NHS England Evidence Review:

Osilodrostat phosphate for the treatment of people with Cushing's disease requiring pharmacological treatment

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Osilodrostat phosphate for the treatment of people with Cushing's disease requiring pharmacological treatment

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of osilodrostat phosphate in people with Cushing's disease compared to standard care.

Cushing's syndrome is an endocrine disorder caused by prolonged exposure to excessive levels of glucocorticoids, which may be due to exposure to exogenous glucocorticoids or to excessive production of the endogenous glucocorticoid cortisol. Approximately 70% of endogenous Cushing's syndrome cases are caused by an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma, a condition called Cushing's disease. People with Cushing's syndrome (excluding people with Cushing's disease) are considered in a separate review.

Cushing's syndrome leads to a broad spectrum of clinical signs and symptoms. The most prevalent manifestations, occurring in ≥70% of patients, include central obesity, facial plethora, proximal myopathy, menstrual irregularity in women, neuropsychiatric symptoms, skin atrophy, red/purple stretchmarks, easy bruising, hypertension, type 2 diabetes, and dyslipidaemia.

Untreated Cushing's syndrome caries a very poor prognosis, with a relative risk of death for those with persistent disease 10-fold greater than those in remission.

It is recommended that the first-line treatment for most patients is surgery to the source of their Cushing's syndrome. Patients will generally need treatment with medication for their Cushing's syndrome at diagnosis to optimise them pre-surgery. Controlling the hypercortisolism reduces surgical risks such as venous thromboembolism and infection. However, a proportion of patients will have persistent or recurrent hypercortisolism after surgery, are not good candidates for, or decline surgery. For these patients, repeat surgery, radiation therapy, or on-going medical therapy may be considered.

Current licensed treatments for endogenous Cushing's syndrome include metyrapone and ketoconazole. Limitations of these treatments include limited clinical effectiveness and risk of adverse events. Osilodrostat phosphate is licensed for the treatment of endogenous Cushing's syndrome in adults. This evidence review proposes osilodrostat phosphate as a pharmacological treatment option for patients with Cushing's disease.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from osilodrostat phosphate more than others and the schedules/doses of osilodrostat phosphate that were used.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of osilodrostat phosphate in the treatment of Cushing's disease. The searches for evidence published since January 2013 were conducted on 18 October 2023 and identified 116 references, and updated searches including the development name for osilodrostat phosphate (LCI699) were conducted on 4 January 2024 and identified a further 69 references. The titles and abstracts were screened, and 19 full text papers were obtained and assessed for relevance. Papers relating to osilodrostat phosphate for the treatment of Cushing's syndrome (excluding Cushing's disease) disease are included in a separate evidence review.

Four studies (two of which each included two component studies) were identified for inclusion in this review on Cushing's disease, reported in seven papers (summarised in Table 1 below).

- LINC2 was a single-arm phase II study reported in Fleseriu et al 2016 in which 19 patients received osilodrostat phosphate for up to 22 weeks. In an extension of LINC2 reported in Fleseriu et al 2022a, 16 of the patients continued to receive osilodrostat phosphate for a total of up to 70 weeks, and a number continued osilodrostat phosphate longer term, the longest being for 6.7 years.
- LINC3 was a phase III study with a randomised withdrawal period within a single-arm study, reported in Pivonello et al 2020 and Fleseriu et al 2022b. In Pivonello et al 2020 there was an initial 26-week single-arm study during which 137 patients received osilodrostat phosphate. This was followed by an eight-week period during which 71 patients who met eligibility criteria based on mean 24-hour urinary free cortisol (UFC) and osilodrostat phosphate dose were randomised to either osilodrostat phosphate or placebo. Sixty-six patients who did not meet the eligibility criteria continued osilodrostat phosphate. From week 35 to the end of the study at week 48 all patients received open label osilodrostat phosphate. In an extension of LINC3 reported in Fleseriu et al 2022b 106 of the patients continued to receive osilodrostat phosphate for a total of up to 72 weeks.
- LINC4 was a phase III study which included a randomised period followed by a single-arm study reported in Gadelha et al 2022 and Gadelha et al 2023. In Gadelha et al 2022 73 patients were randomised to osilodrostat phosphate or placebo for 12 weeks, and all patients then received osilodrostat phosphate for a further 36 weeks. In an extension of LINC4 reported in Gadelha et al 2023 60 of the patients continued to receive osilodrostat phosphate for a total of up to 96 weeks.

LINC3 and LINC4 therefore both included short-term randomised phases (8 weeks and 12 weeks respectively) comparing osilodrostat phosphate with placebo, which were reported in Pivonello et al 2020 (LINC3) and Gadelha et al 2022 (LINC4). They also both reported outcomes from treatment of the whole cohort with osilodrostat phosphate with no comparator, reported in Pivonello et al 2020 and Fleseriu et al 2022b (LINC3) and Gadelha et al 2022 and Gadelha et al 2023 (LINC4). In LINC2, reported in Fleseriu et al 2016 and Fleseriu et al 2022a, only outcomes of treatment with osilodrostat phosphate with no comparator were reported.

- The fourth study included in the review was a retrospective cohort study (Bonnet-Serrano et al 2022) which compared patients treated with osilodrostat phosphate with patients treated with metyrapone and reported disease response at a single point.

No evidence was identified comparing osilodrostat phosphate with ketoconazole and no evidence relating to cost effectiveness was identified.

All the patients recruited to the LINC studies had Cushing's disease, but Bonnet-Serrano et al 2022 included four patients with Cushing's syndrome in their total of 33 patients. All studies

included adults only and a majority of female patients. The study by Bonnet-Serrano et al 2022 was conducted in France, and the remaining studies were multicentre in locations in North America, South America, Europe and Asia; LINC3 included locations in the UK but it was not stated how many patients had been recruited there.

Table 1: Summary of included studies, authors and comparators

Study name	Paper author	Comparisons reported
LINC2	Fleseriu et al 2016 Fleseriu et al 2022a	Osilodrostat phosphate with no comparator
LINC3	Pivonello et al 2020	Osilodrostat phosphate vs placebo Osilodrostat phosphate with no comparator
	Fleseriu et al 2022b	Osilodrostat phosphate with no comparator
LINC4	Gadelha et al 2022	Osilodrostat phosphate vs placebo Osilodrostat phosphate with no comparator
	Gadelha et al 2023	Osilodrostat phosphate with no comparator
	Bonnet-Serrano et al 2022	Osilodrostat phosphate vs metyrapone

In terms of clinical effectiveness:

- **Clinical disease response (critical outcome)**
  - Osilodrostat phosphate vs placebo

    One randomised study (LINC3) provided moderate certainty evidence of improvement or no change in facial rubor, hirsutism, striae, subcutaneous fat pad, dorsal fat pad, proximal muscle atrophy, central obesity and ecchymoses in at least 88% of patients after 48 weeks treatment (consisting of either 48 weeks osilodrostat phosphate or 12 weeks placebo followed by 36 weeks osilodrostat phosphate). There was no statistically significant difference between the treatment groups in the proportion of patients who had improved or not changed with respect to any of the physical characteristics. Physical characteristics with the greatest improvements (reported in at least 40% of all patients) were subcutaneous fat pad, dorsal fat pad, facial rubor and central obesity.
  - Osilodrostat phosphate vs metyrapone

    No evidence relating to clinical disease response was identified for osilodrostat phosphate compared to metyrapone.
  - Osilodrostat phosphate vs no comparator

    One single-arm study (LINC4) provided very low certainty evidence that after 72 weeks treatment with osilodrostat phosphate female hirsutism had improved in 45% and remained stable in 42% of women with normal testosterone, and had improved in 21% and remained stable in 64% of women with raised testosterone. Improvements in female hirsutism were seen in some patients from 12 weeks of treatment onwards.
- **Biochemical disease response (critical outcome)**
  - Osilodrostat phosphate vs placebo

    Two randomised studies (LINC3 and LINC4) provided moderate certainty evidence of a statistically significantly better complete response rate (based on mean urinary free cortisol (UFC) levels)[1] in patients randomised to osilodrostat phosphate compared to patients randomised to placebo after 8 weeks and 12 weeks treatment. One of the randomised studies (LINC3) also provided moderate certainty evidence of no

[1] Controlled or complete response: mean urinary free cortisol (UFC)≤ upper limit of normal (ULN); partially controlled or partial response: mean UFC>ULN and with ≥50% reduction from baseline. Overall response = complete response + partial response. Mean 24-hour UFC reference range: 11-138 nmol/24 hours

statistically significant differences in overall, complete and partial response rates after 48 weeks treatment in patients randomised to 48 weeks osilodrostat phosphate compared to patients randomised to 8 weeks placebo between weeks 27 and 34 and osilodrostat phosphate between weeks 1 to 26 and weeks 35 to 48.

One randomised study (LINC4) provided low certainty evidence that after 12 weeks treatment mean 24-hour UFC levels fell to within the normal range in patients randomised to osilodrostat phosphate but did not fall in patients randomised to placebo, but the two groups were not compared statistically. The same randomised study provided moderate certainty evidence that after 12 weeks randomised treatment there was a statistically significantly greater fall in mean serum cortisol levels in patients randomised to osilodrostat phosphate than in patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate, mean serum cortisol levels had fallen in both groups and there was no statistically significant difference between them in the change in serum cortisol levels.

One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks randomised treatment the early-morning and late-night salivary cortisol levels had fallen more in patients randomised to osilodrostat phosphate than in patients randomised to placebo, but there was no statistically significant difference between the groups in the change in levels. After a further 36 weeks treatment of both groups with osilodrostat phosphate levels had fallen in both groups and there was no statistically significant difference between them in the change in early-morning or late-night salivary cortisol levels.

- Osilodrostat phosphate vs metyrapone

  One retrospective cohort study provided very low certainty evidence that patients treated with osilodrostat phosphate had a statistically significantly lower median serum cortisol level than patients treated with metyrapone at the time of best control of hypercortisolism. No evidence was identified for any other biochemical disease response outcomes comparing osilodrostat phosphate to metyrapone.

- Osilodrostat phosphate vs no comparator

  Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence of overall and complete response rates (based on mean UFC levels) to osilodrostat phosphate of 89.5% and 84.2% respectively after 10 weeks treatment, between 75% and 83% for overall response and between 63% and 81% for complete response at time points between 22 and 87 weeks treatment, and a complete response rate of 63.2% after a median 5.4 years exposure to osilodrostat phosphate.

  Two single-arm studies (LINC2 and LINC4) provided very low certainty evidence that mean 24-hour UFC levels were within the normal range after 22 and 72 weeks treatment with osilodrostat phosphate. They also provided very low certainty evidence that mean serum cortisol levels fell from baseline after 48 and 72 weeks treatment with osilodrostat phosphate, but the levels were within the normal range at all measurement points including baseline.

  Two single-arm studies (LINC2 and LINC4) provided very low certainty evidence that early-morning salivary cortisol levels were above the normal range at baseline and fell to within the normal range after 22 weeks and 48 weeks treatment with osilodrostat phosphate. They also provided very low certainty evidence that late-night salivary cortisol levels fell from baseline after up to 72 weeks treatment with osilodrostat phosphate but remained above the normal range.

- **Sequelae of Cushing's disease (critical outcome)**
  - Osilodrostat phosphate vs placebo

    One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks randomised treatment there was no statistically significant difference in the change in mean weight or waist circumference between patients randomised to osilodrostat phosphate and patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate there remained no statistically significant difference in the change in weight or waist circumference between the two groups.

    One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks randomised treatment there was a statistically significantly greater fall in mean LDL cholesterol and HDL cholesterol in patients randomised to osilodrostat phosphate compared to patients randomised to placebo, but values remained within the normal ranges in both groups at all time points. There was no statistically significant difference at 12 weeks in the change in mean systolic BP, diastolic BP, fasting plasma glucose, HbA1c, total cholesterol or triglycerides between patients randomised to osilodrostat phosphate and patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate there were no statistically significant differences in the changes in any of these measures between the groups. Total cholesterol values were above the normal range in both groups at baseline and fell to within the normal range in the osilodrostat phosphate group by 12 weeks and in the group which had been randomised to placebo by 48 weeks. For all other measures values were within the normal range (where specified) in both groups at all time points.

    One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks randomised treatment there was no statistically significant difference in the change in Beck Depression Inventory (BDI)-II score between patients randomised to osilodrostat phosphate and patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate there remained no statistically significant difference in the change in BDI-II score between the two groups.

  - Osilodrostat phosphate vs metyrapone

    No evidence relating to sequelae of Cushing's disease was identified for osilodrostat phosphate compared to metyrapone.

  - Osilodrostat phosphate vs no comparator

    Two single-arm studies (LINC2 and LINC3) provided very low certainty evidence of a fall in mean weight from baseline after up to 72 weeks treatment with osilodrostat phosphate. Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence of a fall in mean body mass index and two single-arm studies (LINC3 and LINC4) provided very low certainty evidence of a fall in mean waist circumference from baseline after up to 72 weeks treatment with osilodrostat phosphate.

    Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence of a fall in mean systolic BP, diastolic BP, fasting plasma glucose, HbA1c, total cholesterol and triglycerides after between 22 and 72 weeks treatment with osilodrostat phosphate. The three single-arm studies also provided very low certainty evidence of a fall in mean HDL and LDL cholesterol after between 22 and 48 weeks treatment with osilodrostat phosphate.

    Two single-arm studies (LINC3 and LINC4) provided very low certainty evidence of a fall (improvement) in mean BDI-II score after between 48 and a median of 87.1 weeks treatment with osilodrostat phosphate. One single-arm study (LINC3) provided very low

certainty evidence that the percentage fall in BDI-II score at 48 weeks exceeded the minimal clinically important difference (MCID)[2].

- **Reduction in treatment for Cushing's disease sequelae (important outcome)**
  - Osilodrostat phosphate vs placebo

    No evidence relating to reduction in treatment for Cushing's disease sequelae was identified for osilodrostat phosphate compared to placebo.
  - Osilodrostat phosphate vs metyrapone

    No evidence relating to reduction in treatment for Cushing's disease sequelae was identified for osilodrostat phosphate compared to metyrapone.
  - Osilodrostat phosphate vs no comparator

    One single-arm study (LINC3) provided very low certainty evidence that after 48 weeks treatment with osilodrostat phosphate, of the patients taking hypertensive medication at baseline 40% had an increase and 40% had a decrease in their medication, and of the patients taking diabetic medication at baseline 23% had an increase and 49% had a decrease in their medication.
- **Time to improvement (important outcome)**
  - Osilodrostat phosphate vs placebo

    One randomised study (LINC4) provided moderate certainty evidence that the median time to first controlled UFC response for patients treated with osilodrostat phosphate was 35 days.
  - Osilodrostat phosphate vs metyrapone

    No evidence relating to time to improvement was identified for osilodrostat phosphate compared to metyrapone.
  - Osilodrostat phosphate vs no comparator

    One single-arm study (LINC 2) provided very low certainty evidence that mean UFC fell to within the normal range at a mean of 4 weeks after treatment with osilodrostat phosphate. One single-arm study (LINC3) provided very low certainty evidence that the median time to first complete response for patients treated with osilodrostat phosphate was 41.0 days.
- **Quality of life (QoL) (important outcome)**
  - Osilodrostat phosphate vs placebo

    One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks treatment there was no statistically significant difference in the change in mean Cushing QoL score between patients randomised to osilodrostat phosphate and patients randomised to placebo. After a further 36 weeks treatment where both groups received treatment with osilodrostat phosphate, there remained no statistically significant difference in the change in mean Cushing QoL score between the two groups.
  - Osilodrostat phosphate vs metyrapone

    No evidence relating to QoL was identified for osilodrostat phosphate compared to metyrapone.
  - Osilodrostat phosphate vs no comparator

    Two single-arm studies (LINC3 and LINC4) provided very low certainty evidence of an increase (improvement) in mean Cushing QoL score after between 48 and a median of

[2] MCID for BDI-II score defined as 17.5% decrease from baseline in Pivonello et al 2020

87.1 weeks treatment with osilodrostat phosphate. They also provided very low certainty evidence that the change from baseline exceeded the MCID at all timepoints[3].

- **Activities of daily living (ADLs) (important outcome)**
  - No evidence was identified for this outcome.

In terms of safety:

- Osilodrostat phosphate vs placebo

  Two randomised studies (LINC3 and LINC4) provided low certainty evidence that the incidence of any adverse event (AE) was 72-96% in the osilodrostat phosphate group and 66-92% in the placebo group. The incidence of grade 3-4 AEs was 6-21% and 9-20% respectively, and of any serious AE (all grades) was 4.2-6% and 3-4% respectively. One of the randomised studies (LINC3) provided low certainty evidence that AEs related to adrenal hormone precursor accumulation occurred in 6% and 3% respectively, and AEs related to hypocortisolism occurred in 8% and 3% respectively. There were no statistical comparisons between the two groups.

- Osilodrostat phosphate vs metyrapone

  No evidence relating to safety was identified for osilodrostat phosphate compared to metyrapone.

- Osilodrostat phosphate vs no comparator

  Two single-arm studies (LINC3 and LINC4) provided very low certainty evidence that 98.6 to 100% of patients experienced at least one AE of any grade, and that between 38.4% and 60.0% experienced at least one grade 3-4 AE. The incidence of any serious AE was 11.0% to 36.5% and any serious grade 3-4 AE was 12.3% to 28.5%. AEs requiring dose interruption and/or change occurred in 57.5% to 80.3% (all grades) and 17.8% to 30.7% (grade 3-4), and AEs leading to discontinuation occurred in 11.0% to 12.3%. One single-arm study (LINC3) reported one death.

  Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence that the most commonly reported AEs of any grade were nausea, headache, fatigue, adrenal insufficiency, arthralgia, nasopharyngitis, increased blood testosterone and asthenia. The most commonly reported grade 3-4 AEs were adrenal insufficiency, hypertension, headache, vomiting, fatigue and nausea.

  Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence on AEs of special interest. Two studies (LINC2 and LINC3) reported that the AEs of special interest of all grades were adrenal hormone precursor accumulation in 42.3% to 63.1%, hypocortisolism related in 51.1% to 57.9%, QT prolongation related in 3.6% to 5.3%, arrhythmogenic potential in 0.7% to 5.3% and pituitary tumour enlargement related in 0 to 2.2%. The same two studies also reported that Grade 3-4 AEs of special interest were adrenal hormone precursor accumulation related in 16.1% to 21.1%, hypocortisolism related in 10.2% to 10.5%, QT prolongation related in 0 to 0.7% and arrhythmogenic potential in 0 to 0.7%.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

[3] MCID for Cushing QoL score defined as 10.1 point increase from baseline in Pivonello et al 2020

In terms of subgroups:

- No evidence was identified regarding any subgroups of patients that would benefit more from treatment with osilodrostat phosphate.

In terms of osilodrostat phosphate schedules and doses

- All studies used osilodrostat phosphate orally twice daily
- LINC2

  Fleseriu et al 2016

  Follow-up cohort: osilodrostat phosphate was initiated at the penultimate dose that was efficacious and tolerable in LINC 1[4] (starting dose: 4mg/day, n = 1; 20mg/day, n = 3)

  Expansion cohort: osilodrostat phosphate was initiated at 4mg/day if baseline UFC was >1.5 to ≤3 x ULN (n=9), and 10mg/day if baseline UFC was >3 x ULN (n=6).

  For both cohorts, dose was escalated every 2 weeks according to the escalation sequence 10, 20, 40, and 60 mg/day until UFC was ≤ULN. Titration was continued up to week 10 as needed based on efficacy and tolerability. Treatment was then continued at the same dose from week 10 for a further 12 weeks.

  Fleseriu et al 2022a

  Patients were continued on the dose of osilodrostat phosphate they were on at the end of the 22-week treatment period reported in Fleseriu et al 2016. Dose adjustments were permitted based on individual efficacy and tolerability, up to a maximum dose of 30mg twice daily. Median dose from baseline to the end of the study 10.6mg/day (range 1.1 to 47.9 mg/day, interquartile range (IQR) 5.7 to 16.7mg/day).

- LINC3

  Pivonello et al 2020

  Dose of osilodrostat phosphate started at 2mg twice daily for all patients with dose adjustments every 2 weeks based on efficacy and tolerability. The dose range was 1 to 30mg twice a day.

  During the first 26 weeks the mean dose received was 10.0mg per day (standard deviation (SD) 7.3), and mean highest dose was 17.8mg per day (SD 13.6). During the randomised withdrawal phase (week 26 to 34) mean dose was 10.0mg per day (SD 9.6).

  Fleseriu et al 2022b

  Dose started at 2mg twice daily for all patients with dose adjustments as described in Pivonello et al 2020, up to a maximum permitted dose of 30mg twice daily.

  Median osilodrostat phosphate dose from the start of the core study reported in Pivonello et al 2020 to the end of the extension reported in this paper was 7.4mg/day (range 0.8–46.6, IQR 3.5– 13.6).

- LINC4

  Gadelha et al 2022

  Dose of osilodrostat phosphate was started at 2mg twice daily for all patients with dose adjustments approximately every 3 weeks during the placebo-controlled phase (weeks 1 to 12).

[4] LINC1 was a 10-week proof-of-concept study of osilodrostat phosphate in 12 patients with Cushing's disease. Four patients who had participated in LINC1 went on to participate in LINC2.

During the open label phase (weeks 13 to 48) all patients restarted on osilodrostat phosphate 2mg twice daily unless they were on a lower dose at week 12, when they continued to receive the lower dose. Dose adjustments were made as during the placebo-controlled period.

Median osilodrostat phosphate dose from baseline to data cutoff was 5.0 (IQR 3.8 to 9.2) mg/day. At week 48, 84% of patients with normal mean UFC were receiving doses of ≤10 mg/day (≤4 mg/day, n = 28 (56.0%); >4 to 10 mg/day, n = 14 (28.0%); >10 to 20 mg/day, n = 2 (4.0%); or >20 mg/day, n = 6 (12.0%)).

Gadelha et al 2023

Dose was started at the established effective dose from Gadelha et al 2022. Dose adjustments were permitted based on efficacy and tolerability; the maximum permitted dose was 30mg twice daily. Median osilodrostat phosphate dose received during the overall study period was 4.6 (IQR 3.7 to 9.2) mg/day.

- Bonnet-Serrano et al 2022

  Median dose of osilodrostat phosphate 10mg/day (range 2 to 40mg). No further details were provided.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

The certainty of the evidence reported was moderate to low for the randomised studies and very low for the single-arm studies and the retrospective cohort study. Factors reducing confidence in the outcomes of the randomised studies included risk of bias due to uncertainty about whether the groups were similar at baseline, and lack of statistical analysis for some outcomes. Factors reducing confidence in the outcomes of the retrospective cohort study include risk of bias due to uncertainty about whether the groups were similar at baseline, no identification of or adjustment for potential confounders and inclusion of six patients in both the groups being compared. In addition four out of the 33 subjects included in this study had Cushing's syndrome.

Factors reducing confidence in the outcomes of the single-arm studies include risk of bias due to uncertainty about whether the recruitment of subjects was consecutive or complete and limited statistical analyses particularly in the extension studies. There was also a lack of clinical and demographic information about the populations included and unclear reporting of outcomes in the extension studies.

Only one of the studies (LINC3) reported including centres in the UK and it was not stated how many patients were recruited there so it is not possible to comment on the relevance of the study findings to the UK population.

Conclusion

This evidence review includes evidence from four studies, two of which each included two component studies. LINC2 was a single-arm study, LINC3 included both a randomised and a single-arm study, and LINC4 also included both a randomised and a single-arm study. Each of the LINC studies was published in two papers. The two randomised studies compared treatment with osilodrostat phosphate with placebo in patients with Cushing's disease. In addition the review incudes a retrospective cohort study which compared osilodrostat phosphate with metyrapone in patients with Cushing's disease. All studies included adults only and a majority of female subjects.

Osilodrostat phosphate vs placebo

One randomised study provided moderate certainty evidence that there was improvement or no change in all the physical features of hypercortisolism assessed in at least 88% of patients after 48 weeks treatment (consisting of either 48 weeks osilodrostat phosphate or 12 weeks placebo followed by 36 weeks osilodrostat phosphate). There was no statistically significant difference between the treatment groups in the proportion of patients who had improved or not changed with respect to any of the physical characteristics.

Both the randomised studies provided moderate certainty evidence that biochemical disease response was statistically significantly better in patients receiving osilodrostat phosphate compared to patients receiving placebo after a randomisation period of eight to 12 weeks. Both also reported that there was no difference in biochemical disease response between the groups after they had both received a further period of osilodrostat phosphate treatment.

Regarding sequelae of Cushing's disease, one randomised study provided moderate certainty evidence that LDL and HDL cholesterol fell statistically significantly more in patients treated with osilodrostat phosphate for 12 weeks compared to those treated with placebo, but values remained within the normal ranges in both groups at all time points. There were no statistically significant differences between the two groups in the changes in any other measures of the sequelae of Cushing's disease, including weight, blood pressure, fasting plasma glucose, HbA1c, total cholesterol, triglycerides and BDI-II score. Total cholesterol values were above the normal range in both groups at baseline and fell to within the normal range in the osilodrostat phosphate group by 12 weeks and in the group which had been randomised to placebo (who received 12 weeks placebo followed by 36 weeks osilodrostat) by 48 weeks. For all other measures values were within the normal range (where specified) in both groups at all time points.

One randomised study (LINC4) provided moderate certainty evidence that the median time to first controlled UFC response for patients treated with osilodrostat phosphate was 35 days.

One randomised study found moderate certainty evidence that there was no statistically significant difference in the change in Cushing QoL score in patients treated with osilodrostat phosphate for 12 weeks compared to those treated with placebo.

The randomised studies reported AEs, serious AEs and AEs of special interest in the osilodrostat phosphate and placebo groups and while it appeared that there may be fewer of some types of AE in the placebo groups no statistical comparisons were reported.

Osilodrostat phosphate vs metyrapone

The retrospective cohort study provided very low certainty evidence that patients treated with osilodrostat phosphate had a statistically significantly lower median serum cortisol level than those treated with metyrapone at the time of best control of hypercortisolism. No other outcomes were reported comparing treatment with osilodrostat phosphate to metyrapone.

Osilodrostat phosphate vs no comparator

One single-arm study provided very low certainty evidence that after 72 weeks treatment with osilodrostat phosphate female hirsutism improved or remained stable in at least 85% of women, with greater improvements seen in women with normal testosterone than those with raised testosterone and improvements seen in some patients from 12 weeks of treatment onwards.

The three single-arm studies provided very low certainty evidence that complete response rates to osilodrostat phosphate (based on biochemical response) were 84.2% at 10 weeks, between 63% and 81% at time points between 22 and a median of 87 weeks, and 63.2% after a median 5.4 years treatment with osilodrostat phosphate.

The single-arm studies provided very low certainty evidence that most of the measures of the sequelae of Cushing's disease, including weight, blood pressure, fasting plasma glucose, HbA1c, total cholesterol, triglycerides and BDI-II score fell during treatment with osilodrostat phosphate, including a percentage fall (improvement) in the BDI-II score which was reported to exceed the minimal clinically important difference (MCID) defined by the authors.

One single-arm study reported that after 48 weeks treatment with osilodrostat phosphate, of the patients taking hypertensive medication at baseline 40% had an increase and 40% had a decrease in their medication, and of the patients taking diabetic medication at baseline 23% had an increase and 49% had a decrease in their medication. One single-arm study provided very low certainty evidence that the median time to first response to osilodrostat phosphate was 41 days.

Two of the single-arm studies found very low certainty evidence of an increase (improvement) in Cushing QoL score after a median of up to 87.1 weeks treatment with osilodrostat phosphate. They reported increases in the Cushing QoL score which exceeded the MCID defined by the authors at all time points.

Regarding safety, two single-arm studies provided very low certainty evidence that 98.6% to 100% of patients experienced at least one AE while being treated with osilodrostat phosphate, and that between 38.4% and 60.0% experienced at least one grade 3-4 AE.

Two single-arm studies provided very low certainty evidence that AEs requiring dose interruption and/or change occurred in 57.5% to 80.3% of patients treated with osilodrostat phosphate and AEs leading to discontinuation in 11.0% to 12.3% of patients treated with osilodrostat phosphate. One single-arm study reported one death. Three single-arm studies provided very low certainty evidence that the most commonly reported AEs of any grade were nausea, headache, fatigue, adrenal insufficiency, arthralgia, nasopharyngitis, increased blood testosterone and asthenia, and the most commonly reported grade 3-4 AEs were adrenal insufficiency, hypertension, headache, vomiting, fatigue and nausea. Two single-arm studies provided very low certainty evidence that the AEs of special interest of all grades were adrenal hormone precursor accumulation in 42.3% to 63.1%, hypocortisolism related in 51.1% to 57.9%, QT prolongation related in 3.6% to 5.3%, arrhythmogenic potential in 0.7% to 5.3% and pituitary tumour enlargement related in 0 to 2.2%.

No evidence was identified for the important outcome ADLs or for cost effectiveness. No evidence was identified regarding any subgroups of patients that would benefit more from treatment with osilodrostat phosphate. The certainty of the evidence reported was moderate to low for the randomised studies and very low for the single-arm studies and the retrospective cohort study.

The studies included in this review provide moderate certainty evidence that people with Cushing's disease treated with osilodrostat phosphate have a better biochemical disease response than those receiving placebo, with a median time to first response to osilodrostat phosphate of 35 to 41 days. There was very low certainty evidence of a complete response to osilodrostat phosphate ranging from 84.2% at 10 weeks to 63.2% after a median of 5.4 years treatment. There was also moderate certainty evidence that at least 88% of people with Cushing's disease treated with osilodrostat phosphate have a reduction or stabilisation in the physical features of hypercortisolism. There was no statistically significant difference between osilodrostat phosphate and placebo in the change in most other outcomes reported. Adverse events occurred in up to 100% of patients on osilodrostat phosphate, with significant numbers experiencing a more serious adverse event and around half of patients requiring an interruption or change in dose. There was also limited very low certainty evidence that people with

Cushing’s disease treated with osilodrostat phosphate have a better biochemical disease response than those receiving metyrapone.

3. Methodology

Review questions

The review questions for this evidence review are:

1) In people with Cushing's disease, what is the clinical effectiveness of osilodrostat phosphate compared to standard care?
2) In people with Cushing's disease, what is the safety of osilodrostat phosphate compared to standard care?
3) In people with Cushing's disease, what is the cost effectiveness of osilodrostat phosphate compared to standard care?
4) From the evidence selected, are there any subgroups of patients that may benefit from osilodrostat phosphate more than the wider population of interest?
5) From the evidence selected what were the ongoing schedules/doses used for osilodrostat phosphate?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 18 October 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Four studies were identified for inclusion, three of which were reported in six papers. LINC2 was a single-arm phase II study reported in Fleseriu et al 2016 and Fleseriu et al 2022a. LINC3 was a phase II study with a randomised withdrawal period within a single-arm study, reported in Pivonello et al 2020 and Fleseriu et al 2022b. LINC4 was a randomised study followed by a single-arm study reported in Gadelha et al 2022 and Gadelha et al 2023. The randomised studies reported outcomes comparing osilodrostat phosphate to placebo and the single-arm studies reported outcomes for osilodrostat phosphate with no comparator. The randomised studies reported outcomes after eight and 12 weeks of randomisation; the longest follow-up period reported in the single-arm studies was up to median 5.4 years exposure to osilodrostat phosphate. The fourth study was a retrospective cohort study (Bonnet-Serrano et al 2022) which compared patients treated with osilodrostat phosphate with patients treated with metyrapone and reported disease response at a single point.

No studies were identified that reported activities of daily living, and no evidence on cost effectiveness was identified.

Table 2 provides a summary of the included studies and full details are given in Appendix E.

Table 2: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Bonnet-Serrano et al 2022 Retrospective cohort study Cochin, France	Patients with an ACTH-dependent Cushing syndrome. n=33 Treated with osilodrostat phosphate only: n=19 Treated with metyrapone only: n=8 Treated with metyrapone then osilodrostat phosphate: n=6 (these patients were included in both treatment groups for analysis, at a time point they were receiving the relevant treatment) Analysed in osilodrostat phosphate group: n=25 Analysed in metyrapone group: n=14 Whole cohort, n (%) Male: 4 (12.1%) Female: 29 (87.9%) Median age, years: 47 Median BMI (kg/m^2): 29.0 Cushing disease diagnosis: 29 (87.9%) No subgroups reported	**Interventions** Osilodrostat phosphate twice daily Median dose 10 mg (range 2 to 40 mg). **Comparators** Metyrapone three to four times a day Median dose 1250 mg (range 500 to 4000 mg).	**Critical outcomes** • Biochemical disease response
LINC2	Patients aged 18 to 75 years with a confirmed	**Interventions** Osilodrostat phosphate orally twice daily	**Critical outcomes** Fleseriu et al 2016:

Study	Population	Intervention and comparison	Outcomes reported
Reported in Fleseriu et al 2016 and Fleseriu et al 2022a Phase II study (single-arm study) Multicentre, locations of patient recruitment not stated (authors were from USA, Japan, France and Italy)	diagnosis of Cushing's disease Fleseriu et al 2016: n=19 Follow-up cohort: n=4 Expansion cohort: n=15 Fleseriu et al 2022a: n=16 (extension period from week 22 to week 70) Whole cohort • Mean age (SD), years: 36.8 (8.4) • Median age (range), years: 36 (25 to 52) • Sex, n: F14: M5 • Race, n (%): Caucasian: 15 (78.9%); Other: 4 (21.1%) • Median time since diagnosis (range), months: 70.2 (12.2 to 155.2) • Previous surgery, n (%): 17 (89.5%) • Baseline UFC, mean (SD) nmol/24 h [a]: 1371 (2734) No subgroups reported	Fleseriu et al 2016: *Follow-up cohort*: osilodrostat phosphate at the penultimate dose that was efficacious and tolerable in LINC1 (starting dose: 4 mg/day, n = 1; 20 mg/day, n = 3) *Expansion cohort*: osilodrostat phosphate was initiated at 4 mg/day if baseline UFC was >1.5 to ≤3 x ULN (n=9), and 10 mg/day if baseline UFC was >3 x ULN (n=6). For both cohorts, dose was escalated every 2 weeks as needed based on efficacy and tolerability up to week 10. Treatment was then continued at the same dose from week 10 for a further 12 weeks. Fleseriu et al 2022a: Patients were continued on the dose they were on at the end of the 22-week treatment period in Fleseriu et al 2016. Further dose adjustments were made as required. **Comparators** No comparator	• Biochemical disease response [b] at week 10 and week 22 • Sequelae of Cushing's disease at week 22 • Time to improvement Fleseriu et al 2022a: • Biochemical disease response [b] at week 70 and at last observed value • Sequelae of Cushing's disease at last observed value **Important outcomes** Fleseriu et al 2016 and Fleseriu et al 2022a • Safety ○ Adverse events
LINC3 Reported in Pivonello et al 2020 and Fleseriu et al 2022b Phase III study (randomised study (Pivonello et al 2020 only) and single-arm study) Multicentre across 19 countries (exact locations of patient recruitment not stated)	Patients aged 18 to 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 had refused surgery or were not deemed to be surgical candidates. Pivonello et al 2020: n=137 Osilodrostat phosphate: n=36 Placebo: n=35 Not randomised: n=66 Fleseriu et al 2022b: n=106 (extension period from week 48 to week 72) Whole cohort: • Median age, years (IQR) (range): 40.0	**Interventions** Osilodrostat phosphate orally twice daily Pivonello et al 2020: Dose was started at 2mg twice daily for all patients with dose adjustments every 2 weeks up to week 12 based on efficacy and tolerability. The effective dose was continued until week 48, except for the group randomised to placebo who received placebo from week 27 to week 34. Osilodrostat phosphate dose range 1 to 30 mg twice a day. Fleseriu et al 2022b: Patients were continued on open label osilodrostat phosphate. Further dose adjustments were made as required. **Comparators** Pivonello et al 2020: placebo	**Critical outcomes** Pivonello et al 2020: *Outcomes in randomised groups* • Biochemical disease response [b] at week 24, week 34 (after the 8-week randomised withdrawal period) and week 48 *Outcomes in whole cohort* • Biochemical disease response [b] at week 24 and week 48 • Sequelae of Cushing's disease at week 48 Fleseriu et al 2022b • Clinical disease response (female hirsutism) at week 72 • Biochemical disease response [b] at week 72 • Sequelae of Cushing's disease at week 72 **Important outcomes** Pivonello et al 2020

