A multicenter, phase 2 study to evaluate the efficacy and safety of osilodrostat, a new 11β-hydroxylase inhibitor, in Japanese patients with endogenous Cushing’s syndrome other than Cushing’s disease

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Abstract. This phase 2, single-arm, open-label, dose-titration, multicenter study evaluated osilodrostat (11 β-hydroxylase inhibitor) in Japanese patients with endogenous Cushing’s syndrome (CS) caused by adrenal tumor/hyperplasia or ectopic adrenocorticotropic hormone syndrome. The primary endpoint was percent change from baseline to week 12 in mean urinary free cortisol (mUFC) at the individual patient level. Of the nine patients enrolled in the study, seven completed the 12-week core treatment period and two discontinued at or prior to week 12 due to adverse events (AEs). Of the seven patients who completed 12 weeks of study treatment, two completed 48 weeks of study treatment. Median osilodrostat exposure was 12 weeks. Median (range, population) percentage change in mUFC was –94.47% (–99.0% to –52.6%, n = 7) at week 12. At week 12, 6/9 patients were complete responders (mUFC ≤ upper limit of normal [ULN]) and 1/9 was a partial responder (mUFC > ULN but decreased by ≥50% from baseline). Most frequent AEs were adrenal insufficiency (n = 7), gamma-glutamyl transferase increase, malaise, and nasopharyngitis (n = 3 each). Serious AEs were seen in four patients. No deaths occurred in this study. In conclusion, osilodrostat treatment led to a reduction in mUFC in all nine patients with endogenous CS other than Cushing’s disease (CD), regardless of disease type, with >80% reduction seen in 6/7 patients at week 12. The safety profile was consistent with previous reports in CD patients, and the reported AEs were manageable.

Key words: Osilodrostat, 11β-hydroxylase inhibitor, Cushing’s syndrome, Cushing’s disease

ENDOGENOUS CUSHING’S SYNDROME (CS), a rare endocrine disorder characterized by sustained elevated cortisol levels, is associated with higher multiple comorbidities that increase the risk of cardiovascular disease and mortality [1, 2]. In a Japanese survey, out of the 417 CS cases, 36% had Cushing’s disease (CD), 47% had adrenal adenoma, and 17% had other causes of CS [3], which is in contrast to the Western countries where the most common form of CS (about 70%) is CD [4, 5].

Regardless of the type of CS, surgical resection of the underlying tumor remains the standard of care for patients with CS. Medical therapy serves as an option for patients who are not suitable for surgery or have recurrent disease. Medical treatment may be varied by country, based on the underlying cause of CS [6, 7].

In Japan, mitotane, trilostane, and metyrapone have been approved for the treatment of endogenous CS, and pasireotide long-acting release has been approved for the treatment of CD. Based on a number of case reports, metyrapone, a classical 11β-hydroxylase inhibitor, has been traditionally used in Japan and preferred over trilostane and mitotane owing to its favorable risk/benefit profile. However, metyrapone may show suboptimal...
enrolled. Patients with the following types of CS were
e.g. for each type of CS (eligible: ectopic corticotropin syndrome, adrenal ade‐
Patient population

CS was evidenced by an mUFC level >1.3 × ULN and as
cacy of osilodrostat in Japanese patients with various
types of endogenous CS other than CD. The final analy‐
tial 4 weeks, osilodrostat titrations were done weekly, up
to a maximum dose of 10 mg bid, and thereafter doses
were titrated at 2-week intervals. The dose escalation
sequence of osilodrostat was 2, 5, 10, 20, and 30 mg bid.
During period 1, a therapeutic dose for each individual
patient was established, and the efficacy (mean of three
24-h UFC [mUFC] values) and safety of osilodrostat
were evaluated.

During study period 2 (weeks 12–48), the durability of
efficacy and the long-term safety of osilodrostat were
evaluated. Patients who tolerated and agreed to continue
osilodrostat treatment entered study period 2 and contin‐
ued the therapeutic dose achieved in study period 1. Dose
titrations were allowed during this period. Patients
who continued to receive clinical benefit, as assessed by
the study investigator, entered an optional extension
period at the end of the study period. All patients
had either completed week 72 or discontinued early. All
patients had a 30-day safety follow-up after the last dose
of osilodrostat.

