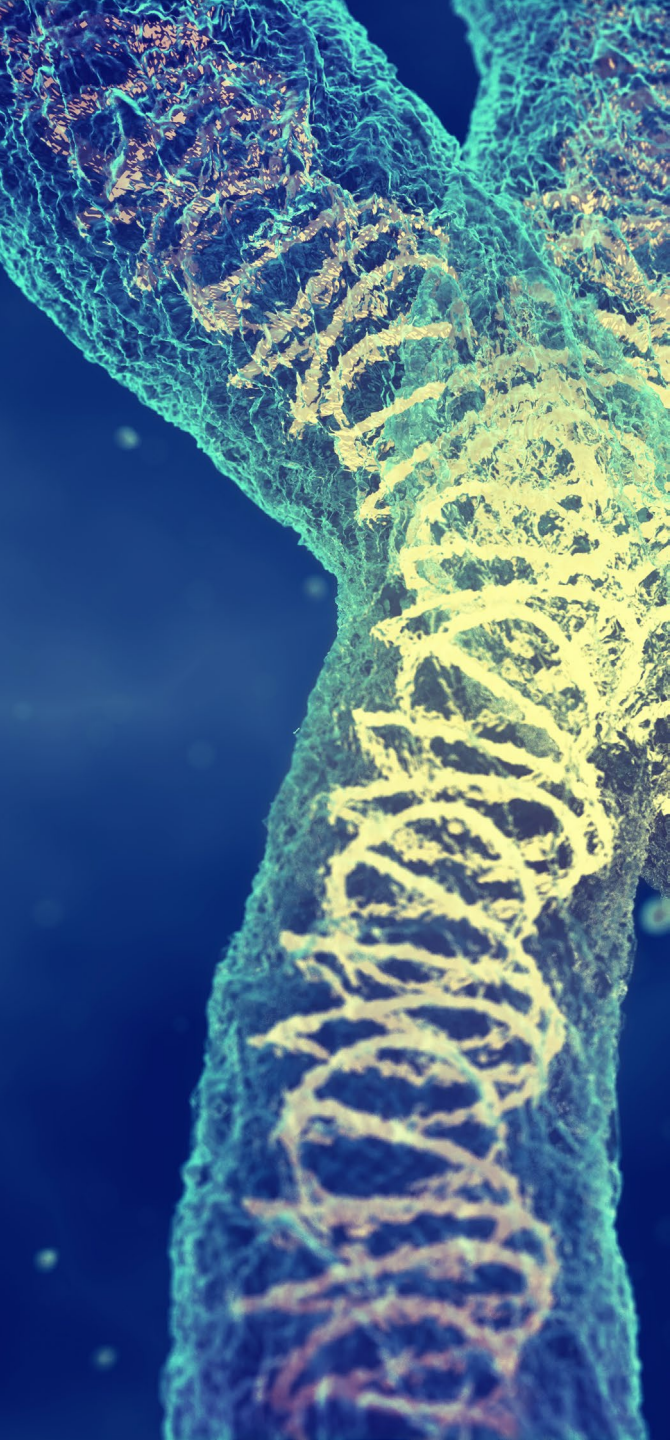


'BLOCK AND REPLACE' ATUMELNANT
(CRN04894) AND PHYSIOLOGIC
HYDROCORTISONE REPLACEMENT
RAPIDLY CONTROLS HYPERCORTISOLISM
IN ACTH-DEPENDENT CUSHING SYNDROME

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AUTHORS AND DISCLOSURES

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BACKGROUND

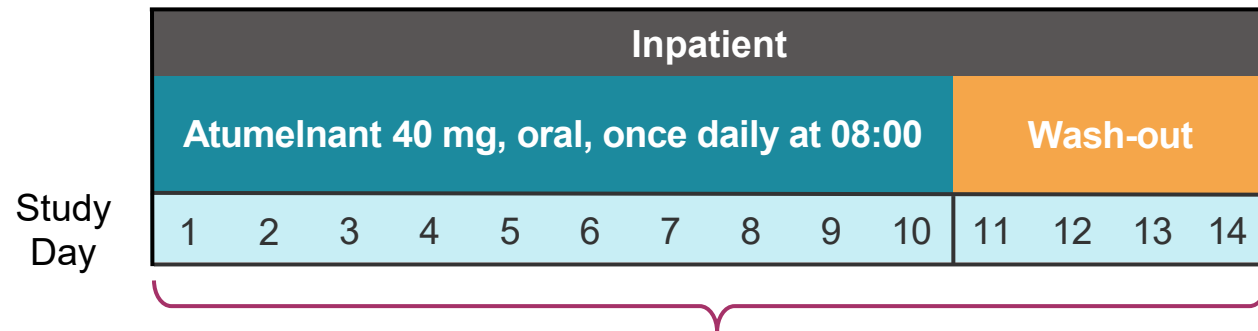
- Medical therapies for Cushing syndrome are suboptimal, with variable efficacy, delay to cortisol normalization, and safety concerns.
- Atumelnant (ATU) is an investigational, once-daily, oral, first-in-class, selective melanocortin type 2 receptor antagonist that blocks ACTH action at the adrenal cortex.
- Previous participants receiving ATU 80 mg (n=6) and 120 mg (n=1) for 10 days developed AM cortisol $<5 \mu\text{g/dL}$ and received physiologic hydrocortisone replacement.
- Here we report data from the 40 mg cohort of the first-in-disease, open-label, dose-finding, phase 1b/2a study of ATU in patients with ACTH-dependent Cushing syndrome (ADCS).

