Efficacy and safety of osilodrostat in patients with Cushing’s disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase

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Summary

Background Cushing’s disease is a rare endocrine disorder characterised by cortisol overproduction with severe complications. Therapies for cortisol reduction are often necessary. Here we report the outcomes from the pivotal phase III study of osilodrostat (a potent oral inhibitor of cytochrome P450 11B1, mitochondrial [11β-hydroxylase]; Novartis Pharma AG, Basel, Switzerland) in patients with Cushing’s disease.

Methods LINC 3 was a prospective, multicentre, open-label, phase III study with a double-blind randomised withdrawal period, that comprised four periods. Patients aged 18–75 years, with confirmed persistent or recurrent Cushing’s disease (defined as mean 24-h urinary free cortisol [UFC] concentration >1.5 times the upper limit of normal [ULN] and morning plasma adrenocorticotropic hormone above the lower limit of normal) who had previously had pituitary surgery or irradiation, or were newly diagnosed and who refused surgery or were not surgical candidates, were recruited from 66 hospital sites and private clinical practices in 19 countries. In period 1, open-label osilodrostat was initiated in all participants and adjusted every 2 weeks (1–30 mg twice daily; film-coated tablets for oral administration) on the basis of mean 24-h UFC concentration and safety until week 12. In period 2, weeks 13–24, osilodrostat was continued at the therapeutic dose determined during period 1. In period 3, beginning at week 26, participants who had a mean 24-h UFC concentration of less than or equal to the ULN at week 24, without up-titration after week 12, were randomly assigned (1:1), via an interactive-response technology, stratified by osilodrostat dose at week 24 and history of pituitary irradiation, to continue osilodrostat or switch to placebo for 8 weeks. Participants and investigators were masked to treatment assignment. Ineligible participants continued open-label osilodrostat. In period 4, weeks 35–48, all participants were given open-label osilodrostat until core-study end. The primary objective was to compare the efficacy of osilodrostat versus placebo at the end of period 3. The primary endpoint was the proportion of participants who had been randomly assigned to treatment or placebo with a complete response (ie, mean 24-h UFC concentration ≤ULN) at the end of the randomised withdrawal period (week 34), without up-titration during this period. The key secondary endpoint was the proportion of participants with a complete response at the end of the single-arm, open-label period (ie, period 2, week 24) without up-titration during weeks 13–24. Analysis was by intention-to-treat for all patients who received at least one dose of osilodrostat (full analysis set; key secondary endpoint) or randomised treatment (randomised analysis set; primary endpoint) and safety was assessed in all enrolled patients who received at least one dose of osilodrostat and had at least one post-baseline safety assessment. LINC 3 is registered with ClinicalTrials.gov, NCT02180217, and is now complete.

Findings Between Nov 12, 2014, and March 22, 2017, 202 patients were screened and 137 were enrolled. The median age was 40·0 years (31·0–49·0) and 106 (77%) participants were female. 72 (53%) participants were eligible for randomisation during the withdrawal phase, of whom 36 were assigned to continue osilodrostat and 35 were assigned to placebo; one patient was not randomly assigned due to investigator decision and continued open-label osilodrostat. More patients maintained a complete response with osilodrostat versus placebo at week 34 [31 [86%] vs ten [29%]; odds ratio 13·7 [95% CI 3·7–53·4]; p<0·0001]. At week 24, 72 (53%; 95% CI 43·9–61·1) of 137 patients maintained a complete response without up-titration after week 12. Most common adverse events (ie, occurred in >25% of patients) were nausea (57 [42%]), headache (46 [34%]), fatigue (39 [28%]), and adrenal insufficiency (38 [28%]). Hypocortisolism occurred in 70 (51%) patients and adverse events related to adrenal hormone precursors occurred in 58 (42%) patients. One patient died, unrelated to study drug, after the core study phase.

Interpretation Twice-daily osilodrostat rapidly reduced mean 24-h UFC and sustained this reduction alongside improvements in clinical signs of hypocortisolism; it was also generally well tolerated. Osilodrostat is an effective new treatment option that is approved in Europe for the treatment of endogenous Cushing’s syndrome and in the USA for Cushing’s disease.

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*Listed in the appendix (pp 1–4)
Introduction

Cushing’s disease is a rare and serious disorder caused by a pituitary tumour that secretes adrenocorticotropic hormone, which stimulates the adrenal glands to overproduce cortisol. Excess cortisol leads to an increased mortality risk largely driven by cardiovascular disease and infections. First-line treatment for most patients is transsphenoidal surgery; however, additional second-line treatments are often needed because persistent or recurrent Cushing’s disease after surgery has been found in approximately a third of patients. For these patients or in situations where surgery or radiotherapy are not possible, medical therapies are used. Several options with various mechanisms of action are available, including a multireceptor antagonist, dopamine receptor agonists, steroidogenesis inhibitors, adrenolytic drugs, and glucocorticoid receptor antagonists. Despite the availability of several medical therapies, Cushing’s disease remains a difficult outcome for patients. For these patients or in situations where surgery or radiotherapy are not possible, medical therapies are used. Several options with various mechanisms of action are available, including a multireceptor antagonist, dopamine receptor agonists, steroidogenesis inhibitors, adrenolytic drugs, and glucocorticoid receptor antagonists. Despite the availability of several medical therapies, Cushing’s disease remains a difficult disease, osilodrostat, a potent oral inhibitor of 11β-hydroxylase, showed promise in fulfilling this unmet need. Here we report the outcomes of a multicentre, open-label, phase III study that assessed the efficacy and safety of osilodrostat in patients with Cushing’s disease (LINC 3) and included a double-blind randomised withdrawal phase. The study consisted of four phases to allow identification of an effective osilodrostat dose within a narrow therapeutic window, to show the sustained safety and efficacy of osilodrostat (without the need for further dose escalation), and to assess osilodrostat against a placebo while minimising the duration of placebo treatment. To our knowledge, this is the first phase III study to include a placebo-control group in patients with Cushing’s disease.