The study protocol and all amendments were reviewed
and approved by the Independent Ethics Committee,
Institutional Review Board, and Research Ethics Board

Materials and Methods

Patient population

Adult patients aged 18–85 yr with confirmed CS were
enrolled. Patients with the following types of CS were
eligible: ectopic corticotropin syndrome, adrenal ade‐
noma, adrenal carcinoma, ACTH-independent macro‐
nodular adrenal hyperplasia/primary macronodular
adrenal hyperplasia (AIMAH/PMAH), or primary pig‐
mented nodular adrenal dysplasia (PPNAD). Confirmed
CS was evidenced by an mUFC level >1.3 × ULN and as
per the other specific eligibility criteria of this study for
each type of CS (e.g., for ectopic corticotropin syn‐
drome, morning plasma ACTH level above lower limit
of normal [LLN], low-dose dexamethasone suppression
test dose not suppress the serum cortisol level next
morning; for adrenal adenoma, AIMAH, and PPNAD, a low
plasma ACTH level [<10 pg/mL or <2.2 pmol/L], evi‐
dence of adrenal tumor/hyperplasia by computed tomog‐
raphy [CT] and/or magnetic resonance imaging [MRI];
and for adrenal carcinoma, evidence of adrenal carci‐
ona by CT and/or MRI). Patients were expected to
have remained in a stable condition for at least 5 months
prior to the study entry. Patients on medical treatment
for hypercortisolism due to CS must have completed
appropriate washout periods of 1 week for steroidogene‐
sis inhibitors (metyrapone, triostane, ketoconazole), 6
months for mitotane, 4 weeks for mifepristone, and at
least 5 half-lives or 30 days, whichever was longer, for
other investigational therapies. Patients with CD or
hypersensitivity to osilodrostat or drugs of similar chem‐
ical classes were not eligible for inclusion in this study.

Study design and treatment

This was a phase 2, single-arm, open-label, dose‐
titration, multicenter study that comprised two study
periods and an optional extension period (Fig. 1).
During the dose-titration period, namely study period
1 (weeks 0–12), patients received an initial dose of 2 mg
bid osilodrostat. Based on the serum cortisol levels that
were measured every week for the initial 4 weeks then
every 2 weeks at a local laboratory or the mUFC levels
measured at the central laboratory, dose levels were
titrated until the mUFC levels were to be normalized. If
hypocortisolism (e.g., serum cortisol value is low less
than LLN or the patient has signs and symptoms of adre‐
nal insufficiency and the serum cortisol value is in the
lower part of the normal range) occurred with the 2 mg
bid dose, the dose was lowered to 1 mg bid. For the ini‐
tial 4 weeks, osilodrostat titrations were done weekly, up
to a maximum dose of 10 mg bid, and thereafter doses
were titrated at 2-week intervals. The dose escalation
sequence of osilodrostat was 2, 5, 10, 20, and 30 mg bid.
During period 1, a therapeutic dose for each individual
patient was established, and the efficacy (mean of three
24-h UFC [mUFC] values) and safety of osilodrostat
were evaluated.
for each participating center. The study was conducted according to the ethical principles of the Declaration of Helsinki. All patients provided written informed consent. This clinical study was registered to ClinicalTrials.gov with the ClinicalTrials.gov Identifier: NCT02468193

Objectives
The primary objective of the study was to assess the percent change from baseline at week 12 in the mUFC levels at the individual patient level. Additional secondary efficacy objectives included the percent change from baseline at weeks 24 and 48 in the mUFC level; absolute and percent changes from baseline in the mUFC level; proportion of patients with complete, partial, and overall response rates; and absolute and percent changes from baseline in the serum cortisol level, steroid hormone levels, and cardiovascular metabolic parameters associated with CS at weeks 12, 24, and 48. The pharmacokinetics and safety of osilodrostat were also evaluated as secondary objectives. In addition, the Cushing's disease Health-Related Quality of Life Questionnaire (Cushing’s QoL) score [14] and Beck Depression Inventory-II (BDI-II) [15] were the primary and secondary patient-reported outcome variables assessed during this study. Complete response rate was defined as the proportion of enrolled patients who had mUFC levels ≤ ULN, and partial response rate was defined as the proportion of enrolled patients who had mUFC levels > ULN and at least a 50% reduction in the mUFC level from baseline.