STUDY DESIGN

KEY ELIGIBILITY CRITERIA

Active ADCS:

- AM ACTH >10 pg/mL
- 24-hr UFC >1.3 upper limit of normal

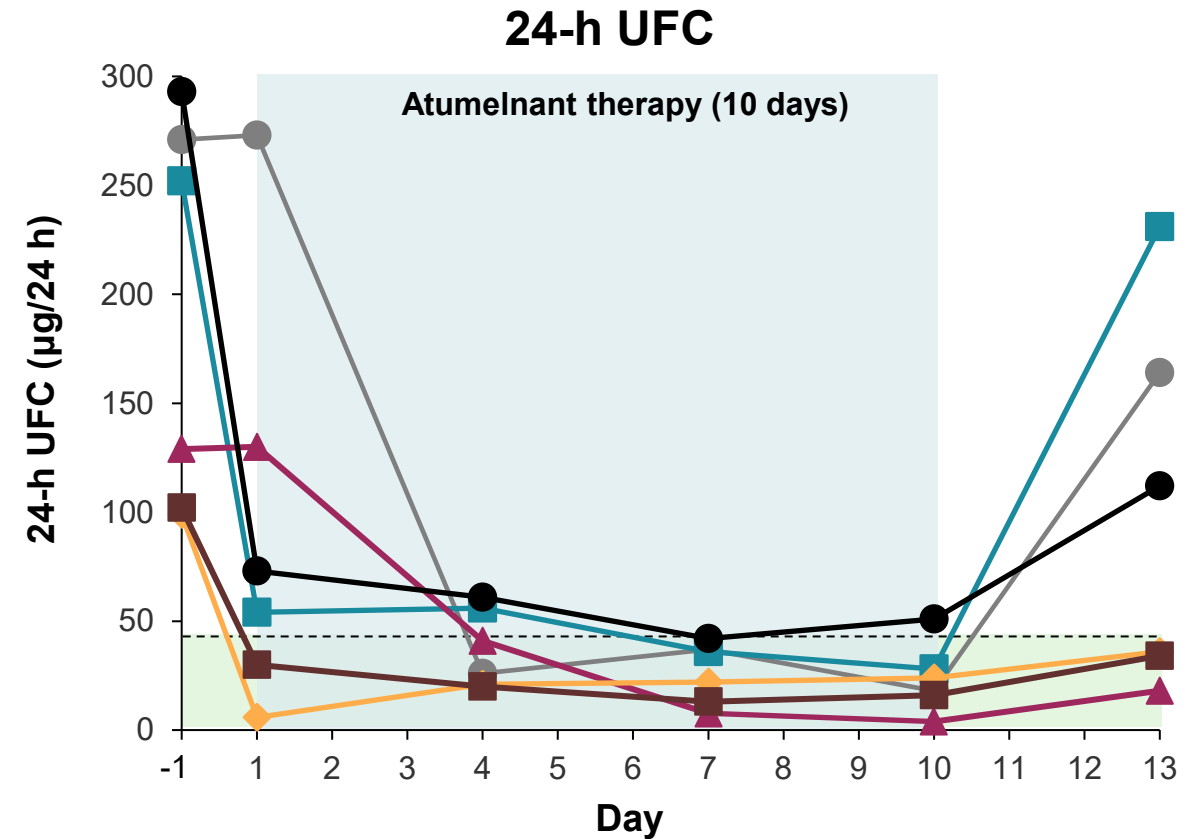
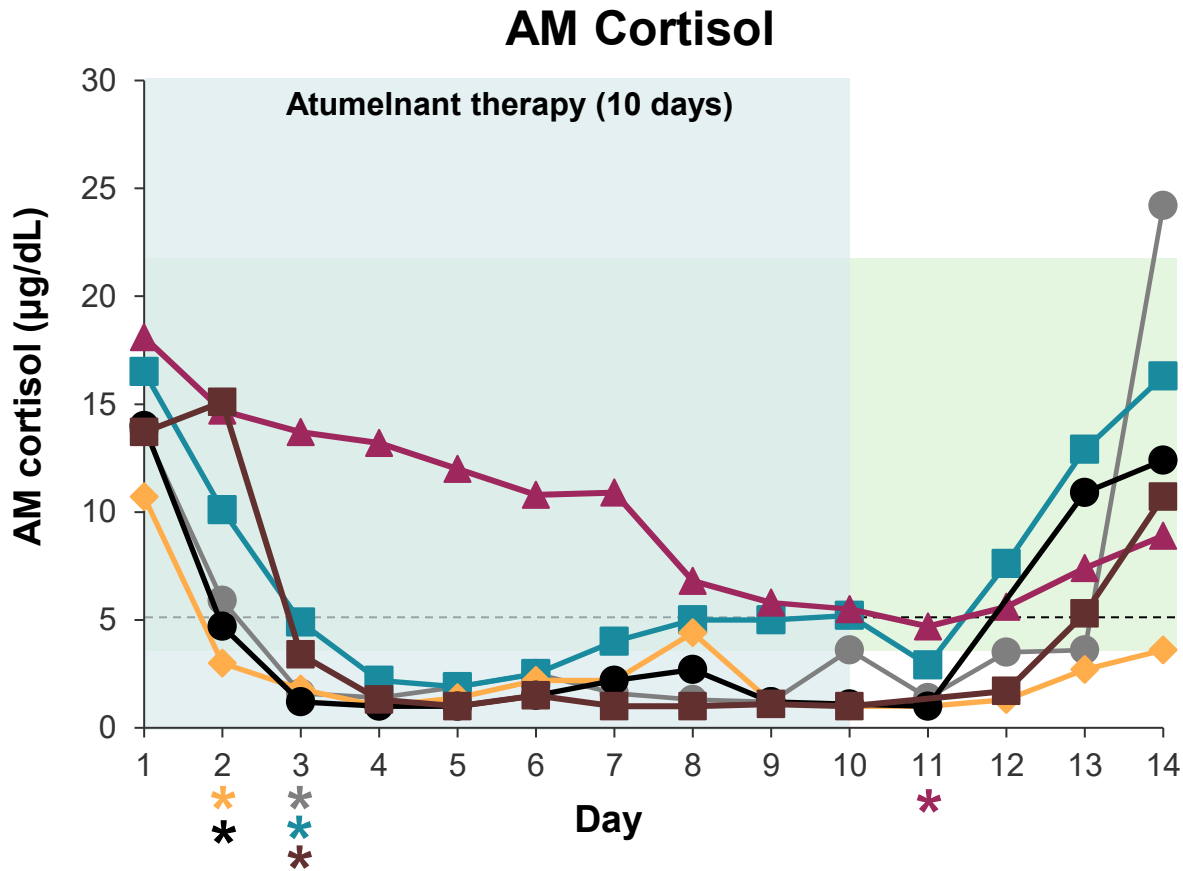


- Daily AM cortisol, ACTH, & AE assessment
- UFC on Day 1, 4, 7, 10, and 14
- Safety labs every 2-3 days

Per protocol, physiologic hydrocortisone replacement was started when AM cortisol was <5 µg/dL, regardless of symptoms (8.9-10.9 mg/m² BSA daily)

PRIOR FINDINGS: AM CORTISOL AND UFC WERE REDUCED WITH ATUMELNANT 80 MG

Participant 1 (EAS) Participant 2 (CD) Participant 3 (CD) Participant 4 (CD) Participant 5 (CD) Participant 6 (CD)



Dashed line = AM Cortisol <5 µg/dL, prompted physiologic hydrocortisone add-back.