Study	Population	Intervention and comparison	Outcomes reported

	(31.0 to 49.0) (19.0 to 70.0)
	• Sex, n (%): F 106 (77%); M 31 (23%)
	• Race, n (%): Caucasian: 89 (65%); Black: 4 (3%); Asian: 39 (28%); Other: 5 (4%)
	• Median (IQR) time since diagnosis, months: 47.2 (19.0 to 88.3)
	• Previous pituitary surgery, n (%): 120 (88%)
	• Mean 24h UFC [a], nmol/24h: 1006 (1590)
	
	No subgroups reported
		Fleseriu et al 2022b: no comparator	*Outcomes in randomised groups*
			• Safety
			  ○ Adverse events in randomised groups during the 8-week randomised withdrawal period
			Outcomes in whole cohort
			• Time to improvement
			• Quality of life at week 48
			• Safety
			  ○ Adverse events
			
			Fleseriu et al 2022b
			• Reduction in treatment for Cushing's disease sequelae at week 48
			• Quality of life at up to week 72
			• Safety
			  ○ Adverse events

LINC4 Reported in Gadelha et al 2022 and Gadelha et al 2023 Phase III study (randomised study (Gadelha et al 2022 only) and single-arm study) Forty centres in 14 countries (Belgium, Brazil, Canada, China, Costa Rica, Greece, Poland, Portugal, Russia, Spain, Switzerland, Thailand, Turkey, USA)	Patients aged 18 to 75 years with a confirmed diagnosis of persistent/recurrent Cushing disease after pituitary surgery and/or irradiation or de novo disease Gadelha et al 2022: n=73 Osilodrostat phosphate: n=48 Placebo: n=25 Gadelha et al 2023: n=60 (extension period week 48 on) Whole cohort: • Median age, years (range): 39.0 (19.0 to 67.0) • Sex, n (%): F61 (83.6%); M12 (16.4%) • Race, n (%): White: 49 (67.1%); Asian: 17 (23.3%); Black/African American: 2 (2.7%); Other: 2 (2.7%); Unknown: 3 (4.1%) • Median (IQR) time since diagnosis, months: 67.4 (26.4 to 93.8) • Previous pituitary surgery, n (%): 64 (87.7%)	**Interventions** Osilodrostat phosphate orally twice daily Gadelha et al 2022: Dose was started at 2mg twice daily for all patients with dose adjustments approximately every 3 weeks during the placebo-controlled phase (weeks 1 to 12). Patients randomised to placebo received placebo until week 12. During the open label phase (weeks 13 to 48) all patients restarted on osilodrostat phosphate 2 mg twice daily unless they were on a lower dose at week 12, when they continued to receive the lower dose. Dose adjustments were made as during the placebo-controlled period. Gadelha et al 2023: Dose was started at the established effective dose from Gadelha et al 2022. Further dose adjustments were made as required. **Comparators** Gadelha et al 2022: placebo Gadelha et al 2023: no comparator	**Critical outcomes** Gadelha et al 2022 *Outcomes in randomised groups* • Clinical disease response (physical features of hypercortisolism) at week 48 • Biochemical disease response [b] at week 12 • Mean 24-hour UFC at week 12 • Serum and salivary cortisol at week 12 and week 48 • Sequelae of Cushing's disease at week 12 and week 48 *Outcomes in whole cohort* • Serum and salivary cortisol at week 12 and week 48 • Sequelae of Cushing's disease at week 12 and week 48 • Biochemical disease response at week 36 and week 48 Gadelha et al 2023 • Biochemical disease response [b] at week 48 and week 72 • Biochemical disease response [b] up to end of treatment • Mean 24-hour UFC at week 72

Study	Population	Intervention and comparison	Outcomes reported

	• Mean (SD) UFC,[a] nmol/24h: 431.7 (388.6)
	
	No subgroups reported
			• Serum and salivary cortisol at week 48 and week 72 treatment
			• Sequelae of Cushing's disease (BDI-II score only) at week 72
			
			Important outcomes
			Gadelha et al 2022
			Outcomes in randomised groups
			• Time to improvement
			• Quality of life at week 12 and week 48
			• Safety
			  ○ Adverse events at week 12
			Outcomes in whole cohort
			• Quality of life at week 12 and week 48
			• Safety
			  ○ Adverse events
			
			Gadelha et al 2023
			• Quality of life at week 72
			• Safety
			  ○ Adverse events over the whole study period

Abbreviations

BDI-II: Beck depression inventory II; BMI: body mass index; F: female; IQR: interquartile range; M: male; n: number; SD: standard deviation; UFC: urinary free cortisol; ULN: upper limit of normal

a Mean UFC calculated as the mean of 2 or 3 samples. Normal range: 11–138 nmol/24 h
b Controlled or complete response: mean UFC≤ ULN; partially controlled or partial response: mean UFC>ULN and with ≥50% reduction from baseline. Overall response = complete response + partial response.

5. Results

In people with Cushing's disease, what is the clinical effectiveness and safety of osilodrostat phosphate compared to standard care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Clinical disease response **Certainty of evidence:** Moderate to very low	This outcome is important to patients because it reflects the clinical improvement that they experience with treatment. In total, one randomised study and one single-arm study provided evidence relating to clinical disease response in people with Cushing's disease. The randomised study reported a range of physical features of hypercortisolism after 48 weeks treatment which included a 12-week randomised period; the single-arm study reported hirsutism in females after up to 72 weeks treatment with osilodrostat phosphate. <u>Facial rubor</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate)** [5] • One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in facial rubor at week 48 in patients randomised to osilodrostat phosphate (n=39); patients randomised to placebo (n=21); and total patients (n=60). Respectively, improvement was reported in 16/39 (41.0%) (95% CI 25.6 to 57.9); 11/21 (52.4%) (95% CI 29.8 to 74.3); 27/60 (45.0%) (95% CI 32.1 to 58.4): no change in 21/39 (53.8%) (95% CI 37.2 to 69.90; 10/21 (47.6%) (95% CI 25.7 to 70.2); 31/60 (51.7%) (95% CI 38.4 to 64.8): and worsening in 2/39 (5.1%) (95% CI 0.6 to 17.3); 0/21 (0%) (95% CI NE); 2/60 (3.3%) (95% CI 0.4 to 11.5). **(MODERATE)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* • No evidence was identified for this outcome. <u>Hirsutism</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate**): • One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in hirsutism at week 48 in patients randomised to osilodrostat phosphate (n=33); patients randomised to placebo (n=15); and total patients (n=48). Respectively, improvement was reported in 5/33 (15.2%) (95% CI 5.1 to 31.9); 3/15 (20.0%) (95% CI 4.3 to 48.1); 8/48 (16.7%) (95% CI 7.5 to 30.2): no change in 24/33 (72.7%) (95% CI 95% CI 54.5 to 86.7); 12/15 (80.0%) (95% CI 51.9 to 95.7); 36/48 (75.0%) (95% CI 60.4 to 86.4): and worsening in 4/33 (12.1%) (95% CI 3.4 to 28.2); 0/15 (0%) (95% CI NE); 4/48 (8.3%) (95% CI 2.3 to 20.0). **(MODERATE)**

[5] Physical features were reported to have been assessed in Gadelha et al 2022 using a semi-quantitative Likert scale; no further details were provided and it was not stated who they were assessed by.

Outcome	Evidence statement
	Osilodrostat phosphate vs metyrapone • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **After up to 72 weeks treatment with osilodrostat phosphate[6]:** • One single-arm study (LINC3, Fleseriu et al 2022b) reported the change in a physician-rated hirsutism score in females with normal and raised testosterone levels. In those with normal testosterone levels the hirsutism score at 12 weeks (n=38); 48 weeks (n=34); 72 weeks (n=38) respectively was reported to be improved in 9/38 (23.7%); 16/34 (47.1%); 7/38 (44.7%): stable in 27/38 (71.1%); 13/34 (38.2%); 16/38 (42.1%): and worsened in 2/38 (5.3%); 5/34 (14.7%); 5/38 (13.2%). In women with raised testosterone level the hirsutism score at 12 weeks (n=48); 48 weeks (n=41); 72 weeks (n=28) respectively was reported to be improved in 3/48 (6.3%); 9/41 (22.0%); 6/28 (21.4%); stable in 41/48 (85.4%); 24/41 (58.5%); 18/28 (64.3%); and worsened in 4/48 (8.3%); 8/41 (19.5%); 4/28 (14.3%). **(VERY LOW)** <u>Supraclavicular fat pad</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in supraclavicular fat pad at week 48 in patients randomised to osilodrostat phosphate (n=39); patients randomised to placebo (n=22); and total patients (n=61). Respectively, improvement was reported in 21/39 (53.8%) (95% CI 37.2 to 69.9); 11/22 (50.0%) (95% CI 28.2 to 71.8); 32/61 (52.5%) (95% CI 39.3 to 65.4): no change in 17/39 (43.6%) (95% CI 27.8 to 60.4); 11/22 (50.0%) (95% CI 28.2 to 71.8); 28/61 (45.9%) (95% CI 33.1 to 59.2): and worsening in 1/39 (2.6%) (95% CI 0.1 to 13.5); 0/22 (0%) (95% CI NE); 1/61 (1.6%) (95% CI 0.0 to 0.8 [sic]). **(MODERATE)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* • No evidence was identified for this outcome. <u>Dorsal fat pad</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in dorsal fat pad at week 48 in patients randomised to osilodrostat phosphate (n=38); patients randomised to placebo (n=22); and total patients (n=60). Respectively, improvement was reported in 20/38 (52.6%) (95% CI 35.8 to 69.0); 10/22 (45.5%) (95% CI 24.4 to 67.8); 30/60 (50.0%) (95% CI 36.8 to 63.2): no change in 16/38 (42.1%) (95% CI 26.3 to 59.2); 10/22 (45.5%) (95% CI 24.4 to 67.8); 26/60 (43.3%) (95% CI 30.6 to 56.8): and worsening in 2/38 (5.3%) (95% CI 0.6 to 17.7); 2/22 (9.1%) (95% CI 1.1 to 29.2); 4/60 (6.7%) (95% CI 1.8 to 16.2). **(MODERATE)**

[6] Assessment of physical features in Fleseriu et al 2022b was based on review of photographs by the investigator (unblinded); features were rated subjectively on a semi-quantitative scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe),

Outcome	Evidence statement
	Osilodrostat phosphate vs metyrapone • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* • No evidence was identified for this outcome. <u>Proximal muscle atrophy</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in proximal muscle atrophy at week 48 in patients randomised to osilodrostat phosphate (n=39); patients randomised to placebo (n=22); and total patients (n=61). Respectively, improvement was reported in 10/39 (25.6%) (95% CI 13.0 to 42.1); 8/22 (36.4%) (95% CI 17.2 to 59.3); 18/61 (29.5%) (95% CI 18.5 to 42.6): no change in 25/39 (64.1%) (95% CI 47.2 to 78.8); 13/22 (59.1%) (95% CI 36.4 to 79.3); 38/61 (62.3%) (95% CI 49.0 to 74.4) : and worsening in 4/39 (10.3%) (95% CI 2.9 to 24.2); 1/22 (4.5%) (95% CI 0.1 to 22.8); 5/61 (8.2%) (95% CI 2.7 to 18.1). **(MODERATE)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* • No evidence was identified for this outcome. <u>Central obesity</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in central obesity at week 48 in patients randomised to osilodrostat phosphate (n=39); patients randomised to placebo (n=22); and total patients (n=61). Respectively, improvement was reported in 16/39 (41.0%) (95% CI 25.6 to 57.9); 9/22 (40.9%) (95% CI 20.7 to 63.6); 25/61 (41.0%) (95% CI 28.6 to 54.3): no change in 19/39 (48.7%) (95% CI 32.4 to 65.2); 12/22 (54.5%) (95% CI 32.2 to 75.6); 31/61 (50.8%) (95% CI 37.7 to 63.9): and worsening in 4/39 (10.3%) (95% CI 2.9 to 24.2); 1/22 (4.5%) (95% CI 0.1 to 22.8); 5/61 (8.2%) (95% CI 2.7 to 18.1). **(MODERATE)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* • No evidence was identified for this outcome. <u>Ecchymosis</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate)**

Outcome	Evidence statement
	• One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in ecchymosis at week 48 in patients randomised to osilodrostat phosphate (n=39); patients randomised to placebo (n=21); and total patients (n=60). Respectively, improvement was reported in 9/39 (23.1%) (95% CI 11.1 to 39.3); 3/21 (14.3%) (95% CI 3.0 to 36.3); 12/60 (20.0%) (95% CI 10.8 to 32.3): no change in 29/39 (74.4%) (95% CI 57.9 to 87.0); 17/21 (81.0%) (95% CI 58.1 to 94.6); 46/60 (76.7%) (95% CI 64.0 to 86.6): and worsening in 1/39 (2.6%) (95% CI 0.1 to 13.5); 1/21 (4.8%) (95% CI 0.1 to 23.8); 2/60 (3.3%) (95% CI 0.4 to 11.5). **(MODERATE)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* • No evidence was identified for this outcome. **Osilodrostat phosphate vs placebo:** **One randomised study (LINC3) provided moderate certainty evidence of improvement or no change in facial rubor, hirsutism, striae, subcutaneous fat pad, dorsal fat pad, proximal muscle atrophy, central obesity and ecchymosis in at least 88% of patients after 48 weeks treatment (consisting of either 48 weeks osilodrostat phosphate or 12 weeks placebo followed by 36 weeks osilodrostat phosphate). There was no statistically significant difference between the treatment groups in the proportion of patients who had improved or not changed with respect to any of the physical features. Physical features with the greatest improvements (reported in at least 40% of all patients) were subcutaneous fat pad, dorsal fat pad, facial rubor and central obesity.** **Osilodrostat phosphate vs metyrapone:** **No evidence was identified for clinical disease response.** **Osilodrostat phosphate vs no comparator:** **One single-arm study (LINC4) provided very low certainty evidence that after 72 weeks treatment with osilodrostat phosphate female hirsutism had improved in 45% and remained stable in 42% of women with normal testosterone, and had improved in 21% and remained stable in 64% of women with raised testosterone. Improvements in female hirsutism were seen in some patients from 12 weeks of treatment onwards.**
Biochemical disease response **Certainty of evidence:** Moderate to very low	This outcome is important to patients because biochemical improvement is a measure of disease response to treatment. In total, two randomised studies and three single-arm studies (reported in six papers) and one retrospective cohort study provided evidence relating to biochemical disease response in people with Cushing's disease. The two randomised studies were conducted during a time-limited randomised double-blind placebo-controlled period within two of the single-arm studies. Patients who took part in the randomised studies also had periods of open label treatment with osilodrostat phosphate which were reported in the single-arm studies. The third single-arm study provided non-comparative evidence only. The randomised studies reported biochemical disease response outcomes after 8 and 12 weeks of randomisation, and the single-arm studies reported biochemical disease response outcomes after between 10 weeks and a median of 5.4 years of osilodrostat phosphate. The retrospective cohort study reported biochemical disease response at the time of best control of hypercortisolism for each patient.

Outcome	Evidence statement
	Response to treatment (based on mean 24-hour UFC unless otherwise stated)[7] *Osilodrostat phosphate vs placebo* **After 8 weeks randomised treatment** • One randomised study (LINC3, Pivonello et al 2020) (n=71) reported complete response rate (n (%) (95% CI)) in patients randomised to osilodrostat phosphate (n=36) compared to patients randomised to placebo (n=34): randomised to osilodrostat phosphate: 31/36 (86.1%) (95% CI 70.5% to 95.3%); randomised to placebo: 10/34 (29.4%) (95% CI 15.1% to 47.5%). This difference was *statistically significant*: OR 13.7 (95% CI 3.7 to 53.4), p<0.0001. **(MODERATE)** **After 12 weeks randomised treatment** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported complete response rate (n (%)) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25): randomised to osilodrostat phosphate: 37/48 (77.1%); randomised to placebo: 2/25 (8.0%). This difference was *statistically significant*: OR 43.4 (95% CI 7.1 to 343.2), p < 0.0001. **(MODERATE)** **After 48 weeks treatment, including 8 weeks randomisation and 40 weeks open label osilodrostat phosphate** • One randomised study (LINC3, Pivonello et al 2020) (n=71) reported overall, complete and partial response rates (n (%) (95% CI)) in patients randomised to osilodrostat phosphate (n=36) compared to patients randomised to placebo (n=35) after a total of 48 weeks treatment (patients randomised to osilodrostat phosphate received 48 weeks osilodrostat phosphate and patients randomised to placebo received placebo between weeks 27 and 34 and osilodrostat phosphate between weeks 1 to 26 and weeks 35 to 48). Randomised to osilodrostat phosphate: overall response 34 (94.4%) (95% CI 81.3% to 99.3%), complete response 32 (88.9%) (95% CI 73.9% to 96.9%), partial response 2 (5.6%) (95% CI 0.7% to 18.7%); randomised to placebo: overall response 31 (88.6%) (95% CI 73.3% to 96.8%), complete response: 27 (77.1%) (95% CI 59.9% to 89.6%), partial response 4 (11.4%) (95% CI 3.2% to 26.7%)**.** The differences between the groups were *not statistically significant*. **(MODERATE)** *Osilodrostat phosphate vs metyrapone* **At the point of best control of hypercortisolism** • One retrospective cohort study (Bonnet-Serrano et al 2022) (n=33) reported median serum cortisol (nmol/L) ([8]) in patients treated with osilodrostat phosphate compared to patients treated with metyrapone: osilodrostat phosphate group, 175 nmol/L (22 to 421); metyrapone group, 307 (68 to 547) nmol/L; p = 0.025. The difference between the two groups was *statistically significant*. **(VERY LOW)** *Osilodrostat phosphate vs no comparator* **After 10 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported response rates (n (%) (95% CI)) of overall response: 17 (89.5%) (95% CI 66.9% to 98.7%); controlled: 16 (84.2%) (95% CI 60.4% to 96.6%); partially controlled: 1 (5.3%) (95% CI 0.1% to 26.0%)**. (VERY LOW)** **After 22 weeks treatment with osilodrostat phosphate**

[7] Controlled or complete response: mean UFC≤ULN; partially controlled or partial response: mean UFC>ULN and with ≥50% reduction from baseline. Overall response = complete response + partial response. Mean 24-hour UFC reference range: 11-138 nmol/24 hours

[8] Figures within brackets reported in the paper appear to be the range; this would be consistent with some other reporting in this paper but was not stated for these outcomes.