Statistical analysis
The planned study enrollment was 10 patients. The sample size is reflective of the rarity of this condition; hence, data will be primarily described on an individual basis except for a few endpoints, including mUFC response rate and change from baseline in mUFC. The full analysis set consisted of all enrolled patients who received at least one dose of osilodrostat. The safety analysis set consisted of all patients who received at least one dose of osilodrostat and had at least one valid post-baseline safety assessment.

Due to the limited sample size and patients enrolled with various disease types, no statistical hypothesis was set up for this study. Data from all participating patients from all centers were combined for the summary. However, given the small sample size, data were primarily described on an individual basis or by disease type (ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, AIMAH, and PPNAD).

Results
Characteristics of patients
Data reported here are based on the final analysis results after all patients completed or discontinued the study (data cut-off date: October 29, 2018). A total of nine patients were enrolled in this study, of which seven

Fig. 1 Study design

Osilodrostat in Cushing’s syndrome
patients completed study period 1, two patients completed study period 2, and none completed the optional extension period (Fig. 2). Six patients discontinued, with adverse events (AEs; \( n = 4 \)) followed by patient/guardian decision (\( n = 2 \)) as the primary reasons for discontinuation (Fig. 2).

Out of the nine patients (median age, 46.0 yr [range: 20–75 yr]), five had adrenal adenoma, three had ectopic corticotropin syndrome, and one had AIMAH. The primary site of cancer in patients with ectopic corticotropin syndrome was the thymus (metastasis site: sacral bone) in one patient and unknown for the remaining two patients. The majority of patients were less than 65 yr of age and female (Table 1). The median duration of exposure was 12.00 weeks (range: 1.3–81.9 weeks) at final cut-off (Table 2).

**Efficacy, symptoms, and other biomarkers**

All nine patients showed a decrease in the mUFC levels regardless of the disease type (Fig. 3). Median mUFC (\( n = 9 \)) decreased from 841.80 nmol/24 h at baseline to 77.10 nmol/24 h at week 12 (\( n = 7 \)). At week 12, a greater than 80% reduction in the mUFC levels from baseline was noted in all patients except in one patient with adrenal adenoma (−52.6% change from baseline; patient 6) (Table 3). Although the remaining patients (patients 8 and 9) had discontinued prior to week 12, the percent changes from baseline at the end of study treatment were −96.1% at days 30–33 and −95.7% at days 61–64. One patient (patient 2) appears to have lost control of mUFC around week 16 by off-treatment but this patient showed a response to osilodrostat similar to other patients. (Of note, the patient permanently discontinued osilodrostat and preferred surgery to achieve complete remission.)

Two patients (patients 5 and 6) underwent adrenalectomy on day 19 and day 22 after the last osilodrostat dose, respectively. Two patients (patients 2 and 3) permanently discontinued osilodrostat due to undergoing surgery, but they had not undergone surgery yet during the safety follow-up period. Of note, surgery data after study treatment were collected for only the safety follow-up period (i.e., 30 days after the last osilodrostat dose) according to the protocol.

At baseline (\( n = 9 \)), the median mUFC was 841.80 nmol/24 h. Notable reductions were initially observed in the median mUFC at week 4 (Table 4). By week 8, the median mUFC levels were reduced to within the normal range (11.0–138.0 nmol/24 h) and were maintained up to week 12. The median mUFC and median percent change in the mUFC values from baseline at week 12 (\( n = 7 \)) were 77.10 nmol/24 h and −94.47%, respectively; at week 24 (\( n = 3 \)) were 63.90 nmol/24 h and −91.57%, respectively; and at week 48 (\( n = 2 \)) were 511.30 nmol/24 h and −95.04%, respectively (Table 4). Mean

| Discontinued at or prior to Week 12 (\( n = 2 \); 22.2%) |
| Completed Week 12 and did not enter Study period II (\( n = 3 \); 33.3%) |
| Discontinued at or prior to Week 48 but after Week 12 (\( n = 2 \); 22.2%) |
| Completed Week 48 and did not enter Optional extension period (\( n = 0 \)) |
| Discontinued study in Optional extension period (\( n = 2 \); 22.2%) |
| Primary reason for discontinuation: AE (\( n = 2 \)) |
| Patients enrolled and treated (\( N = 9 \); 100%) |
| Completed Week 12 (\( n = 7 \); 77.8%) |
| Completed Week 12 and entered Study period 2 (\( n = 4 \); 44.4%) |
| Completed Week 48 (\( n = 2 \); 22.2%) |
| Completed Week 48 and entered Optional extension period (\( n = 2 \); 22.2%) |
| Completed the Optional extension period (\( n = 0 \)) |
| Study Period 1 (Week 0–12) |
| Study Period 2 (Week 12–48) |
| Optional extension Period (Week 48–72) |

*One patient discontinued with AE (grade 3 hypokalemia) that started at day −1 (i.e. before treatment).

