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Original Research

Osilodrostat dose impact on efficacy/safety in Cushing's disease: large, pooled analysis of LINC 2, 3, and 4

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Abstract

Objectives: Evaluate how osilodrostat dose and baseline mean urinary free cortisol (mUFC) affect treatment outcomes and provide evidence-based guidance on personalized medical treatment for patients with Cushing's disease.

Methods/design: Individual-patient data from the Phase II LINC 2 and Phase III LINC 3 and LINC 4 core and extension periods were pooled, excluding periods when patients received placebo (LINC 3 and LINC 4). Outcomes were evaluated in patients with available data across common time points.

Results: Two hundred and twenty-nine patients were treated: starting osilodrostat dose 2 mg twice daily, median average dose per patient 6.8 mg/day for a mean of 113.7 weeks (standard deviation 73.1). mUFC control (not exceeding the upper limit of normal) was achieved within 4-12 weeks in most patients and sustained throughout. Median time to first mUFC control was 35 days, longer with increasing baseline mUFC. Most common dose for first mUFC control was 4 mg/day (33.2% of patients; median dose 10 mg/day [range 2-60]). Adverse events (AEs) generally occurred more often during dose titration (baseline to week 12) than long-term treatment (week >12), but could occur at any time. AEs were manageable in most patients; $n = 37$ (16.2%) discontinued because of AEs.

Conclusions: In this analysis of the largest and longest prospective interventional studies of an adrenal steroidogenesis inhibitor to date, osilodrostat provided rapid and sustained mUFC control, with dose decreases possible over the long term. AE frequency generally decreased over time, with no relationship with osilodrostat dose. Personalized adjustment of osilodrostat dose is important to optimize outcomes for patients with Cushing's disease.

Clinical trial registration numbers: LINC 2 (NCT01331239); LINC 3 (NCT02180217); and LINC 4 (NCT02697734).

Keywords: hypercortisolism, Cushing's disease, osilodrostat, 11β-hydroxylase, long-term treatment

Significance

These findings, based on the largest Cushing's disease patient population prospectively treated with a steroidogenesis inhibitor to date, provide practical, evidence-based guidance on personalized treatment approaches with osilodrostat that can be applied in clinical practice to optimize the management of patients with Cushing's disease. Besides efficacy and safety findings, we evaluated multiple additional parameters, including the dose required to achieve cortisol normalization and how baseline cortisol levels may affect treatment outcomes. Taken together, the results underscore the need for personalized management of patients with Cushing's disease.

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Introduction

Cushing's disease (CD) is caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma and is the most common etiology of endogenous Cushing's syndrome.[1,2] Prolonged exposure to elevated cortisol levels causes substantial comorbidities, impaired health-related quality of life (QoL), and increased mortality risk; therefore, normalizing cortisol is the primary treatment goal.[2-7]

Selective transsphenoidal resection of the corticotroph adenoma is the recommended first-line treatment for patients with CD; however, up to one-third of patients do not achieve sustained remission, and over one-quarter experience disease recurrence.[8,9] Medical therapy is usually the second-line treatment for persistent or recurrent disease.[1]

Osilodrostat is a potent oral inhibitor primarily of 11β-hydroxylase, the enzyme catalyzing the final step of cortisol synthesis and inhibiting aldosterone synthase.[10] LINC 2, LINC 3, and LINC 4 were clinical trials that assessed the efficacy and safety of osilodrostat in patients with CD.[8,11,12] Osilodrostat provided rapid reductions in 24-h mean urinary free cortisol (mUFC) levels, which were maintained for long periods.[8,11-15] Sustained improvements were also observed in clinical features of hypercortisolism and patient QoL.[8,11,13-15]

Overall, osilodrostat was well tolerated.[8,11-15] The most common adverse events (AEs) were related to hypocortisolism and accumulation of adrenal hormone precursors, generally mild to moderate in severity, and manageable without permanent treatment discontinuation in most patients.[8,11-15] Lifelong management of CD requires individualized treatment to maintain biochemical control and minimize AE risk.[1] This manuscript reports findings from a large, pooled analysis of LINC 2, LINC 3, and LINC 4, providing evidence-based guidance on personalized treatment approaches to optimize the management of patients with CD.

Materials and methods

Patients

Eligibility criteria were similar across parent studies, although LINC 2 (NCT01331239) and LINC 3 (NCT02180217) enrolled patients with mUFC > 1.5 × upper limit of normal (ULN; 138 nmol/24 h [50 µg/24 h]) and LINC 4 (NCT02697734) enrolled patients with mUFC > 1.3 × ULN.[8,11,12]

Patients who achieved clinical benefit (study investigator assessed) with osilodrostat at the end of each core phase could enter the optional extension phase of their study.[13-15] Studies were conducted in accordance with the Declaration of Helsinki, with an independent ethics committee or institutional review board at each site approving the study protocol; patients provided written informed consent, including additional consent for the extension.

Study design

Study details were published previously.[8,11-15] Notable differences in study design, besides the minimum degree of mUFC elevation in eligible patients, were the inclusion of randomized, double-blind, placebo-controlled periods in LINC 3 and LINC 4 and speed of dose escalation (Figure 1). Information on dosing and titration is provided in Figure 1 and the supplementary material.

Assessments and analyses

Data from common time points were analyzed based on patients with available data; for parameters with insufficient data, common time points between at least 2 studies were analyzed.

Efficacy analyses included proportion of patients with mUFC control (≤ULN), time to first mUFC control, osilodrostat dose required for mUFC control, and time to loss of mUFC control (defined as time [weeks] from first measurement of mUFC control to first mUFC > 1.3 × ULN on 2 consecutive visits after achieving control at the highest tolerated osilodrostat dose, unrelated to dose interruption or reduction for safety reasons) in all patients and according to baseline mUFC level. Reasons for loss of mUFC control were not evaluated.

Safety was assessed by overall incidence, incidence by time interval, and management of AEs, in all patients and according to the baseline mUFC level. Additional analyses included mean mUFC level and mean osilodrostat dose at the time of the most common (≥20% of all patients) AEs and hypocortisolism-related AEs, as well as the impact of the total number of osilodrostat dose up-titrations on the occurrence of these AEs. Change in tumor volume over time was assessed in all patients with available data and according to baseline tumor size. Pituitary magnetic resonance imaging was performed locally according to standardized image-acquisition guidelines, and the images were assessed centrally. Measurement of pituitary tumor volume was performed by independent neuroradiologists.

Statistical methods

Individual-patient data from LINC 2 ($n = 19/19$), LINC 3 ($n = 137/137$) and LINC 4 ($n = 73/73$) were pooled and analyzed; periods during which patients received placebo in LINC 3 and LINC 4 (8 and 12 weeks, respectively) were excluded.

Categorical data are presented by frequencies and percentages, and continuous data are summarized by mean and standard deviation (SD) or median and minimum–maximum, unless otherwise specified.

Cox proportional-hazards models were used to analyze predictors of first mUFC control (mUFC ≤ ULN) and determinant factors for first hypocortisolism-related AE.

Correlations between total daily osilodrostat dose and mUFC, serum cortisol, late-night salivary cortisol (LNSC), and ACTH levels over time were performed, and between ACTH levels and tumor volume over time, for which extreme outliers were excluded (defined as observations >Q3 + 3 × IQR or <Q1 − 3 × IQR; IQR, interquartile range; Q, quartile).

See the supplementary material for additional information on assessments, analyses, and statistical methods.

Results

Study population

The pooled analysis included 229 patients. Baseline characteristics were consistent with the parent studies (Table 1).[8,11,13] Most patients had microadenomas (76.4%), undergone pituitary surgery (87.8%), and received prior medical therapy for CD (83.8%).