PARTICIPANTS IN 40 MG COHORT

6 women with Cushing disease (pituitary)

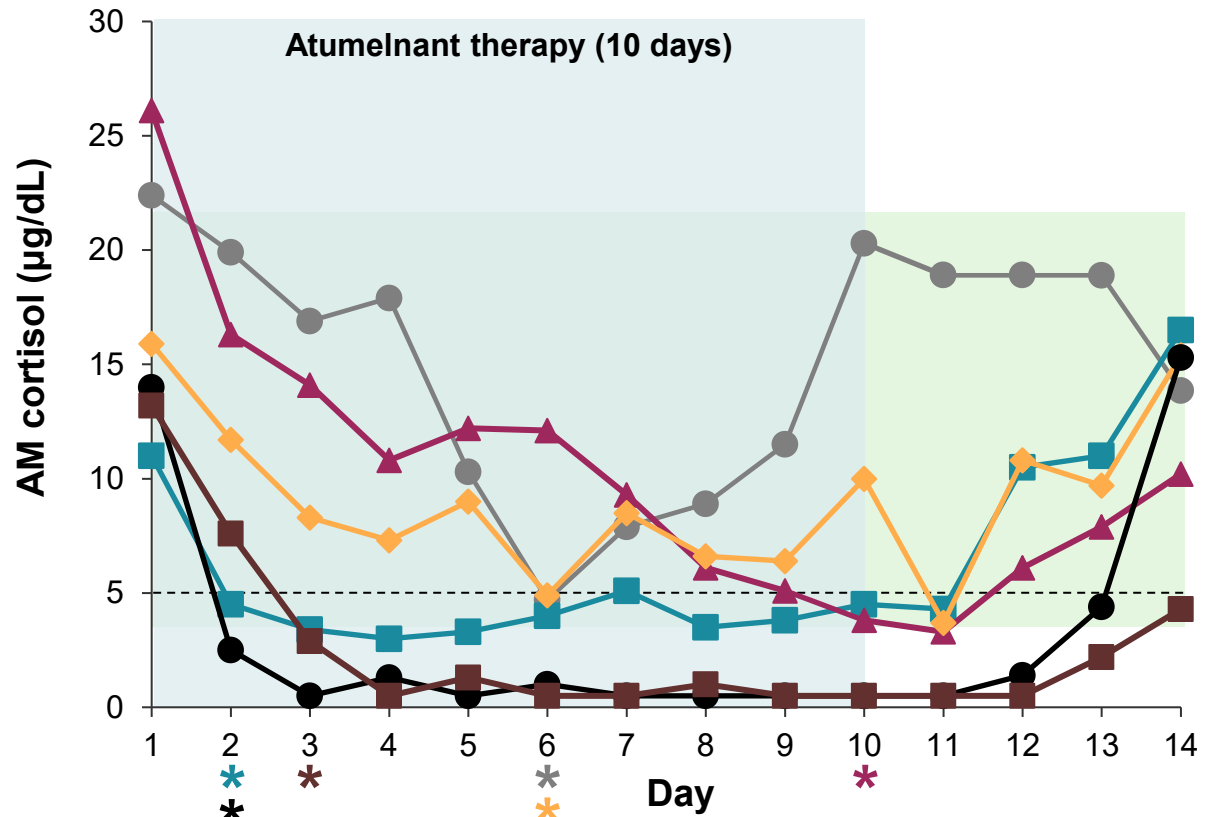
Median baseline characteristics:

- Age 41.5 years (range: 18-58)
- AM ACTH: 35.4 pg/mL (range: 9.5-67.2) [RR <46]
- UFC: 353 µg/d (range: 35-1655) [RR <45]
- UFC elevation: 7.8 x ULN (range: 0.8-37)

ATUMELNANT 40 MG: ALL PARTICIPANTS DEVELOPED AM CORTISOL <5 MCG/DL

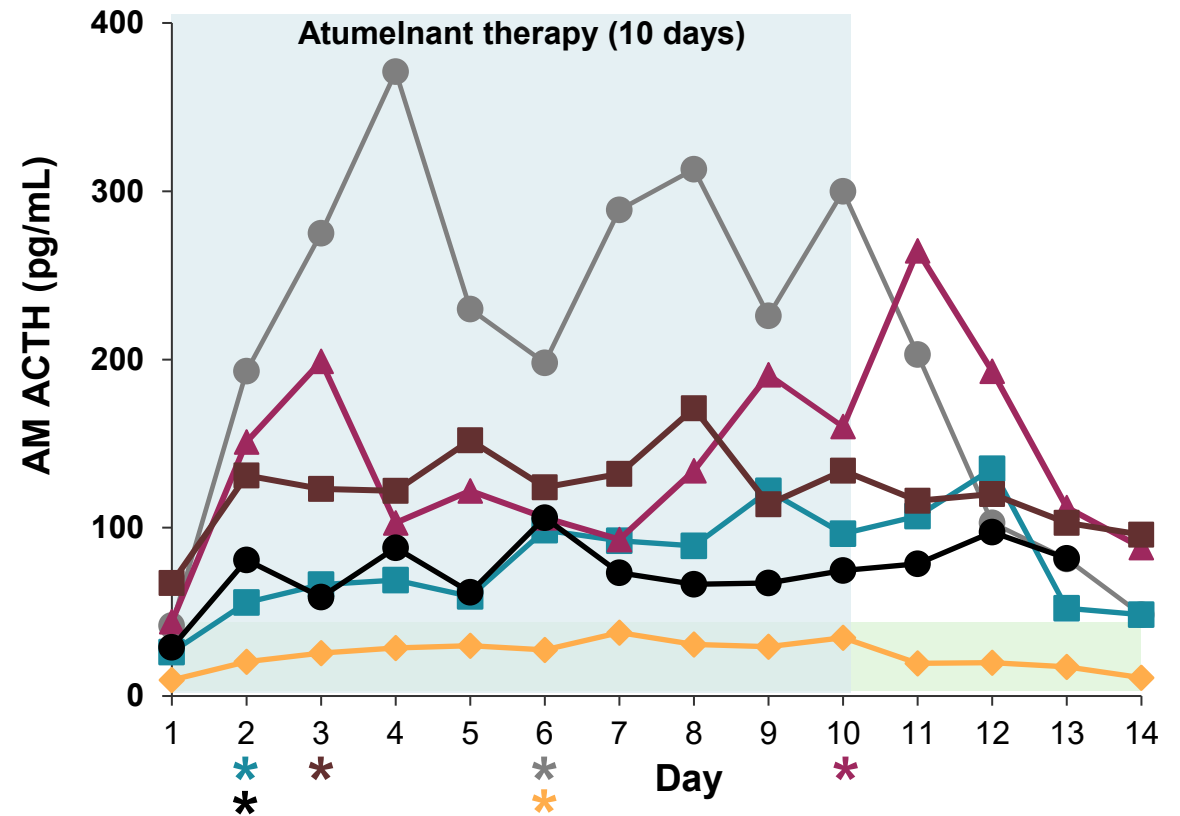
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AM Cortisol



