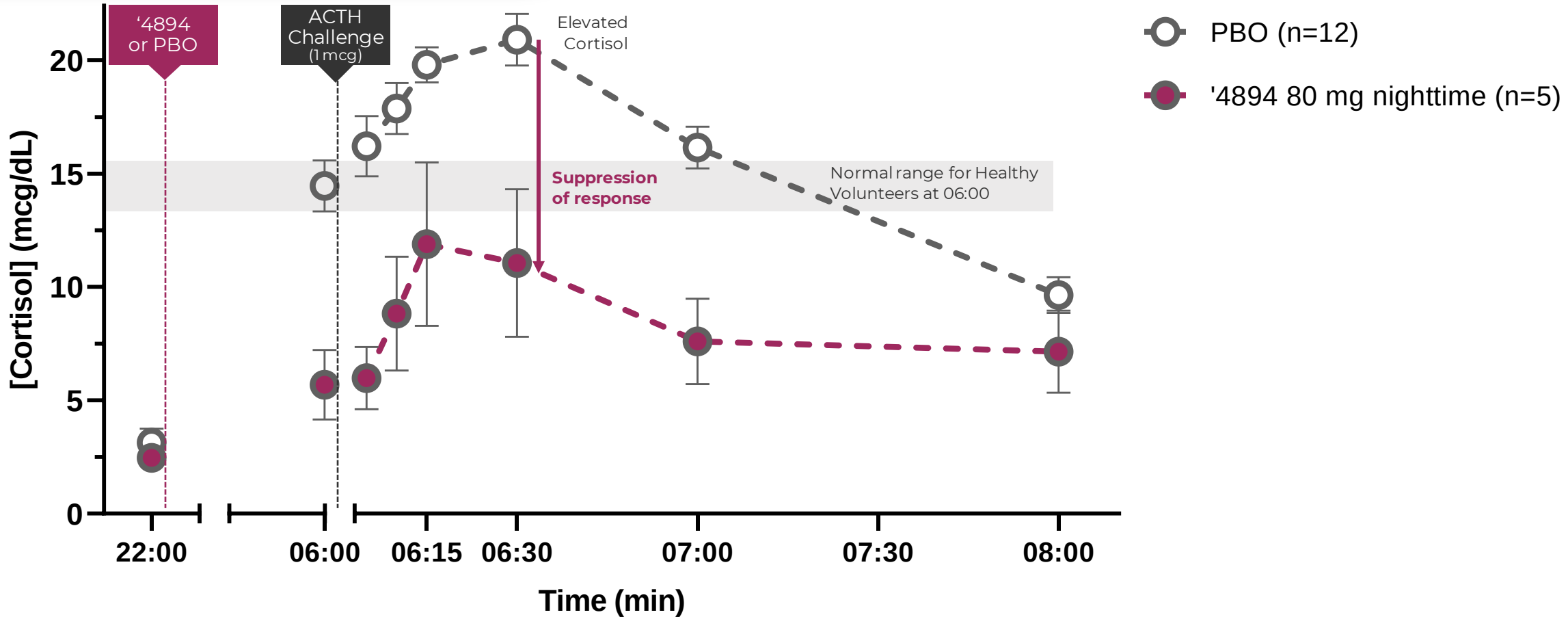
Crinetics Pharmaceuticals

Atumelnant Maintained Cortisol Below Normal Levels After ACTH Challenge Test on Top of Sustained Elevated ACTH

ACTH Challenge



Data shown are mean ± SEM; one subject in 80 mg MAD arm did not receive ACTH challenge; Placebo