Osilodrostat dose and exposure

Mean (SD) osilodrostat exposure overall was 113.7 weeks (73.1), consistent across baseline mUFC groups (<2×ULN,

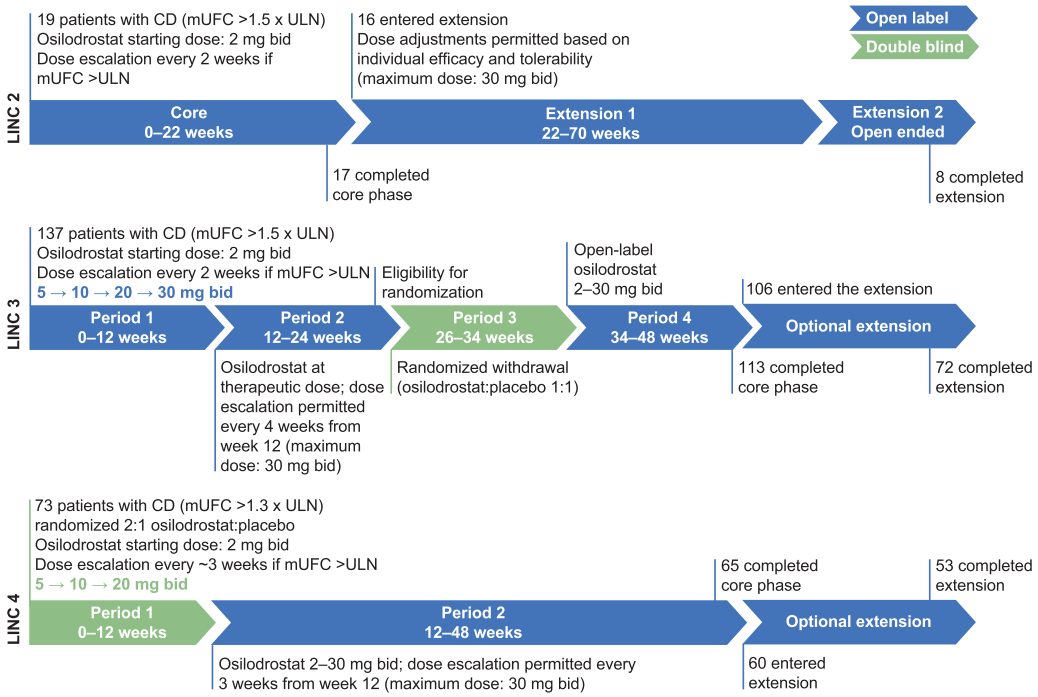

Figure 1. Study design and dosing schedule of LINC 2, LINC 3, and LINC 4. bid, twice daily.

$n = 60$, 115.3 weeks [67.7]; 2-5×ULN, $n = 111$, 111.5 weeks [74.1]; >5×ULN, $n = 58$, 116.1 weeks [77.5]).

Median (minimum–maximum) average daily dose per patient overall was 6.8 mg/day (1.0-47.0) and increased with baseline mUFC level (baseline mUFC < 2×ULN, 4.9 mg/day [1.0-22.0]; 2-5×ULN, 7.7 mg/day [1.0-47.0]; >5×ULN, 7.2 mg/day [1.0-46.0]).

Median (minimum–maximum) osilodrostat dose received for the longest duration was 6.0 mg/day (0.0-60.0) overall (baseline mUFC < 2×ULN, 4.0 mg/day [1.0-40.0]; 2-5×ULN, 8.0 mg/day [1.0-60.0]; >5×ULN, 5.5 mg/day [0.0-60.0]).

The most common osilodrostat doses over time are summarized in the supplementary material.

Most patients had at least 1 dose increase (Figure 2A) or decrease (Figure 2B) at any time point and at least 1 dose increase from baseline to week 12, regardless of baseline mUFC level. The most common reasons for osilodrostat dose increases were "as per protocol" (62.3%, $n = 591/949$) and "re-escalation" (12.3%, $n = 117/949$). For dose decreases, these were "adverse event" (39.6%, $n = 343/866$), "as per protocol" (24.1%, $n = 209/866$), and "dosing error" (21.0%, $n = 182/866$).

Most patients (78.9%, $n = 161/204$) achieved their individual maximum osilodrostat dose during the first 12 weeks, with the dose decreased in many patients thereafter (supplementary material).

In this study, 33.2% of patients achieved first mUFC control with a dose of 4 mg/day (50.0% of patients with baseline mUFC < 2×ULN, 30.6% with 2-5×ULN, and 20.7% with >5×ULN), 31.9% with 10 mg/day (25.0% with baseline mUFC < 2×ULN, 36.9% with 2-5×ULN, and 29.3% with >5×ULN), and 17.0% with 20 mg/day (13.3% with baseline mUFC < 2×ULN, 17.1% with 2-5×ULN, and 20.7% with >5×ULN). Median (minimum–maximum) osilodrostat dose leading to first mUFC control was 10 mg/day (2-60) overall (baseline mUFC < 2×ULN, 4 mg/day [2-40]; 2-5 and >5×ULN, both 10 mg/day [2-60]).

mUFC control

Mean mUFC control (≤ULN) was achieved at week 4 for patients with baseline mUFC < 2×ULN (baseline, 1.4×ULN; week 4, 1.0×ULN), at week 6 for baseline mUFC 2-5×ULN (baseline, 3.1×ULN; week 6, 0.9×ULN), and at week 12 for baseline mUFC > 5×ULN (baseline, 17.0×ULN; week 12, 0.9×ULN; Figure 3A). Mean mUFC levels were generally maintained to week 108 in all groups, regardless of the baseline mUFC level. The majority of patients achieved mUFC control by week 8 of osilodrostat treatment (week 2, 20.7% of all patients; week 8, 70.6%), which was maintained to week 108 (62.8%; Figure 3B). Median (95% confidence interval [CI]) time to first mUFC control was 35.0 days (34.0-41.0) overall and increased with the baseline mUFC level (<2×ULN, 28.0 days [17.0-34.0]; 2-5×ULN, 40.0 days [34.0-42.0]; >5×ULN, 52.0 days [41.0-56.0]). Patients aged <65 years and those with no prior medical therapy for CD were more likely to achieve mUFC control more quickly than older patients and those with prior medical therapy (supplementary material). Few patients experienced loss of mUFC control (baseline mUFC < 2×ULN, 3.3% [$n = 2/60$]; 2-5×ULN, 2.7% [$n = 3/111$]; >5×ULN, 5.2% [$n = 3/58$]).

Serum cortisol and LNSC

Mean (SD) serum cortisol levels decreased from baseline to week 12 and remained stable to week 108 of osilodrostat treatment (Figure S1). In the baseline mUFC 2-5 and >5×ULN groups, mean (SD) serum cortisol levels decreased from 1.1×ULN (0.4) and 1.3×ULN (0.5), respectively, to within the normal range by week 2 of osilodrostat treatment (0.9×ULN [0.3] and 1.0×ULN [0.4], respectively). Mean (SD) LNSC also decreased from baseline to week 12 and

Table 1. Baseline characteristics of the pooled patient population.