Dashed line = <5 µg/dL, prompted physiologic hydrocortisone add-back.

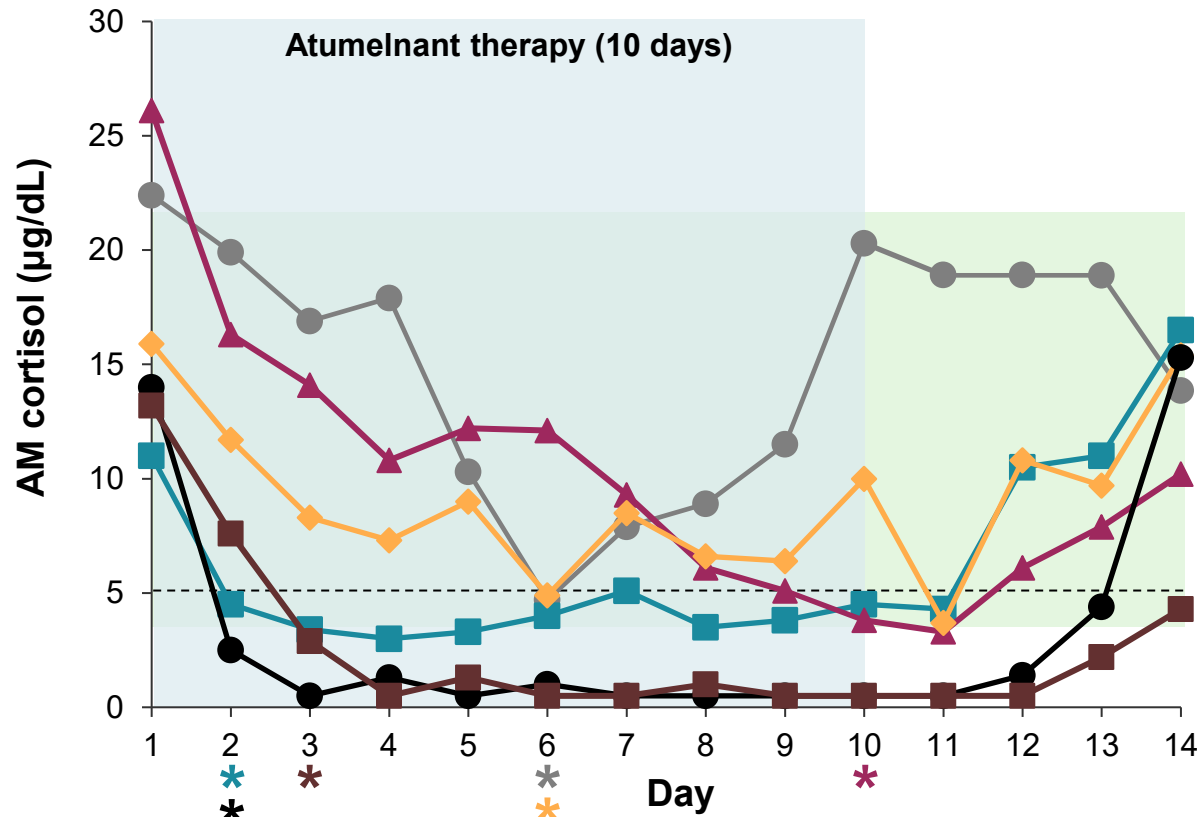
AM ACTH



ATUMELNANT 40 MG: ALL PARTICIPANTS DEVELOPED AM CORTISOL <5 MCG/DL

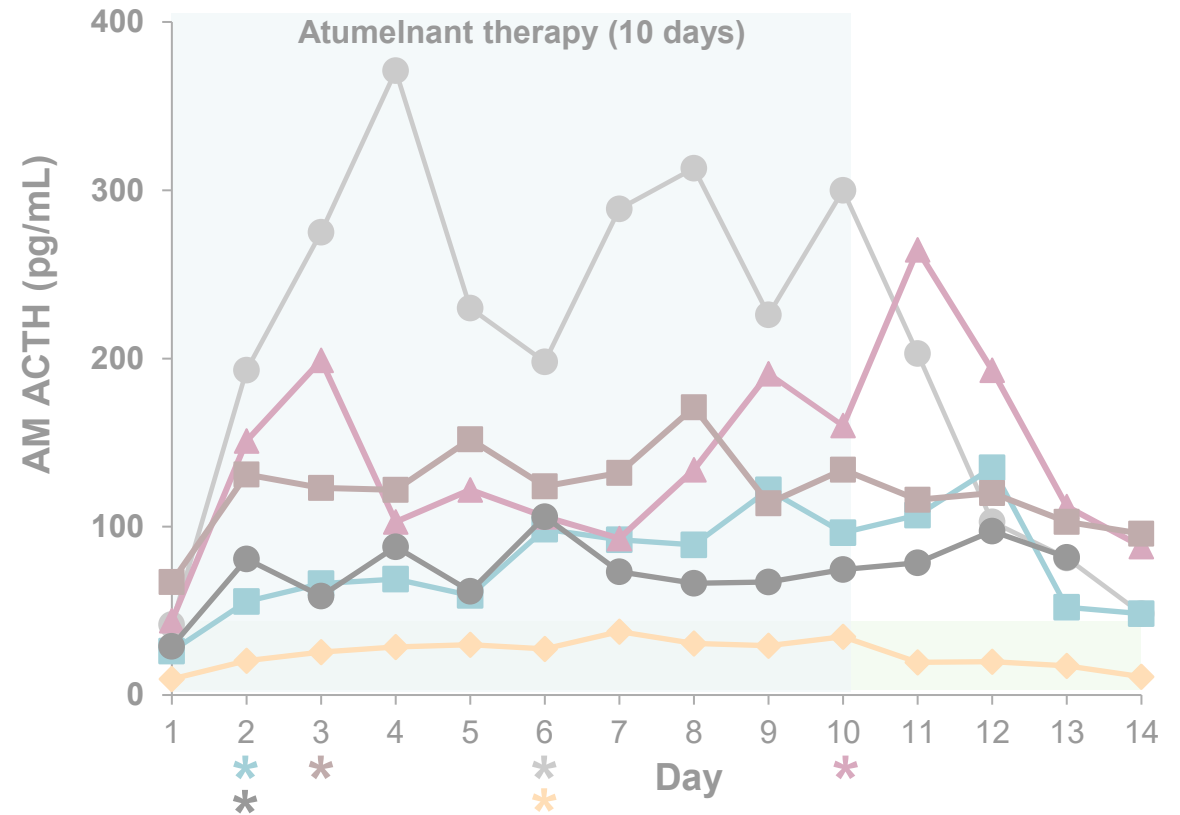
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AM Cortisol



