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POSTER NO. **SAT-671**

Safety and Effectiveness of Osilodrostat in Patients With Non-pituitary Cushing's Syndrome: Results From the Retrospective Observational LINC 7 Study

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INTRODUCTION

- Cushing's disease, caused by a pituitary adenoma, is the most common form of endogenous Cushing's syndrome (60–70% of cases)[1]
  - Some patients present with non-pituitary causes of Cushing's syndrome, such as ectopic ACTH-secreting syndrome, adrenal tumors (adenomas and carcinomas), and bilateral nodular or macronodular adrenal hyperplasia[1,2]
  - The severity of hypercortisolism in patients with adrenal Cushing's syndrome is similar to that in patients with Cushing's disease, but it is greater in patients with ectopic Cushing's syndrome[3–5]
  - Chronic hypercortisolism in non-pituitary Cushing's syndrome leads to increased morbidity and mortality[1,2]
- Osilodrostat, a potent oral 11β-hydroxylase inhibitor, is an effective and well-tolerated long-term therapy for patients with Cushing's syndrome, as demonstrated in pivotal Phase II (LINC 2) and III (LINC 3, LINC 4) trials in patients with Cushing's disease[6–11] and a Phase II study in Japanese patients with non-pituitary Cushing's syndrome[12]
- Osilodrostat is approved for patients with endogenous Cushing's syndrome (EMA) and Cushing's disease for whom pituitary surgery is not an option or has not been curative (FDA)
- LINC 7 (NCT05633953) was a retrospective, non-interventional study conducted to evaluate the safety and effectiveness of osilodrostat in a heterogeneous cohort of patients with non-pituitary Cushing's syndrome in a real-world setting

CONCLUSIONS

- **Osilodrostat provides rapid and sustained control of cortisol in patients with non-pituitary Cushing's syndrome**
  - **Non-pituitary Cushing's syndrome is often associated with severe disease, reflected by the 29 (28.2%) patients who died during the study, most commonly because of neoplasm progression**
- **Overall, the proportion of patients with mUFC ≤ULN and any cortisol parameter ≤ULN generally increased over time**
  - **Patients with adrenal tumors and adrenal hyperplasia had higher rates of mUFC normalization than patients with EAS**
- **Overall, mean mUFC and serum cortisol levels generally decreased during the study**
  - **mUFC generally decreased over time in all etiology subgroups; however, data are limited by small patient numbers and missing assessments at some time points**
- **The safety profile of osilodrostat was consistent with that known in Cushing's disease and the known morbidity in the study population**
  - **In the safety population, 30.1% of patients experienced TEAEs related to hypocortisolism**
  - **Patients with EAS had a higher death rate than patients with adrenal tumors and adrenal hyperplasia**
- **Overall, findings from this retrospective, real-world study show that osilodrostat is an effective and well-tolerated treatment option for patients with varying etiologies of non-pituitary Cushing's syndrome**

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials.

Alternatively, please visit the link: **https://bit.ly/3yBktVH**

ACKNOWLEDGMENTS

We thank Beth Harrahill, Mudskipper Business Limited (funded by Recordati AG [Rare Diseases Branch]), for providing medical editorial assistance, as well as the site investigators, study coordinators and patients who participated in the trial.

DISCLOSURES

The LINC 7 study was funded by Recordati AG (Rare Diseases Branch).

METHODS

- LINC 7 was a retrospective, observational, multicenter study in patients with non-pituitary Cushing's syndrome conducted in France
- Adult patients with non-pituitary Cushing's syndrome were evaluated retrospectively for up to 36 months and included those who initiated osilodrostat:
  - During the follow-up period between the French ATU (April 2019; temporary authorization for use granted prior to commercial availability) and commercialization of osilodrostat in France (June 2020)
  - In routine clinical practice between commercialization of osilodrostat in France (June 2020) and the study start date (December 16, 2022)
- The analysis populations were:
  - **Safety population:** All enrolled patients who met all inclusion/exclusion criteria and have received osilodrostat treatment for non-pituitary Cushing's syndrome
  - **ITT population:** All enrolled patients who met all inclusion/exclusion criteria and have received osilodrostat treatment for non-pituitary Cushing's syndrome, with a potential follow-up of ≥12 weeks
  - **mITT population:** All patients in the ITT population, excluding patients who did not have an mUFC measurement at week 12 for any reason except safety
  - **On-treatment population:** All participants taking osilodrostat at a defined time point or period
- Selected outcomes were analyzed in the following etiologies of Cushing's syndrome: **ectopic ACTH syndrome** (EAS), **adrenal tumors** (adrenal adenoma or adrenocortical carcinoma), and bilateral nodular or macronodular **adrenal hyperplasia**
- The **primary endpoint** was the proportion of patients with mUFC ≤ULN at week 12, based on the **mITT population**
- Secondary and exploratory endpoints included:
  - Proportion of patients with normalization of any cortisol parameter (mUFC, LNSC, morning serum cortisol) at certain time points
  - Proportion of patients with mUFC and any cortisol parameter ≤ULN at the last on-treatment assessment
  - Change in cardiovascular and metabolic parameters, recorded every 4 or 12 weeks, depending on clinical practice (see poster SAT-670 for details)
  - Occurrence of TEAEs
- Safety data are reported for all patients
- There was no formal statistical hypothesis testing; all analyses are descriptive