Demographic variable	All patients $n = 229$
Age, years	
Mean (SD)	40.8 (12.8)
Median (mininum–maximum)	39.0 (19-70)
Sex, *n* (%)	
Female	181 (79.0)
Male	48 (21.0)
Race, *n* (%)	
White	153 (66.8)
Asian	57 (24.9)
Black	9 (3.9)
Native American	1 (0.4)
Other	6 (2.6)
Unknown	3 (1.3)
Previous pituitary surgery, *n* (%)	
Yes	201 (87.8)
No	28 (12.2)
Previous medical therapy for CD, *n* (%)	
Yes	192 (83.8)
No	37 (16.2)
Time from diagnosis to first osilodrostat dose, months	
Mean (SD)	67.5 (55.9)
Median (minimum–maximum)	57.6 (2-287)
Baseline mUFC	
Mean (SD), nmol/24 h	853.2 (1496.2)
Mean (SD), µg/24 h	309.1 (542.1)
Mean (SD), ×ULN[a]	6.2 (10.8)
Median (minimum–maximum), nmol/24 h	400.2 (21-10 647)
Median (minimum–maximum), ×ULN[a]	2.9 (0.2-77.2)
<2×ULN, *n* (%)	60 (26.2)
2-5×ULN, *n* (%)	111 (48.5)
>5×ULN, *n* (%)	58 (25.3)
Adenoma classification, *n* (%)	
Microadenoma	175 (76.4)
Macroadenoma	50 (21.8)
Unknown	4 (1.7)

[a]ULN = 138 nmol/24 h (50µg/24 h).

remained generally stable, although above the normal range, to week 108, regardless of baseline mUFC (Figure S2). From baseline to week 12, the proportion of patients with LNSC ≤ ULN increased: from 6.7% to 15.7% of patients with baseline mUFC < 2×ULN, from 3.4% to 23.5% of patients with baseline mUFC 2-5×ULN, and from 0.6% to 10.4% of patients with baseline mUFC > 5×ULN. The proportion of patients with LNSC within the normal range remained relatively stable in all groups thereafter.

There was no correlation between total daily osilodrostat dose and mUFC, serum cortisol, or LNSC levels over time (supplementary material).

AEs regardless of osilodrostat relationship

The most common AEs (≥20% of all patients and by baseline mUFC level) are summarized in Table S1; the 3 most frequent overall were nausea (43.2%), headache (36.7%), and fatigue (34.9%). They occurred mostly during the first 48 weeks, with decreasing incidence over time (Figure 4A) and no clear trend between the time of occurrence and the baseline mUFC level. At the time of the event, mean mUFC ranged from 0.8 to 1.9×ULN, and mean osilodrostat dose ranged from 7.2 to 12.3 mg/day (Figure 4B). The number of osilodrostat dose increases was unrelated to the occurrence of these AEs (Figure S3).

Grade 3/4 AEs occurred in 59.4% of all patients; hypertension was the only event to be reported in ≥10% of all patients (12.7%). Serious AEs (SAEs) occurred in 31.0% of all patients; adrenal insufficiency (AI) was the only SAE to occur in ≥5% of all patients (5.7%; Table S1).

Management of AEs

Temporary osilodrostat interruption for AEs was most commonly (≥12.5% of all patients) reported for AI (26.2%), nausea (15.3%), and fatigue (12.7%; Table S1). Median duration of dose interruption to manage the most common AEs (≥20% of all patients) ranged from 3.5 days (headache) to 12.5 days (AI; Figure S4); there was no trend between baseline mUFC level and mean osilodrostat dose at the time of temporary interruption for these AEs (Figure 4C).

Additional therapy was most commonly (≥15% of all patients) required to manage headache (23.1%), AI (17.5%), and urinary tract infection (16.2%; Table S1). Most commonly (≥15% of all patients) used concomitant medications (where recorded) were paracetamol (39.7%, *n* = 85/214), hydrocortisone (18.7%, *n* = 40/214), and ibuprofen (17.8%, *n* = 38/214).

The most common investigator-reported AEs (≥2.5% of all patients) leading to permanent osilodrostat discontinuation were AI (3.5%), benign pituitary tumor (3.1%), and pituitary tumor (2.6%; Table S1).

Data on management of AEs by baseline mUFC level are included in Table S1.

Hypocortisolism-related AEs

Overview

Hypocortisolism-related AEs (reported by study investigators based on clinical judgment and grouped in accordance with the study protocol to avoid under-reporting) were reported in 46.3% of all patients (Table 2), mostly during the first 12 weeks of treatment (Figure 5A).

Grade 3/4 AEs were reported in 8.7% of all patients (Table 2), and SAEs occurred in 8.3%, most commonly (≥5% of all patients) AI (5.7%).

In all patients for whom AI was reported as an AE, the median (minimum–maximum) duration of AI was 19 days (1-1677) (baseline mUFC < 2×ULN, 14 days [1-256]; 2-5×ULN, 19 days [5-555]; >5×ULN, 30 days [2-1677]). In patients of Asian origin, the median duration of AI was 39 days (2-1677) and in patients of non-Asian origin, 15 days (1-555).

Management

Most patients (41.0%) were managed with temporary osilodrostat dose interruption (baseline mUFC < 2×ULN, 38.3%; 2-5×ULN, 34.2%; >5×ULN, 56.9%; Table 2). Median (minimum–maximum) duration of osilodrostat dose interruption was 9.0 days (1.0-234.0) for patients with baseline mUFC < 2×ULN (*n* = 25), 15.5 days (1.0-43.0) for 2-5×ULN (*n* = 26), and 18.0 days (1.0-470.0) for >5×ULN (*n* = 33).

Osilodrostat dose was adjusted in 2.6% and permanently discontinued in 3.5% of all patients. In all cases, discontinuation was because of AI (Table 2).

Additional therapy was required in 21.4% of all patients (Table 2); glucocorticoids were prescribed in all patients (*n* = 48/48).

AEs of AI resolved within 1 week in 25.0% of all patients, within 2 weeks in 50.0%, within 4 weeks in 69.1%, and