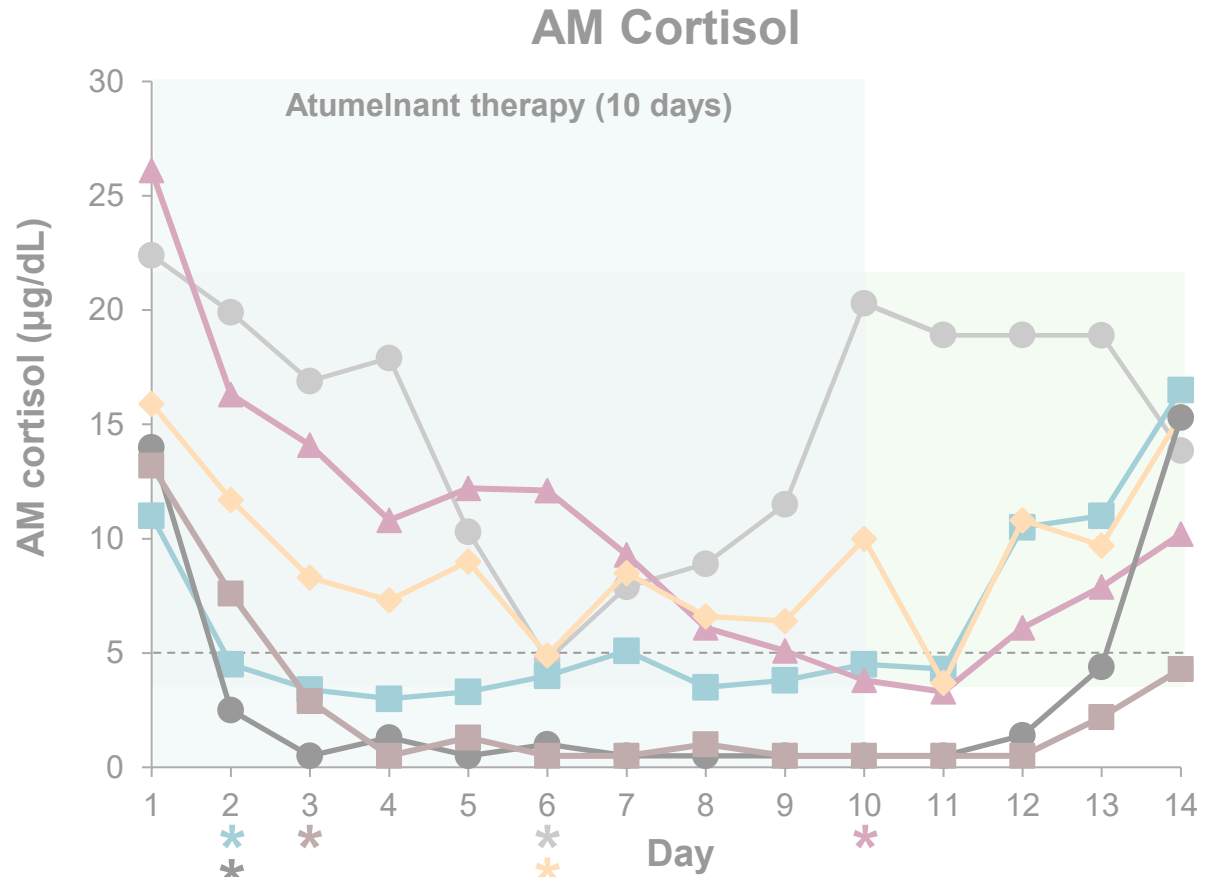
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AM ACTH