Methods

Study design and participants

In this prospective, multicentre, open-label study, which included a double-blind randomised withdrawal phase, osilodrostat rapidly reduces mean urinary free cortisol (UFC) concentrations, leading to normalised mean UFC concentrations in most patients (15 [79%] of 19) at week 22. Treatment was generally well tolerated, with the most common adverse events including nausea, diarrhoea, asthenia, and adrenal insufficiency, which were mostly mild or moderate in severity. Here we report the outcomes of a multicentre, open-label, phase III study that assessed the efficacy and safety of osilodrostat in patients with Cushing’s disease (LINC 3) and included a double-blind randomised withdrawal phase. The study consisted of four phases to allow identification of an effective osilodrostat dose within a narrow therapeutic window, to show the sustained safety and efficacy of osilodrostat (without the need for further dose escalation), and to assess osilodrostat against a placebo while minimising the duration of placebo treatment. To our knowledge, this is the first phase III study to include a placebo-control group in patients with Cushing’s disease.
after a 24-week, open-label, single-arm treatment period, patients with Cushing’s disease were recruited from 66 hospital sites and private clinical practices across 19 countries; a list of sites is provided in the appendix (pp 1–3). Patients were eligible if they were aged 18–75 years with confirmed persistent or recurrent Cushing’s disease after pituitary surgery or irradiation, or both, or if they had not had previous surgery or radiotherapy and refused surgery or were not deemed to be surgical candidates. Confirmed active Cushing’s disease was determined at screening from the mean of two or three 24-h UFC concentrations of more than 1·5 times the upper limit of normal (ULN; 138 nmol/24 h or 50 μg/24 h) and morning plasma adrenocorticotropin hormone above the lower limit of normal (LLN; 1·6 pmol/L [males] and 1·1 pmol/L [females]). Additionally, patients were required to have evidence of a pituitary origin for the excess adrenocorticotropin hormone based on one or more of the following criteria: a pituitary tumour of more than 6 mm in diameter by MRI; a central-to-peripheral bilateral inferior petrosal sinus sampling gradient of more than 2 pre-stimulation or more than 3 post-stimulation with either corticotrophin-releasing hormone or desmopressin acetate stimulation; or histopathological and immuno-histochemical confirmation of an adrenocorticotropin hormone-producing pituitary tumour in patients who have previously had pituitary surgery. Patients receiving other medical therapies for Cushing’s disease could be included after a washout period as follows: 1 week for steroidogenesis inhibitors (eg, ketoconazole and metyrapone); 4 weeks for dopamine agonists (eg, cabergoline) or peroxisome proliferator-activated receptor-γ agonists (eg, rosiglitazone, pioglitazone); 4 weeks for mifepristone; 1 week for short-acting pasireotide; 8 weeks for long-acting pasireotide; and 6 months for mitotane, followed by rescreening if required. Exclusion criteria included the following: stereotactic radiosurgery in the past 2 years; conventional radiotherapy in the past 3 years; pituitary surgery in the past 29 days; receipt of glucocorticoid replacement therapy after surgery within the past week or five half-lives (whichever is longer) before screening; treatment with other investigational drugs within 30 days or five half-lives (whichever was longer); a history of hypersensitivity to osilodrostat or therapies of a similar chemical class; and presence or high risk of compression of optic chiasm. A complete list of exclusion criteria is provided in the appendix (p 5). Although not a specific exclusion criterion, no participant had previously received osilodrostat.

All patients provided written informed consent before participation. A redacted version of the protocol is provided in the appendix (pp 20–169). The study was done in accordance with the Declaration of Helsinki, with an independent ethics committee or institutional review board at each site approving the study protocol. Study conduct was overseen by the Study Steering Committee (listed in the appendix [p 1]).

Randomisation and masking

For the double-blind, randomised withdrawal phase starting at week 26, eligible patients were randomly assigned (1:1) via interactive-response technology (IRT) to either continue osilodrostat at the same therapeutically effective dose or receive matching placebo. Randomisation was stratified by osilodrostat dose at week 24 (≤5 mg or >5 mg twice a day) and history of pituitary irradiation (yes or no). Participants were only submitted for randomisation after their treating investigator confirmed they met full randomisation criteria. A randomisation number was then assigned by the IRT to link the patient to a treatment group and unique medication number. Treatment identity was concealed with identical packaging, labelling, schedule of administration, and tablet appearance and odour. To ensure that randomisation was concealed, a randomisation list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomisation numbers. Participants, investigators, and the study sponsor as required were masked to treatment allocation from the time of random assignment until completion of the core study (week 48).

Figure 1: Study design and dosing schedule

Patients were eligible for randomisation if they had mean 24-h UFC concentration of less than or equal to the ULN at week 24 and no dose up-titration of osilodrostat during weeks 13–24. UFC=urinary free cortisol. ULN=upper limit of normal. *Based on efficacy and tolerability.
Articles

Procedures
There were four study periods in the core phase of the study (figure 1). All participants initiated open-label oral osilodrostat 2 mg twice daily (taken roughly every 12 h; 1 mg, 5 mg, 10 mg, or 20 mg film-coated tablets for oral administration; Novartis Pharma AG, Basel, Switzerland), with dose adjustments every 2 weeks (range 1–30 mg twice a day) up to week 12 (study period 1) on the basis of efficacy and tolerability. Decisions to reduce osilodrostat dose were made by the treating investigator. Dose was increased according to a twice-a-day 2 mg, 5 mg, 10 mg, 20 mg, and 30 mg escalation sequence if mean 24-h UFC concentration (mean of three 24-h samples) exceeded the ULN. Throughout the study, osilodrostat dose was reduced if a patient’s mean 24-h UFC concentration was below the LLN (normal range: 11–138 nmol/24 h or 4–50 µg/24 h), or if their mean 24-h UFC concentration was in the lower part of the normal range in patients with symptoms of hypocortisolism or adrenal insufficiency. From weeks 13 to 24 (study period 2), osilodrostat was continued at the therapeutic dose determined during study period 1. Osilodrostat dose was increased in participants whose mean 24-h UFC concentration increased to more than the ULN. Dose increases, if tolerated, were managed by a phone call to the patient between visits or by an unscheduled visit as soon as possible after receipt of mean 24-h UFC results, but these participants were not entered into the randomised withdrawal phase in the next study period. Participants remained on open-label osilodrostat until they received their randomised treatment at week 26. Participants were eligible to enter the randomised withdrawal phase at week 26 if they had mean 24-h UFC concentrations of less than or equal to the ULN at week 24 without a dose increase after week 12; patients were randomly assigned (1:1), in a double-blind manner, to continue osilodrostat at the same therapeutic dose or to receive matching placebo for 8 weeks without further dose increases (study period 3). Dose reductions or interruptions were permitted for safety reasons and did not preclude the possibility of a complete response at week 34. During study period 3, participants who were not eligible for randomisation continued open-label osilodrostat. After week 34, all participants received open-label osilodrostat until week 48 (study period 4).

The dose of osilodrostat could be adjusted throughout the study, depending on efficacy and tolerability. The dose schedule for osilodrostat was based, in part, on modelling data that estimated that a dose of 4–5 mg twice a day would achieve a plasma concentration above the in-vitro 50% inhibitory concentration of 11β-hydroxylase (2·5 nM) for a full 24-h period (Novartis Pharma AG, Basel, Switzerland, unpublished data). Furthermore, a phase II study found that the dose of osilodrostat required to normalise mean 24-h UFC concentrations ranged from 2 mg twice a day to 50 mg twice a day after individual dose titration.12 The lower starting dose of 2 mg twice a day and progressive up-titration to a maximum dose of 30 mg twice a day (based on individual clinical response and tolerability) were chosen to reduce potential risks of hypocortisolism or adrenal insufficiency.

Participants could enter an optional, open-label extension phase for up to week 72 as a minimum. The study is now complete (last patient visit occurred on Dec 4, 2019).