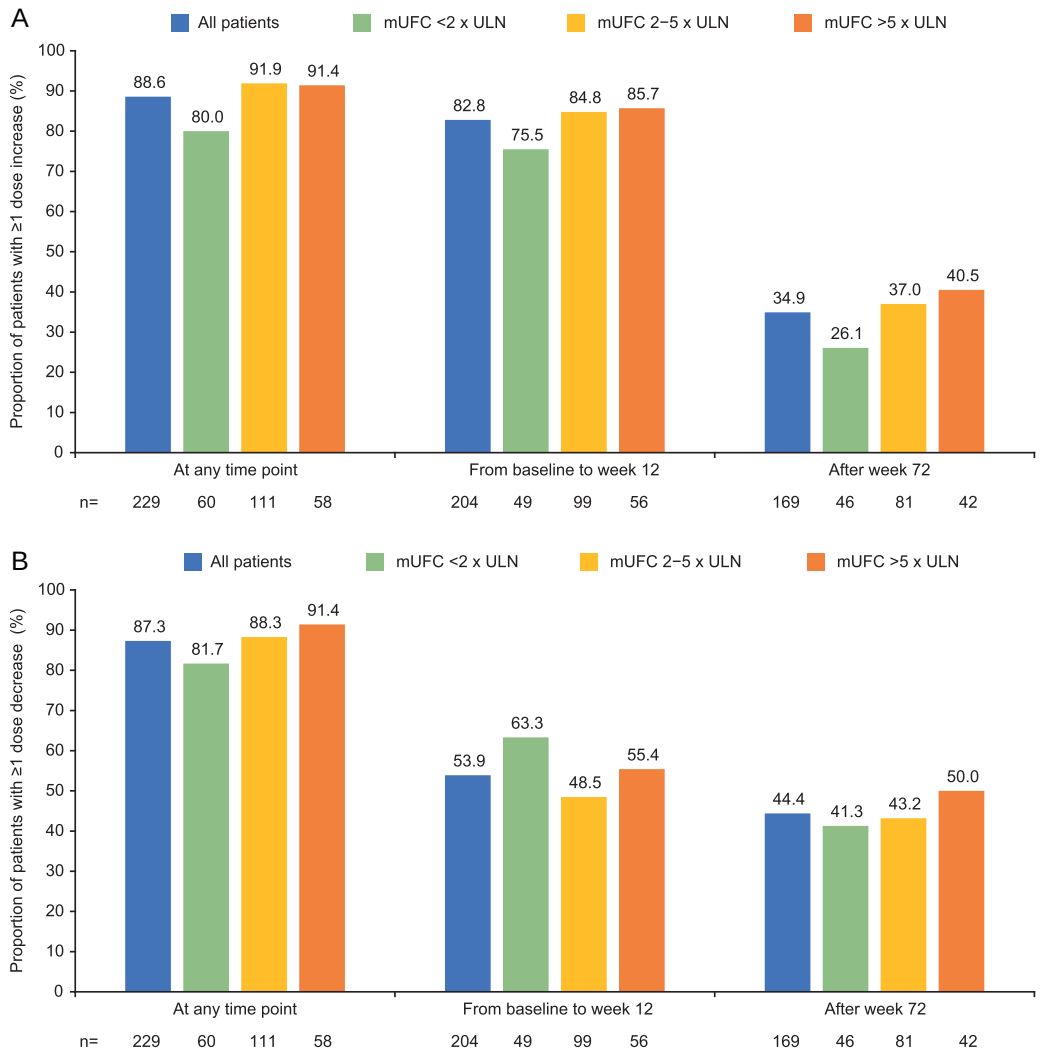

Figure 2. Proportion of patients with ≥1 (A) dose increase or (B) dose decrease over time and by baseline mUFC level.

within 8 weeks in 79.4%. In 5.9% of patients, AI had not resolved by the end of the study.

Factors that may affect hypocortisolism-related AEs

Patients with less severe hypercortisolism at baseline (mUFC < 2 or 2-5×ULN) and no prior medical therapy had a significantly lower risk of experiencing a (first) hypocortisolism-related AE than those with baseline mUFC > 5×ULN (<2×ULN, hazard ratio [HR] 0.6, 95% CI 0.4-1.0; 2-5×ULN, HR 0.5, 95% CI 0.3-0.8; $P = .0056$) and prior medical therapy (no prior medical therapy, HR 0.5, 95% CI 0.3-1.0; $P = .0569$), respectively.

Concomitant medications prescribed 7 days before to 3 days after 90 hypocortisolism-related AEs were recorded. At least 1 anti-infectious medication was prescribed during this time for 21 events (23.3%; AI, $n = 15/56$; glucocorticoid deficiency, $n = 3/21$; acute adrenocortical insufficiency, $n = 3/7$; decreased UFC, $n = 0/3$; decreased cortisol, $n = 0/2$; steroid-withdrawal syndrome, $n = 0/1$). Of these, antibiotics were prescribed in 33.3% ($n = 30/90$), antifungals in 3.3% ($n = 3/90$), and antivirals in 2.2% ($n = 2/90$).

At the time of the event, the mean mUFC level ranged from 0.2 to 1.3×ULN, and the mean osilodrostat dose ranged from 7.0 to 13.0 mg/day (Figure 5B). For AI, mean mUFC was 0.8×ULN (range 0.01-19), and mean dose was 7.0 mg/day. Serum cortisol at the time was not assessed in all patients.

The most common osilodrostat doses (≥15% of patients) at the time of the first event were 10 mg/day (17.9%, $n = 19/106$) and 4 or 20 mg/day (both 15.1%, $n = 16/106$).

In general, the more the osilodrostat dose was increased, the more AI events were reported (Figure 6).

In patients with hypocortisolism-related AEs, mean mUFC and LNSC decreased during the first 8-12 weeks, then stabilized (Figure S5). Mean 11-deoxycorticosterone increased from baseline to week 8, then stabilized. Neutrophil count, sodium levels, and potassium levels remained within normal limits (Figure S5).

Accumulation of adrenal hormone precursors and arrhythmogenic potential/QT prolongation AEs

AEs related to the accumulation of adrenal hormone precursors and arrhythmogenic potential/QT prolongation led to osilodrostat discontinuation in 3 and 1 patient, respectively. Further data are included in the supplementary material (including testosterone levels over time; Figure S6).

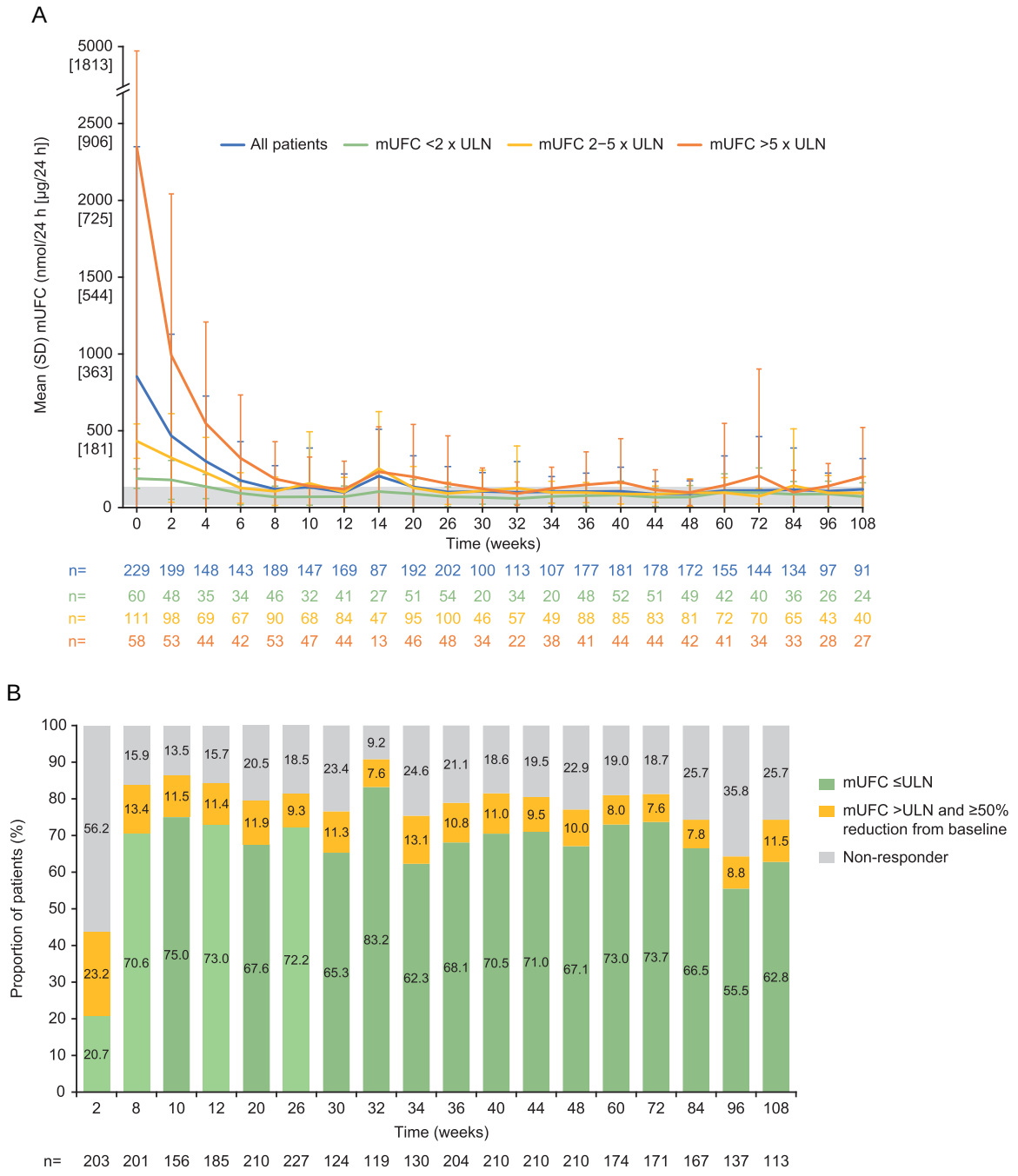

Figure 3. (A) Mean (SD) mUFC levels over time and by baseline mUFC level and (B) proportion of patients with mUFC ≤ ULN, with mUFC > ULN and ≥50% reduction from baseline, and who were non-responders over time. As there were few common time points between the 3 clinical trials, data are presented for time points that were common for at least 2 studies. Gray shading indicates the normal range for mUFC (11-138 nmol/24 h [4-50 µg/24 h]).