RESULTS

Patient population

- **103 patients were enrolled** (**safety population**); **77 patients** were included in the **ITT population** and **52 patients** in the **mITT population**
- Overall, 60 patients discontinued osilodrostat treatment, most commonly because of death (n=30) and planned surgery for Cushing's syndrome (n=15; scan QR code for data)
  - The most common reason for discontinuation was death in patients with **EAS** (n=25/53) and planned surgery related to Cushing's syndrome in patients with **adrenal tumors** and **adrenal hyperplasia** (n=8/36 and n=4/14, respectively; scan QR code for data)

Baseline characteristics by etiology of CS

	Safety population (N=103)	EAS (n=53)	Adrenal tumors* (n=36)	Adrenal hyperplasia (n=14)
Age, mean (SD), years	59.3 (15.5)	61.5 (12.9)	56.0 (18.9)	59.3 (14.6)
Sex, n (%)				
Male	40 (38.8)	25 (47.2)	9 (25.0)	6 (42.9)
Female	63 (61.2)	28 (52.8)	27 (75.0)	8 (57.1)
Weight, mean (SD), kg	76.6 (22.3)	74.4 (21.3)	77.6 (24.2)	80.7 (21.3)
BMI, mean (SD), kg/m²	27.8 (6.9)	26.7 (6.5)	28.3 (7.7)	29.9 (6.1)
mUFC, mean (SD), µg/24 h; x ULN	1518.6 (3679.8); (21.8 [47.8] x ULN)	2534.6 (4881.4); (NA)	498.0 (535.3); (NA)	83.4 (118.1); (NA)

*Adrenocortical carcinoma, n=19; adrenal adenoma, n=17

- Scan the QR code for baseline characteristics and data showing the type of intervention and method of osilodrostat use by treatment population

Osilodrostat dose and exposure in all enrolled patients

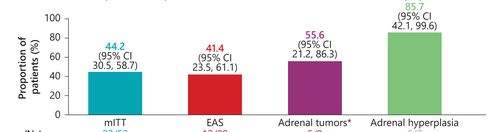
	Safety population (N=103)	EAS (n=53)	Adrenal tumors (n=36)	Adrenal hyperplasia (n=14)
Osilodrostat exposure, median (min–max), days*	164 (1–1178)	245 (10–846)	74 (1–873)	194 (28–1178)
Osilodrostat dose, median (min–max), mg/day				
Baseline	5.0 (1–60)	7.0 (1–60)	4.0 (1–60)	4.0 (1–10)
Week 12	6.0 (1–120)	10.0 (0–60)	4.0 (0–60)	1.5 (0–12)
Week 36	10.0 (1–120)	15.5 (0–50)	8.0 (2–120)	4.0 (1–12)

*Based on patients with available end-of-treatment dates

- The median (min–max) duration of osilodrostat exposure in the **ITT population** and **mITT population** was 280 (33–1178) and 285 (53–1178) days, respectively
- In the **safety population**, 73.8% of patients had at least one dose change during the study; 53.4% had a dose increase, 36.9% had a dose decrease

1. The primary endpoint was met; overall, 23/52 patients in the mITT population had mUFC ≤ULN at week 12: EAS, n=12/29; adrenal tumors, n=5/9; adrenal hyperplasia, n=6/7

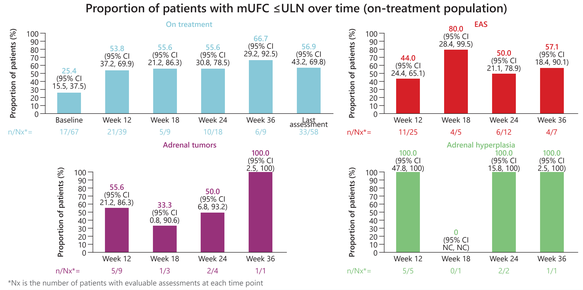
Proportion of patients with mUFC ≤ULN at week 12 (mITT population)



*Adrenocortical carcinoma, n=6; adrenal adenoma, n=5; †Nx is the number of patients with evaluable assessments

- Overall, 53.8% (n=21/39) of patients in the **on-treatment population** had mUFC ≤ULN at week 12; the proportion of patients with mUFC ≤ULN increased over time
  - Patients with **adrenal tumors** and **adrenal hyperplasia** had higher rates of mUFC normalization than patients with **EAS**

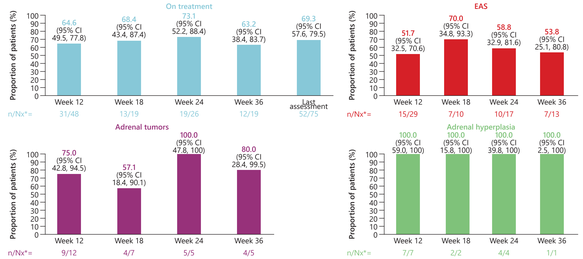
Proportion of patients with mUFC ≤ULN over time (on-treatment population)