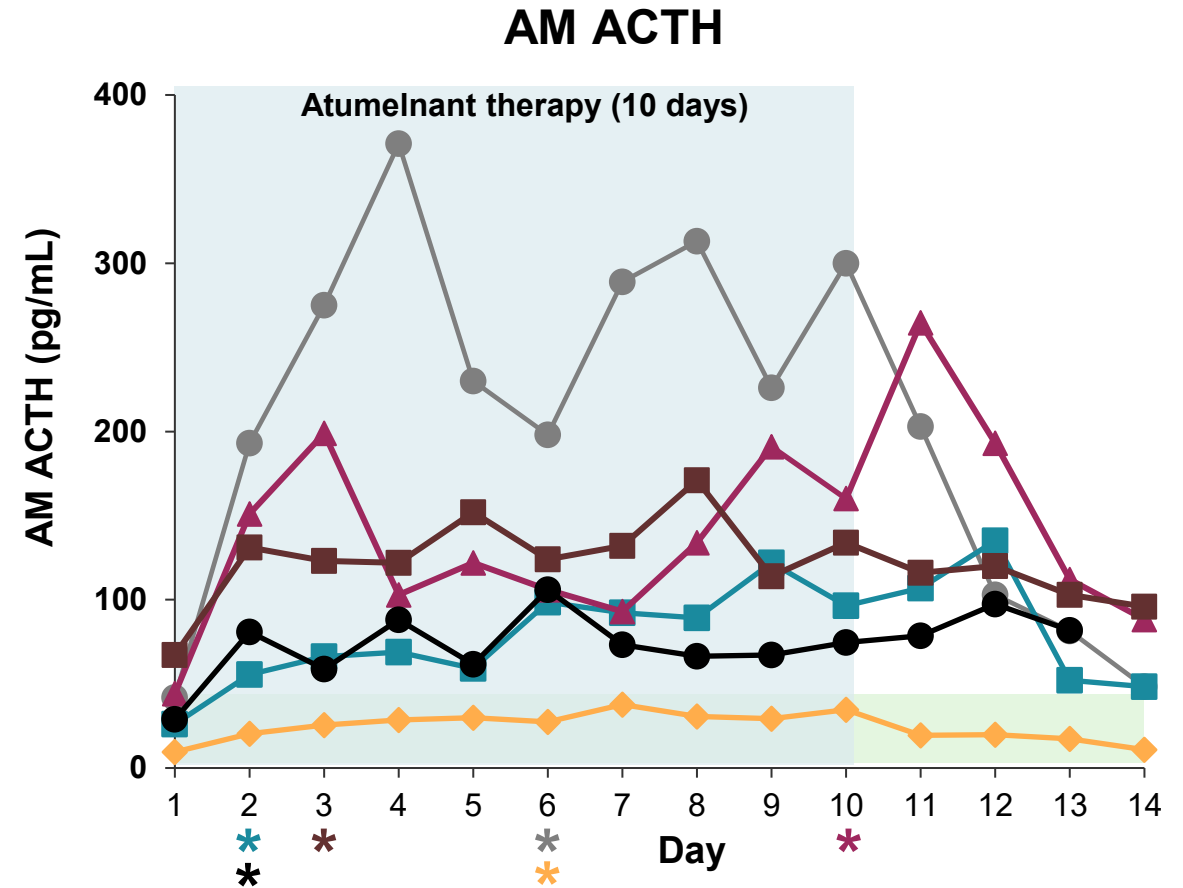


ATUMELNANT 40 MG: ALL PARTICIPANTS DEVELOPED AM CORTISOL <5 MCG/DL

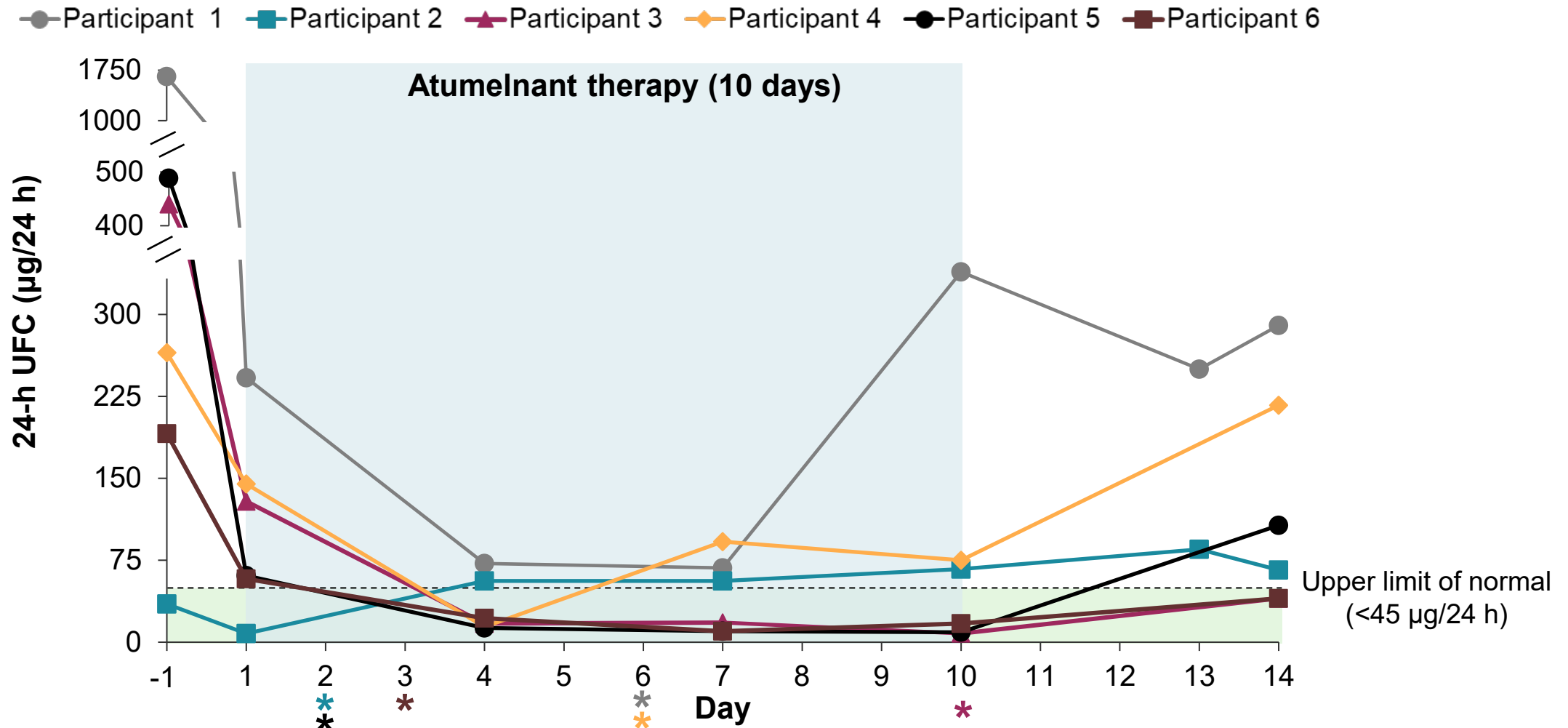
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Dashed line = <5 µg/dL, prompted physiologic hydrocortisone add-back.



ATUMELNANT 40 MG NORMALIZED 24-HR UFC BY DAY 4 IN 4/6 SUBJECTS



AM cortisol <5 µg/dL, prompted physiologic hydrocortisone add-back.