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Fig. 2 Patient disposition

AE, adverse event.
(±SD) mUFC over time is shown in Fig. 4.

Of the nine enrolled patients, five had received prior metyrapone treatment. At week 12, the median percent changes in the mUFC values were −98.97% and −86.65% in patients with and without prior exposure to metyrapone, respectively (Table 3).

At week 12, an overall response was observed in 7/9 patients (77.8%); of these, six were complete responders and one was a partial responder. Two patients who discontinued the study prior to week 12 were counted as non-responders for the calculation of the response rate at week 12. At week 24 (n = 3), two patients were complete responders and one patient was a partial responder. At week 48 (n = 2), one patient was a complete responder and one patient was a partial responder (Table 5).

The reductions in serum cortisol levels were consistent with the reductions in mUFC levels. The median morning serum cortisol level decreased from 535.0 nmol/L at baseline (n = 9) to 235.0 nmol/L at week 12 (n = 7) with a −56.07% median percent change from baseline. At weeks 24 (n = 3) and 48 (n = 2), the median percent changes from baseline were −68.96% and −67.39%, respectively.

For all six patients with ACTH-independent CS (i.e., AIMAH and adrenal adenoma), plasma ACTH levels remained low around detection limit throughout the study compared with baseline. There were three patients with ectopic corticotropin syndrome, but only one (patient 7) had data for more than 12 weeks. In this patient, plasma ACTH levels decreased (range: 25.8–88.8 pmol/L) up to day 239 and then increased (range: 98.1–142.3 pmol/L) up to the end of treatment (day 477) compared with baseline (94.6 pmol/L). In addition to ACTH, aldosterone, adrenal hormone precursors (11-deoxycortisol, 11-deoxycorticosterone), and sex hormones (estradiol, testosterone) were also monitored in this study; however, overall, no clinically obvious relevant changes were observed due to the small number of patients and the short treatment exposure with dose reductions and/or interruption of the study drug (Suppl Table 1).

In most patients, marginal improvements were observed in most cardiovascular metabolic parameters (including fasting glucose, hemoglobin A1c [HbA1c], total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglyceride, waist circumference, systolic blood pressure [BP], diastolic

| Table 1 | Demographics (full analysis set) |
|---------|----------------------------------|
| Demographic variable | All patients (N = 9) |
| Median (range) age, yr | 46.0 (20–75) |
| ≥65 yr, n (%) | 3 (33.3) |
| Female, n (%) | 7 (77.8) |
| Weight, median (range), kg | 59.30 (47.0–106.5) |
| Height, median (range), cm | 156.00 (145.0–170.0) |
| BMI, median (range), kg/m² | 23.876 (19.31–38.19) |
| Type of disease, n (%) | |
| AIMAH | 1 (11.1) |
| Adrenal adenoma | 5 (55.6) |
| Ectopic corticotropin syndrome | 3 (33.3) |
| Previous treatment, n (%)* | |
| Surgery | 1 (11.1) |
| Medication† | 5 (55.6) |
| Radiotherapy | 0 (0.0) |

AIMAH, ACTH-independent macronodular adrenal hyperplasia; BMI, body mass index; CS, Cushing’s syndrome.