*Nx is the number of patients with evaluable assessments at each time point

2. At week 12, 64.6% of patients in the on-treatment population had any cortisol parameter ≤ULN; the proportion of patients with any cortisol parameter ≤ULN generally increased over time. Patients with adrenal tumors and adrenal hyperplasia had higher rates of normalization of any cortisol parameter than patients with EAS

Proportion of patients with any cortisol parameter ≤ULN over time (on-treatment population)

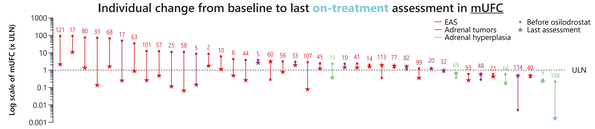


Any cortisol parameter includes mUFC, LNSC and morning serum cortisol. *Nx is the number of patients with evaluable assessments at each time point

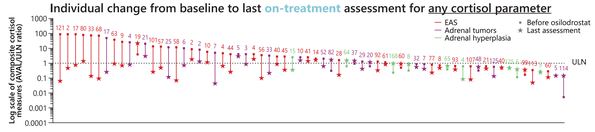
- Overall, median (95% CI) time to mUFC ≤ULN and any cortisol parameter ≤ULN was 2.9 (2.5, 6.2) and 1.4 (1.1, 2.5) months, respectively

3. Most patients had a decrease in mUFC or any cortisol parameter from baseline to last on-treatment assessment

Individual change from baseline to last **on-treatment** assessment in **mUFC**



Individual change from baseline to last **on-treatment** assessment for **any cortisol parameter**

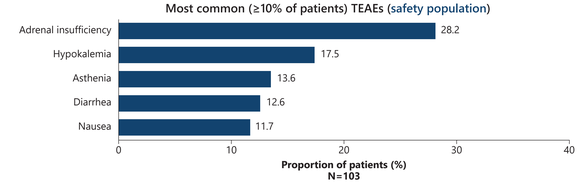


Numbers represent the number of weeks on treatment

- In the **on-treatment population**, mean mUFC decreased rapidly from baseline to week 8; mean mUFC then generally remained stable throughout the study (scan QR code for data)
- Mean mUFC typically decreased from baseline to week 8 in patients with **EAS**, **adrenal tumors**, and **adrenal hyperplasia** and then generally remained stable throughout the study (scan QR code for data)
- In the **on-treatment** population, mean serum cortisol levels decreased rapidly from baseline to week 8; a more gradual decrease was observed throughout the study (scan QR code for data)
- Trends show a general decrease in mean serum cortisol levels from baseline in patients with **EAS**, **adrenal tumors** and **adrenal hyperplasia**; however, data are limited by small patient numbers (scan QR code for data)

4. Overall, the safety profile was consistent with the known safety profile of osilodrostat in patients with Cushing's disease and the known morbidity in the study population

Most common (≥10% of patients) TEAEs (**safety population**)



- Serious TEAEs were reported in 50.5% (n=52/103) of patients, most commonly related to neoplasm progression (13.6%; n=14/103)
- 29 patients died during the study because of a serious TEAE (EAS, n=24; ACC, n=5), most commonly because of neoplasm progression (10.7%; n=11/103)
  - Only one death was suspected to be related to osilodrostat treatment

Management of TEAEs*

Dose adjustment or temporary dose interruption: **21.4%** (n=22/103)

Osilodrostat discontinuation: **34.0%** (n=35/103)

*Data for management of TEAEs with additional therapy not available

- Overall, the most common TEAE leading to osilodrostat discontinuation, as reported by the study investigator, was neoplasm progression (n=11/35)

Overview of AEs by etiology of CS

Patients, n (%)	EAS (n=53)	Adrenal tumors (n=36)	Adrenal hyperplasia (n=14)
Patients with any TEAE	47 (88.7)	28 (77.8)	12 (85.7)
Patients with any serious TEAE	33 (62.3)	12 (33.3)	7 (50.0)
Patients with any TEAE leading to osilodrostat discontinuation	26 (49.1)	6 (16.7)	3 (21.4)
Death	24 (45.3)	5 (13.9)	0

5. Overall, hypocortisolism-related TEAEs were reported in 30.1% (n=31/103) of patients: EAS, 32.1% (n=17); adrenal tumors, 22.2% (n=8); adrenal hyperplasia, 42.9% (n=6)

30.1% of patients experienced a hypocortisolism-related TEAE

Patients, n (%)	Safety population (N=103)	EAS (n=53)	Adrenal tumors (n=36)	Adrenal hyperplasia (n=14)
Adrenal insufficiency	29 (28.2)	16 (30.2)	7 (19.4)	6 (42.9)
Glucocorticoid deficiency	3 (2.9)	1 (1.9)	1 (2.8)	1 (7.1)
Acute adrenocortical insufficiency	1 (1.0)	0	1 (2.8)	0

- Certain TEAEs were expected based on osilodrostat pharmacology; scan the QR code for details of such TEAEs that occurred during the study period