Outcomes
The primary objective was to compare the response rate at the end of period 3 between patients randomly assigned to continue osilodrostat versus those assigned to placebo. The primary endpoint was the proportion of participants who had been randomly assigned to treatment in the randomised withdrawal phase who maintained a complete response (ie, mean 24-h UFC concentration <ULN) to osilodrostat therapy or matching placebo at the end of the 8-week randomised withdrawal period (period 3, week 34), without any dose increase during this period. Patients discontinued the randomised withdrawal period and were considered non-responders for the primary endpoint if their mean 24-h UFC concentration increased to more than 1·5 times the ULN and they had at least two urine samples with UFC concentrations more than 1·5 times the ULN at a single visit. These patients resumed open-label osilodrostat.

The key secondary endpoint was the proportion of participants who had a complete response at the end of the single-arm, open-label period (ie, period 2, week 24) without up-titration during weeks 13–24. Other secondary endpoints included the following: rates of complete response and partial response (mean 24-h UFC concentration >ULN but ≤50% reduction from baseline) at weeks 12, 24, and 48 and last available assessment; change from baseline in mean 24-h UFC concentration, cardiovascular-related parameters (fasting plasma glucose, HbA₁c, fasting lipid profile, sitting systolic and diastolic blood pressure, bodyweight, BMI, and waist circumference), and patient-reported outcomes (health-related quality of life [HRQoL] assessed using the Cushing’s quality-of-life questionnaire [CushingQoL],13 the Beck Depression Inventory,14 and EuroQoL 5-dimension 5-level (EQ-5D-5L) instrument;15 maximum plasma concentration of osilodrostat (C₀₋₅₀); and safety. The following secondary endpoints will be published separately: time to last control of mean 24-h UFC (ie, number of days from randomisation to the last complete response during period 3); change in categorical signs of Cushing’s disease from baseline over time (ie, facial rubor, hirsutism, striae, supraclavicular and dorsal fat pads, proximal muscle wasting, central obesity, and bruising); change in EQ-5D-5L score from baseline over time; change in bone mineral density from baseline over time; and time to escape (ie, number of days from first complete response to the first mean 24-h UFC concentration above 2·5×ULN with at least two individual UFC results above 2·5×ULN).

A minimum important difference (the smallest change in treatment outcome that an individual patient would
identify as important) in CushingQoL score of 10·1 was defined on the basis of the distribution method of a 0·5 SD unit change using baseline data, with a 1-week recall period. A minimum important difference for improvement in Beck Depression Inventory score was a 17·5% reduction in scores from baseline, as described

Figure 2: Study profile
Adverse events leading to discontinuation are described as reported by the treating investigator; some patients had multiple adverse events that led to discontinuation. *Including unacceptable test procedure results, laboratory values, past medical history, and use of excluded medications. †Including rash (n=1); visual impairment (n=1); headache, paresis cranial nerve, and pituitary tumour benign (n=1); blood pressure increased (n=1); asthma (n=1); pituitary tumour benign (n=1); and malignant pituitary tumour (n=1). §One patient who was randomly assigned to placebo did not receive their allocated treatment because of an adverse event (glucocorticoid deficiency), which required dose interruption; the patient subsequently discontinued because of an adverse event (hyponatraemia). ¶Pituitary tumour (n=1). ||Increased adrenocorticotropic hormone and pituitary tumour (n=1).
Mean 24-h UFC concentration was measured at a central laboratory (Q² Solutions, Global Laboratory Services, Morrisville, NC, USA) using liquid chromatography-tandem mass spectrometry (LC-MS/MS; Thermo Finnigan, San Jose, CA, USA; normal range 11–138 nmol/24 h or 4–50 μg/24 h). Safety and tolerability were assessed by the investigators throughout the study, as required, by monitoring adverse events according to Common Terminology Criteria for Adverse Events (CTCAE; version 4.03), which were coded using Medical Dictionary for Regulatory Activities terminology.

Adverse events of special interest (anticipated adverse events) were those related to an increase in adrenal hormone precursors, hypocortisolism, pituitary tumour enlargement, QT interval prolongation, and arrhythmogenic potential. Electrocardiograms (ECGs) were done every 2–4 weeks throughout the study and notable ECG abnormalities were recorded (eg, Fridericia’s corrected QT [QTcF] >480 ms or >60 ms increase from baseline).

Clinical and laboratory evaluations, assessed by the central laboratory, included total testosterone (LC-MS/MS), plasma adrenocorticotropic hormone (Immulate 2000 ACTH kit; PIIKAC-18, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA), early-morning serum cortisol (LC-MS/MS), serum 11-deoxycorticisol (LC-MS/MS), late-night salivary cortisol (LC-MS/MS), plasma aldosterone (LC-MS/MS), dehydroepiandrosterone sulfate (Chemiluminescent Immunoassay; UniCel Dxl 800 Access Immunoassay System; Beckman Coulter, Brea, CA, USA), 11-deoxycorticosterone (LC-MS/MS), active renin (Chemiluminescent Immunoassay; Liaison XL Direct Renin kit, DiaSorin, Vercelli, Italy), serum oestradiol (LC-MS/MS), and oestrone (LC-MS/MS). A list of normal ranges is in the appendix (pp 7–8). Pituitary MRI with gadolinium enhancement was done at each study site according to standardised image acquisition guidelines; assessment of pituitary volume was done by an independent review committee of neuroradiologists who were masked to randomised treatment and the timepoint at which the image was taken (appendix p 6). Mean percentage changes in tumour volume from baseline to week 48 were assessed for all patients with evaluable measurements and by maximum tumour diameter at baseline (<6 mm, 6–<10 mm, or ≥10 mm). For efficacy and safety evaluations, the last available pre-dose assessment within 35 days before or on the first day of osilodrostat treatment (before the first dose) was taken as the baseline assessment. Plasma samples from all participants were assayed for osilodrostat concentration with an LC-MS/MS (lower limit of quantification for osilodrostat was 0.10 ng/mL).

The study included other exploratory endpoints, which will be reported separately.