Pituitary-tumor enlargement AEs

Overview

Pituitary-tumor enlargement AEs were reported in 12.2% of all patients (Table 2), with incidence generally increasing over time (Figure 5A). Grade 3/4 AEs were reported in 5.2% of all patients (Table 2) and SAEs in 5.7%, most commonly (≥2.5% of all patients) pituitary tumor (2.6%).

Management

One patient with a pituitary-tumor enlargement AE (benign tumor; baseline mUFC > 5×ULN) had temporary osilodrostat interruption; data on duration were not available.

Osilodrostat was permanently discontinued in 6.6% of patients, most commonly (≥2.5% of all patients) for benign pituitary tumor (3.1%) and pituitary tumor (2.6%; Table 2).

The most common osilodrostat doses (≥15% of patients) at the time of the first event were 2 and 10 mg/day (both 17.9%, $n = 5/28$).

Tumor volume and plasma ACTH levels

The proportion of patients with ≥20% increase in tumor volume from baseline was 28.6% ($n = 32/112$) at month 5 and 38.3% ($n = 31/81$) at month 16. The proportion with ≥20% decrease in tumor volume from baseline was 27.7% ($n = 31/112$) at

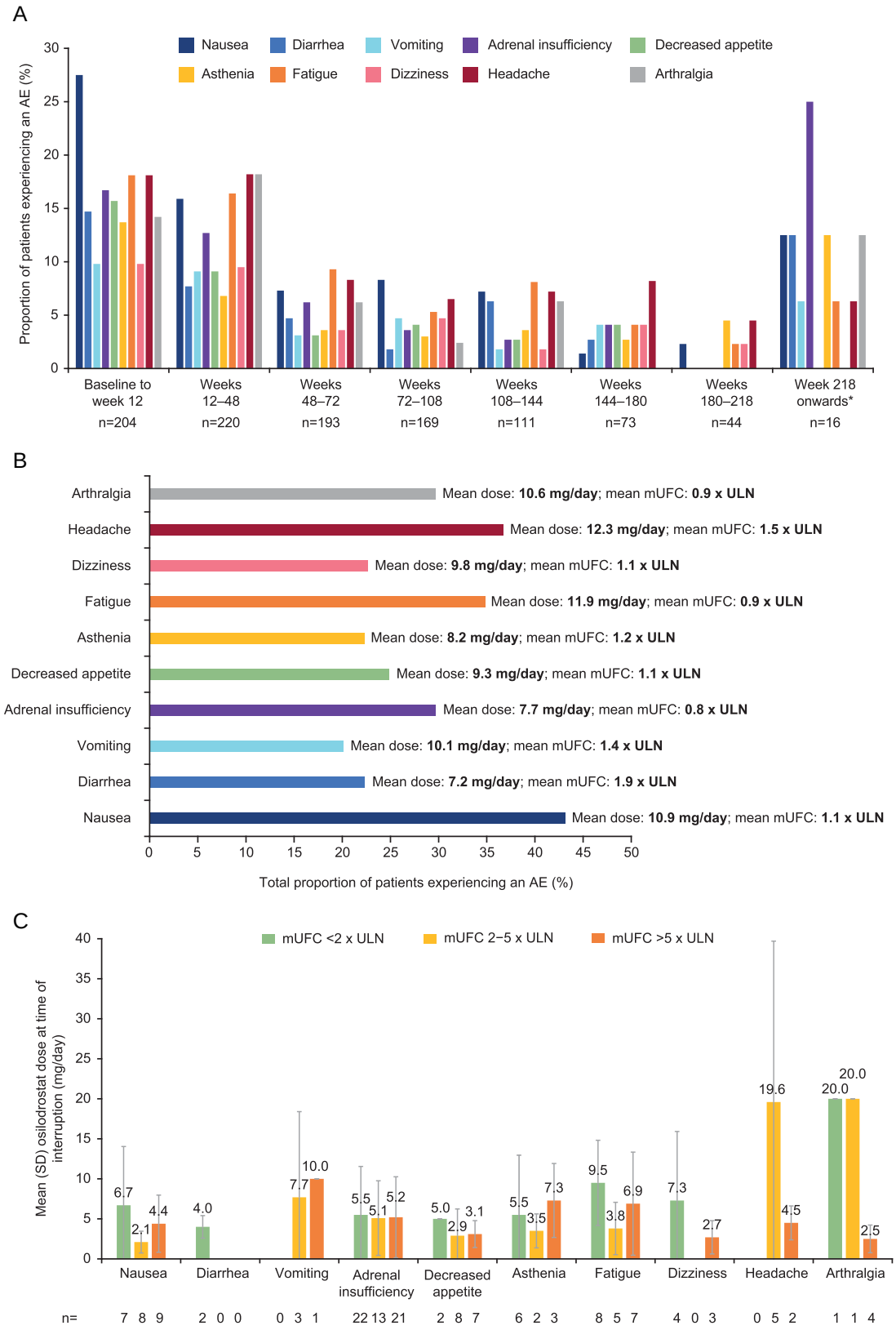

Figure 4. (A) Occurrence of most common AEs (≥20% of all patients), regardless of relationship with osilodrostat, by time interval, (B) mean osilodrostat dose and mUFC levels at time of most common AEs (≥20% of all patients), regardless of relationship with osilodrostat, and (C) mean (SD) osilodrostat dose at time of interruption for the most common AEs (≥20% of all patients), regardless of relationship with osilodrostat. AEs were reported at the discretion of the investigator, with no specific guidance given on definitions. *Maximum duration of osilodrostat treatment of 351 weeks.

month 5 and 29.6% ($n = 24/81$) at month 16, and 32.1% of patients ($n = 26/81$) had stable tumor volume from baseline to month 16. Tumor volume over time is shown in Figure S7.

There was no trend over time towards increasing tumor volume with increasing osilodrostat dose (Figure S8). Mean (SD) ACTH levels increased steadily and remained > ULN in all

Table 2. Overview of AEs related to hypocortisolism, accumulation of adrenal hormone precursors, arrhythmogenic potential and QT prolongation, and pituitary-tumor enlargement in all patients, and by baseline mUFC level.