ABBREVIATIONS

ACC, adrenocortical carcinoma; ACTH, adrenocorticotropic hormone; AE, adverse event; ATU, Autorisation Temporaire d'Utilisation; AVAL, analysis value; BMI, body mass index; CI, confidence interval; EAS, ectopic ACTH secretion; ITT, intention to treat; LNSC, late-night salivary cortisol; max, maximum; min, minimum; mITT, modified intention to treat; mUFC, mean urinary free cortisol; NA, not available; NC, not calculable; SD, standard deviation; TEAE, treatment-emergent adverse event; ULN, upper limit of normal

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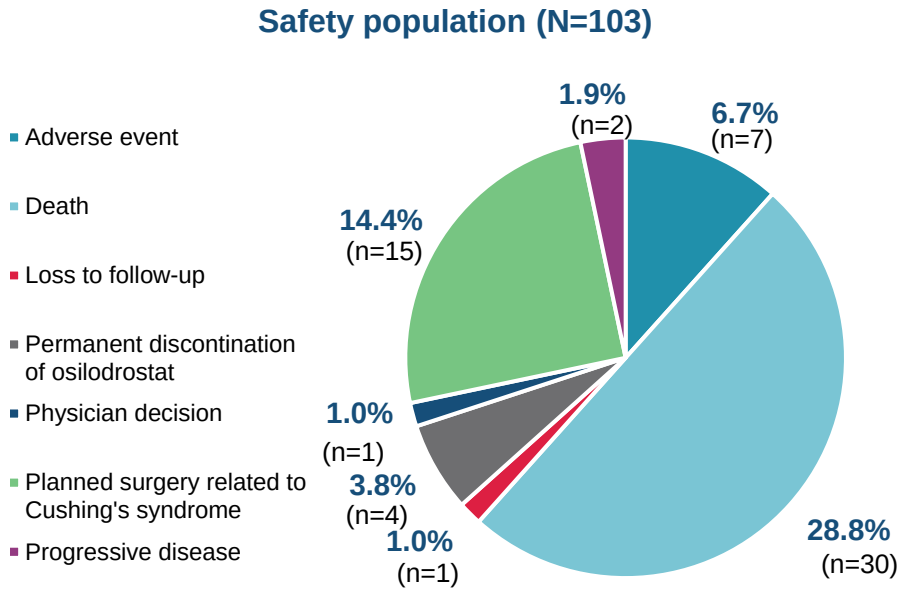
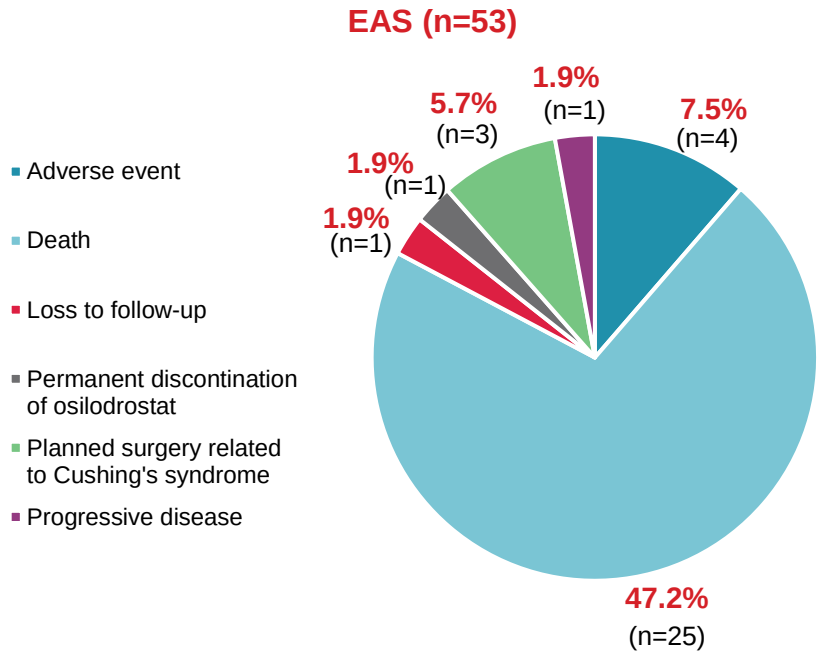
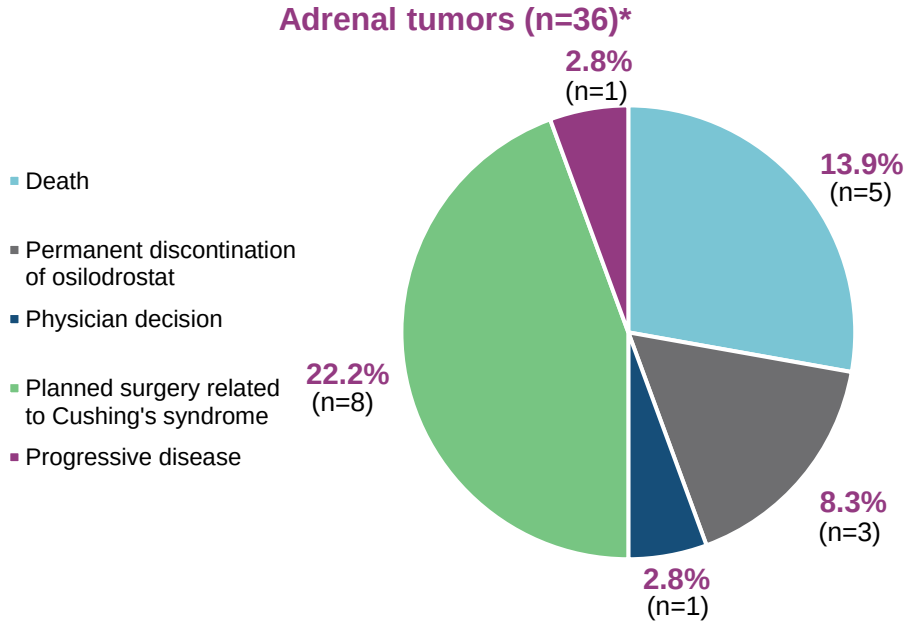
Safety and Effectiveness of Osilodrostat in Patients With Non-pituitary Cushing’s Syndrome: Results From the Retrospective Observational LINC 7 Study