Outcome	Evidence statement
	• One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported response rates (n (%) (95% CI)) of overall response: 15 (78.9%) (95% CI 54.4% to 94.0%); controlled: 15 (78.9%) (95% CI 54.4% to 94.0%); partially controlled: 0 (0%) (95% CI 0% to 17.7%). **(VERY LOW)** **After 24 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported response rates (n (%) (95% CI)) of overall response: 113 (82.5%) (95% CI 75.1% to 88.4%); complete response: 93 (67.9%) (95% CI 59.4% to 75.6%); partial response: 20 (14.6%) (95% CI 9.2% to 21.6%). **(VERY LOW)** **After 36 weeks treatment [9]** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported a complete response rate (n (%) (95% CI)) of 59 (80.8%) (95% CI 69.9% to 89.1%). **(VERY LOW)** **After 48 weeks treatment [10]** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported response rates (n (%) (95% CI)) of overall response: 104 (75.9%) (95% CI 67.9% to 82.8%); complete response: 91 (66.4%) (95% CI 57.9% to 74.3%); partial response: 13 (9.5%) (5.2% to 15.7%). **(VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported response rates (n (%)) of overall response: 58 (79.5%); complete response: 50 (68.5%); partial response: 8 (11.0%). **(VERY LOW)** **After 60 weeks treatment [11]** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a complete response rate (n (%) (95% CI)) of 86 (81.1%) (95% CI 72.4% to 88.1%). **(VERY LOW)** **After 70 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2022a) (n=16) reported response rates (n (%)) of overall response: 13 (81.3%); complete response: 12 (75%); partial response: 1 (6.3%). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a complete response rate (n (%) (95% CI)) of 86 (81.1%) (95% CI 72.4% to 88.1%)**. (VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2023) (n=60) reported response rates (n (%)) of overall response: 45 (75%); complete response: 40 (66.7%); partial response: 5 (8.3%). **(VERY LOW)** **Up to the end of treatment (median 87.1 (range 2.0 to 126.6) weeks) [12]** • One single-arm study (LINC4, Gadelha et al 2023) (n=58) reported response rates (n (%)) of overall response: 47 (81%); complete response: 42 (72.4%); partial response: 5 (8.6%). **(VERY LOW)**

[9] Patients in Gadelha et al 2022 randomised to placebo received 12 weeks placebo followed by osilodrostat phosphate to the end of treatment; patients randomised to osilodrostat phosphate received osilodrostat phosphate throughout.
[10] Patients in Pivonello et al 2020 randomised to placebo received 26 weeks osilodrostat phosphate followed by 8 weeks placebo and 14 weeks osilodrostat phosphate; patients randomised to osilodrostat phosphate received 48 weeks osilodrostat phosphate.
[11] Patients in Fleseriu et al 2022b who had been randomised to placebo in Pivonello et al 2020 received 26 weeks osilodrostat phosphate followed by 8 weeks placebo and osilodrostat phosphate to the end of treatment; patients randomised to osilodrostat phosphate received osilodrostat phosphate throughout.
[12] Patients in Gadelha et al 2023 who had been randomised to placebo in Gadelha et al 2022 received 12 weeks placebo followed by osilodrostat phosphate to the end of treatment; patients randomised to osilodrostat phosphate received osilodrostat phosphate throughout.

Outcome	Evidence statement
	At the last observed value (median exposure to osilodrostat phosphate 5.4 (range 0.04 to 6.7) years) • One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported response rates (n (%) (95% CI)) of complete response 12 (63.2%), partial response 5 (26.3%). **(VERY LOW)** <u>24-hour urinary free cortisol (UFC)</u> [13] *Osilodrostat phosphate vs placebo* **After 12 weeks randomised treatment** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) 24-hour UFC levels (nmol/24h) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25). Randomised to osilodrostat phosphate: baseline 421.4 (291.3), week 12 98.2 (122.5); randomised to placebo: baseline 451.5 (535.1), week 12: 411.3 (389.9). The 12-week result for the osilodrostat phosphate group was within the reference range but the results were not compared statistically. **(LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **After 22 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported a mean (SE) 24-hour UFC (nmol/24h) of 1371 (2734) at baseline and 92 (124) at 22 weeks. **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2023) (n=48) reported a mean (SE) 24-hour UFC (nmol/24h) of 90.5 (122.6). **(VERY LOW)** <u>Serum cortisol</u> [14] *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) serum cortisol levels (nmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25). Randomised to osilodrostat phosphate: baseline 565.8 (169.0), week 12 295.6 (160.4), week 48 354.0 (114.6); randomised to placebo: baseline 486.1 (198.1), week 12: 560.1 (204.4), week 48 353.7 (145.5). They also reported mean (95% CI) change in serum cortisol levels from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12 −276.0 (95% CI −330.2 to −221.7), week 48 -210.7 (95% CI −261.5 to −159.9); randomised to placebo: week 12: 73.0 (95% CI −5.2 to 151.2), week 48 -131.0 (95% CI −236.1 to −26.0). The change at 12 weeks was *statistically significantly greater* in the osilodrostat phosphate group. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator*

[13] Mean 24-hour UFC reference range, all studies: 11-138 nmol/24 hours
[14] Serum cortisol reference range male and female, ≥18 years old, all studies: 127–567 nmol/L

Outcome	Evidence statement
	After 48 weeks treatment • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported (mean (SD)) serum cortisol levels (nmol/L) of 538.1 (182.3) at baseline and 353.9 (124.9) at week 48. Mean change from baseline at week 48 was -182.9 (95% CI -231.5 to -134.3). **(VERY LOW)** **After up to 72 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2023) (n=46 to 73) reported (mean (SD)) serum cortisol levels (nmol/L) of 538.1 (182.3) at baseline (n=73), 353.9 (124.9) at week 48 (n=64) and 319.1 (129.8) at week 72 (n=46). **(VERY LOW)** • One single-arm study (LINC3, Fleseriu et al 2022b) (n not stated) reported that mean serum cortisol levels were within the normal range at week 48 and throughout the extension period (up to 72 weeks)**. (VERY LOW)** <u>Early-morning salivary cortisol</u> [15] *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) early-morning salivary cortisol levels (nmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25). Randomised to osilodrostat phosphate: baseline 17.2 (30.0), week 12 5.8 (7.0), week 48 4.7 (2.9); randomised to placebo: baseline 14.1 (12.3), week 12 14.1 (10.0), week 48 6.9 (7.7). They also reported mean (95% CI) change in early-morning salivary cortisol levels from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12 -11.6 (95% CI −20.5 to −2.7), week 48 −11.8 (95% CI −21.8 to −1.8); randomised to placebo: week 12: −0.3 (95% CI −5.1 to 4.4), week 48 −6.0 (95% CI −10.8 to −1.1). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported mean (SE) morning salivary cortisol levels (nmol/L) of 24 (41) at baseline and 5 (6) at week 22. **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) early-morning salivary cortisol levels (nmol/L) of 16.1 (25.3) at baseline and 5.4 (5.2) at week 48. Mean change from baseline at week 48 was −9.8 (95% CI −16.4 to −3.1). **(VERY LOW)** <u>Late-night salivary cortisol</u> [16] *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)**

[15] Early-morning salivary cortisol reference range, all studies: 1.1–15.5 nmol/L
[16] Late-night salivary cortisol reference range, male and female, ≥18 years old, all studies: ≤2.5 nmol

Outcome	Evidence statement
	• One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) late-night salivary cortisol levels (nmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25). Randomised to osilodrostat phosphate: baseline 11.7 (28.7), week 12 3.5 (2.3), week 48 3.5 (2.6); randomised to placebo: baseline 9.0 (6.7), week 12: 10.3 (6.5), week 48 4.0 (2.5). They also reported mean (95% CI) change in late-night salivary cortisol levels from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12 −8.5 (95% CI −17.3 to 0.3), week 48 -9.3 (95% CI −18.5 to −0.2); randomised to placebo: week 12: 1.3 (95% CI −2.4 to 5.1), week 48 −5.0 (95% CI −7.6 to −2.5). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **After 48 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported (mean (SD)) late-night salivary cortisol levels (nmol/L) of 10.8 (23.5) at baseline and 3.7 (2.6) at week 48. Mean change from baseline at week 48 was -7.8 (95% CI −13.8 to −1.9). **(VERY LOW)** **After up to 72 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2023) (n=46 to 73) reported (mean (SD)) late-night salivary cortisol levels (nmol/L) of 10.8 (23.5) at baseline (n=73), 3.7 (2.6) at week 48 (n=63) and 3.8 (3.0) at week 72 (n=46). **(VERY LOW)** • One single-arm study (LINC3, Fleseriu et al 2022b) (n not stated) reported that mean (SD) late-night salivary cortisol (nmol/L) was 2.7 (SD 1.6) at week 48 and remained consistently lower than baseline but above the reference range during the extension period (up to 72 weeks)**. (VERY LOW)** **Osilodrostat phosphate vs placebo:** **Two randomised studies (LINC3 and LINC4) provided moderate certainty evidence of a statistically significantly better complete response rate (based on mean UFC levels) in patients randomised to osilodrostat phosphate compared to patients randomised to placebo after 8 weeks and 12 weeks treatment. One of the randomised studies (LINC3) provided moderate certainty evidence of no statistically significant differences in overall, complete and partial response rates after 48 weeks treatment in patients randomised to 48 weeks osilodrostat phosphate compared to patients randomised to 8 weeks placebo between weeks 27 and 34 and osilodrostat phosphate between weeks 1 to 26 and weeks 35 to 48.** **One randomised study (LINC4) provided low certainty evidence that after 12 weeks treatment mean 24-hour UFC levels fell to within the normal range in patients randomised to osilodrostat phosphate but did not fall in patients randomised to placebo, but the two groups were not compared statistically. The same randomised study provided moderate certainty evidence that after 12 weeks randomised treatment there was a statistically significantly greater fall in mean serum cortisol levels in patients randomised to osilodrostat phosphate than in patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate mean serum cortisol levels had fallen in both groups and there was no statistically significant difference between them in the change in serum cortisol levels.** **One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks randomised treatment the early-morning and late-night**

Outcome	Evidence statement
	salivary cortisol levels had fallen more in patients randomised to osilodrostat phosphate than in patients randomised to placebo, but there was no statistically significant difference between the groups in the change in levels. After a further 36 weeks treatment of both groups with osilodrostat phosphate levels had fallen in both groups and there was no statistically significant difference between them in the change in early-morning or late-night salivary cortisol levels. **Osilodrostat phosphate vs metyrapone:** **One retrospective cohort study provided very low certainty evidence that patients treated with osilodrostat phosphate had a statistically significantly lower median serum cortisol level than patients treated with metyrapone at the time of best control of hypercortisolism. No evidence was identified for any other biochemical disease response outcomes comparing osilodrostat phosphate to metyrapone.** **Osilodrostat phosphate vs no comparator:** **Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence of overall and complete response rates (based on mean UFC levels) to osilodrostat phosphate of 89.5% and 84.2% respectively after 10 weeks treatment, between 75% and 83% for overall response and between 63% and 81% for complete response at time points between 22 and a median of 87 weeks treatment, and a complete response rate of 63.2% after a median 5.4 years exposure to osilodrostat phosphate.** **Two single-arm studies (LINC2 and LINC4) provided very low certainty evidence that mean 24-hour UFC levels were within the normal range after 22 and 72 weeks treatment with osilodrostat phosphate. They also provided very low certainty evidence that mean serum cortisol levels fell from baseline after 48 and 72 weeks treatment with osilodrostat phosphate, but the levels were within the normal range at all measurement points including baseline.** **Two single-arm studies (LINC2 and LINC4) provided very low certainty evidence that early-morning salivary cortisol levels were above the normal range at baseline and fell to within the normal range after 22 weeks and 48 weeks treatment with osilodrostat phosphate. They also provided very low certainty evidence that late-night salivary cortisol levels fell from baseline after up to 72 weeks treatment with osilodrostat phosphate but remained above the normal range.**
Sequelae of Cushing's disease **Certainty of evidence:** Moderate to very low	This outcome is important for patients because it measures improvements in the physical health consequences of Cushing's disease. The associated morbidity is high due to complications such as diabetes, hypertension, metabolic syndrome, low mood, a predisposition to infection and impacts on bone health. In total, one randomised study and three single-arm studies (reported in six papers) provided evidence relating to sequelae of Cushing's disease. The randomised study was conducted during a time-limited randomised double-blind placebo-controlled period within one of the single-arm studies. Patients who took part in the randomised study also had a period of open label treatment with osilodrostat phosphate which was reported in the single-arm studies. Two of the single-arm studies provided non-comparative evidence only. The randomised study reported outcomes relating to sequelae of Cushing's disease after 12 weeks of randomisation, and the single-arm studies reported outcomes relating to sequelae of Cushing's disease after between 22 weeks and a median of 5.4 years of osilodrostat phosphate. **<u>Weight, body mass index (BMI) and waist circumference</u>** *Osilodrostat phosphate vs placebo* <u>Weight</u>

Outcome	Evidence statement
	After up to 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate) • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) weight (kg) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 78.8 (17.5), week 12: 78.1 (17.9), week 48: 74.1 (16.6); randomised to placebo: 77.3 (16.9), week 12: 75.7 (15.7), week 48 72.5 (17.4). They also reported mean (95% CI) change in weight from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12 −0.8 (95% CI −1.7 to 0.1), week 48 -3.6 (95% CI −5.7 to −1.6); randomised to placebo: week 12: -3.6 (95% CI −5.7 to −1.6), week 48 −5.5 (95% CI −8.3 to −2.7). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** <u>Waist circumference.</u> **After up to 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) waist circumference (cm) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 102.5 (17.0), week 12: 101.4 (17.7), week 48: 97.3 (17.0); randomised to placebo: 103.4 (15.5), week 12: 102.1 (15.1), week 48 97.8 (17.2). They also reported mean (95% CI) change in waist circumference from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12 -1.0 (95% CI −2.3 to 0.3), week 48 −4.1 (95% CI −6.0 to −2.2); randomised to placebo: week 12: −0.5 (95% CI −1.9 to 1.0), week 48 −5.3 (95% CI −7.9 to −2.8). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for these outcomes. *Osilodrostat phosphate vs no comparator* <u>Weight</u> **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) weight (kg): baseline: 85.1 (24.0); week 22: 85.6 (26.2); change from baseline: –1.5 (3.8). **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) weight (kg): baseline: 80.8 (22.4); week 48: 75.5 (20.7); change from baseline: -3.8 (95% CI -4.8 to -2.7). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) weight (kg): baseline: 78.3 (17.2); Week 48: 73.5 (16.8); change from baseline: −4.3 (95% CI −5.9 to −2.6). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in weight (kg) from baseline of -4.7 (6.6). **(VERY LOW)** <u>BMI</u> **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) body mass index (kg/m^2): baseline: 30.7 (7.0); week 22: 30.1 (7.9); change from baseline: –0.5 (1.4). **(VERY LOW)**

Outcome	Evidence statement
	After 48 weeks treatment • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) body mass index (kg/m^2): baseline: 30.3 (7.8); Week 48: 28.4 (7.1); change from baseline: -1.4 (95% CI -1.8 to 1.0). (**VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in body mass index (kg/m^2) from baseline of -1.8 (2.5). **(VERY LOW)** <u>Waist circumference</u> **After 48 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) waist circumference (cm): baseline: 102.8 (16.4); week 48: 97.5 (16.9); change from baseline: −4.5 (95% CI −6.0 to −3.0). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in waist circumference (cm) from baseline of -6.2 (8.5). **(VERY LOW)** **<u>Cardiovascular and metabolic outcomes</u>** *Osilodrostat phosphate vs placebo* <u>Systolic BP</u> **After up to 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate) [17]** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) systolic BP (mm Hg) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 132.4 (19.2), week 12: 125.5 (13.7), week 48: 123.0 (15.4); randomised to placebo: baseline: 130.0 (17.7), week 12: 127.4 (14.9), week 48: 117.0 (16.2). They also reported mean (95% CI) change in systolic BP from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −7.1 (95% CI −12.6 to −1.6), week 48: −9.1 (95% CI −15.2 to −2.9); randomised to placebo: week 12: −0.9 (95% CI −5.8 to 4.1), week 48: −11.0 (−20.8, −1.1). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** <u>Diastolic BP</u> • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) diastolic BP (mm Hg) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 87.2 (12.7), week 12: 125.5 (13.7), week 48: 81.7 (11.0); randomised to placebo: baseline: 88.2 (10.8), week 12: 87.0 (11.2), week 48: 83.5 (10.4). They also reported mean (95% CI) change in diastolic BP from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −4.8 (95% CI −8.2 to −1.5), week 48: −4.4 (95% CI −8.1 to −0.7); randomised to placebo: week 12: −1.4 (95% CI −5.5 to 2.8), week 48: −3.9 (95% CI −9.8 to 2.0). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)**

[17] Reference ranges, Gadelha et al 2022: fasting plasma glucose, 70–115 mg/dL (13–49 years), 70–125 mg/dL (≥50 years); HbA1c, ≤6.4%; total cholesterol, 0–5.2 mmol/L (≥20 years); HDL cholesterol, >0.89 mmol/L; LDL cholesterol, 0–3.4 mmol/L (≥20 years); triglycerides, 0–2.2 mmol/L.