	All patients ($n = 229$)	Baseline mUFC < 2×ULN ($n = 60$)	Baseline mUFC 2-5×ULN ($n = 111$)	Baseline mUFC > 5×ULN ($n = 58$)
Hypocortisolism-related AEs[a]				
All grades (≥10% in any group)	106 (46.3)	27 (45.0)	42 (37.8)	37 (63.8)
Adrenal insufficiency	68 (29.7)	18 (30.0)	23 (20.7)	27 (46.6)
Glucocorticoid deficiency	29 (12.7)	4 (6.7)	15 (13.5)	10 (17.2)
Decreased UFC	12 (5.2)	7 (11.7)	3 (2.7)	2 (3.4)
Grade 3/4 AEs (≥2.5% in any group)	20 (8.7)	4 (6.7)	8 (7.2)	8 (13.8)
Adrenal insufficiency	11 (4.8)	3 (5.0)	4 (3.6)	4 (6.9)
Glucocorticoid deficiency	5 (2.2)	0 (0.0)	3 (2.7)	2 (3.4)
Acute adrenocortical insufficiency	4 (1.7)	1 (1.7)	1 (0.9)	2 (3.4)
AEs leading to osilodrostat discontinuation (adrenal insufficiency)	8 (3.5)	1 (1.7)	2 (1.8)	5 (8.6)
AEs leading to dose interruption (≥2.5% in any group)	94 (41.0)	23 (38.3)	38 (34.2)	33 (56.9)
Adrenal insufficiency	60 (26.2)	16 (26.7)	20 (18.0)	24 (41.4)
Glucocorticoid deficiency	26 (11.4)	2 (3.3)	15 (13.5)	9 (15.5)
Decreased UFC	10 (4.4)	5 (8.3)	3 (2.7)	2 (3.4)
Acute adrenocortical insufficiency	5 (2.2)	2 (3.3)	1 (0.9)	2 (3.4)
AEs leading to dose adjustment (≥1.5% in any group)	6 (2.6)	1 (1.7)	3 (2.7)	2 (3.4)
Adrenal insufficiency	5 (2.2)	1 (1.7)	2 (1.8)	2 (3.4)
AEs requiring additional therapy (≥5% in any group)[b]	49 (21.4)	14 (23.3)	18 (16.2)	17 (29.3)
Adrenal insufficiency	40 (17.5)	13 (21.7)	13 (11.7)	14 (24.1)
AEs related to the accumulation of adrenal hormone precursors[a]				
All grades (≥10% in any group)	137 (59.8)	33 (55.0)	69 (62.2)	35 (60.3)
Hypertension	44 (19.2)	10 (16.7)	18 (16.2)	16 (27.6)
Increased blood testosterone	34 (14.8)	7 (11.7)	20 (18.0)	7 (12.1)
Peripheral edema	34 (14.8)	6 (10.0)	18 (16.2)	10 (17.2)
Hypokalemia	29 (12.7)	5 (8.3)	17 (15.3)	7 (12.1)
Acne	26 (11.4)	4 (6.7)	17 (15.3)	5 (8.6)
Hirsutism	21 (9.2)	6 (10.0)	8 (7.2)	7 (12.1)
Grade 3/4 AEs (≥2.5% in any group)	40 (17.5)	9 (15.0)	16 (14.4)	15 (25.9)
Hypertension	29 (12.7)	5 (8.3)	11 (9.9)	13 (22.4)
Hypokalemia	8 (3.5)	3 (5.0)	3 (2.7)	2 (3.4)
AEs leading to osilodrostat discontinuation (≥2.5% in any group)	3 (1.3)	2 (3.3)	1 (0.9)	0 (0.0)
Hypokalemia	2 (0.9)	2 (3.3)	0 (0.0)	0 (0.0)
AEs leading to dose interruption (≥2.5% in any group)	19 (8.3)	2 (3.3)	10 (9.0)	7 (12.1)
Edema	6 (2.6)	0 (0.0)	4 (3.6)	2 (3.4)
Hypokalemia	3 (1.3)	1 (1.7)	0 (0.0)	2 (3.4)
AEs leading to dose adjustment	2 (0.9)	0 (0.0)	2 (1.8)	0 (0.0)
Acne	1 (0.4)	0 (0.0)	1 (0.9)	0 (0.0)
Hypertension	1 (0.4)	0 (0.0)	1 (0.9)	0 (0.0)
AEs requiring additional therapy (≥5% in any group)[b]	88 (38.4)	15 (25.0)	47 (42.3)	26 (44.8)
Hypertension	33 (14.4)	6 (10.0)	13 (11.7)	14 (24.1)
Hypokalemia	25 (10.9)	4 (6.7)	16 (14.4)	5 (8.6)
Acne	12 (5.2)	2 (3.3)	9 (8.1)	1 (1.7)
Peripheral edema	9 (3.9)	1 (1.7)	6 (5.4)	2 (3.4)
AEs related to arrhythmogenic potential and QT prolongation[a]				
All grades	11 (4.8)	1 (1.7)	4 (3.6)	6 (10.3)
Grade 3/4 AEs	3 (1.3)	0 (0.0)	1 (0.9)	2 (3.4)
AEs leading to osilodrostat discontinuation	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.7)
AEs leading to dose interruption	7 (3.1)	0 (0.0)	2 (1.8)	5 (8.6)
AEs requiring additional therapy[b]	1 (0.4)	0 (0.0)	1 (0.9)	0 (0.0)
AEs related to pituitary-tumor enlargement[a]				
All grades (≥10% in any group)	28 (12.2)	5 (8.3)	13 (11.7)	10 (17.2)
Benign pituitary tumor	14 (6.1)	1 (1.7)	6 (5.4)	7 (12.1)
Grade 3/4 AEs (≥2.5% in any group)	12 (5.2)	3 (5.0)	5 (4.5)	4 (6.9)
Benign pituitary tumor	5 (2.2)	1 (1.7)	2 (1.8)	2 (3.4)
Pituitary tumor	5 (2.2)	2 (3.3)	2 (1.8)	1 (1.7)
AEs leading to osilodrostat discontinuation (≥2.5% in any group)	15 (6.6)	3 (5.0)	7 (6.3)	5 (8.6)
Benign pituitary tumor	7 (3.1)	0 (0.0)	3 (2.7)	4 (6.9)
Pituitary tumor	6 (2.6)	3 (5.0)	3 (2.7)	0 (0.0)
AEs leading to dose interruption (benign pituitary tumor)	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.7)
AEs requiring additional therapy (≥2.5% in any group)[b]	14 (6.1)	2 (3.3)	9 (8.1)	3 (5.2)
Pituitary tumor	6 (2.6)	1 (1.7)	4 (3.6)	1 (1.7)
Benign pituitary tumor	4 (1.7)	0 (0.0)	2 (1.8)	2 (3.4)

All data are given as n (%). AEs were reported at the discretion of the investigator, with no specific guidance given on definitions.
UFC, urinary free cortisol.
[a]Number of patients with ≥1 event.
[b]Additional therapy includes concomitant medications and non-drug therapies.