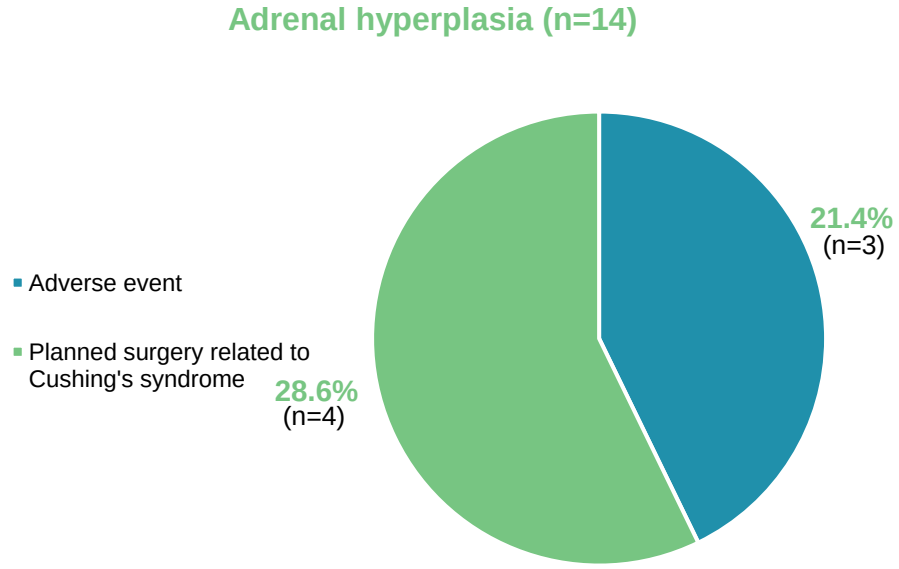
QR code content

Reasons for discontinuation









*Adrenocortical carcinoma, n=19; adrenal adenoma, n=17. EAS, ectopic adrenocorticotropic hormone syndrome

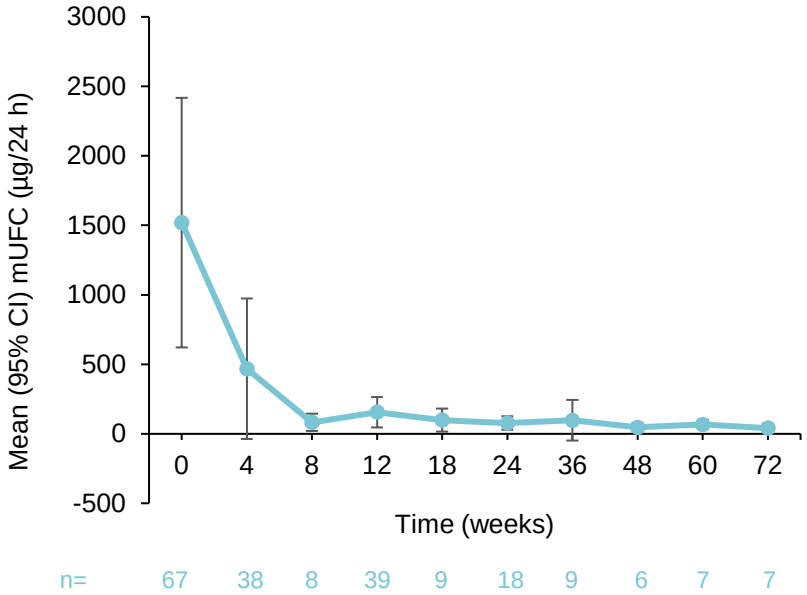
Baseline characteristics by treatment population