### Statistical analysis

The sample size calculation was based on the primary endpoint. To detect a clinically meaningful difference of 40% in complete response rate (mean 24-h UFC concentration ≤ULN) between 70% of patients in the osilodrostat group and 30% in the placebo group, a sample size of 33 participants per group was required on the basis of a two-sided Cochran-Mantel-Haenszel test at the two-sided 0.05 level of statistical significance with 87% power. Assuming that 50% or more of participants who were enrolled would be eligible for random assignment to treatment in the randomised withdrawal phase, 132 participants needed to be enrolled. The primary analysis was based on the comparison of the proportion of participants with mean 24-h UFC concentration of less than or equal to the ULN without a dose increase at the end of the 8-week randomised withdrawal period (ie, at week 34) between participants randomly assigned to continue osilodrostat versus placebo. The statistical null hypothesis was that there would be no difference in the complete response rates between the two randomly assigned treatment groups. For the primary endpoint, we did testing using the randomised analysis set composed of all participants who had been randomly assigned to a group who received at least one dose of assigned treatment (osilodrostat or placebo) during period 3, following the

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**Table 1: Demographics and baseline characteristics of all patients and by randomised treatment group in randomised withdrawal period**

<table>
<thead>
<tr>
<th></th>
<th>Osilodrostat (n=36)</th>
<th>Placebo (n=35)*</th>
<th>Non-randomised (n=66)</th>
<th>All patients (n=137)</th>
</tr>
</thead>
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<tr>
<td><strong>Age, years</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Median</td>
<td>41.0</td>
<td>40.0</td>
<td>37.5</td>
<td>40.0</td>
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<tr>
<td>Range</td>
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<td>(31.0–55.0)</td>
<td>(28.0–47.0)</td>
<td>(31.0–49.0)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
<td>6 (17%)</td>
<td>3 (9%)</td>
<td>12 (18%)</td>
<td>31 (23%)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (83%)</td>
<td>23 (63%)</td>
<td>54 (82%)</td>
<td>106 (77%)</td>
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<tr>
<td><strong>Race</strong></td>
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</tr>
<tr>
<td>Caucasian</td>
<td>27 (75%)</td>
<td>23 (66%)</td>
<td>39 (59%)</td>
<td>89 (65%)</td>
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<td>Black</td>
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<td>3 (9%)</td>
<td>1 (2%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (19%)</td>
<td>7 (20%)</td>
<td>25 (38%)</td>
<td>39 (28%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (6%)</td>
<td>2 (6%)</td>
<td>1 (2%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td><strong>Time since diagnosis, months</strong></td>
<td>53 (6)</td>
<td>76 (8)</td>
<td>34.7</td>
<td>47.2</td>
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<td><strong>Previous pituitary irradiation</strong></td>
<td>32 (89%)</td>
<td>33 (94%)</td>
<td>55 (83%)</td>
<td>120 (88%)</td>
</tr>
<tr>
<td><strong>Previous medical therapy for Cushing’s disease</strong></td>
<td>26 (72%)</td>
<td>24 (69%)</td>
<td>52 (79%)</td>
<td>102 (74%)</td>
</tr>
</tbody>
</table>

Mean 24-h UFC, nmol/24 h

- Mean: 890 (1276; 64 × ULN), 560 (549; 4 × ULN), 1306 (2012; 9.5 × ULN), 1006 (1590; 7.3 × ULN)
- Median: 457 (268–777; 358 (20–652; 2 × ULN), 1167 (148–1246; 4.0 × ULN), 476 (314–919; 3.4 × ULN)

Data are median (IQR), n (%), or mean (SD), with multiple of ULN where appropriate. ULN for mean 24-h UFC concentration is 138 nmol/24 h. UFC = urinary free cortisol. ULN = upper limit of normal. *One patient in the placebo group (woman aged 25 years with persistent or recurrent Cushing’s disease after previous pituitary surgery; mean 24-h UFC concentration at screening of 2037.2 nmol/24 h [14.8 × ULN]) was entered into the randomised withdrawal phase but did not receive any allocated treatment during the period.
intention-to-treat principle. If the Cochran-Mantel-Haenszel exact test two-sided p value was less than 0.05 and the odds ratio (OR) was more than 1, the null hypothesis would be rejected and the complete response rate in the osilodrostat group would be considered higher than that in the placebo group. We did a prespecified analysis of the primary endpoint by randomisation strata. p values are not shown for the analysis by randomisation strata because multiplicity adjustment was not applied.

For the key secondary endpoint, the statistical null hypothesis was that the complete response rate at the end of the 24-week open-label period of osilodrostat treatment was 30% or less. Analysis of the key secondary endpoint was based on the two-sided 95% CI using the Clopper-Pearson method. If the lower bound of this 95% CI was 30% or more, the secondary null hypothesis would be rejected, and a complete response rate of 30% or more after 24 weeks of treatment with osilodrostat would be concluded. Testing on the key secondary endpoint was only done if the null hypothesis for the primary objective was rejected to ensure preservation of the overall two-sided type 1 error at 5%. We analysed the key secondary endpoint using the full analysis set (ie, all enrolled participants who received at least one dose of osilodrostat). Other secondary efficacy endpoints were analysed using the full analysis set or the randomised analysis set as appropriate.

We summarised changes from baseline in secondary endpoint parameters descriptively. Safety was analysed for all patients who received at least one dose of osilodrostat and had at least one valid safety assessment, or for patients who received at least one dose of randomised treatment and had at least one valid safety assessment during the randomised withdrawal period. We assessed safety using all data from the first visit of the first patient until the time the last patient completed or discontinued the core study (ie, safety is reported beyond 48 weeks for some participants). We tabulated the number and proportion of patients with adverse events by preferred term and CTCAE grade. For patients who discontinued the randomised

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**Figure 3:** Changes in mean 24-h UFC concentration during the randomised withdrawal phase, by randomised treatment group (A) and from baseline to week 24 (B).

Mean 24-h UFC concentration ULN was 138 nmol/24 h. Each vertical set of datapoints is for one participant. For panel B, patients are shown in order of decreasing baseline mean 24-h UFC concentration. Five patients had mean 24-h UFC concentrations of ≤ULN at baseline; however, mean 24-h UFC was ≥1·5 times the ULN at screening, thus the patients met the eligibility criterion. RR=response rate. UFC=urinary free cortisol. ULN=upper limit of normal.
withdrawal period and resumed open-label osilodrostat, we report adverse events that occurred after withdrawal of randomly assigned treatment as part of the open-label osilodrostat phase. We calculated the proportion of patients who maintained a complete response for at least 6 months from the time of their first complete response (patients who were randomly assigned to placebo were excluded); patients who discontinued within 6 months of their first complete response were classed as non-responders for this analysis. We did post-hoc pairwise correlation analyses to assess the associations between adrenocorticotropic hormone and mean 24-h UFC concentrations, and between 11-deoxycorticosterone concentrations and systolic blood pressure and serum potassium concentrations. We assessed changes in androgen and oestrogen levels and the occurrence of associated adverse events overall and by sex. We assessed changes in tumour volume overall and by maximum tumour diameter at baseline (<10 mm or ≥10 mm).

We did all statistical analyses using SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT02180217.

### Role of funding source
The funder of the study contributed to study design, data collection, data analysis, data interpretation, writing of the report, and decision to submit the report for publication. The funder also paid for the services of professional medical writers, who provided editorial assistance in developing the outline and subsequent drafts of the manuscript. All authors had full access to all the study data and were responsible for interpreting the data, writing the manuscript, and the decision to submit for publication.