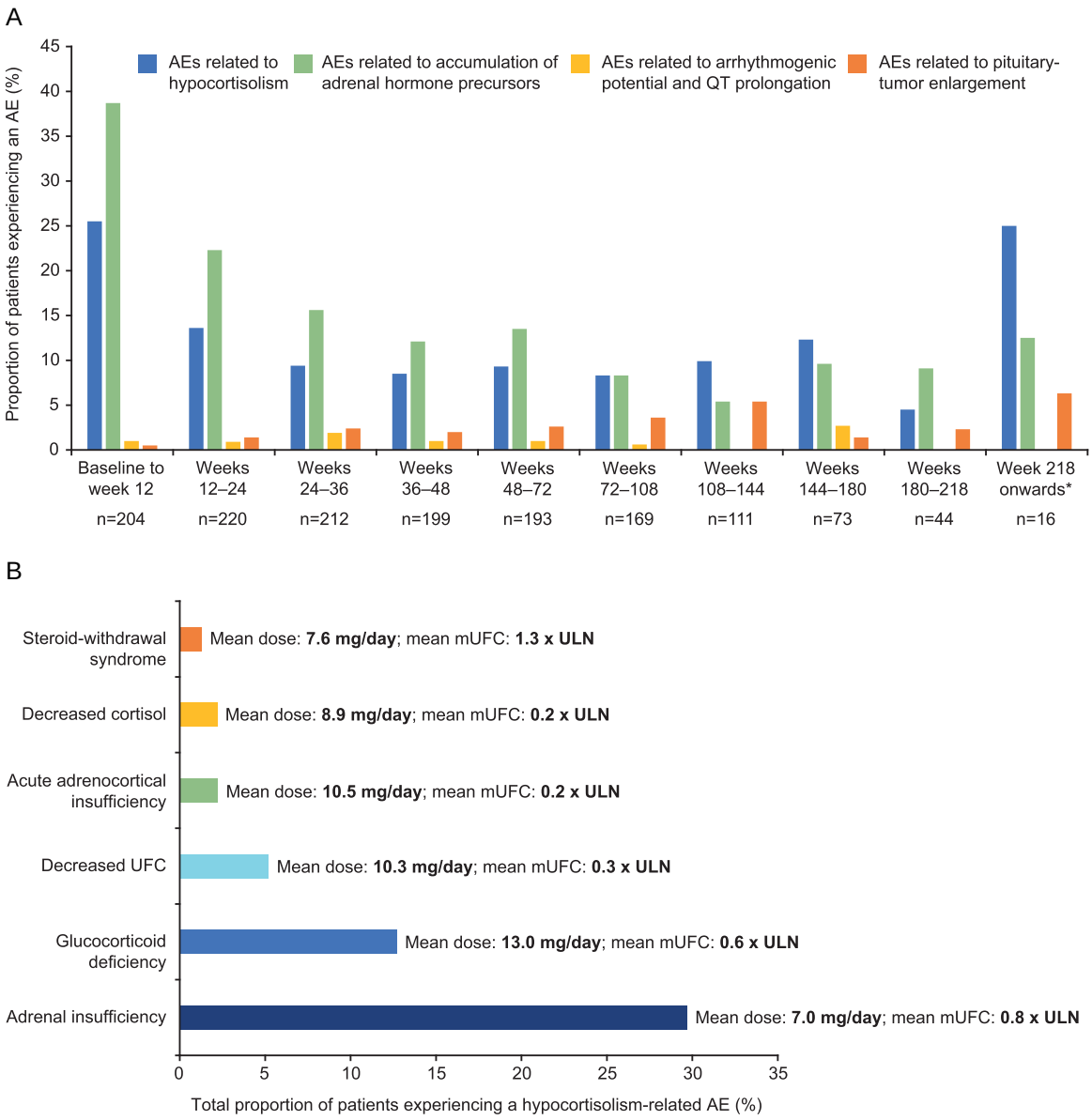

Figure 5. (A) Occurrence of AEs related to hypocortisolism, accumulation of adrenal hormone precursors, arrhythmogenic potential and QT prolongation, and pituitary-tumor enlargement by time interval, and (B) mean osilodrostat dose and mUFC levels at time of hypocortisolism-related AEs. AEs were reported at the discretion of the investigator, with no specific guidance given on definitions. *Maximum duration of osilodrostat treatment of 351 weeks.

patients (Figure S9). There were no trends over time between ACTH level and total daily osilodrostat dose or tumor volume (Table S2).

Osilodrostat was permanently discontinued in 0.4% of patients ($n = 1$), and the dose was interrupted in 2.6%, because of an AE of increased ACTH.

Discussion

Patients with CD require effective and well-tolerated long-term medical treatment options to meet their individual needs when surgery is not successful or the disease recurs.[1] This pooled analysis includes patients from 3 osilodrostat clinical trials, the largest and longest prospective interventional studies of an adrenal steroidogenesis inhibitor to date. As far as we know, it is the first to evaluate several outcomes during steroidogenesis inhibitor treatment, including how baseline cortisol levels and osilodrostat dose changes may affect efficacy and safety outcomes. It provides comprehensive and valuable insights into the effects of short- and long-term osilodrostat dosing on mUFC control and AE risk.

Data on predictors of biochemical response to adrenal steroidogenesis inhibitors are sparse.[1,2,6] The current analysis showed that patients with baseline mUFC < 2×ULN generally achieved mUFC control faster than those with mUFC 2-5 or >5×ULN, requiring a lower median osilodrostat dose to do so; however, the dose needed for first mUFC control varied considerably, with no apparent association between osilodrostat dose and first mUFC control, potentially owing to differences in the sensitivity of the adrenal cortex to osilodrostat, as indicated *in vitro*.[10]

While the median average osilodrostat dose was 6.8 mg/day (slightly higher than the starting dose of 4 mg/day), the median average dose was ~5 mg/day in patients with baseline mUFC < 2×ULN and >7 mg/day for baseline mUFC ≥ 2×ULN.

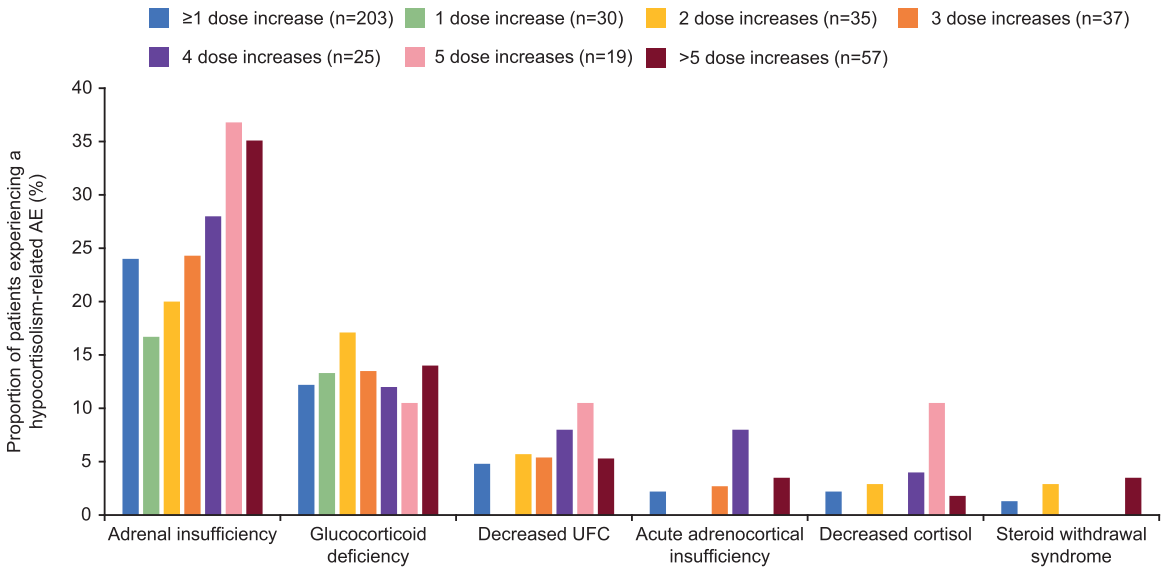

Figure 6. Number of osilodrostat dose increases and occurrence of hypocortisolism-related AEs. AEs were reported at the discretion of the investigator, with no specific guidance given on definitions.

Although most patients had at least 1 dose increase or decrease throughout the studies, the incidence of dose adjustments in patients with baseline mUFC < 2×ULN was generally lower. Based on the study titration protocols, approximately 80% of patients achieved their individual maximum osilodrostat dose during the first 12 weeks of treatment. However, almost 60% of patients required dose down-titration thereafter, most often within the first 12 weeks, suggesting that osilodrostat up-titration at the beginning of treatment may have been too rapid or to a higher dose than needed in some patients.

There was no correlation between total daily osilodrostat dose and mUFC, serum cortisol, or LNSC levels over time. Although the number of patients was limited in some subgroups, patients <65 years old and with no prior medication for hypercortisolism achieved mUFC control faster than older patients and those with prior medical therapy.

Osilodrostat was generally well tolerated for the duration of treatment assessed (mean [SD] exposure 113.7 weeks [73.1]), consistent with previous reports.[8,11-15] Approximately 15% of patients permanently discontinued treatment because of AEs.