	Safety population (N=103)	ITT population (n=77)	mITT population (n=52)
Etiology of Cushing's syndrome, n (%)			
Ectopic ACTH secretion	53 (51.5)	46 (59.7)	32 (61.5)
Macronodular adrenal hyperplasia	14 (13.6)	11 (14.3)	9 (17.3)
Adrenocortical carcinoma	19 (18.4)	10 (13.0)	6 (11.5)
Adrenal adenoma	17 (16.5)	10 (13.0)	5 (9.6)
Age, mean (SD), years	59.3 (15.5)	59.3 (15.1)	57.6 (14.3)
Sex, n (%)			
Male	40 (38.8)	30 (39.0)	22 (42.3)
Female	63 (61.2)	47 (61.0)	30 (57.7)
Weight, mean (SD), kg	76.6 (22.3)	76.2 (23.8)	75.2 (21.3)
BMI, mean (SD), kg/m^2	27.8 (6.9)	27.8 (7.3)	27.2 (6.3)
mUFC, mean (SD), µg/24 h; x ULN	1518.6 (3679.8) (21.8 [47.8] x ULN)	1198.7 (2162.7) (17.5 [30.75] x ULN)	–
Type of intervention			
Treatment naïve	63 (61.2)	46 (44.7)	27 (26.2)
Switch group*	7 (6.8)	6 (5.8)	3 (2.9)
Combination therapy	33 (32.0)	25 (24.3)	22 (21.4)
Method of osilodrostat use			
Block and replace	39 (37.9)	31 (30.1)	22 (21.4)
Initial titration followed by block and replace†	26 (25.2)	21 (20.4)	18 (17.5)
Titration only‡	38 (36.9)	25 (24.3)	12 (11.7)

*Switch group: All patients who were treated with osilodrostat as monotherapy but were taking any medical therapy for Cushing's syndrome and discontinued these prior to the start of osilodrostat; †Initial titration followed by block and replace: Patients who initiated osilodrostat and after at least 2 weeks started taking glucocorticoids as concomitant medication; ‡Titration only: Patients who did not take glucocorticoids as concomitant medications while taking osilodrostat
ACTH, adrenocorticotropic hormone; BMI, body mass index; ITT, intention to treat; mITT, modified intention to treat; mUFC, mean urinary free cortisol; SD, standard deviation; ULN, upper limit of normal