Outcome	Evidence statement
	Fasting plasma glucose • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) fasting plasma glucose (mg/dl) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 97.3 (18.1), week 12: 92.0 (15.5), week 48: 90.5 (12.9); randomised to placebo: baseline: 91.4 (15.2), week 12: 91.1 (11.2), week 48: 90.7 (13.7). They also reported mean (95% CI) change in fasting plasma glucose from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −4.3 (95% CI −8.9 to 0.2), week 48: −5.6 (95% CI −10.1 to −1.1); randomised to placebo: week 12: −1.7 (95% CI −6.3 to 2.9), week 48: 1.8 (95% CI −4.5 to 8.1). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups and levels were within the normal range in both groups at all time points. **(MODERATE/LOW)** HbA1c • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) HbA1c (%) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 6.0 (0.9), week 12: 5.7 (0.7), week 48: 5.8 (0.6); randomised to placebo: baseline: 5.7 (0.6), week 12: 5.6 (0.6), week 48: 5.7 (0.5). They also reported mean (95% CI) change in HbA1c from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −0.2 (95% CI −0.4 to −0.1), week 48: −0.2 (95% CI −0.4 to 0.0); randomised to placebo: week 12: 0.0 (95% CI −0.2 to 0.1), week 48: 0.1 (95% CI −0.1 to 0.2). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups and levels were within the normal range in both groups at all time points. **(MODERATE/LOW)** Total cholesterol • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) total cholesterol (mmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 5.7 (1.3), week 12: 4.9 (1.2), week 48: 5.1 (1.3); randomised to placebo: baseline: 5.3 (1.2), week 12: 5.3 (1.3), week 48: 4.9 (1.2). They also reported mean (95% CI) change in total cholesterol from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −0.8 (95% CI −1.1 to −0.5), week 48: −0.6 (95% CI −1.0 to −0.1); randomised to placebo: week 12: 0.0 (95% CI −0.2 to 0.3), week 48: -0.4 (95% CI −0.9 to 0.1). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups; levels were above the normal range in both groups at baseline and in the placebo group at week 12 but within the normal range at all other timepoints. **(MODERATE/LOW)** LDL cholesterol • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) LDL cholesterol (mmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 3.4 (1.1), week 12: 3.0 (1.0), week 48: 3.0 (1.0); randomised to placebo: baseline: 3.0 (1.1), week 12: 3.1 (1.1), week 48: 2.8 (1.1). They also reported mean (95% CI) change in LDL cholesterol from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −0.5 (95% CI −0.7 to −0.2), week 48: −0.5 (95% CI −0.8 to −0.2); randomised to placebo: week 12: 0.1 (95% CI −0.1 to 0.3), week 48: −0.2 (95% CI −0.6 to 0.2). The fall in LDL cholesterol was *statistically significantly greater* in the osilodrostat phosphate group at week 12 but not

Outcome	Evidence statement
	at week 48, but levels remained within the normal range in both groups at all time points. **(MODERATE/LOW)** HDL cholesterol • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) HDL cholesterol (mmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 1.6 (0.4), week 12: 1.3 (0.3), week 48: 1.4 (0.3); randomised to placebo: 1.5 (0.4), week 12: 1.5 (0.5), week 48: 1.4 (0.4). They also reported mean (95% CI) change in HDL cholesterol from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −0.3 (95% CI −0.4 to −0.2), week 48: −0.2 (95% CI −0.3 to −0.1); randomised to placebo: week 12: 0.0 (95% CI −0.1 to 0.1), week 48: −0.1 (95% CI −0.3 to 0.0). There was a *statistically significant fall* in HDL cholesterol in the osilodrostat phosphate group but not in the placebo group, but levels remained within the normal range in both groups at all time points. **(MODERATE/LOW)** Triglycerides • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) triglycerides (mmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 1.5 (0.8), week 12: 1.5 (0.8), week 48: 1.5 (1.0); randomised to placebo: baseline: 1.7 (0.9), week 12: 1.5 (0.8), week 48: 1.5 (0.8). They also reported mean (95% CI) change in triglycerides from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: 0.0 (95% CI −0.1 to 0.2), week 48: 0.1 (95% CI −0.2 to 0.4); randomised to placebo: week 12: −0.2 (95% CI −0.4 to 0.0), week 48: −0.2 (95% CI −0.5 to 0.0). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups and levels were within the normal range in both groups at all time points. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for these outcomes. *Osilodrostat phosphate vs no comparator* Systolic BP **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) systolic BP (mm Hg): baseline: 132.6 (11.6); week 22: 131.9 (17.8); change from baseline: –1.0 (16.2). **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) systolic BP (mm Hg): baseline: 132.2 (15.1); week 48: 121.7 (13.7); change from baseline: -9.8 (95% CI -12.7 to -6.9). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) systolic BP (mm Hg): baseline: 131.5 (18.6); week 48: 120.9 (15.8); change from baseline: −9.7 (95% CI −14.9 to −4.6). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in systolic BP (mm Hg) from baseline of -10.1 (18.1). **(VERY LOW)**

Outcome	Evidence statement
	Diastolic BP **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) diastolic BP (mm Hg): baseline: 85.1 (6.5); week 22: 86.0 (8.9); change from baseline: 1.3 (9.7). **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) diastolic BP (mm Hg): baseline: 85.3 (10.6); week 48: 78.9 (10.1); change from baseline: -6.3 (95% CI -8.4 to -4.2). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) diastolic BP (mm Hg): baseline: 87.5 (12.0); week 48: 82.3 (10.8); change from baseline: −4.2 (95% CI −7.3 to −1.2). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in diastolic BP (mm Hg) from baseline of -5.8 (11.3). **(VERY LOW)** Fasting plasma glucose **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) fasting plasma glucose (mg/dl) [18]: baseline: 105.6 (49.0); week 22: 81.2 (9.0); change from baseline: -14.9 (28.9). **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) fasting plasma glucose (mg/dl) [19]: baseline: 99.2 (29.8); week 48: 87.2 (18.9); change from baseline: -9.5 (95% CI -14.3 to -4.8). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) fasting plasma glucose (mg/dl)[20]: baseline: 95.3 (17.3); week 48: 90.6 (13.1); change from baseline: −3.1 (95% CI −6.8 to 0.6). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in fasting plasma glucose (mmol/L)[21] from baseline of -0.3 (1.1). **(VERY LOW)** HbA1c **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) HbA1c (%)[22]: baseline: 5.7 (0.7); week 22: 5.5 (0.6); change from baseline: -0.2 (0.3). **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) HbA1c (%): baseline: 6.0 (1.0); week 48: 5.6 (0.8); change from baseline: -0.4 (95% CI -0.5 to -0.2). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) HbA1c (%): baseline: 5.9 (0.2); week 48: 5.7 (0.5); change from baseline: −0.1 (95% CI −0.2 to 0.0). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in HbA1c (%) from baseline of -0.4 (0.6). **(VERY LOW)**

[18] Normal range Fleseriu et al 2016: fasting plasma glucose 70 to 110 mg/dL
[19] Reference range Pivonello et al 2020: plasma glucose 70 to 125 mg/dL
[20] Reference range Gadelha et al 2022: fasting plasma glucose, 70–115 mg/dL
[21] Reference range Fleseriu et al 2022b: plasma glucose, 3.9–5.5 mmol/L
[22] Reference range in all studies: HbA1c ≤6.4%

Outcome	Evidence statement
	Total cholesterol **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) total cholesterol (mmol/L)[23]: baseline: 5.3 (1.4); week 22: 4.6 (0.8); change from baseline: -0.7 (1.4). **(VERY LOW)** **After 48 weeks treatment** [24] • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) total cholesterol (mmol/L): baseline: 5.3 (1.2); week 48: 4.8 (1.0); change from baseline: -0.5 (95% CI -0.7 to -0.3). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) total cholesterol (mmol/L): baseline: 5.5 (1.3); week 48: 5.0 (1.3); change from baseline: −0.5 (95% CI −0.8 to -0.2). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in total cholesterol (mmol/L)[25] from baseline of -0.4 (0.9). **(VERY LOW)** HDL cholesterol **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) HDL cholesterol (mmol/L)[26]: baseline: 1.7 (0.9); week 22: 1.3 (0.4); change from baseline: -0.5 (0.8). **(VERY LOW)** **After 48 weeks treatment** [27] • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) HDL cholesterol (mmol/L): baseline: 1.6 (0.5); week 48: 1.3 (0.3); change from baseline: -0.3 (95% CI -0.3 to -0.2). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) HDL cholesterol (mmol/L): baseline: 1.6 (0.4); week 48: 1.4 (0.4); change from baseline: −0.2 (95% CI −0.3 to -0.1). **(VERY LOW)** LDL cholesterol **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) LDL cholesterol (mmol/L) [28]: baseline: 3.3 (1.7); week 22: 2.8 (0.6); change from baseline: -0.6 (1.6). **(VERY LOW)** **After 48 weeks treatment** [29] • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) LDL cholesterol (mmol/L): baseline: 3.0 (1.0); week 48: 2.8 (1.0); change from baseline: -0.2 (95% CI -0.4 to -0.1). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) LDL cholesterol (mmol/L): baseline: 3.3 (1.1); week 48: 2.9 (1.1); change from baseline: −0.4 (95% CI −0.6 to -0.1). **(VERY LOW)** Triglycerides **After 22 weeks treatment**

[23] Normal range Fleseriu et al 2016: total cholesterol 3.9 to 6.5 mmol/L
[24] Reference range Pivonello et al 2020 and Gadelha et al 2022: total cholesterol 0 to 5.2 mmol/L
[25] Normal ranges Fleseriu et al 2022b: total cholesterol, ≤4.4 mmol/L in people aged <19 years and ≤5.2 mmol/L in people aged ≥20 years
[26] Normal range Fleseriu et al 2016: HDL-cholesterol 1 to 1.7 mmol/L
[27] Reference range Pivonello et al 2020 and Gadelha et al 2022: HDL cholesterol >0.89 mmol/L
[28] Normal range Fleseriu et al 2016: LDL-cholesterol 0 to 4.2 mmol/L
[29] Reference range Pivonello et al 2020 and Gadelha et al 2022: LDL cholesterol 0 to 3.4 mmol/L

Outcome	Evidence statement
	• One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) triglycerides (mmol/L)[30]: baseline: 1.5 (0.6); week 22: 1.3 (0.6); change from baseline: -0.7 (1.4). **(VERY LOW)** **After 48 weeks treatment [31]** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) triglycerides (mmol/L): baseline: 1.5 (1.3); week 48: 1.4 (0.9); change from baseline: -0.1 (95% CI -0.2 to 0.1). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) triglycerides (mmol/L): baseline: 1.6 (0.8); week 48: 1.5 (0.9); change from baseline: 0 (95% CI −0.2 to 0.2). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in triglycerides (mmol/L) from baseline of -0.1 (0.6). **(VERY LOW)** <u>Beck depression inventory II (BDI-II) score</u> [32] *Osilodrostat phosphate vs placebo* **After up to 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) BDI-II score in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 12.2 (10.2), week 12: 10.3 (8.5), week 48: 6.7 (6.7); randomised to placebo: baseline: 8.4 (7.8), week 12: 4.7 (6.1), week 48: 4.1 (7.5). They also reported mean (95% CI) change in BDI-II score from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −1.4 (95% CI −3.7 to 1.0), week 48: −4.3 (95% CI −6.7 to −2.0); randomised to placebo: week 12: −3.9 (95% CI −6.2 to −1.6); week 48: −4.0 (95% CI −7.5 to −0.6). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) BDI-II score: baseline: 16.8 (10.6); week 48: 10.7 (10.7); change from baseline: -5.8 (95% CI -7.6 to -4.1); mean % change from baseline: -31.8% (95% CI -44.3% to -19.3%). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) BDI-II score: baseline: 10.9 (9.6); week 48: 5.8 (7.9); change from baseline: -4.2 (95% CI −6.1 to -2.3). **(VERY LOW)** **After 72 weeks treatment**

[30] Normal range Fleseriu et al 2016: triglycerides 0.6 to 1.7 mmol/L

[31] Reference range Pivonello et al 2020, Gadelha et al 2022 and Fleseriu et al 2022b: triglycerides 0 to 2.2 mmol/L

[32] Decrease in BDI-II score indicates benefit

Outcome	Evidence statement
	• One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in BDI-II score from baseline of -6.7 (10.7). **(VERY LOW)** **Up to the end of treatment (median 87.1 (range 2.0 to 126.6 weeks))** • One single-arm study (LINC4, Gadelha et al 2023) (n=48 at week 72, n=13 at the end of treatment) reported a mean (SD) BDI-II score of 6.5 (7.0), mean change from baseline -4.1 (9.3) at week 72, and 6.2 (7.1), mean change from baseline -4.5 (7.9) at the end of treatment. **(VERY LOW)** **Osilodrostat phosphate vs placebo:** **One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks randomised treatment there was no statistically significant difference in the change in mean weight or waist circumference between patients randomised to osilodrostat phosphate and patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate there remained no statistically significant difference in the change in weight or waist circumference between the two groups.** **One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks randomised treatment there was a statistically significantly greater fall in mean LDL cholesterol and HDL cholesterol in patients randomised to osilodrostat phosphate compared to patients randomised to placebo, but values remained within the normal ranges in both groups at all time points. There was no statistically significant difference at 12 weeks in the change in mean systolic BP, diastolic BP, fasting plasma glucose, HbA1c, total cholesterol or triglycerides between patients randomised to osilodrostat phosphate and patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate there were no statistically significant differences in the changes in any of these measures between the groups. Total cholesterol values were above the normal range in both groups at baseline and fell to within the normal range in the osilodrostat phosphate group by 12 weeks and in the group which had been randomised to placebo by 48 weeks. For all other measures values were within the normal range (where specified) in both groups at all time points.** **One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks randomised treatment there was no statistically significant difference in the change in BDI-II score between patients randomised to osilodrostat phosphate and patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate there remained no statistically significant difference in the change in BDI-II score between the two groups.** **Osilodrostat phosphate vs metyrapone:** **No evidence was identified for sequelae of Cushing's disease.** **Osilodrostat phosphate vs no comparator:** **Two single-arm studies (LINC2 and LINC3) provided very low certainty evidence of a fall in mean weight from baseline after up to 72 weeks treatment with osilodrostat phosphate. Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence of a fall in mean body mass index and two single-arm studies provided very low certainty evidence of a fall in mean waist circumference from baseline after up to 72 weeks treatment with osilodrostat phosphate.** **Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence of a fall in mean systolic BP, diastolic BP, fasting plasma glucose, HbA1c, total cholesterol and triglycerides after between 22 and 72 weeks treatment with osilodrostat phosphate. The three single-arm studies also provided very low certainty evidence of a fall in mean HDL and LDL**

Outcome	Evidence statement
	cholesterol after between 22 and 48 weeks treatment with osilodrostat phosphate. **Two single-arm studies (LINC3 and LINC4) provided very low certainty evidence of a fall (improvement) in mean BDI-II score after between 48 and a median of 87.1 weeks treatment with osilodrostat phosphate. One single-arm study (LINC3) provided very low certainty evidence that the percentage fall in BDI-II score at 48 weeks exceeded the MCID[33].**
Important outcomes	
Reduction in treatment for Cushing's disease sequelae **Certainty of evidence:** Very low	This is important to patients because they may be getting symptomatic relief with improvement in their physical health consequences of Cushing's disease, for example improvement in diabetes or hypertension. It may also provide them benefit as it reduces their medication burden. In total, one single-arm study provided evidence relating to reduction in treatment for Cushing's disease sequelae. *Osilodrostat phosphate vs placebo* • No evidence was identified for this outcome. *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **At 48 weeks follow-up[34]:** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=85 taking hypertensive medication at baseline) reported that compared to baseline 34/85 (40%) had increased their dose or number of medications and 34/85 (40%) had decreased their dose or stopped the medication. (**VERY LOW)** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=43 taking diabetic medication at baseline) reported that compared to baseline 10/43 (23%) had increased their dose or number of medications and 21/43 (49%) had decreased their dose or stopped the medication. (**VERY LOW)** **Osilodrostat phosphate vs placebo:** **No evidence was identified for reduction in treatment for Cushing's disease sequelae.** **Osilodrostat phosphate vs metyrapone:** **No evidence was identified for reduction in treatment for Cushing's disease sequelae.** **Osilodrostat phosphate vs no comparator:** **One single-arm study (LINC3) provided very low certainty evidence that after 48 weeks treatment with osilodrostat phosphate, of the patients taking hypertensive medication at baseline 40% had an increase and 40% had a decrease in their medication, and of the patients taking diabetic medication at baseline 23% had an increase and 49% had a decrease in their medication.**
Time to improvement **Certainty of evidence:** Low to very low	This is important to patients because current medicine for Cushing's disease differ with regards to their mechanism of action and time course of pharmacological

[33] Defined as 17.5% decrease from baseline in Pivonello et al 2020

[34] Patients in Fleseriu et al 2022b who had been randomised to placebo in Pivonello et al 2020, received 26 weeks osilodrostat phosphate followed by 8 weeks placebo and osilodrostat phosphate to the end of treatment; patients randomised to osilodrostat phosphate received osilodrostat phosphate throughout. It was not stated how many patients included in these outcomes had been randomised to osilodrostat phosphate or placebo.

Outcome	Evidence statement
	effect. A treatment that works more quickly is more likely to reduce the risk of subsequent sequelae of Cushing's disease developing. In total, one randomised study and two single-arm studies (reported in three papers) provided evidence relating to time to improvement. Patients in the randomised study who were initially randomised to placebo later crossed over to open-label treatment with osilodrostat phosphate. *Osilodrostat phosphate vs placebo* **After an unspecified duration of follow-up** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported median time to first controlled UFC response of 35 (95% CI 34.0 to 52.0) days in patients randomised to osilodrostat phosphate (n=48), and not reached in patients randomised to placebo (n=25). They also reported that the median time to first controlled UFC response was 35 days in patients randomised to placebo once they had crossed over to osilodrostat phosphate. **(LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome *Osilodrostat phosphate vs no comparator* **After an unspecified duration of follow-up** • One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported that the mean (SE) 24-hour UFC was 1371 at baseline and fell to within the normal range by week 4. **(VERY LOW)** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported that the median time to first complete response was 41.0 days (IQR 27.0 to 56.0 days). (**VERY LOW)** **Osilodrostat phosphate vs placebo** **One randomised study (LINC4) provided moderate certainty evidence that the median time to first controlled UFC response for patients treated with osilodrostat phosphate was 35 days.** **Osilodrostat phosphate vs metyrapone** **No evidence was identified for time to improvement.** **Osilodrostat phosphate vs no comparator:** **One single-arm study (LINC2) provided very low certainty evidence that mean UFC fell to within the normal range at a mean of 4 weeks. One single-arm study (LINC3) provided very low certainty evidence that the median time to first complete response was 41.0 days.**
Quality of life **Certainty of evidence:** Moderate to very low	Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making. In total, one randomised study and two single-arm studies (reported in four papers) provided evidence relating to quality of life. Patients in the randomised study who were randomised to osilodrostat phosphate received 48 weeks osilodrostat phosphate, while those randomised to placebo received 12 weeks placebo followed by 36 weeks osilodrostat phosphate. The randomised study reported outcomes relating to quality of life after 12 and 48 weeks treatment, and the single-arm studies reported outcomes relating to quality of life after between 48 weeks and a median of 87.1 weeks treatment with osilodrostat phosphate.