* Four patients, with adrenal adenoma, were naive to any treatment for CS.
† All five patients received metyrapone (three of them had a complete response and one patient each had a partial response and no response as the best response to metyrapone [last regimen prior to washout before entering study]). Of them, one patient with ectopic corticotropin syndrome (patient 7) received cisplatin, irinotecan, and amrubicin in addition to metyrapone and had prior surgery.

| Table 2 | Osilodrostat dose and duration of exposure (safety analysis set) |
|---------|---------------------------------------------------------------|
| Demographic variable | All patients at final cut-off (N = 9) |
| Median exposure (range), weeks | 12.00 (1.3–81.9) |
| >8 weeks of exposure, n (%) | 7 (77.8) |
| >16 weeks of exposure, n (%) | 4 (44.4) |
| >48 weeks of exposure, n (%) | 2 (22.2) |
| Median highest dose (range), mg/day | 5.0 (2–10) |
| Median average dose (range), mg/day | 2.143 (1.16–7.54) |
| Median dose with longest duration (range), mg/day | 2.0 (1–10) |
| Median average dose (range) excluding dose interruption (0 mg/day), mg/day | 2.571 (1.17–7.54) |
| Median dose with longest duration (range) excluding dose interruption (0 mg/day), mg/day | 2.0 (1–10) |
Fig. 3 Absolute values of mUFC (nmol/24 h) over time with actual dose data by patient. (a) AIMAH ($n = 1$); (b) Adrenal adenoma ($n = 5$); Ectopic corticotropin syndrome ($n = 3$).

AIMAH, ACTH-independent macronodular adrenal hyperplasia; mUFC, mean urinary free cortisol.
BP) at week 12 (Suppl Tables 2–4). Overall, no clinically relevant differences were observed in any of the quality of life (QoL) scores evaluated (Cushing’s QoL and BDI-II) at week 12.

There was an increasing trend in the osilodrostat plasma concentrations at 1–2 h post-dose, with increasing incident dose noted. The geometric mean concentrations were 2.45–10.9, 2.87–13.9, 21.1–23.2, and 18.9–37.8 ng/mL for the 1, 2, 3, and 5 mg doses, respectively. With osilodrostat, there was no exposure-response relationship with percent change of mUFC from baseline and was not considered as clinically relevant with change of QTcF (QT interval, Fridericia correction) from baseline.

For the patient with AIMAH who had the longest follow-up (patient 1), a consistent and sustained normalization of serum cortisol level was observed throughout

### Table 3 Absolute mUFC values and absolute changes from baseline for seven patients who completed week 12/day 85

| Patients                  | mUFC values at baseline, nmol/24 h | mUFC values at week 12, nmol/24 h | Change from baseline, nmol/24 h | Percent change from baseline, % |
|---------------------------|-----------------------------------|-----------------------------------|---------------------------------|--------------------------------|
| AIMAH                     |                                   |                                   |                                 |                                |
| Patient 1                 | 7,469.0                           | 77.1                              | −7,391.9                        | −99.0                          |
| Adrenal adenoma           |                                   |                                   |                                 |                                |
| Patient 2                 | 277.9                             | 6.2                               | −271.7                          | −97.8                          |
| Patient 3                 | 431.8                             | 23.9                              | −407.9                          | −94.5                          |
| Patient 4                 | 841.8                             | 71.5                              | −770.3                          | −91.5                          |
| Patient 5                 | 516.0                             | 93.9                              | −422.1                          | −81.8                          |
| Patient 6                 | 298.2                             | 141.2                             | −157.0                          | −52.6                          |
| Ectopic corticotropin syndrome |                                   |                                   |                                 |                                |
| Patient 7                 | 10,595.6                          | 108.1                             | −10,487.5                       | −99.0                          |

Normal range of mUFC: 11.0–138.0 nmol/24 h.
AIMAH, ACTH-independent macronodular adrenal hyperplasia; mUFC, mean urinary free cortisol.

### Table 4 Actual mUFC values for all patients and by prior metyrapone treatment (full analysis set)

| Prior metyrapone (N = 5) | No prior metyrapone (N = 4) | All (N = 9) |
|--------------------------|-----------------------------|-------------|
| Actual value, nmol/24 h  | Percent change from baseline, % | Actual value, nmol/24 h | Percent change from baseline, % |
| Baseline                 | —                           | 9           | —                           |
| Median (range)           | 7,469.00 (431.8, 10,595.6)  | 407.10 (277.9, 841.8)         | 841.80 (277.9, 10,595.6)       |
| Week 4                   | 4                           | 4            | 8                           | 8                             |
| Median (range)           | 181.95 (47.9, 635.8)         | 185.70 (26.1, 193.7)           | 185.70 (26.1, 635.8)           |
| Week 8                   | 4                           | 4            | 8                           | 8                             |
| Median (range)           | 156.30 (13.3, 723.5)         | 58.70 (9.0, 539.0)             | 72.60 (–9.0, 723.5)            |
| Week 12                  | 3                           | 4            | 7                           | 7                             |
| Median (range)           | 77.10 (23.9, 108.1)          | 82.70 (6.2, 141.2)             | 77.10 (6.2, 141.2)             |
| Week 24                  | 3                           | —            | 3                           | 3                             |
| Median (range)           | 63.90 (40.9, 893.6)          | —            | 63.90 (40.9, 893.6)          |
| Week 48                  | 2                           | —            | 2                           | 2                             |
| Median (range)           | 511.30 (67.5, 955.1)         | —            | 511.30 (67.5, 955.1)         |
the study period for about 1.5 yr (day 606) with osilodrostat (range of dosage: 0.5–6 mg/day). In addition, an overall clinically improvement in cardiovascular-related metabolic parameters was also observed in this patient.