IMPROVEMENT IN CUSHING SYNDROME FEATURES

Clinical feature	Improved
Hypertension	3/6
Brain fog	3/6
Insomnia	4/5
Anxiety	3/4
Poor concentration	3/4
Fatigue	3/3
Swelling/bloating	3/3
Depression	2/2
Impaired memory	2/2

Lab feature	Resolution
↑ Testosterone	3/5
Leukocytosis	3/3
Neutrophilia	2/3

SAFETY

- Well-tolerated; all subjects completed 10 days of atumelnant 40 mg
- Most AEs were mild to moderate and consistent with adrenal insufficiency (AI)
 - 4 participants developed headache, anorexia, nausea and malaise at time of AM cortisol $<5 \mu\text{g/dL}$
 - Fatigue, diarrhea, arthralgia, feeling faint, pruritus occurred in 2-4 participants
 - Most symptoms improved with HC replacement
- Serious AEs
 - Adrenal insufficiency in all participants, as expected
- Safety labs
 - ALT 1.2 ULN (n=1); ALT 2.1 ULN and AST 1.6 ULN (n=1)
 - Bilirubin, ALP and creatinine remained normal

CONCLUSIONS

- In ACTH-dependent CS, 10 days of daily oral atumelnant 40 mg
 - Rapid lowering of serum and urine cortisol, 4/6 normalized UFC
 - UFC remained \leq ULN in 3/6 despite physiologic HC replacement
 - Improvement of signs and symptoms of hypercortisolism
 - A compensatory increase in ACTH occurred
 - Symptoms of AI improved with initiation of HC replacement
- As with the previously reported cohort, combination 'Block & Replace' therapy with atumelnant and physiologic HC was well tolerated

ACKNOWLEDGEMENTS

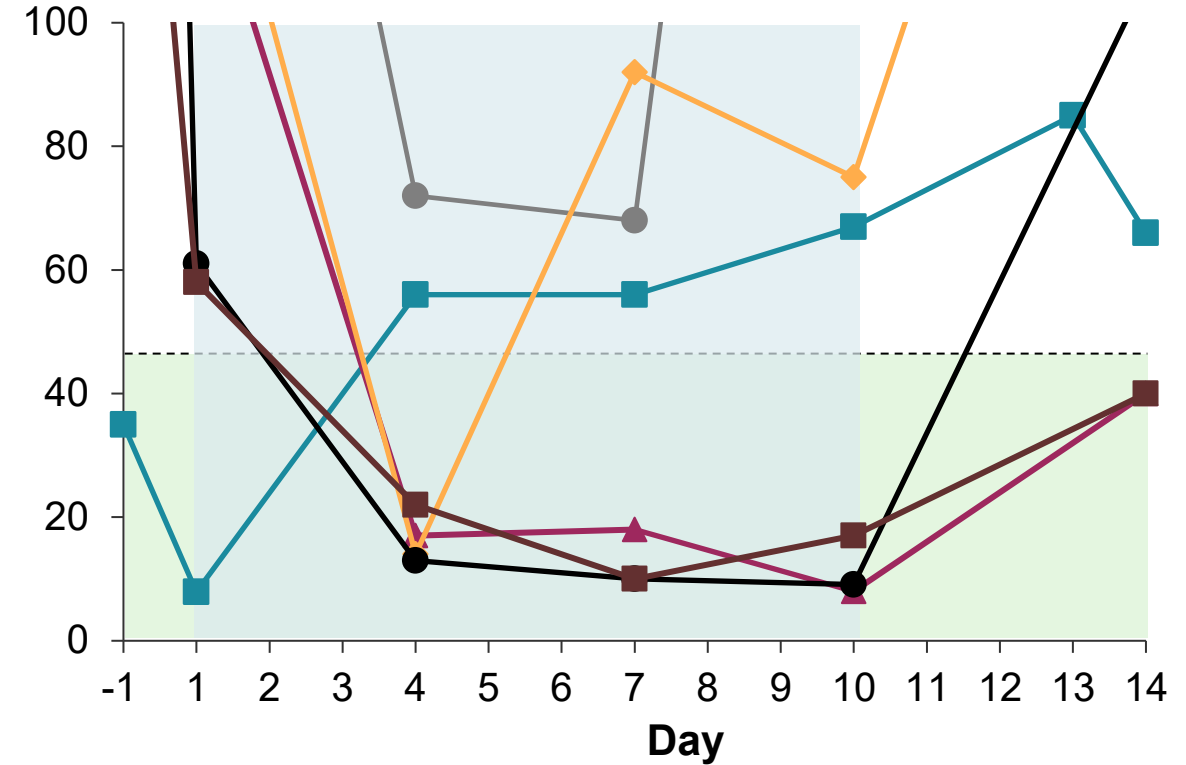
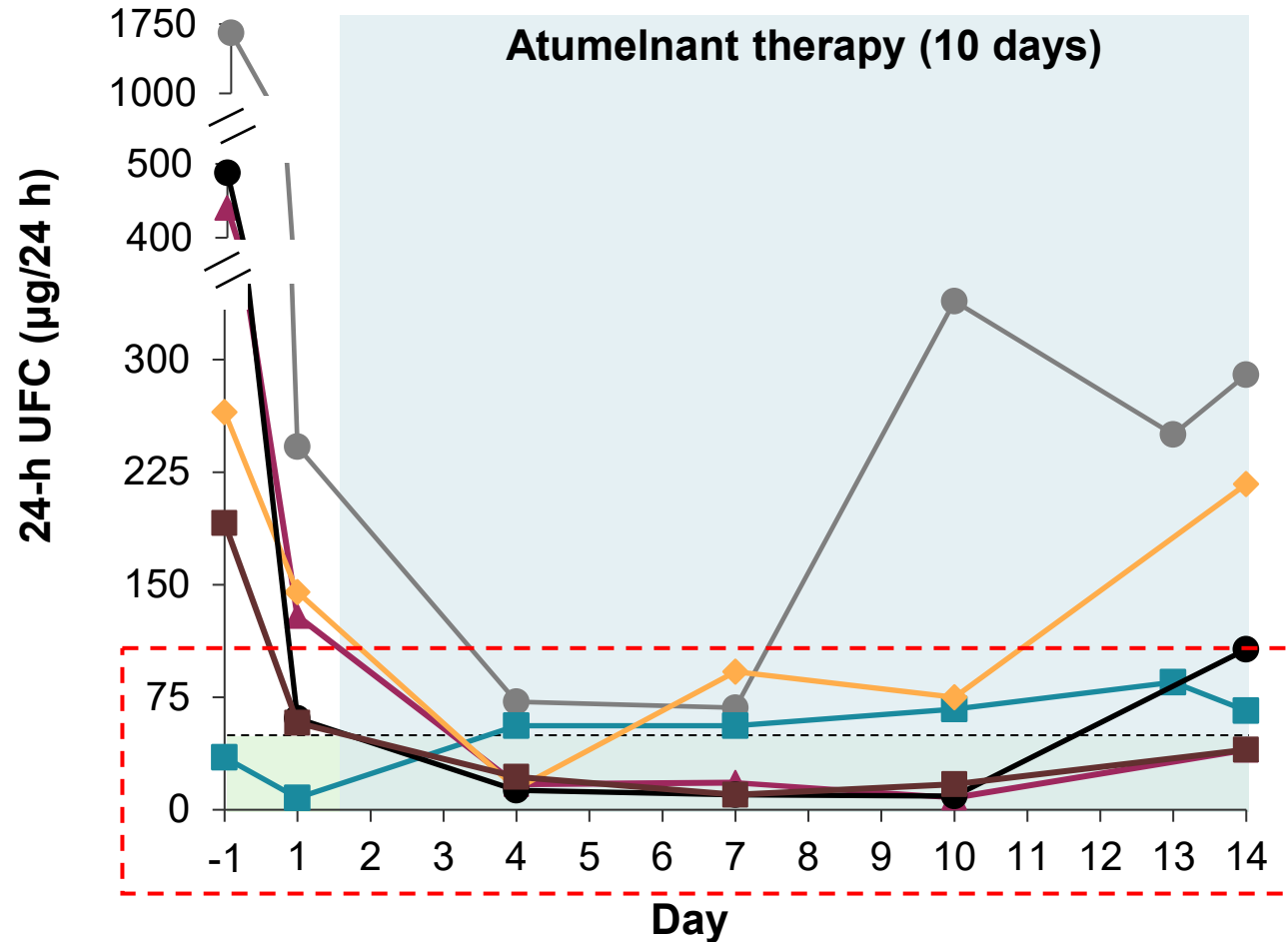
Thank you to the study patients, nurses/study coordinators, clinical staff, who made this study possible