Outcome	Evidence statement
	Osilodrostat phosphate vs placebo **After up to 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) Cushing quality of life score in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 49.1 (19.6), week 12: 56.1 (22.1), week 48: 62.8 (22.2); randomised to placebo: baseline: 56.9 (19.0), week 12: 65.6 (17.6), week 48: 69.9 (16.9). They also reported mean (95% CI) change in Cushing quality of life score from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: 6.2 (95% CI 1.7 to 10.6), week 48: 11.7 (95% CI 6.6 to 16.7); randomised to placebo: week 12: 8.6 (95% CI 3.5 to 13.7); week 48: 12.8 (95% CI 6.5 to 19.1). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome *Osilodrostat phosphate vs no comparator* **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) Cushing quality of life score: baseline: 42.2 (19.1); week 48: 58.3 (21.3); change from baseline: 14.1 (95% CI 10.9 to 17.3). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) Cushing quality of life score: baseline: 51.8 (19.6); week 48: 65.3 (20.7); change from baseline: 12.0 (95% CI 8.2 to 15.9). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in Cushing quality of life score from baseline of 15.1 (19.4). **(VERY LOW)** **Up to the end of treatment (median 87.1 (range 2.0 to 126.6 weeks))** • One single-arm study (LINC4, Gadelha et al 2023) (n=48 at week 72, n=13 at the end of treatment) reported a mean (SD) Cushing quality of life score of 66.4 (19.6), mean change from baseline 15.2 (19.0) at week 72, and 69.0 (20.9), mean change from baseline 17.1 (17.1) at the end of treatment. **(VERY LOW)** **Osilodrostat phosphate vs placebo** **One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks treatment there was no statistically significant difference in the change in mean Cushing QoL score between patients randomised to osilodrostat phosphate and patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate there remained no statistically significant difference in the change in mean Cushing QoL score between the two groups.** **Osilodrostat phosphate vs metyrapone** **No evidence was identified for QoL.** **Osilodrostat phosphate vs no comparator** **Two single-arm studies (LINC3 and LINC4) provided very low certainty evidence of an increase (improvement) in mean Cushing QoL score after between 48 and a median of 87.1 weeks treatment with osilodrostat**

Outcome	Evidence statement
	phosphate. They also provided very low certainty evidence that the change from baseline exceeded the MCID at all timepoints[35].
Activities of daily living (ADLs) **Certainty of evidence:** Not applicable	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. **No evidence was identified for this outcome.**
Safety	
Adverse events **Certainty of evidence:** Low to very low	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. In total, two randomised studies and three single-arm studies (reported in six papers) provided evidence relating to adverse events in people with Cushing's disease. The two randomised studies were conducted during a time-limited randomised double-blind placebo-controlled period within two of the single-arm studies. The randomised studies reported adverse events during the randomised treatment periods (8 and 12 weeks in the two studies), and the single-arm studies reported adverse events after between 22 weeks and a median of 5.4 years of osilodrostat phosphate. *Osilodrostat phosphate vs placebo* <u>Any adverse event</u> **During the 8-week randomised treatment period** • One randomised study (LINC3, Pivonello et al 2020) (n=71) reported that in patients randomised to osilodrostat phosphate (n=35) and those randomised to placebo (n=35) the incidence of any AE (all grades) was 26 (72%) and 23 (66%), and of grade 3-4 AEs was 2 (6%) and 3 (9%) respectively. The incidence of any serious AE (all grades) was 2 (6%) and 1 (3%), and of any serious grade 3-4 AE was 1 (3%) and 1 (3%) respectively. **(LOW)** **During the 12-week randomised treatment period** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported that in patients randomised to osilodrostat phosphate (n=48) and those randomised to placebo (n=25) respectively the incidence of any AE was 46 (95.8%) and 23 (92.0%), of any serious AE was 2 (4.2%) and 1 (4.0%), of AEs leading to discontinuation was 1 (2.1%) and 0, of grade 1–2 AEs was 36 (75.0%) and 18 (72.0%) and of grade 3–4 AEs was 10 (20.8%) and 5 (20.0%). **(LOW)** <u>Most common adverse events</u> **During the 8-week randomised treatment period** • One randomised study (LINC3, Pivonello et al 2020) (n=71) reported that in patients randomised to osilodrostat phosphate (n=35) and those randomised to placebo respectively (n=35) the most common AEs were: nausea, 4 (11%) and 0; anaemia, 3 (8%) and 3 (9%) and fatigue, 2 (6%) and 3 (9%). **(LOW)**

[35] Defined as 10.1-point increase from baseline in Pivonello et al 2020

Outcome	Evidence statement
	During the 12-week randomised treatment period • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported that in patients randomised to osilodrostat phosphate (n=48) and those randomised to placebo (n=25) respectively the most common AEs were: decreased appetite, 18 (37.5%) and 4 (16.0%); arthralgia, 17 (35.4%) and 2 (8.0%); fatigue, 12 (25.0%) 4 (16.0%); nausea, 15 (31.3%) and 3 (12.0%) and hypertension, 8 (16.7%) and 7 (28.0%). **(LOW)** <u>Adverse events of special interest</u> **During the 8-week randomised treatment period** • One randomised study (LINC3, Pivonello et al 2020) (n=71) reported that in patients randomised to osilodrostat phosphate (n=35) and those randomised to placebo (n=35) respectively the incidence of AEs of special interest was: related to adrenal hormone precursor accumulation, 2 (6%) and 1 (3%); related to hypocortisolism, 3 (8%) and 1 (3%). No incidences were reported of AEs related to pituitary tumour enlargement, QT interval prolongation or arrhythmogenic potential on ECG. **(LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for adverse events. *Osilodrostat phosphate vs no comparator* <u>Any adverse event</u> **After up to 48 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported that the incidence of any AE of all grades was 100%, and of any grade 3-4 AE was 56.9%. The incidence of any serious AE was 36.5% and any serious grade 3-4 AE was 28.5%. AEs requiring dose interruption and/or change occurred in 77.4% (all grades) and 28.5% (grade 3-4). One death was reported. **(VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported that the incidence of any AE of all grades was 100%, and of any grade 3-4 AE was 38.4%. The incidence of any serious AE was 11.0% and of AEs leading to discontinuation was 11.0%. **(VERY LOW)** **After up to 72 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=137) reported that the incidence of any AE of all grades was 100%, and of any grade 3-4 AE was 60.6%. AEs leading to discontinuation occurred in 18.2% (all grades) and 12.4% (grades 3-4). AEs requiring dose adjustment or interruption occurred in 80.3% (all grades) and 30.7% (grades 3-4). **(VERY LOW)** **After a median 87.1 weeks exposure to osilodrostat phosphate** • One single-arm study (LINC4, Gadelha et al 2023) (n=73) reported that incidence of any AE of all grades was 98.6% and of any grade 3-4 AE was 39.7%. The incidence of any serious AE was 13.7% and any serious grade 3-4 AE was 12.3%. AEs leading to discontinuation occurred in 12.3% (all grades) and 2.7% (grade 3-4); AEs leading to dose adjustment or interruption occurred in 57.5% (all grades) and 17.8% (grades 3-4). AEs requiring additional therapy occurred in 91.8% (all grades) and 30.1% (grade 3-4). **(VERY LOW)** <u>Most common adverse events</u> **After up to 22 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported that the most common AEs of all grades (between 5 (26.3%) and 7 (36.8%) reported of each) were nausea, diarrhoea, asthenia, adrenal insufficiency, nasopharyngitis, increased testosterone, increased adrenal precursors and

Outcome	Evidence statement
	increased ACTH. Grade 3-4 AEs reported (1 (5.3%) of each reported) were adrenal insufficiency and increased testosterone. **(VERY LOW)** **After up to 48 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported that the most common AEs of all grades (between 30 (21.9%) and 57 (41.6%) reported) were nausea, headache, fatigue, adrenal insufficiency, nasopharyngitis and vomiting. The most common grade 3-4 AEs (n, (%)) were adrenal insufficiency; 6 (4.4%); headache, 4 (2.9%); vomiting, 4 (2.9%); nausea, 3 (2.2%), fatigue, 3 (2.2%). **(VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported that the most common AEs of all grades (between 15 (20.5%) and 33 (45.2%) reported) were decreased appetite, arthralgia, fatigue, nausea, headache, myalgia, dizziness, adrenal insufficiency, increased blood testosterone, diarrhoea, hypertension, asthenia and upper respiratory tract infection. **(VERY LOW)** **After up to 70 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC2, Fleseriu et al 2022a) (n=16) reported that the most common AEs of all grades (between 4 and 7 reported of each) were adrenal insufficiency, arthralgia, headache and diarrhoea. Grade 3-4 AEs (1 of each reported) were adrenal insufficiency, headache, abdominal pain, increased lipase, pituitary-dependant Cushing's syndrome, gastroenteritis, non-cardiac chest pain and decreased weight. **(VERY LOW)** **After up to 72 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=137) reported that the most common AEs of all grades (between 28 (20.4%) and 50 (36.5%) each) were nausea, headache, fatigue, adrenal insufficiency, vomiting, nasopharyngitis and glucocorticoid deficiency. The most common grade 3-4 AEs (n, (%)) were hypertension, 16 (11.7%); headache, 6 (4.4%); adrenal insufficiency, 6 (4.4%); glucocorticoid deficiency, 5 (3.6%); vomiting, 5 (3.6%); fatigue, 3 (2.2%); nausea, 3 (2.2%). **(VERY LOW)** **After a median 87.1 weeks exposure to osilodrostat phosphate:** • One single-arm study (LINC4, Gadelha et al 2023) (n=73) reported that the most common AEs of all grades (between 16 (21.9%) and 34 (46.6%) reported) were decreased appetite, arthralgia, fatigue, nausea, headache, dizziness, adrenal insufficiency, increased blood testosterone, myalgia, asthenia, diarrhoea, hypertension, upper respiratory tract infection. The most common grade 3-4 AEs (n, (%)) were hypertension, 9 (12.3%); myalgia, 5 (6.8%); adrenal insufficiency,3 (4.1%); fatigue, 3 (4.1%); arthralgia, 2 (2.7%); asthenia, 2 (2.7%). **(VERY LOW)** <u>Adverse events of special interest</u> **After up to 48 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported that the AEs of special interest of all grades (n, (%)) were adrenal hormone precursor accumulation related, 58 (42.3%); hypocortisolism related, 70 (51.1%); pituitary tumour enlargement related, 3 (2.2%); QT prolongation related, 5 (3.6%); arrhythmogenic potential, 1 (0.7%). Grade 3-4 AEs of special interest (n, (%)) were adrenal hormone precursor accumulation related, 22 (16.1%); hypocortisolism related, 14 (10.2%); QT prolongation related, 1 (0.7%); arrhythmogenic potential, 1 (0.7%). **(VERY LOW)** **After a median 87.1 weeks exposure to osilodrostat phosphate:** • One single-arm study (LINC4, Gadelha et al 2023) reported the incidence of AEs of special interest (%) at weeks 1-12 (n=48), weeks 12-24 (n=71), weeks 24-36 (n=69), weeks 36-48 (n=68), weeks 48-60 (n=64) and weeks 60 onwards (n=59). The incidence of AEs related to hypocortisolism during these time periods was 14.6%, 12.7%, 7.2%, 5.9%, 0 and 8.5% respectively. The incidence of AEs related to arrhythmogenic potential and

Outcome	Evidence statement
	QT prolongation during these time periods was 0, 1.4%, 1.4%, 1.5%, 0 and 0 respectively. **(VERY LOW)** **After median 5.4 years exposure to osilodrostat phosphate** • One single-arm study (LINC2, Fleseriu et al 2022a) (n=19) reported that the most common AEs of special interest of all grades (n) were related to accumulation of adrenal hormone precursors, 12; related to hypocortisolism, 11; related to arrhythmogenic potential, 1; related to QT prolongation, 1. Grade 3-4 AEs reported were related to accumulation of adrenal hormone precursors, 4; and related to hypocortisolism, 2**. (VERY LOW)** **Osilodrostat phosphate vs placebo** **Two randomised studies (LINC3 and LINC4) provided low certainty evidence that the incidence of any AE was 72-96% in the osilodrostat phosphate group and 66-92% in the placebo group. The incidence of grade 3-4 AEs was 6-21% and 9-20% respectively, and of any serious AE (all grades) was 4.2-6% and 3-4% respectively. One of the randomised studies (LINC3) provided low certainty evidence that AEs related to adrenal hormone precursor accumulation occurred in 6% and 3% respectively, and AEs related to hypocortisolism occurred in 8% and 3% respectively. There were no statistical comparisons between the two groups.** **Osilodrostat phosphate vs metyrapone** **No evidence was identified for adverse events.** **Osilodrostat phosphate vs no comparator** **Two single-arm studies(LINC3 and LINC4) provided very low certainty evidence that 98.6 to 100% of patients experienced at least one AE of any grade, and that between 38.4% and 60.0% experienced at least one grade 3-4 AE. The incidence of any serious AE was 11.0% to 36.5% and any serious grade 3-4 AE was 12.3% to 28.5%. AEs requiring dose interruption and/or change occurred in 57.5% to 80.3% (all grades) and 17.8% to 30.7% (grade 3-4), and AEs leading to discontinuation occurred in 11.0% to 12.3%. One single-arm study (LINC3) reported one death.** **Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence that the most commonly reported AEs of any grade were nausea, headache, fatigue, adrenal insufficiency, arthralgia, nasopharyngitis, increased blood testosterone and asthenia. The most commonly reported grade 3-4 AEs were adrenal insufficiency, hypertension, headache, vomiting, fatigue and nausea.** **Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence on AEs of special interest. Two studies (LINC2 and LINC3) reported that the AEs of special interest of all grades were adrenal hormone precursor accumulation in 42.3% to 63.1%, hypocortisolism related in 51.1% to 57.9%, QT prolongation related in 3.6% to 5.3%, arrhythmogenic potential in 0.7% to 5.3% and pituitary tumour enlargement related in 0 to 2.2%. Two studies also reported that Grade 3-4 AEs of special interest were adrenal hormone precursor accumulation related in 16.1% to 21.1%, hypocortisolism related in 10.2% to 10.5%, QT prolongation related in 0 to 0.7% and arrhythmogenic potential in 0 to 0.7%.**

Abbreviations

ACTH: adrenocorticotrophic hormone; AE: adverse event; BDI-II: Beck's Depression Inventory-II; BP: blood pressure; CI: confidence interval; HbA1c: glycated haemoglobin; HDL: high density lipoprotein; IQR: interquartile range; LDL: low density lipoprotein; MCID: minimal clinically important difference; NE: not evaluable; OR: odds ratio; SD: standard deviation; SE: standard error; UFC: urinary free cortisol

In people with Cushing's disease, what is the cost effectiveness of osilodrostat phosphate compared to standard care?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified for cost effectiveness.

From the evidence selected, are there any subgroups of patients that may benefit from osilodrostat phosphate more than the wider population of interest?

Outcome	Evidence statement
Subgroups	No evidence was identified regarding any subgroups of patients that would benefit more from treatment with osilodrostat phosphate.

From the evidence selected, what were the ongoing schedules/doses used for osilodrostat phosphate?

Outcome	Evidence statement
Osilodrostat phosphate schedules and doses	All studies used osilodrostat phosphate orally twice daily. Bonnet-Serrano et al 2022 Median dose 10mg/day (range 2 to 40mg). No further details were provided. **LINC2** Fleseriu et al 2016 *Follow-up cohort*: osilodrostat phosphate was initiated at the penultimate dose that was efficacious and tolerable in LINC 1 (starting dose: 4 mg/day, n = 1; 20 mg/day, n = 3) *Expansion cohort*: osilodrostat phosphate was initiated at 4 mg/day if baseline UFC was >1.5 to ≤3 x ULN (n=9), and 10 mg/day if baseline UFC was >3 x ULN (n=6). For both cohorts, dose was escalated every 2 weeks according to the escalation sequence 10, 20, 40, and 60 mg/day until UFC was ≤ULN. Titration was continued up to week 10 as needed based on efficacy and tolerability. Treatment was then continued at the same dose from week 10 for a further 12 weeks. If UFC was in the lower normal range or below the lower normal limit, and if the patient had symptoms suggestive of adrenal insufficiency, a dose reduction or interruption was considered. Fleseriu et al 2022a Patients were continued on the dose they were on at the end of the 22-week treatment period reported in Fleseriu et al 2016. Dose adjustments were permitted based on individual efficacy and tolerability, up to a maximum dose of 30mg twice daily. Median dose from baseline to the end of the study 10.6 mg/day (range 1.1 to 47.9 mg/day, IQR 5.7 to 16.7 mg/day). **LINC3** Pivonello et al 2020 Dose started at 2mg twice daily for all patients with dose adjustments every 2 weeks based on efficacy and tolerability. The dose range was 1 to 30 mg twice a day. During the first 26 weeks the mean dose received was 10.0 mg per day (SD 7.3), and mean highest dose was 17.8 mg per day (SD 13.6). During the randomised withdrawal phase (week 26 to 34) mean dose was 10.0 mg per day (SD 9.6).