**Safety**

All patients experienced at least one AE (Table 6). The most common AE was adrenal insufficiency (all grade, 77.8% and grade 3, 22.2%; Table 7). No grade 4 events or deaths occurred in this study. Four patients (44.4%) had serious AEs (SAEs; adrenal insufficiency in two patients; myocardial infarction, pneumonia [in the same patient with adrenal insufficiency], and psychiatric symptom, each in one patient); all SAEs were grade 3, with only adrenal insufficiency in two patients suspected to be related to the study drug by the investigator. The AEs that led to study drug discontinuation were myocardial infarction (grade 3), abdominal distention (grade 1), and reactive psychosis (grade 2), each in one patient. Adrenal insufficiency was the most frequently recorded AE requiring dose adjustments or dose interruptions.

The AEs of special interest (i.e., AEs potentially related to osilodrostat treatment based on the mechanism of action) are shown in Table 8. The high incidence of hypocortisolism-related AEs was seen during the 12-week dose-titration phase, but results should be interpreted with caution because the median duration of treatment in this study was 12 weeks and long-term exposure was limited. Most of the patients with hypocortisolism-related AEs required dose adjustments or interruptions and treatment with glucocorticoids, but none of the patients discontinued study treatment due to this event.

Grade 3/4 shifts were observed after baseline in the biochemistry variable for elevated alanine aminotransferase (ALT; \( n = 3 \)), decreased potassium (\( n = 2 \)), elevated gamma-glutamyl transferase (GGT; \( n = 2 \)), elevated triglycerides (\( n = 1 \)), and urate (\( n = 1 \)) levels. Three patients with elevated GGT levels and/or ALT laboratory abnormality had a pre-existing medical history of metabolic syndrome. Overall, no clinically relevant change from baseline in vital signs was observed. New QTcF of >480 ms and ≤500 ms (as well as >60 ms increase from baseline) was observed in one patient, which occurred after myocardial infarction (SAE). This myocardial

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**Table 5** Proportions of mUFC responders by visit (full analysis set)

|                    | Complete response | Partial response | Overall          |
|--------------------|------------------|-----------------|-----------------|
|                    | \( n (%) \) [95% CI] | \( n (%) \) [95% CI] | \( n (%) \) [95% CI] |
| Week 12 (\( n = 9 \)) | 6 (66.7) [29.9–92.5] | 1 (11.1) [0.3–48.2] | 7 (77.8) [40.0–97.2] |
| Week 24 (\( n = 3 \)) | 2 (66.7) [9.4–99.2] | 1 (33.3) [0.8–90.6] | 3 (100) [29.2–100.0] |
| Week 48 (\( n = 2 \)) | 1 (50.0) [1.3–98.7] | 1 (50.0) [1.3–98.7] | 2 (100) [15.8–100.0] |

CI, confidence interval; mUFC, mean urinary free cortisol.

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Fig. 4  Mean (±SD) of mUFC over time
mUFC, mean urinary free cortisol.

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infarction was not suspected by the investigator to be drug related.