### Results
Between Nov 12, 2014, and March 22, 2017, 202 patients were screened and 137 were enrolled to receive open-label osilodrostat (figure 2). 84 patients completed a mandated washout period for other medical therapies for Cushings’s disease before enrolment. Of these patients, 36 were previously on ketoconazole, 24 were on long-acting or short-acting pasireotide, 18 were on cabergoline, four were on mifepristone, one was on metyrapone, and one was on mitotane. The median age was 40·0 years (IQR 31·0–49·0) and 106 (77%) participants were female (table 1). At week 26, 71 (52%) patients who were eligible for the randomised withdrawal phase were randomly assigned to continue osilodrostat (n=36) or matching placebo (n=35).

19 patients discontinued treatment before the randomised withdrawal phase, and one patient met randomisation criteria but was not randomly assigned in accordance with the investigator’s decision, staying on open-label osilodrostat. Of the remaining 46 patients not randomly assigned to treatment, 20 did not meet the mean 24-h UFC normalisation criteria at week 24, and 26 had dose increases during weeks 13–24, although 19 of these 26 patients later met the mean 24-h UFC normalisation criteria at week 24. Among the enrolled patients, 106 (77%) entered the extension phase, which is now complete.

Baseline patient characteristics were generally balanced between the treatment groups of the randomised withdrawal phase, although the median of the mean 24-h UFC concentrations was higher in patients in the osilodrostat group than among those in the placebo group (457 nmol/24 h [IQR 268–777] vs 358 nmol/24 h [210–652]; normal range 11–138 nmol/24 h; table 1). However, the median of the mean 24-h UFC concentrations were similar between these two groups at the start of the randomised withdrawal period (week 26: 57·0 nmol/24 h [IQR 44·2–87·5] vs 57·0 nmol/24 h [40·5–96·6]).

By week 24, 85 (62%) patients were receiving an osilodrostat dose of 5·0 mg or lower twice a day, irrespective of severity of increased mean 24-h UFC concentration at baseline, with only eight (6%) of 137 patients requiring a dose of more than 10·0 mg twice a day. During the first 26 weeks, mean dose received was 10·0 mg per day (SD 7·3), and mean highest dose was 17·8 mg per day (13·6). 100 (73%) patients had a dose reduction during the first 26 weeks. During the randomised withdrawal phase, mean dose was 10·0 mg per day (SD 9·6). 121 (88%) patients were treated for more than 24 weeks, with 105 (77%) patients exposed to

<table>
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<tr>
<th>Table 2: Proportion of participants who met the primary efficacy endpoint at week 34, by randomly assigned treatment group and randomisation strata</th>
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<tbody>
<tr>
<td><strong>Responders</strong></td>
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<tr>
<td><strong>All participants randomly assigned to treatment</strong></td>
</tr>
<tr>
<td>Osilodrostat</td>
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<tr>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Osilodrostat dose at week 24 of ≥5 mg twice daily</strong></td>
</tr>
<tr>
<td>With history of pituitary irradiation</td>
</tr>
<tr>
<td>Osilodrostat</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>Without history of pituitary irradiation</td>
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<tr>
<td>Osilodrostat</td>
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<tr>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Osilodrostat dose at week 24 of &gt;5 mg twice daily</strong></td>
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<tr>
<td>With history of pituitary irradiation</td>
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<td>Osilodrostat</td>
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<td>Placebo</td>
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<tr>
<td>Without history of pituitary irradiation</td>
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<tr>
<td>Osilodrostat</td>
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<tr>
<td>Placebo</td>
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Data are n/N (%; 95% CI) or odds ratio with 95% CI in parentheses. Odds ratio calculated using the Cochran-Mantel-Haenszel exact test. The Cochran-Mantel-Haenszel test incorporates the impact of the stratification factors on the odds ratio and associated p value; p values are not shown for the analysis by randomisation strata because multiplicity adjustment was not applied. Responders are defined as participants who met the primary endpoint. NE=not evaluable.
osilodrostat for at least 48 weeks (core phase). Median exposure was 74–7 weeks (IQR 48.1–117.0; including the 48-week core phase plus extension data up to the data cut-off date [Feb 21, 2018], when all patients had completed the core period of the study or discontinued early). 42 (31%) of 137 patients received at least one dose of osilodrostat different to that planned in the protocol.

At the end of the randomised withdrawal phase (week 34; study period 3), significantly more patients who continued osilodrostat treatment maintained a complete response, without a dose increase above the level at week 26, versus those who were on placebo (31 [86%] of 36 vs ten [29%] of 34; OR 13.7; 95% CI 3.7–53.4; p<0.0001; figure 3, table 2; intrapatient changes in mean 24-h UFC concentrations are shown in the appendix [p 13]). One patient randomly assigned to the placebo group did not receive treatment because of an adverse event (glucocorticoid deficiency), which required drug interruption. A consistent treatment effect was observed irrespective of randomisation stratum (week 24 dose of ≤5 or >5 mg twice a day, and history of pituitary irradiation; table 2).

Of the ten patients randomly assigned to the placebo group who maintained a complete response at the end of the randomised withdrawal period, at baseline seven had mean 24-h UFC concentrations of less than 2 times the ULN, two had mean 24-h UFC concentrations of 2–5 times the ULN, and one had a mean 24-h UFC concentration of more than 5 times the ULN. All ten patients had previous neurosurgery, all of which took place at least 6 months before enrolment, and one patient had received previous pituitary irradiation. Of the three patients with baseline mean 24-h UFC concentration of more than 2 times the ULN, all were receiving osilodrostat at 2 mg or lower twice a day at week 24.

The key secondary endpoint was also met. At week 24 (end of study period 2), 72 (53%; 95% CI 43.9–61.1) of 137 patients maintained a complete response without a dose increase after week 12 (end of study period 1). Irrespective of dose increase, 93 (68%) of 137 patients had a mean 24-h UFC concentration of less than or equal to the ULN, two had mean 24-h UFC concentrations of 2–5 times the ULN, and one had a mean 24-h UFC concentration of more than 5 times the ULN. All ten patients who were randomly assigned to the placebo group did not receive treatment because of an adverse event (glucocorticoid deficiency), which required drug interruption. A consistent treatment effect was observed irrespective of randomisation stratum (week 24 dose of ≤5 or >5 mg twice a day, and history of pituitary irradiation; table 2).

Most enrolled patients (132 [96%] of 137) had a mean 24-h UFC concentration of less than or equal to the ULN at least once during the study, with no differences observed between men and women (data not shown); median time to first complete response was 41·0 days (IQR 27·0–56·0). Excluding patients who were randomly assigned to placebo, 64 (66%) of 97 patients who had a complete response during the study period maintained a complete response for at least 6 months. At the end of the core phase (week 48), 91 (66%) enrolled patients had a complete response, and 13 (9%) enrolled patients had a partial response (mean 24-h UFC concentration above the ULN but ≥50% reduction from baseline; data for weeks 12, 24, and 48 are in the appendix [p 9]).