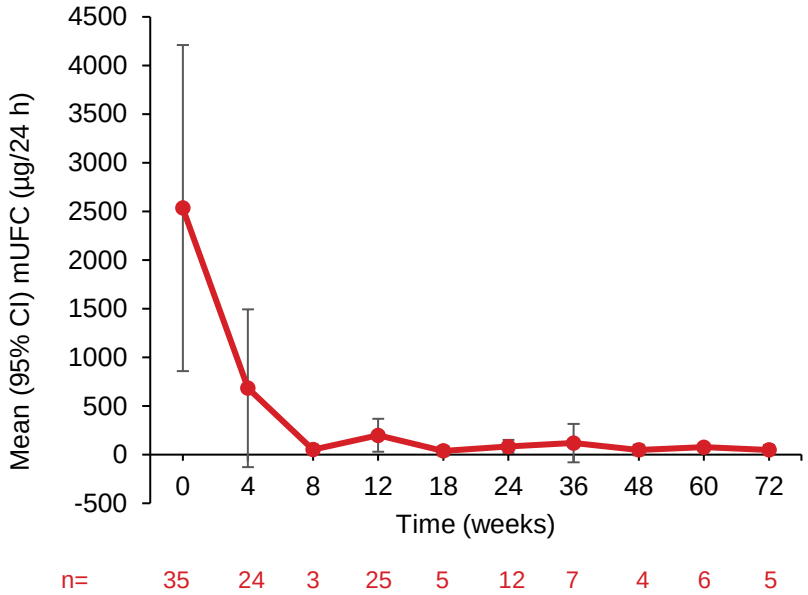
Mean (95% CI) mUFC levels over time

On treatment



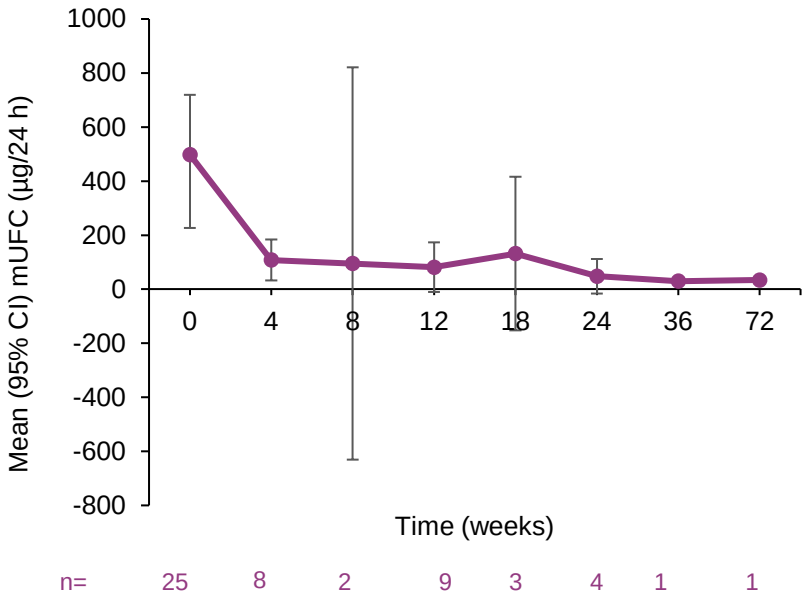
n=	67	38	8	39	9	18	9	6	7	7

EAS



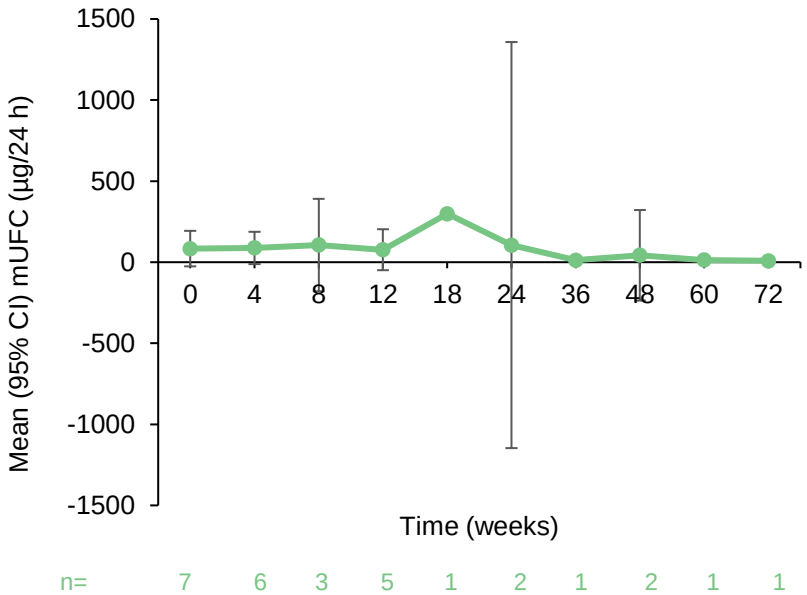
n=	35	24	3	25	5	12	7	4	6	5

Adrenal tumors



n=	25	8	2	9	3	4	1	1

Adrenal hyperplasia

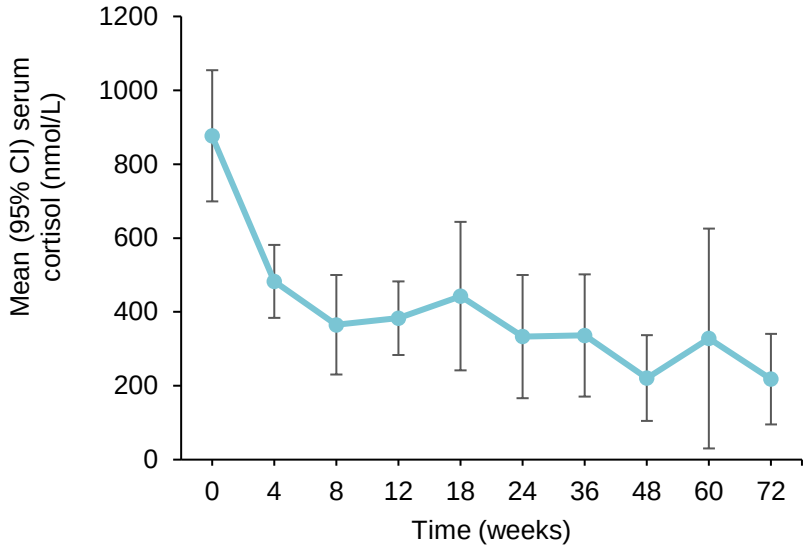


n=	7	6	3	5	1	2	1	2	1	1

CI, confidence interval

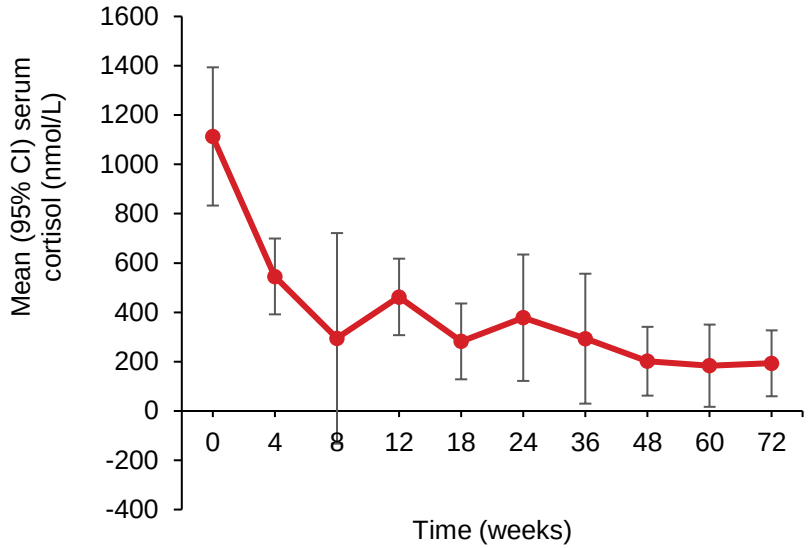
Mean (95% CI) serum cortisol levels over time