Outcome	Evidence statement
	Fleseriu et al 2022b Dose started at 2mg twice daily for all patients with dose adjustments as described in Pivonello et al 2020, up to a maximum permitted dose of 30 mg twice daily. Median osilodrostat phosphate dose from the start of the core study reported in Pivonello et al 2020 to the end of the extension reported in this paper was 7.4 mg/day (range 0.8–46.6, IQR 3.5– 13.6). **LINC4** Gadelha et al 2022 Dose was started at 2mg twice daily for all patients with dose adjustments approximately every 3 weeks during the placebo-controlled phase (weeks 1 to 12). During the open label phase (weeks 13 to 48) all patients restarted on osilodrostat phosphate 2mg twice daily unless they were on a lower dose at week 12, when they continued to receive the lower dose. Dose adjustments were made as during the placebo-controlled period. Median osilodrostat phosphate dose from baseline to data cutoff was 5.0 (IQR 3.8 to 9.2) mg/day. At week 48, 84% of patients with normal mean UFC were receiving doses of ≤10 mg/day (≤4 mg/day, n = 28 (56.0%); >4 to 10 mg/day, n = 14 (28.0%); >10 to 20 mg/day, n = 2 (4.0%); >20 mg/day, n = 6 (12.0%)). Gadelha et al 2023 Dose was started at the established effective dose from Gadelha et al 2022. Dose adjustments were permitted based on efficacy and tolerability; the maximum permitted dose was 30 mg twice daily. Median osilodrostat phosphate dose received during the overall study period was 4.6 (IQR 3.7 to 9.2) mg/day.
Abbreviations IQR: interquartile range; UFC: urinary free cortisol; ULN: upper limit of normal	

6. Discussion

This evidence review examines the clinical effectiveness, safety and cost effectiveness of osilodrostat phosphate compared to current standard care for patients with Cushing's disease requiring pharmacological treatment. The critical outcomes of interest were clinical disease response, biochemical disease response and sequelae of Cushing's disease and the important outcomes were reduction in treatment for Cushing's disease sequelae, time to improvement, quality of life (QoL), activities of daily living (ADLs) and safety outcomes. Evidence on cost effectiveness was also sought.

The review includes four studies, three of which were reported in six papers. For these three studies (the LINC studies) an initial paper was published reporting the first phase of the study, which was followed by a second paper reporting an extension study with longer term follow-up of some of the same patients. LINC2 was a single-arm phase II study reported in Fleseriu et al 2016 and Fleseriu et al 2022a. LINC3 was a phase III study with a randomised withdrawal period within a single-arm study, reported in Pivonello et al 2020 and Fleseriu et al 2022b. LINC4 was a phase III study which included a randomised period followed by a single-arm study reported in Gadelha et al 2022 and Gadelha et al 2023. The randomised studies (LINC3 and LINC4) reported outcomes comparing osilodrostat phosphate to placebo and the single-arm studies (LINC2, LINC3 and LINC4) reported outcomes for osilodrostat phosphate with no comparator. The fourth study was a retrospective cohort study (Bonnet-Serrano et al 2022) which compared patients treated with osilodrostat phosphate with patients treated with metyrapone and reported disease response at a single point.

Evidence was available for clinical disease response, biochemical disease response, sequelae of Cushing's disease, reduction in treatment for Cushing's disease sequelae, time to improvement, QoL and safety. No studies were identified that reported ADLs and no evidence on cost effectiveness was identified. Minimal clinically important differences (MCIDs) were defined in one single-arm study for the Beck Depression Inventory (BDI) II score and the Cushing QoL score, but no other MCIDs were defined. The clinical significance of many reported changes was not clear; while normal ranges were provided for some of the biochemical outcomes most of these measures were within the normal range at all time points in both the osilodrostat phosphate and placebo groups. No evidence was identified regarding any subgroups of patients that would benefit more from treatment with osilodrostat phosphate.

The studies all included adult patients only and more females than males. Between 19 and 137 subjects were recruited but the numbers followed up in the extension studies were lower. All patients were reported to have Cushing's disease apart from four out 33 in Bonnet-Serrano et al 2022 who had Cushing's syndrome; there was no separate reporting of outcomes for Cushing's disease patients in this paper. Bonnet-Serrano et al 2022 took place in France and the single-arm and randomised studies were multicentre in locations in North America, South America, Europe and Asia. The LINC3 study included locations in the UK but it was not stated how many patients had been recruited there.

All the single-arm and randomised studies reported a similar approach to adjustment of the dose of osilodrostat phosphate, based on efficacy and tolerability. The median doses of osilodrostat phosphate reported in all studies ranged from 4.6 to 10.6 mg/day.

In both the randomised studies there appeared to be some baseline differences between the groups but no statistical comparisons were reported. Both reported that patients, investigators and assessors were blinded during the randomised treatment period. Outcomes were measured in a standardised way and analyses were intention-to-treat, apart from one patient in Pivonello et al 2020 who did not receive their allocated treatment (placebo) because of an adverse event, and was not included in the biochemical disease response outcome comparing the two groups

but was included in other outcomes. In Gadelha et al 2022 no statistical analyses were reported for many of the comparisons between osilodrostat phosphate and placebo; some comparisons were shown in figures from which data could not be extracted.

In the retrospective cohort study (Bonnet-Serrano et al 2022) there appeared to be differences between the groups being compared but no statistical comparisons were reported and potential confounders were not identified or adjusted for in the analysis. It was not stated why patients had been allocated to different treatments and a number of potentially eligible patients were excluded from the analysis because their hypercortisolism was insufficiently controlled. Median treatment duration with metyrapone was 33.5 months (range 0.5 to 66 months) compared with only 7 months (range 0.75 to 96 months) for osilodrostat phosphate. Six patients were switched from metyrapone to osilodrostat phosphate, four because of uncontrolled hypercortisolism which was stated to be due to poor tolerance or low compliance to therapy and two because metyrapone was out of stock. These patients were included in both treatment groups in the analysis; six of the patients in each group are therefore being compared against themselves. The median serum cortisol level reported was taken from the blood sample corresponding to the period of best control of hypercortisolism. It therefore only represents a single timepoint and does not provide any information about longer term effects or duration of response.

In the LINC2 study recruitment was not consecutive or complete, and in LINC3 and LINC4 recruitment was unclear. All three single-arm studies reported outcomes for the cohort initially recruited in the first paper, and an extension study including some but not all of the original cohort in the second paper. All three reported clinical and demographic details for the original cohorts but not for the extension cohorts. In Fleseriu et al 2022a (the second LINC2 paper), Fleseriu et al 2022b (the second LINC3 paper) and Gadelha et al 2023 (the second LINC4 paper) outcomes were not clearly reported, most being either in narrative text or figures from which data could not be extracted, and few or no statistical analyses were reported. In Gadelha et al 2023 some inconsistencies were noted between figures and text.

The certainty of the evidence reported was moderate to low for the randomised studies and very low for the single-arm studies and the retrospective cohort study. Factors reducing confidence in the outcomes of the randomised studies included risk of bias due to uncertainty about whether the groups were similar at baseline, and lack of statistical analysis for some outcomes. Factors reducing confidence in the outcomes of the retrospective cohort study include risk of bias due to uncertainty about whether the groups were similar at baseline, no identification of or adjustment for potential confounders and inclusion of six patients in both groups being compared. In addition four out of the 33 included subjects had Cushing’s syndrome.

Factors reducing confidence in the outcomes of the single-arm studies include risk of bias due to uncertainty about whether the recruitment of subjects was consecutive or complete, limited statistical analyses particularly in the extension studies, and lack of clinical and demographic information and unclear reporting of outcomes in the extension studies.

7. Conclusion

This evidence review includes evidence from four studies, two of which each included two component studies. LINC2 was a single-arm study, LINC3 included both a randomised and a single-arm study, and LINC4 also included both a randomised and a single-arm study. Each of the LINC studies was published in two papers. The two randomised studies compared treatment with osilodrostat phosphate with placebo in patients with Cushing's disease. In addition the review incudes a retrospective cohort study which compared osilodrostat phosphate with metyrapone in patients with Cushing's disease. All studies included adults only and a majority of female subjects.

Osilodrostat phosphate vs placebo

One randomised study provided moderate certainty evidence that there was improvement or no change in all the physical features of hypercortisolism assessed in at least 88% of patients after 48 weeks treatment (consisting of either 48 weeks osilodrostat phosphate or 12 weeks placebo followed by 36 weeks osilodrostat phosphate). There was no statistically significant difference between the treatment groups in the proportion of patients who had improved or not changed with respect to any of the physical characteristics.

Both the randomised studies provided moderate certainty evidence that biochemical disease response was statistically significantly better in patients receiving osilodrostat phosphate compared to patients receiving placebo after a randomisation period of eight to 12 weeks. Both also reported that there was no difference in biochemical disease response between the groups after they had both received a further period of osilodrostat phosphate treatment.

Regarding sequelae of Cushing's disease, one randomised study provided moderate certainty evidence that LDL and HDL cholesterol fell statistically significantly more in patients treated with osilodrostat phosphate for 12 weeks compared to those treated with placebo, but values remained within the normal ranges in both groups at all time points. There were no statistically significant differences between the two groups in the changes in any other measures of the sequelae of Cushing's disease, including weight, blood pressure, fasting plasma glucose, HbA1c, total cholesterol, triglycerides and BDI-II score. Total cholesterol values were above the normal range in both groups at baseline and fell to within the normal range in the osilodrostat phosphate group by 12 weeks and in the group which had been randomised to placebo (who received 12 weeks placebo followed by 36 weeks osilodrostat) by 48 weeks. For all other measures values were within the normal range (where specified) in both groups at all time points.

One randomised study (LINC4) provided moderate certainty evidence that the median time to first controlled UFC response for patients treated with osilodrostat phosphate was 35 days.

One randomised study found moderate certainty evidence that there was no statistically significant difference in the change in Cushing QoL score in patients treated with osilodrostat phosphate for 12 weeks compared to those treated with placebo.

The randomised studies reported AEs, serious AEs and AEs of special interest in the osilodrostat phosphate and placebo groups and while it appeared that there may be fewer of some types of AE in the placebo groups no statistical comparisons were reported.

Osilodrostat phosphate vs metyrapone

The retrospective cohort study provided very low certainty evidence that patients treated with osilodrostat phosphate had a statistically significantly lower median serum cortisol level than

those treated with metyrapone at the time of best control of hypercortisolism. No other outcomes were reported comparing treatment with osilodrostat phosphate to metyrapone.

Osilodrostat phosphate vs no comparator

One single-arm study provided very low certainty evidence that after 72 weeks treatment with osilodrostat phosphate female hirsutism improved or remained stable in at least 85% of women, with greater improvements seen in women with normal testosterone than those with raised testosterone and improvements seen in some patients from 12 weeks of treatment onwards.

The three single-arm studies provided very low certainty evidence that complete response rates to osilodrostat phosphate (based on biochemical response) were 84.2% at 10 weeks, between 63% and 81% at time points between 22 and a median of 87 weeks, and 63.2% after a median 5.4 years treatment with osilodrostat phosphate.

The single-arm studies provided very low certainty evidence that most of the measures of the sequelae of Cushing's disease, including weight, blood pressure, fasting plasma glucose, HbA1c, total cholesterol, triglycerides and BDI-II score fell during treatment with osilodrostat phosphate, including a percentage fall (improvement) in the BDI-II score which was reported to exceed the minimal clinically important difference (MCID) defined by the authors.

One single-arm study reported that after 48 weeks treatment with osilodrostat phosphate, of the patients taking hypertensive medication at baseline 40% had an increase and 40% had a decrease in their medication, and of the patients taking diabetic medication at baseline 23% had an increase and 49% had a decrease in their medication. One single-arm study provided very low certainty evidence that the median time to first response to osilodrostat phosphate was 41 days.

Two of the single-arm studies found very low certainty evidence of an increase (improvement) in Cushing QoL score after a median of up to 87.1 weeks treatment with osilodrostat phosphate. They reported increases in the Cushing QoL score which exceeded the MCID defined by the authors at all time points.

Regarding safety, two single-arm studies provided very low certainty evidence that 98.6% to 100% of patients experienced at least one AE while being treated with osilodrostat phosphate, and that between 38.4% and 60.0% experienced at least one grade 3-4 AE.

Two single-arm studies provided very low certainty evidence that AEs requiring dose interruption and/or change occurred in 57.5% to 80.3% of patients treated with osilodrostat phosphate and AEs leading to discontinuation in 11.0% to 12.3% of patients treated with osilodrostat phosphate. One single-arm study reported one death. Three single-arm studies provided very low certainty evidence that the most commonly reported AEs of any grade were nausea, headache, fatigue, adrenal insufficiency, arthralgia, nasopharyngitis, increased blood testosterone and asthenia, and the most commonly reported grade 3-4 AEs were adrenal insufficiency, hypertension, headache, vomiting, fatigue and nausea. Two single-arm studies provided very low certainty evidence that the AEs of special interest of all grades were adrenal hormone precursor accumulation in 42.3% to 63.1%, hypocortisolism related in 51.1% to 57.9%, QT prolongation related in 3.6% to 5.3%, arrhythmogenic potential in 0.7% to 5.3% and pituitary tumour enlargement related in 0 to 2.2%.

No evidence was identified for the important outcome ADLs or for cost effectiveness. No evidence was identified regarding any subgroups of patients that would benefit more from treatment with osilodrostat phosphate. The certainty of the evidence reported was moderate to low for the randomised studies and very low for the single-arm studies and the retrospective cohort study.

The studies included in this review provide moderate certainty evidence that people with Cushing's disease treated with osilodrostat phosphate have a better biochemical disease response than those receiving placebo, with a median time to first response to osilodrostat phosphate of 35 to 41 days. There was very low certainty evidence of a complete response to osilodrostat phosphate ranging from 84.2% at 10 weeks to 63.2% after a median of 5.4 years treatment. There was also moderate certainty evidence that at least 88% of people with Cushing's disease treated with osilodrostat phosphate have a reduction or stabilisation in the physical features of hypercortisolism. There was no statistically significant difference between osilodrostat phosphate and placebo in the change in most other outcomes reported. Adverse events occurred in up to 100% of patients on osilodrostat phosphate, with significant numbers experiencing a more serious adverse event and around half of patients requiring an interruption or change in dose. There was also limited very low certainty evidence that people with Cushing's disease treated with osilodrostat phosphate have a better biochemical disease response than those receiving metyrapone.

Appendix A PICO document

The review questions for this evidence review are:

1) In people with Cushing's disease, what is the clinical effectiveness of osilodrostat phosphate compared to standard care?
2) In people with Cushing's disease, what is the safety of osilodrostat phosphate compared to standard care?
3) In people with Cushing's disease, what is the cost effectiveness of osilodrostat phosphate compared to standard care?
4) From the evidence selected, are there any subgroups of patients that may benefit from osilodrostat phosphate more than the wider population of interest?
5) From the evidence selected, what were the ongoing schedules/doses used for osilodrostat phosphate?

P –Population and Indication	People with Cushing's disease requiring pharmacological treatments, who are either waiting for, not suitable for, or not responding to interventions including surgery. [Reasons for requiring pharmacological therapy could include: - Optimisation pre-surgery or radiotherapy - Response to surgery is inadequate e.g., persistent hypercortisolism post-surgery. - Recurrence of the Cushing's disease following successful surgery - Contraindications to surgery due to co-morbidities resulting in unsuitability for surgery. - Patient refusal of surgery or radiotherapy] [Pharmacological bridging may be given prior to radiotherapy or whilst awaiting surgery]
I – Intervention	Oral osilodrostat phosphate [Patients may be receiving supportive care to treat the physical sequelae of Cushing's syndrome such as treatment for diabetes, hypertension, hyperlipidaemia]
C – Comparator(s)	Standard care which is • No adrenal steroidogenesis inhibitors • Ketoconazole • Metyrapone [Patients may be receiving supportive care.]
O – Outcomes	**Clinical Effectiveness** Minimally clinically important differences (MCIDs) are not known unless stated. Outcomes measured at 3 – 6 months are of particular interest. *Critical to decision-making:* ○ **Clinical disease response** *This outcome is important to patients because it reflects the clinical improvement that they experience with treatment.* [For example, but not limited to, clinical response, improvement in performance score]

	○ **Biochemical disease response** *This outcome is important to patients because biochemical improvement is a measure of disease response to treatment.* [Specifically, serum cortisol levels, mean urinary free cortisol (mUFC) levels (complete response: mUFC < the upper limit of normal (ULN)), salivary cortisol. Other biochemical markers are not of interest] ○ **Sequelae of Cushing's disease** *This outcome is important for patients because it measures improvements in the physical health consequences of Cushing's disease. The associated morbidity is high due to complications such as diabetes, hypertension, metabolic syndrome, low mood, a predisposition to infection and impacts on bone health.* [For example, but not limited to, clinician estimated control of Type 2 Diabetes (as measured by HbA1c or fasting glucose), blood pressure control, blood lipid level (total cholesterol, LDL, triglycerides), bone mineral density, fragility fractures, Beck's Depression Inventory) or patient described improvements in symptoms with subjective/self-reported assessment.] *Important to decision-making:* ○ **Reduction in treatment for Cushing's disease sequelae** *This is important to patients because they may be getting symptomatic relief with improvement in their physical health consequences of Cushing's disease, for example improvement in diabetes or hypertension. It may also provide them benefit as it reduces their medication burden.* [For example, reduction in insulin requirement for diabetes, reduction in requirement for anti-hypertensives, reduction in need for statin.] ○ **Time to improvement** *This is important to patients because current medicine for Cushing's disease differ with regards to their mechanism of action and time course of pharmacological effect. A treatment that works more quickly is more likely to reduce the risk of subsequent sequelae of Cushing's disease developing.* [This may be quantitively or narratively reported in the literature.] ○ **Quality of life** *Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being, and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making.* [Quality of life can be measured using the Cushing's Quality-of-Life scoring questionnaire. Other terms used to describe or indicate quality of life include patient-reported quality of life, health related quality of life, visual analogue scale] ○ **Activities of daily living (ADLs)** *ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation.* [ADLs can be measured using assessments such as: ○ Timed task completion (e.g., timed repeatable test such as dressing, meal preparation or patient specific ADL goal) ○ ADLs assessment using a tool (e.g., Barthel Index (BI) or Independence in Activities of Daily Living (ADL)

	○ Subjective/self-reported assessment (e.g., by the individual, carer, or MDT. This could include self-reported questionnaires such as participation in work and other activities).] **<u>Safety</u>** *These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.* [Examples include, but not limited to: ○ Toxicity ○ Frequency of adverse events ○ Frequency of grade 3 or 4 adverse events ○ Adverse events leading to discontinuation. ○ Treatment related adverse events] Of particular relevance are QTc prolongation and Hypocortisolism (nausea, vomiting, fatigue, low blood pressure, abdominal pain, loss of appetite, dizziness and syncope). [Hypocortisolism may be the desired effect if the treatment is part of a block and replace regime. Treatment of Cushing's disease will sometimes produce a glucocorticoid withdrawal syndrome as the cortisol level is normalised. This can be difficult to distinguish from hypocortisolism that results in negative outcomes for patients.] **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2013-2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library and TRIP database were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints, guidelines, case reports and resource utilisation studies were excluded.