Hypocortisolism-related AEs were most frequent during the dose-titration periods (first 12 weeks of treatment). Importantly, hypocortisolism-related AEs were less frequent overall in LINC 4 (27.4%, $n = 20/73$), which had a slower up-titration schedule (every ~3 weeks in the first 12 weeks), than in LINC 3 (51.1%, $n = 70/137$), in which patients were up-titrated more quickly (every 2 weeks in the first 12 weeks).[8,11] This suggests that more gradual osilodrostat dose increases may mitigate hypocortisolism-related AEs without affecting biochemical control, as demonstrated by the similar median times to mUFC control in both studies.[8,11] While an up-titration schedule was mandated in all clinical trials analyzed, dosing and titration should be personalized for each patient in clinical practice, in accordance with country-specific recommendations.[16-18] Notably, patients of Asian ancestry are more sensitive to osilodrostat than non-Asian patients, requiring lower osilodrostat doses and careful titration to avoid hypocortisolism-related side effects such as AI.[18]

Anti-infectious medications were commonly prescribed during AI events, suggesting that concomitant infections could have been a precipitating factor. Thus, patients with intercurrent illnesses should be advised to either decrease the dose or pause osilodrostat treatment for a few days and to administer glucocorticoids to prevent AI.[19]

Hypocortisolism-related AEs were reported with the highest incidence in patients with baseline mUFC > 5×ULN who likely experienced a greater proportional decrease in cortisol levels during osilodrostat treatment. As AEs were reported by the study investigators based on their clinical judgment, with no specific guidance or protocol-mandated requirement for confirmation by measurement of serum cortisol, it is possible that some reported AI cases were symptoms of glucocorticoid-withdrawal syndrome (GWS), particularly as mUFC was within the normal range for some patients at the time of reported events. Differentiating between GWS and AI can be challenging because of overlapping symptoms.[20]

AEs related to the accumulation of adrenal hormone precursors were also common, occurring mostly during the first 12 weeks of osilodrostat treatment, with a general decrease in incidence thereafter and rarely leading to permanent osilodrostat discontinuation. Hypertension was the most frequently experienced precursor-accumulation-related AE (all patients, 19.2%); occurrence may have been affected by the severity of hypercortisolism prior to osilodrostat treatment, as the highest incidence was reported in patients with baseline mUFC > 5×ULN. Additional therapy, such as aldosterone antagonists and/or potassium supplements, was required in some patients; the lowest use was in patients with baseline mUFC < 2×ULN. Mean testosterone levels increased in both female and male patients. In females, greater increases occurred in those with baseline mUFC > 2×ULN, which could be related to higher doses of osilodrostat being received. Importantly, testosterone levels returned to within the normal range over time in all subgroups, consistent with previous studies.[13-15] In males, mean testosterone levels increased to a similar extent regardless of baseline mUFC and remained within the normal range.

Tumor volume remained stable or decreased by ≥20% from baseline to month 16 of osilodrostat treatment in >60% of

patients. The proportion with ≥20% increase in tumor volume rose from 28.6% at month 5 to 38.3% at month 16. AEs related to pituitary-tumor enlargement occurred mostly in patients with baseline mUFC > 5×ULN, with some instances leading to permanent osilodrostat discontinuation (all patients, 6.6%) and additional therapy (all patients, 6.1%). Almost half of patients with pituitary-tumor enlargement AEs had grade 3/4 events (severe, medically significant or life-threatening; all patients, 5.2%), with a similar number experiencing SAEs. Unlike AEs related to hypocortisolism and accumulation of adrenal hormone precursors, the incidence of AEs related to pituitary-tumor enlargement generally increased over time. Although mean ACTH levels increased steadily from baseline to week 108 in all patients, no correlations were identified between ACTH levels and total daily osilodrostat dose or tumor volume over time, the latter of which has been demonstrated with other medical therapies for CD.[21,22]

This analysis had several limitations. As mUFC was measured every 2-3 weeks during the early stages of each study, the exact time when mUFC control was achieved cannot be determined. In addition, because of the differences in study design, patients may have had different levels of osilodrostat exposure at various time points, although placebo-controlled periods were excluded. Furthermore, osilodrostat dose-titration decisions were made by a group of independent endocrinologists during the double-blind dose-titration period of LINC 4, whereas decisions were made at the investigators' discretion during the dose-titration period of LINC 3. It was also not possible to confirm the specific reasons behind the dose "re-escalation" and "dosing error". AEs were also reported according to the investigators' discretion, with no standardized definitions provided. Furthermore, the study protocols did not mandate assessment of early-morning serum cortisol in patients with suspected AI, and reasons for loss of mUFC control were not evaluated. Finally, data from week 180 onwards in this pooled analysis should be interpreted with caution because of small patient sample sizes.

Conclusions

These data from the largest pooled analysis to date demonstrate that the osilodrostat dose needed for first mUFC control was ≤10 mg/day in most patients, with dose decreases possible over the long term; however, it varied, with higher doses required over a longer period for patients with more severe disease at baseline. Patients aged <65 years and those with no prior medical therapy for CD were more likely to achieve mUFC control faster than older patients and those with prior medical therapy.

AEs related to hypocortisolism and accumulation of adrenal hormone precursors were mostly manageable without the need for permanent osilodrostat discontinuation. As demonstrated previously, rates of hypocortisolism-related AEs were higher with faster osilodrostat up-titration,[8,11,14,15] further highlighting the importance of individualized treatment regimens to optimize clinical outcomes. Most AEs occurred during dose titration, with decreasing occurrence over time; however, AEs can also occur later during treatment. Lifelong monitoring for long-term maintenance of normal cortisol levels and to detect AEs early to ensure prompt intervention is advised.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Authors' contributions

Maria Fleseriu (Conceptualization [lead], Investigation [equal], Writing—review & editing [lead]), Rosario Pivonello (Investigation [equal], Writing—review & editing [equal]), Andre Lacroix (Investigation [equal], Writing—review & editing [equal]), Beverly Biller (Conceptualization [equal], Investigation [equal], Writing—review & editing [equal]), Richard Feelders (Investigation [equal], Writing—review & editing [equal]), Monica Gadelha (Conceptualization [equal], Investigation [equal], Writing—review & editing [equal]), Jérôme Bertherat (Investigation [equal], Writing—review & editing [equal]), Zhanna Belaya (Investigation [equal], Writing—review & editing [equal]), Andrea Piacentini (Formal analysis [lead], Validation [lead], Writing—review & editing [equal]), Alberto Pedroncelli (Conceptualization [equal], Writing—review & editing [equal]), and John Newell-Price (Conceptualization [equal], Investigation [equal], Writing—review & editing [equal])

Conflict of interest: M.F. reports grants to her university from Crinetics and Sparrow and occasional scientific consulting fees from Crinetics, Recordati Rare Diseases, Sparrow, and Xeris Pharmaceuticals; she served on the LINC 3 steering committee. R.P. has received research funding from Recordati AG, Corcept Therapeutics, Strongbridge Biopharma, Neurocrine Biosciences, and Spruce Biosciences and served as a consultant for Corcept Therapeutics, Recordati AG, Crinetics Pharmaceuticals, and H Lundbeck A/S. A.L. reports grants and personal consulting fees from Novartis, Recordati, Corcept Therapeutics, and Pfizer. B.M.K.B. reports occasional consulting honoraria from Lundbeck, Recordati Rare Diseases, and Xeris Pharmaceuticals (Strongbridge); she served on the LINC 3 steering committee. R.F. reports consultancy for HRA Pharma, Recordati, and Corcept Therapeutics. M.G. has received speaker fees from Novartis, Recordati, Ipsen, Crinetics, and Novo Nordisk and attended advisory boards for Novartis, Novo Nordisk, Recordati, and Crinetics Pharmaceuticals. J.B. reports research funding from Novartis, Pfizer, Neurocrine, and HRA Pharma and consultancy for HRA Pharma, Novartis, Corcept Therapeutics, Crinetics, and Recordati. Z.B. has nothing to disclose. A.P. is an employee of Recordati. A.M.P. was an employee of Recordati when the analyses were conducted. J.N.-P. reports research grants and consultancy payments to his university from Crinetics, Diurnal, HRA Pharma, and Recordati Rare Diseases.

Data availability

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request. Recordati Rare Diseases will share the complete de-identified patient dataset, study protocol, statistical analysis plan, and informed consent form upon request, effective immediately following publication, with no end date.

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