On treatment



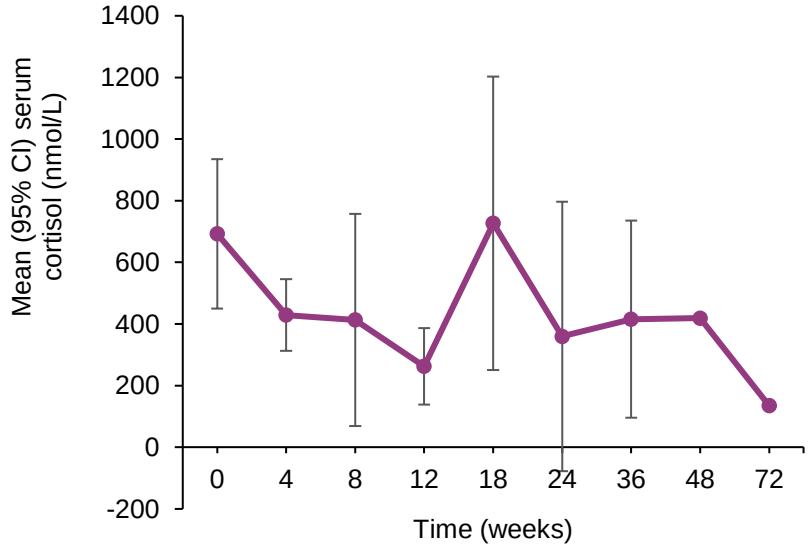
n=	70	52	14	36	16	22	15	10	11	9

EAS



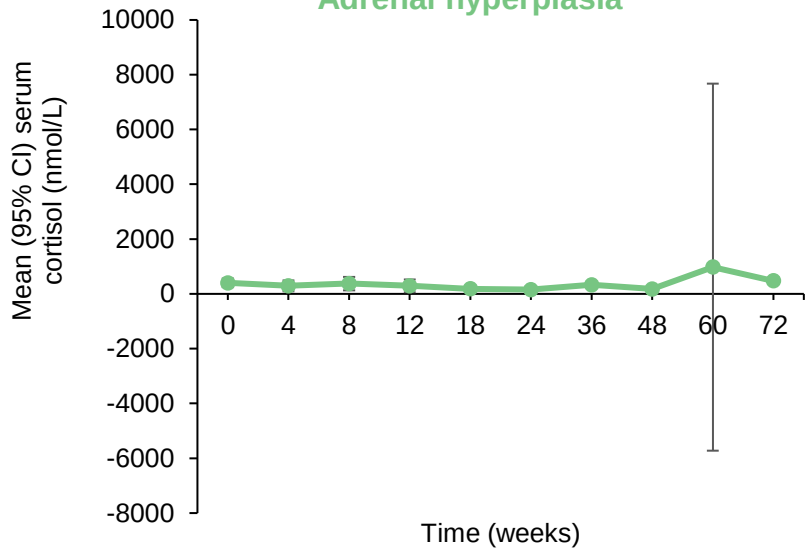
n=	37	31	4	21	9	14	9	8	9	7

Adrenal tumors



n=	24	15	5	10	6	4	5	1	1

Adrenal hyperplasia



n=	9	6	5	5	1	4	1	1	2	1

Expected TEAEs based on osilodrostat pharmacology

	Patients, n (%)			
	Safety population (N=103)	EAS (n=53)	Adrenal tumors (n=36)	Adrenal hyperplasia (n=14)
Patients with any TEAE	50 (48.5)	25 (47.2)	14 (38.9)	11 (78.6)
Hypocortisolism related	31 (30.1)	17 (32.1)	8 (22.2)	6 (42.9)
Adrenal insufficiency	29 (28.2)	16 (30.2)	7 (19.4)	6 (42.9)
Glucocorticoid deficiency	3 (2.9)	1 (1.9)	1 (2.8)	1 (7.1)
Acute adrenocortical insufficiency	1 (1.0)	0	1 (2.8)	0
Metabolism and nutrition disorders	18 (17.5)	9 (17.0)	6 (16.7)	3 (21.4)
Hypokalemia	18 (17.5)	9 (17.0)	6 (16.7)	3 (21.4)
General disorders and administration-site conditions	7 (6.8)	2 (3.8)	2 (5.6)	3 (21.4)
Peripheral edema	6 (5.8)	2 (3.8)	2 (5.6)	2 (14.3)
Edema	1 (1.0)	0	0	1 (7.1)
Vascular disorders	6 (5.8)	3 (5.7)	1 (2.8)	2 (14.3)
Hypertension	6 (5.8)	3 (5.7)	1 (2.8)	2 (14.3)
Investigations	3 (2.9)	1 (1.9)	2 (5.6)	0
Electrocardiogram QT prolonged	2 (1.9)	1 (1.9)	1 (2.8)	0
Increased systolic blood pressure	1 (1.0)	0	1 (2.8)	0
Cardiac disorders	2 (1.9)	1 (1.9)	1 (2.8)	0
Cardiorespiratory arrest	2 (1.9)	1 (1.9)	1 (2.8)	0
Nervous system disorders	2 (1.9)	1 (1.9)	1 (2.8)	0
Loss of consciousness	2 (1.9)	1 (1.9)	1 (2.8)	0

TEAE, treatment-emergent adverse event