### Table 6  Overview of AEs (safety analysis set)

| Category                                      | All grades n (%) | Grade 3 n (%) |
|-----------------------------------------------|------------------|---------------|
| AEs                                           | 9 (100)          | 6 (66.7)      |
| Suspected to be drug related                  | 8 (88.9)         | 4 (44.4)      |
| On-treatment deaths                           | 0                | 0             |
| Serious AEs                                   | 4 (44.4)         | 4 (44.4)      |
| Suspected to be drug related                  | 2 (22.2)         | 2 (22.2)      |
| AEs leading to discontinuation                | 3* (33.3)        | 1* (11.1)     |
| Suspected to be drug related                  | 1 (11.1)         | 0             |
| AEs requiring dose interruption and/or change | 7 (77.8)         | 3 (33.3)      |
| Suspected to be drug related                  | 7 (77.8)         | 3 (33.3)      |
| AEs requiring additional therapy              | 8 (88.9)         | 5 (55.6)      |
| Suspected to be drug related                  | 5 (55.6)         | 2 (22.2)      |
| AEs of special interest                       | 7 (77.8)         | 3 (33.3)      |
| Suspected to be drug related                  | 6 (66.7)         | 2 (22.2)      |

No grade 4 events were observed.

*One patient had grade 3 hypokalemia leading to discontinuation that started at day –1 (i.e., before on-treatment period) and is not counted in any AE summary tables. AE, adverse event.

### Table 7  Adverse events by preferred term in >20% of patients (safety analysis set)

| MedDRA Preferred term                  | All grades n (%) | Grade 3 n (%) |
|----------------------------------------|------------------|---------------|
| Total                                  | 9 (100)          | 6 (66.7)      |
| Adrenal insufficiency*                 | 7 (77.8)         | 2 (22.2)      |
| Gamma-glutamyl transferase increased   | 3 (33.3)         | 1 (11.1)      |
| Malaise                                | 3 (33.3)         | 0             |
| Nasopharyngitis                        | 3 (33.3)         | 0             |
| Alanine aminotransferase increased     | 2 (22.2)         | 2 (22.2)      |
| Aspartate aminotransferase increased   | 2 (22.2)         | 0             |
| Blood alkaline phosphatase increased   | 2 (22.2)         | 0             |
| Constipation                           | 2 (22.2)         | 0             |
| Dermatitis acneiform                   | 2 (22.2)         | 0             |
| Hypokalemia                            | 2 (22.2)         | 1 (11.1)      |
| Pruritus                               | 2 (22.2)         | 0             |
| Rash                                   | 2 (22.2)         | 0             |

No grade 4 events observed.

* Adrenal insufficiency includes the reported terms of adrenal insufficiency, hypoadrenalism and adrenal gland hypofunction.

MedDRA, Medical Dictionary of Regulatory Activities.

Discussion

To the best of our knowledge, this is the first study to report efficacy and safety of osilodrostat in patients with
The primary objective of this phase 2, single-arm, open-label, dose-titration, multicenter study was to assess the percent change from baseline in the mUFC level at the patient level at week 12 in patients with endogenous CS other than CD in Japan. The patients enrolled in this study demonstrated a rapid and consistent reduction in mUFC level over time with osilodrostat treatment irrespective of the disease type (AIMAH, ectopic corticotropin syndrome, and adrenal adenoma). At week 12, a greater than 80% reduction in mUFC levels was observed in six patients despite the interruption of study drug just before week 12 (days 71–84) due to an AE in one patient. The remaining two patients who discontinued prior to week 12 had a >95% reduction in mUFC levels at the end of study treatment. Most patients achieved normal mUFC levels by week 12. The reductions in mUFC levels with osilodrostat were generally maintained after week 12; however, the data should be interpreted cautiously as the number of patients was small in this study.

The overall response rate at week 12 was high (77.8% [7/9]; six complete responders and one partial responder), which is similar to the findings in the LINC-3 study in patients with CD [13]. Two patients who discontinued prior to week 12 had a >95% reduction in mUFC levels at the end of study treatment. Most patients achieved normal mUFC levels by week 12. The reductions in mUFC levels with osilodrostat were generally maintained after week 12; however, the data should be interpreted cautiously as the number of patients was small in this study.

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The most common treatment for CS in Japan is metyrapone, which needs to be administered 4 times/day, and the proportion of patients who have mUFC < ULN by metyrapone monotherapy is around 40% [8]. The percent change from baseline in mUFC was evaluated in patients with and without prior metyrapone treatment. There were similar rapid mUFC reductions in both groups, indicating the efficacy of osilodrostat regardless of prior metyrapone treatment. Interestingly, similar reductions were observed despite the fact that baseline mUFC levels were higher in patients with prior metyrapone treatment and that patients had a variable response to prior metyrapone. Since no head-to-head comparisons are available for the same patients, results should be interpreted with caution.