Overall, the mean of the mean 24-h UFC concentration decreased rapidly during the initial 12-week dose-titration period (study period 1), then remained below baseline values throughout the study (appendix p 14). Mean morning serum and late-night salivary cortisol concentrations also decreased rapidly in the first 12 weeks, then remained below baseline values; however, slight increases were seen in patients randomly assigned to the placebo group between weeks 28 and 34 (appendix p 14).

**Table 3: Adverse events during the randomised withdrawal phase, by randomly assigned treatment group**

<table>
<thead>
<tr>
<th></th>
<th>Osilodrostat (n=36)</th>
<th>Placebo (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any adverse event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All grades</td>
<td>26 (72%)</td>
<td>23 (66%)</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>Any serious adverse event</strong></td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>Adverse events requiring dose adjustment</strong></td>
<td>7 (19%)</td>
<td>5 (14%)</td>
</tr>
<tr>
<td><strong>Anticipated adverse events of special interest</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Related to adrenal hormone precursor accumulation</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Related to hypocortisol</td>
<td>3 (8%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Related to pituitary tumour enlargement</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Related to QT prolongation</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Arhythmogenic potential on ECG</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Most common study-emergent adverse events*: Nausea 4 (11%) 0 0 0, Anaemia 3 (8%) 0 3 (9%) 0, Arthralgia 3 (8%) 0 0 0, Headache 3 (8%) 0 0 0, Asthenia 2 (6%) 0 0 0, Blood corticotropin increased 2 (6%) 0 1 (3%) 1 (3%), Constipation 2 (6%) 0 0 0, Depression 2 (6%) 0 1 (3%) 0, Dizziness 2 (6%) 0 1 (3%) 0, Fatigue 2 (6%) 0 3 (9%) 1 (3%), Hirsutism 2 (6%) 0 1 (3%) 0, Nasopharyngitis 2 (6%) 0 1 (3%) 0, UFC decreased 2 (6%) 0 1 (3%) 0, Cough 1 (3%) 0 2 (6%) 0, Insomnia 1 (3%) 0 2 (6%) 0, Urinary tract infection 1 (3%) 0 2 (6%) 0, Diarrhoea 0 0 2 (6%) 0, Gastro-oesophageal reflux disease 0 0 2 (6%) 0.

Patients with multiple events in the same category are counted only once in that category. ECG=electrocardiogram. NA=not assessed. UFC=urinary free cortisol. *Occurring in ≥5% of patients in either group.
Overall, improvements were observed from baseline in most of the assessed cardiovascular-related metabolic parameters associated with hypercortisolism, including bodyweight, BMI, fasting plasma glucose, systolic and diastolic blood pressure, and total and LDL cholesterol (appendix p 10). A slight decrease from baseline in HDL cholesterol was observed at week 48 (–0.3 mmol/L, 95% CI –0.3 to –0.2). At baseline, mean CushingQoL score was 42–2 (SD 19–1) and mean Beck Depression Inventory score was 16–8 (10–6). Both scores improved, with mean CushingQoL score increasing by 52–4% (95% CI 32–3 to 72–7), and Beck Depression Inventory score decreasing by 31–8% (95% CI –44–3 to –19–3), by week 48 (appendix p 11). Changes in CushingQoL score reached the distribution-based minimum important difference of a 10–1-point change from baseline at weeks 26, 30, 32, 34, and 48 (data for week 48 shown in appendix [p 10], otherwise data not shown). Changes in Beck Depression Inventory score reached the minimum important difference of a 17–5% reduction from baseline at weeks 24, 26, 28, 30, and 48 (data for week 48 shown in appendix [p 10], otherwise data not shown). Most improvements in clinical and laboratory parameters were evident during the dose-titration period (up to week 12; study period 1) and were generally maintained throughout the study (appendix p 11), including the 8-week randomised withdrawal period, although this was a short timeframe.

For patients with evaluable assessments, mean \(C_{\text{max}}\) increased with increasing doses of osilodrostat during the initial 12-week dose-titration period. At the end of the dose-titration period (week 12), mean plasma osilodrostat concentration was 4–5 ng/mL 2 h after a 1 mg (n=16) incident dose and 54–0 ng/mL 2 h after a 10 mg (n=20) incident dose.

All patients had at least one investigator-reported adverse event during the study, most frequently nausea (57 [42%]), headache (46 [34%]), fatigue (39 [28%]), and adrenal insufficiency (38 [28%]; appendix p 12). The most frequently reported grade 3–4 adverse events were adrenal insufficiency (six [4%]), glucocorticoid deficiency (five [4%]), headache (four [3%]), and vomiting (four [3%]).

A similar proportion of patients randomly assigned to continue osilodrostat treatment or switch to placebo had adverse events during the randomised withdrawal period (26 [72%] of 36 in the osilodrostat group and 23 [66%] of 35 in the placebo group). The most commonly reported adverse events in the osilodrostat group during the randomised withdrawal were nausea (four [11%] vs zero in the placebo group), anaemia (three [8%] vs three [9%]), arthralgia (three [8%] vs zero), and headache (three [8%] vs zero; table 3). Arthralgia was often considered by the treating investigator to be related to the underlying disease or otheropathologies (including injuries).

Hypocortisolism-related adverse events were clinically assessed and reported by the investigators in 70 (51%) patients at any point during the study (appendix p 12), most commonly being classified as adrenal insufficiency (38 [28%] of 137) or glucocorticoid deficiency (29 [21%]), which reflect the same condition. These events mostly occurred and resolved during the dose-titration period (study period 1), which were typically single episodes of grade 1–2 severity, and were managed by dose reductions or interruptions and corticosteroid supplementation when clinically indicated (data now shown). 25 (36%) of 70 patients with one or more hypocortisolism-related adverse event required treatment with glucocorticoids. Generally, mean 24-h UFC measurements closest to the occurrence of these events did not decrease to below the LLN (ie, the adverse event occurred concurrently with a rapid decrease in pathologically high cortisol concentrations, which were still >ULN or within the normal range; data not shown). No association was observed between the dose of osilodrostat or baseline mean 24-h UFC concentration and the occurrence of hypocortisolism-related adverse events (data not shown).

Five (4%) enrolled patients had an increase in alaninaminotransferase or aspartate aminotransferase enzymes above 3 times the ULN, which were typically mild and reversed spontaneously or after dose adjustment. Adverse events potentially related to increases in adrenal hormone precursors occurred in 58 (42%) patients during the study (mostly grade 1–2; appendix p 12), most commonly reported as hypokalaemia (18 [13%]) and hypertension (17 [12%]). Although serum potassium concentrations were generally maintained within the normal range, we observed a pattern of greater decreases in mean serum potassium levels with increasing osilodrostat \(C_{\text{max}}\) (appendix p 15). Seven patients had newly occurring grade 3–4 hypokalaemia, among whom the lowest reported serum potassium concentration observed was 2.4 mmol/L (normal range was 3.5–5.3 mmol/L). Episodes of hypokalaemia were treated with potassium supplements, spironolactone, dose reduction or interruption, or a combination of these approaches.