THANK YOU



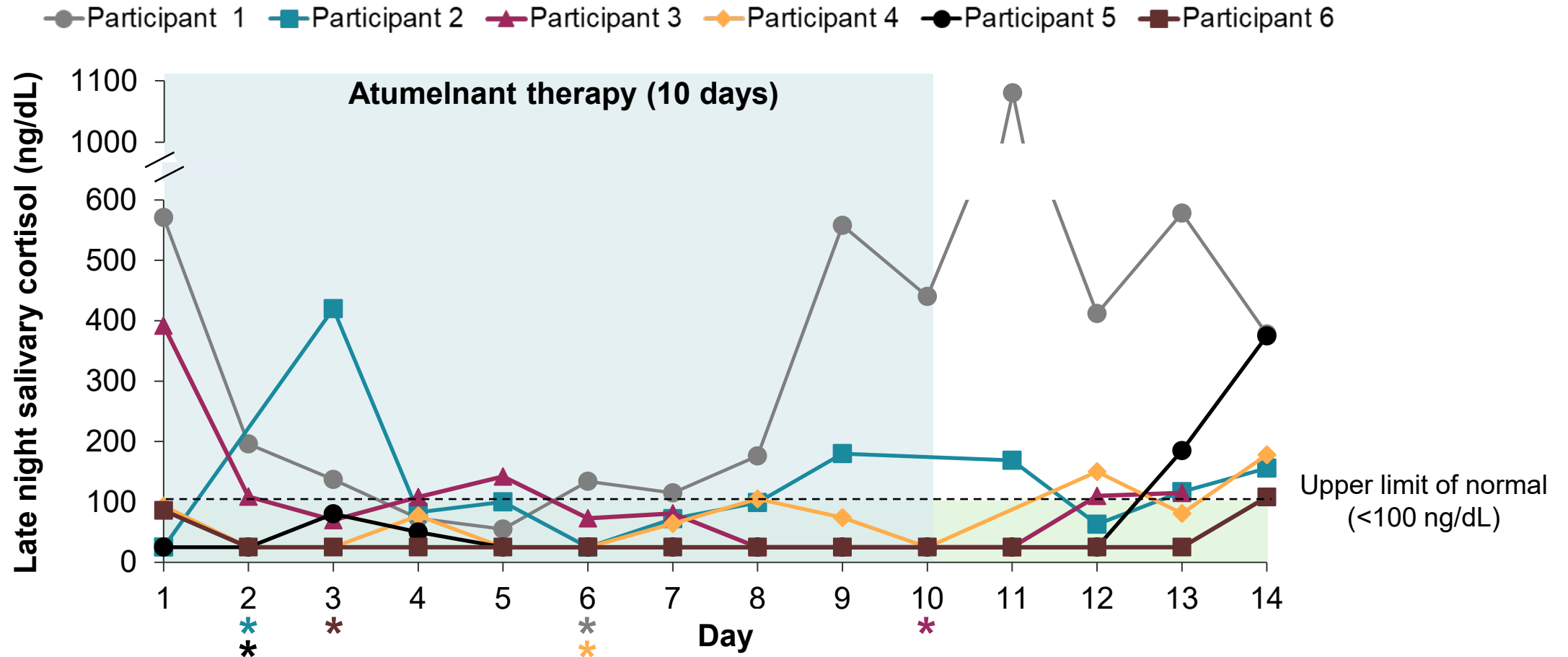
ATUMELNANT 40 MG NORMALIZED 24-HR UFC BY DAY 4 IN 4/6 SUBJECTS

● Participant 1 ■ Participant 2 ▲ Participant 3 ◆ Participant 4 ● Participant 5 ■ Participant 6



AM cortisol <5 µg/dL, prompted physiologic hydrocortisone add-back.

LATE NIGHT SALIVARY CORTISOL



*AM cortisol < 5 µg/dL (dashed line), prompting physiologic hydrocortisone add-back.
 Participant 2, Day 5 value reported as <100 ng/dL. Participant 5, Day 4 value reported as <50 ng/dL.