The reduction in serum cortisol levels was consistent with that in mUFC levels throughout the study. Based on the mechanism of action of osilodrostat as an inhibitor of both cortisol and aldosterone synthesis [11], potential decrease in aldosterone and potential increase in adrenal hormone precursors and sexual steroids were anticipated [10]. However, in the current study, no clinically obvious relevant changes were observed overall in other steroid hormone levels due to the small number of patients and the short treatment exposure with dose reductions and/or interruption of study drug. In addition, three patients had adrenal hormone precursor accumulation-related events (Table 7), but none of these were suspected to be study drug related by the investigator, and grade 3 events were reported in only one patient (hypokalemia). Therefore, the changes in these hormones indicate minimal clinical impact on the patients. Improvements were observed in most cardiovascular-related metabolic parameters at week 12 despite the short exposure. Overall, the QoL scores at week 12 were similar to those at baseline, indicating osilodrostat treatment at least sustained the QoL of patients. Moreover, due to the short treatment exposure, no major clinically relevant changes in QoL were expected.

The most frequent AEs in the study (i.e. adrenal insufficiency) were one of the hypocortisolism-related AEs as expected based on the mechanism of action of osilodrostat, and these events were manageable with dose adjustments or interruptions and treatment with glucocorticoids. To manage the hypocortisolism-related AEs

| Table 8  | AEs of special interest by AE category and preferred term (safety analysis set) |
|----------|--------------------------------------------------------------------------------|
| AE of special interest | MedDRA Preferred term | All grades | Grade 3 |
| Any AE of special interest | 7 (77.8) | 3 (33.3) |
| Hypocortisolism-related AEs | 7 (77.8) | 2 (22.2) |
| Adrenal insufficiency* | 7 (77.8) | 2 (22.2) |
| Steroid withdrawal syndrome† | 1 (11.1) | 1 (11.1) |
| Adrenal hormone precursor accumulation-related AEs | 3 (33.3) | 1 (11.1) |
| Hypokalemia | 2 (22.2) | 1 (11.1) |
| Weight increased | 1 (11.1) | 0 |

AE, adverse event; MedDRA, Medical Dictionary of Regulatory Activities.
* Adrenal insufficiency includes the reported terms of adrenal insufficiency, hypoadrenalism and adrenal gland hypofunction.
† Steroid withdrawal syndrome includes the reported term of glucocorticoid withdrawal syndrome.
such as glucocorticoid deficiency or adrenal insufficiency, it is recommended that cortisol levels should be monitored at regular intervals. In addition, patients should be alerted to the signs and symptoms associated with hypocortisolism (e.g., nausea, vomiting, fatigue, abdominal pain, loss of appetite and dizziness). If hypocortisolism is suspected, cortisol levels should be measured and temporary dose reduction or interruption of osilodrostat considered. If necessary, treatment with glucocorticoids should be initiated. The other reported AEs included elevated level of liver enzymes, malaise, and nasopharyngitis, constipation, dermatitis acneiform, hypokalemia, pruritus, and rash. Four patients (44.4%) had SAEs. No grade 4 events or deaths were observed. Three patients discontinued study treatment due to AEs (myocardial infarction, abdominal distention, or reactive psychosis) during the on-treatment period, but only one patient had an AE (abdominal distention; grade 1) suspected to be study drug related. Overall, the safety profile observed in this study was consistent with the previously known safety profile of osilodrostat [13] and no new safety signals were identified.

Some of the limitations of the study include its small sample size and open-label study design. Due to the limited sample size and variety of patients and types of disease, no statistical hypothesis was set up for this study. It should also be noted that the study is being conducted only in Japanese patients with endogenous CS (other than CD). To further substantiate the results, studies with larger sample sizes, including patients from across the globe, are warranted.

The results of this study in patients with endogenous CS other than CD, along with other studies in CD, indicate that osilodrostat is effective for patients with all types of endogenous CS. Osilodrostat is generally tolerated with a manageable AE profile. Thus, osilodrostat is a viable option for the treatment of patients with endogenous CS regardless of disease type.

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Tomomi Kaneko, Tamami Takeda, Akina Suzuki, Masahiko Sato are employees of Novartis Pharm K.K. The remaining authors have nothing to disclose.

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