No male participants had adverse events related to increases in androgens or oestrogens during the study. In female participants, adverse events of hirsutism (12 [11%] of 106), acne (12 [11%]), and hypertrichosis (one [1%]) were reported; all were grade 1–2 and none led to study discontinuation. An adverse event of QT interval prolongation was reported in five (4%) patients (QTcF values <480 ms at all timepoints); all were reported as non-serious, which resulted in dose adjustment or interruption in three patients and discontinuation in one patient. One (1%) patient had an arrhythmogenic-potential-related adverse event of syncope, which was not suspected to be related to the study drug and spontaneously resolved.

18 (13%) patients discontinued treatment because of an adverse event by the time of the data cut-off, most commonly adrenal insufficiency (four [3%]) and pituitary tumour (four [3%]), reported as pituitary tumour enlargement, pituitary tumour volume increase, increased adenoma size, or pituitary tumour growth. Of the four patients who discontinued because of an adverse
event of the pituitary tumour, two had macroadenomas and two had microadenomas at baseline. 81 (59%) patients had a measurable pituitary tumour at baseline (13 [16%] had a macroadenoma [≥10 mm] and 68 [84%] had a microadenoma [<10 mm]). 79 (58%) patients had a measurable tumour at both baseline and at least one post-baseline assessment. A similar proportion of patients had either a decrease of 20% or more or an increase of 20% or more from baseline in tumour volume at week 24 (20 [30%] of 66 evaluable patients had a ≥20% increase and 19 [29%] had ≥20% decrease) and week 48 (24 [38%] of 64 evaluable patients had a ≥20% increase and 21 [33%] had a ≥20% decrease). Similar results were observed irrespective of maximum tumour diameter at baseline (<10 mm or ≥10 mm; data not shown). Four patients with an increase of 20% or more and 13 with a decrease of 20% or more in tumour volume from baseline had received previous pituitary irradiation. In patients with no tumour identifiable at baseline, none had evidence of a newly measurable pituitary tumour identified by MRI during the study.

One death occurred, which was not considered to be related to the study drug; the patient died by suicide during the extension phase (day 551) in the context of an extensive psychiatric history. The patient, who was randomly assigned to the placebo group, had a mean 24-h UFC concentration within the normal range during osilodrostat treatment. All enrolled patients received concomitant medications and clinically relevant non-drug therapies during the study. The most common concomitant medications (received by >20% of patients) were paracetamol (61 [45%] of 137), spironolactone (32 [23%]), colecalciferol (36 [26%]), and levothyroxine (34 [25%]). Concomitant medications were mainly prescribed to manage adverse hormone levels were greater than the ULN (18·4 pmol/L [SD 35·5]) at baseline and increased during the study to 50·0 pmol/L (69·7) at week 48. No association was observed between adrenocorticotropic hormone and cortisol concentrations (Pearson’s correlation coefficient at week 48: −0·10; appendix p 13). Mean adrenocorticotropic hormone concentration was seen in both male and female participants during the first 12 weeks of the study, which stabilised thereafter (appendix p 17). In male participants, mean testosterone concentrations increased from 9·5 nmol/L (SD 5·8) at baseline to 17·7 nmol/L (8·0) at week 48. For individual male participants, testosterone concentrations generally increased from the low end of the normal range to the middle of the normal range, with no values above the ULN reported for last available values. For some male patients, testosterone increased from below the LLN into the normal range during osilodrostat treatment (data not shown). In female participants, mean testosterone concentrations increased from 1·3 nmol/L (SD 1·2) at baseline to 2·6 nmol/L (2·4) at week 48. In male and female participants, a mild increase in gonadotropin concentrations was seen from baseline (data not shown), although we cannot exclude effects of spontaneous recovery of post-surgical damage of the gonadotropin pituitary cells. Compared with baseline, gradual reductions were seen in plasma aldosterone and dehydroepiandrosterone sulphate, and gradual increases were seen in 11-deoxycorticosterone, renin, serum oestradiol, and oestrone (appendix p 18). No clear pattern was observed between absolute 11-deoxycorticosterone concentrations and systolic blood pressure or serum potassium concentrations, or between changes from baseline in these parameters (data not shown).

**Discussion**

This large prospective study is, to our knowledge, the first phase III trial of a medical therapy for patients with Cushing’s disease to include a randomised, double-blind, placebo-controlled period. The study met both its primary and key secondary endpoints. At the end of the 8-week, randomised withdrawal phase (study period 3), a significantly higher proportion of patients in the osilodrostat group maintained a complete response versus placebo. These findings were seen irrespective of randomisation strata, confirming that previous irradiation and higher osilodrostat dose were not driving factors for mean 24-h UFC response.

For the patients who were given placebo who maintained a complete response, the last mean 24-h UFC concentration during the withdrawal phase was higher than that at week 24 in nine of ten patients but still within the normal range, with all nine patients showing a progressive increase in mean 24-h UFC during this period; a longer withdrawal period would likely have resulted in a higher proportion of patients who were given placebo having increased mean 24-h UFC concentrations. These results
are consistent with findings from a 10-week proof-of-concept study of osilodrostat in patients with Cushing’s disease (n=12), in which mean 24-h UFC concentrations remained below the ULN in two (17%) patients with an evaluable assessment after a 2-week washout of osilodrostat, although mean 24-h UFC concentration was based on a single sample in these patients. This finding that ten patients who were randomly assigned to placebo maintained a complete response at the end of the randomised withdrawal period might have been influenced by most of these patients having mild increases in mean 24-h UFC concentrations at baseline (less than 2 times the ULN in seven patients), or by fluctuations in mean 24-h UFC concentrations, or both. However, the significant difference in complete response between the two randomised groups strongly indicates a benefit with osilodrostat. A delay in cortisol recovery after withdrawal of osilodrostat in some patients is also a possibility. We did not observe an association between adrenocorticotropic hormone and cortisol concentrations in our study. Additionally, a delay in cortisol increase above the ULN in some patients is not fully explained by the reversible inhibitory effect of osilodrostat on 11β-hydroxylase, and no evidence supports a cytolytic effect of osilodrostat on adrenal tissue or extended duration of action on the hypothalamic–pituitary–adrenal axis. As such, the reason underlying a delayed increase in cortisol above the ULN in some patients after osilodrostat withdrawal is unknown and further investigation would be of interest.

Participants had a rapid reduction in mean 24-h UFC concentration during the initial 24-week open-label phase, which included the dose-titration (study period 1) and therapeutic-dose periods (study period 2). More than half (53%) of participants enrolled achieved the key secondary endpoint of mean 24-h UFC concentration of less than or equal to the ULN at week 24 without dose up-titration after week 12. Furthermore, most patients (96%) achieved a complete response at some point during osilodrostat treatment, with 66% of patients maintaining a complete response for at least 6 months after their first response, indicating that osilodrostat provides sustained control of mean 24-h UFC concentrations in most patients. The lower proportion of patients with a complete response at the end of the core phase than at any point during the study might be explained by day-to-day fluctuations in mean 24-h UFC measurements, or the classification of patients who discontinued before week 48 as non-responders at this timepoint. Decreases in mean morning serum and late-night salivary cortisol accompanied the decreases in mean 24-h UFC concentration, further strengthening our conclusion of a benefit with osilodrostat treatment for patients with Cushing’s disease. In a recent phase III study of the investigational drug levoketoconazole, a steroidogenesis inhibitor, 29 (31%) of 94 patients with Cushing’s syndrome achieved a mean 24-h UFC concentration of less than or equal to the ULN after an initial dose-titration period and 6 months of maintenance therapy (without a dose increase during the maintenance phase).10

Reductions in mean 24-h UFC concentration during 48 weeks of osilodrostat treatment were accompanied by improvements in weight, BMI, fasting plasma glucose, systolic and diastolic blood pressure, and total cholesterol. Improvements occurred soon after osilodrostat initiation and were sustained until the end of the study. Given the known clinical burden of cardiovascular risk associated with Cushing’s disease, the improvement in clinical features shown here indicates important benefits of osilodrostat. By improving multiple cardiovascular risk factors, our findings are likely to be clinically relevant. The slight decrease in HDL cholesterol observed at week 48 was similar to that described in a study of mifepristone (a glucocorticoid receptor antagonist) for the treatment of Cushing’s syndrome: further investigation concluded that such a reduction would not adversely affect cardiovascular risk.16 At baseline, the mean CushingQoL score (42 [SD 19]) showed the substantial effect of hypercortisolism on the quality of life of patients enrolled in our study. Osilodrostat led to clinically meaningful improvements in HRQoL throughout the study from week 12, including in CushingQoL score, despite considerable impairments at baseline associated with extended duration of hypercortisolism.10 Clinically meaningful improvements in depression as assessed by the Beck Depression Inventory score were also evident throughout the study, representing clinical benefit after starting osilodrostat treatment. Future evaluation of other manifestations of cortisol excess, including menstrual abnormalities (which often resolve after normalisation of cortisol concentrations17), facial rubor, striae, muscle wasting, and bone loss, would be of considerable interest given the potential deleterious effects they can exert on quality of life and morbidity.3

Osilodrostat was generally well tolerated and commonly reported adverse events were as expected on the basis of its mechanism of action. Adverse events were consistent with those reported during the 22-week phase II study of osilodrostat.11 Most patients (82%) completed the 48-week study, and as of data cut-off, the rate of discontinuations due to adverse events was low (13%) and one death had occurred, which was not attributed to osilodrostat. The most commonly reported adverse events of special interest (associated with osilodrostat) were related to hypoglycaemia, highlighting the potency of osilodrostat; these events were generally managed with dose adjustments or corticosteroid supplementation, or both. These adverse events were mostly mild to moderate in severity and mainly occurred during the initial dose-titration period, as was also found when using either metyrapone18 or ketoconazole19 in previous studies. Because most adverse events occurred during the rapid dose up-titration period (forced dose increases every 2 weeks if mean 24-h UFC concentration was >ULN), we anticipate that smaller dose increases or more gradual
Articles

Limitations to this study included the short length (8 weeks) of the randomised withdrawal period, which was not long enough to confirm whether withdrawal of osilodrostat would have resulted in worsening clinical signs and symptoms of hypercortisolism. Longer-term follow-up to assess both duration of efficacy and long-term safety will be important. Additionally, no patients older than 70 years were enrolled in our study, so further assessment of osilodrostat in older patients might be of interest. Assessment of serum or salivary cortisol levels, or both, across a 24-h period would be valuable to further explore the pharmacodynamic effect of twice-daily osilodrostat, including on the restoration of cortisol diurnal rhythm, which is frequently disrupted in patients with Cushing’s disease.28 Notably, nearly all patients received concomitant medications during the study, including antihypertensive and antidiabetic medications, and we are unable to exclude the possibility that these medications might have affected some findings. Further examination of the effects of osilodrostat on the clinical signs of Cushing’s disease, and the reasons for changes in concomitant medications and the association between such medications and clinical outcomes would be valuable.

In summary, the results of this prospective, phase III study, which included a double-blind randomised withdrawal phase, show that osilodrostat rapidly reduces mean 24-h UFC and serum cortisol concentrations and sustains these reductions alongside improvements in clinical signs of hypercortisolism, CushingQoL score, and depression without unexpected side-effects. Alongside careful dose adjustments and monitoring of known risks associated with osilodrostat, our findings indicate a positive benefit-risk consideration of treatment for most patients with Cushing’s disease.

Contributors

RP, MF, JN-P, XB, JF, AS, FG, and BMKB, as part of the academic investigator steering committee, and AMP, LT, Alap, and the funder designed the study. RP, MF, JN-P, XB, JF, AS, FG, RA, RL, EJL, JHK, ALaC, and BMKB all enrolled patients in the study. Data were collected by investigators of the LINC 3 Study Group using the funder’s data management systems. PO and the funder’s statistical team analysed the data. A data-sharing and kick-off meeting was held with all authors and an outline prepared by a professional medical writer based on interpretation provided by the authors. Each new draft of the manuscript subsequently prepared by the medical writer was reviewed and revised in line with direction and feedback from all authors. All authors approved the final version of the manuscript and made the final decision to submit.

Declaration of interests

RP reports grants and personal fees from Novartis, Pfizer, HRA Pharma, Viopharma, Shire, and Ipsen; personal fees from Ferring and Italfarmaco; and grants from Concept Therapeutics, Cortendo AB, and Institut Bioclinique SA. MF reports grants to her university and personal consulting fees from Strongbridge and Novartis and grants to her university from Millendo. JN-P reports grants from Novartis, HRA Pharma, and Diurnal; and research grants and consultancy payments to his university from Novartis, HRA Pharma, and Diurnal. XB reports personal fees from Novartis, Idiosa, and Ipsen. JF reports grants, investigator fees, and consulting fees from Novartis and consulting fees from Concept Therapeutics. RA reports grants and
personal fees from Strongbridge Biopharma, Novartis, Millendo, Spruce Biosciences, Corcept Therapeutics, and Neurocrine Biosciences; and personal fees from Corcept Therapeutics, Janssen Pharmaceuticals, Diurnal, LTD, Selenity Therapeutics, Quest Diagnostics, and Adrenas Therapeutics. ALa reports grants from Novartis, Corcept Therapeutics, Strongbridge Biopharma, and GIWL Research; and personal fees from Novartis and Corcept Therapeutics. ALa, PO, IT, and AMP report employment by Novartis. BMKB reports grants and personal fees from Novartis and Strongbridge; and grants from Millendo. All other authors declare no competing interests.

Data sharing
Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trial, in line with applicable laws and regulations. This trial data availability is in accordance with the criteria and process described on www.clinicalstudydatarequest.com. Data will be made available to requests upon publication with no time limit specified.

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