Following the receipt of additional information that the development name for osilodrostat phosphate was LCI699, an updated search was conducted including this search term.

A single search was conducted for osilodrostat phosphate for the treatment of Cushing's syndrome (excluding those with Cushing's disease) and Cushing's disease.

Original search dates: 1 January 2013 to 17 October 2023

Medline search strategy

1	Cushing Syndrome/
2	cushing*.ti,ab,kf.
3	hypercortisolism.ti,ab,kf.
4	Pituitary ACTH Hypersecretion/
5	(acth adj (dependent or independent or hypersecret* or secret*)).ti,ab,kf.
6	1 or 2 or 3 or 4 or 5
7	(osilodrostat or isturisa or cy11b1).ti,ab,kf.
8	6 and 7
9	exp animals/ not humans/
10	8 not 9
11	steroidogenesis inhibitor?.ti,ab,kf.
12	limit 11 to ("systematic review" or "reviews (maximizes specificity)")
13	10 or 12

Updated search dates: 1 January 2013 to 3 January 2024

Medline search strategy

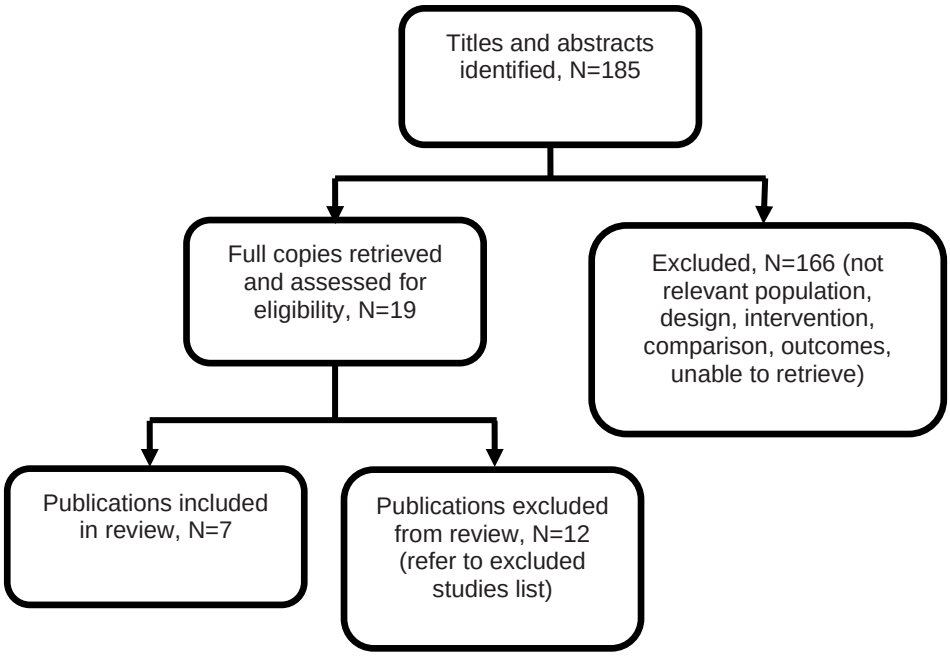
1	Cushing Syndrome/
2	cushing*.ti,ab,kf.
3	hypercortisolism.ti,ab,kf.
4	Pituitary ACTH Hypersecretion/
5	(acth adj (dependent or independent or hypersecret* or secret*)).ti,ab,kf.
6	1 or 2 or 3 or 4 or 5
7	(osilodrostat or isturisa or cy11b1).ti,ab,kf.
8	6 and 7
9	exp animals/ not humans/
10	8 not 9
11	steroidogenesis inhibitor?.ti,ab,kf.

12 limit 11 to ("systematic review" or "reviews (maximizes specificity)")
13 10 or 12
14 LCI699.ti,ab,kf.
15 6 and 14
16 13 or 15

Appendix C Evidence selection

The combined updated literature searches for osilodrostat phosphate in the treatment of Cushing's syndrome (excluding those with Cushing's disease) and Cushing's disease identified 185 references. These were screened using their titles and abstracts and 19 references were obtained in full text and assessed for relevance. Of these, seven references relating to osilodrostat phosphate for the treatment of Cushing's disease are included in this evidence review. The 12 references excluded are listed in Appendix D. Studies relating to osilodrostat phosphate for the treatment of Cushing's syndrome (excluding those with Cushing's disease) are considered in a separate evidence review.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Pivonello R, Fleseriu M, Newell-Price J, Bertagna X, Findling J, Shimatsu A, et al. 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. The Lancet Diabetes & Endocrinology. 2020;8(9):748-61.	Included
Fleseriu M, Newell-Price J, Pivonello R, Shimatsu A, Auchus RJ, Scaroni C, et al. Long-term outcomes of osilodrostat in Cushing's disease: LINC 3 study extension. Eur J Endocrinol. 2022;187(4):531-541.	Included
Gadelha M, Bex M, Feelders RA, Heaney AP, Auchus RJ, Gilis-Januszewska A, et al. Randomized Trial of Osilodrostat for the Treatment of Cushing Disease. The Journal of Clinical Endocrinology & Metabolism. 2022;107(7):e2882-e95.	Included

Appendix D Excluded studies table

Study reference	Reason for exclusion
Anonymous. Correction to Lancet Diabetes Endocrinol 2020; 8: 762-72 (The Lancet Diabetes & Endocrinology (2020) 8(9) (748-761), (S2213858720302400), (10.1016/S2213-8587(20)30240-0)). The Lancet Diabetes and Endocrinology. 2020;8(9):e4.	Correction to Pivonello et al (2020); corrections have been implemented in the full text paper.
Bertagna X, Pivonello R, Fleseriu M, Zhang Y, Robinson P, Taylor A, et al. LCI699, a potent 11beta-hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing's disease: results from a multicenter, proof-of-concept study. Journal of Clinical Endocrinology & Metabolism. 2014;99(4):1375-83.	Proof-of-concept study, n=12 with Cushing's disease treated with varying doses of osilodrostat phosphate with 10-week follow-up and no additional outcomes reported. Larger studies with longer follow-up and more comprehensive reporting of outcomes have been included.
Detomas M, Altieri B, Deutschbein T, Fassnacht M, Dischinger U. Metyrapone Versus Osilodrostat in the Short-Term Therapy of Endogenous Cushing's Syndrome: Results From a Single Center Cohort Study. Frontiers in Endocrinology. 2022;13:903545.	The majority of the study population had Cushing's syndrome and those with Cushing's disease (n=7) were not analysed separately. The studies included in this review had larger study populations with Cushing's disease. This paper was included in the review of osilodrostat phosphate for the treatment of Cushing's syndrome.
Dormoy A, Haissaguerre M, Vitellius G, Do Cao C, Geslot A, Drui D, et al. Efficacy and Safety of Osilodrostat in Paraneoplastic Cushing Syndrome: A Real-World Multicenter Study in France. Journal of Clinical Endocrinology & Metabolism. 2023;108(6):1475-87.	The study population had Cushing's syndrome
Dougherty JA, Desai DS, Herrera JB. Osilodrostat: A Novel Steroidogenesis Inhibitor to Treat Cushing's Disease. Annals of Pharmacotherapy. 2021;55(8):1050-60.	Non-systematic review of Cushing's disease; relevant studies included in this review were returned by the search and considered separately.
Dzialach L, Sobolewska J, Respondek W, Szamotulska K, Witek P. Cushing's Disease: Long-Term Effectiveness and Safety of Osilodrostat in a Polish Group of Patients with Persistent Hypercortisolemia in the Experience of a Single Center. Biomedicines. 2023;11(12):06.	Small study (n=6 with Cushing's disease treated with osilodrostat phosphate) and no additional outcomes reported. Larger studies with more comprehensive outcomes have been included in the review.
Fleseriu M, Castinetti F. Updates on the role of adrenal steroidogenesis inhibitors in Cushing's syndrome: a focus on novel therapies. Pituitary. 2016;19(6):643-53.	Non-systematic review of Cushing's syndrome and Disease; relevant studies included in this review were returned by the search and considered separately.
Ghalawinji A, Drezet L, Chaffanjon P, Muller M, Sturm N, Simiand A, et al. Discontinuation of drug treatment in Cushing's disease not cured by pituitary surgery. Journal of Clinical Endocrinology & Metabolism. 2023;14:14.	Retrospective study, n=29 patients with Cushing's disease receiving a range of drug treatments (most more than one). Only n=8 received osilodrostat phosphate at some point. Main outcome was type of treatment (drugs/ surgery/ radiotherapy) leading to control of Cushing's disease. Reporting of control in relation to specific drug treatment was unclear and lacked detail.
Simoes Correa Galendi J, Correa Neto ANS, Demetres M, Boguszewski CL, Nogueira V. Effectiveness of Medical Treatment of Cushing's Disease: A Systematic Review and Meta-Analysis. Frontiers in Endocrinology. 2021;12:732240.	Systematic review of Cushing's disease; relevant studies included in this review were returned by the search and considered separately.
Tabarin A, Haissaguerre M, Lassole H, Jannin A, Paepegaey AC, Chabre O, Young J. Efficacy and	The study population had Cushing's syndrome

tolerance of osilodrostat in patients with Cushing's syndrome due to adrenocortical carcinomas. European Journal of Endocrinology. 2022;186(2):K1-K4.	
Tanaka T, Satoh F, Ujihara M, Midorikawa S, Kaneko T, Takeda T, et al. A multicenter, phase 2 study to evaluate the efficacy and safety of osilodrostat, a new 11beta-hydroxylase inhibitor, in Japanese patients with endogenous Cushing's syndrome other than Cushing's disease. Endocrine Journal. 2020;67(8):841-52.	The study population had Cushing’s syndrome
Tritos NA. Adrenally Directed Medical Therapies for Cushing Syndrome. Journal of Clinical Endocrinology & Metabolism. 2021;106(1):16-25.	Non-systematic review of Cushing's syndrome.

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Bonnet-Serrano F, Poirier J, Vaczlavik A, Laguillier-Morizot C, Blanchet B, Baron S, et al. Differences in the spectrum of steroidogenic enzyme inhibition between Osilodrostat and Metyrapone in ACTH-dependent Cushing syndrome patients. European Journal of Endocrinology. 2022;187(2):315-22. **Study location** Cochin, France **Study type** Retrospective cohort study **Study aim** To compare steroidogenic profiles in patients treated with either Osilodrostat or Metyrapone for adrenocorticotrophic hormone (ACTH)-dependent Cushing's syndrome **Study dates** March 2019 to December 2021	Patients with an ACTH-dependent Cushing syndrome. **Inclusion criteria** • All patients visiting Cochin hospital endocrinology department between March 2019 and December 2021, for whom an adrenal steroidogenic profile with ultra-high-performance liquid chromatography-mass spectrometry (UPLC-MS/MS) assay was performed in clinical care, in the context of treatment by either Osilodrostat or Metyrapone for an ACTH-dependent Cushing syndrome. **Exclusion criteria** • Patients whose hypercortisolism was not controlled under treatment (UFC>142 nmol/24 h) • Patients whose treatment had been	**Interventions** Osilodrostat phosphate twice a day: median dose 10 mg (range 2 to 40 mg). Median treatment duration 7 months (range 0.75 to 96 months). **Comparators** Metyrapone three to four times a day, median dose 1250 mg (range 500 to 4000 mg). Median treatment duration 33.5 months (range 0.5 to 66 months). Patients were also prescribed exogenous glucocorticoid (dexamethasone or hydrocortisone) supplementation as required (13 out of 25 (52%) of patients treated with Osilodrostat phosphate and 4 out of 14 (28%) of patients treated with Metyrapone).	**Critical outcomes** **Biochemical disease response** *Median serum cortisol level* [36] Osilodrostat phosphate group (n=25): 175 (22 to 421) nmol/L Metyrapone group (n=14): 307 (68 to 547) nmol/L p = 0.025	This study was appraised using the JBI checklist for case series. 1. Unclear 2. No 3. Yes 4. No 5. No 6. N/A 7. Yes 8. Unclear 9. N/A 10. N/A 11. No This was a retrospective cohort study which used information from one hospital's electronic medical records. It was not stated why different patients had been allocated to different treatments initially, and it was not clear whether the groups were similar at baseline. There appeared to be some differences in baseline characteristics but no statistical comparisons were made. Potential confounders were not identified or accounted for in the analysis. Six patients switched from metyrapone to osilodrostat phosphate, four because of uncontrolled hypercortisolism which

[36] Figures within brackets reported in the paper appear to be the range; this would be consistent with some other reporting in this paper but was not stated for these outcomes.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	disrupted for an evaluation free of treatment **Total sample size** n=33 Treated with osilodrostat phosphate only: n=19 Treated with metyrapone only: n=8 Treated with metyrapone then osilodrostat phosphate: n=6 (these patients were included in both treatment groups for analysis, at the time point they were receiving the relevant treatment) Analysed in osilodrostat phosphate group: n=25 Analysed in metyrapone group: n=14 **Baseline characteristics (n)** Osilodrostat phosphate only (n=19); metyrapone only (n=8); both drugs (n=6); total (n=33) Male: 3; 1; 0; 4 (12.1%) Female: 16; 7; 6; 29 (87.9%) Median age, years: 45; 49; 55; 47 Median BMI (kg/m^2): 29.8; 25.5; 31.0; 29.0			was stated to be due to poor tolerance or low compliance to therapy and two because metyrapone was out of stock. These patients were included in both groups in the analysis; six of the patients in each group are therefore being compared against themselves. The median serum cortisol level reported was taken from the blood sample corresponding to the period of best control of hypercortisolism. It therefore only represents a single timepoint and does not provide any information about longer term effects or duration of response. Out of the potential study subjects initially identified, three out of 28 treated with osilodrostat phosphate and four out of 18 treated with metyrapone were excluded from analysis because of insufficient control of hypercortisolism. Four of the thirty-three patients included in the study had ectopic ACTH-dependent Cushing's syndrome and the remaining 29 had Cushing's disease. There was no separate analysis of the patients with Cushing's disease. **Source of funding** The authors stated that the study was supported in part by the Agence Nationale de la Recherche Fondation du Centre hospitalier de l'Universite de Montreal (fellowship

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Cushing disease diagnosis: 16; 7; 6; 29 (87.9%) *Hypercortisolism-related complications at diagnosis (n)* Hypertension: 8; 5; 6; 19 (57.6%) Diabetes or glucose intolerance: 7; 4; 5; 16 (48.5%) Low bone density: 10; 4; 6; 20 (60.6%) Neuropsychiatric affection: 11; 5; 2; 18 (54.5%) Hyperandrogenism: 6; 1; 2; 9 (27.3%) Thrombosis: 3; 0; 1; 4 (12.1%) Infection: 0; 0; 0; 0 (0%) *Median UFC at time of sampling (nmol/24 h):* Osilodrostat phosphate: 39.8 Metyrapone: 45.8 Both drugs, osilodrostat phosphate sample: 19.0 Both drugs, metyrapone sample: 87.0 Total: 44.4			training/research grant received as funding by one of the authors (J P)).
Fleseriu M, Pivonello R, Young J, Hamrahian AH, Molitch ME, Shimizu C, et al. Osilodrostat, a potent oral 11beta-hydroxylase inhibitor: 22-week, prospective, Phase II study	Patients aged 18 to 75 years with a confirmed diagnosis of Cushing's disease **Inclusion criteria**	**Interventions** Osilodrostat phosphate orally twice daily *Follow-up cohort*: osilodrostat phosphate at the penultimate dose that	**Critical outcomes** Outcomes were measured up to 22 weeks after starting treatment.	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. No 5. No

Study details	Population	Interventions	Study outcomes	Appraisal and funding
in Cushing's disease. Pituitary. 2016;19(2):138-48. **Study location** Multicentre, locations not stated (authors were from the USA, Japan, France and Italy). **Study type** Phase II study (LINC2) (single-arm study) **Study aim** To assess osilodrostat in patients with Cushing's disease over a longer period of time and in more patients than previous studies. **Study dates** January to December 2013	• Urinary free cortisol (UFC) levels above the upper limit of normal (ULN): ○ follow-up cohort: UFC>ULN ○ expansion cohort: UFC >1.5xULN • Morning plasma ACTH level above the lower limit of normal • Evidence of a pituitary origin for the excess ACTH[37] **Exclusion Criteria** • Major surgery within one month prior to screening • Poorly controlled diabetes mellitus as evidenced by HbA1c levels >9 % • Compression of the optic chiasm • History of, or risk factors for, prolonged QTcF • Renal impairment **Total sample size** n=19 Follow-up cohort: n=4	was efficacious and tolerable in LINC 1 (starting dose: 4 mg/day, n = 1; 20 mg/day, n = 3) *Expansion cohort*: osilodrostat phosphate was initiated at 4 mg/day if baseline UFC was >1.5 to ≤3 x ULN (n=9), and 10 mg/day if baseline UFC was >3 x ULN (n=6). For both cohorts, dose was escalated every 2 weeks according to the escalation sequence 10, 20, 40, and 60 mg/day until UFC was ≤ULN. Titration was continued up to week 10 as needed based on efficacy and tolerability. Treatment was then continued at the same dose from week 10 for a further 12 weeks. If UFC was in the lower normal range or below the lower normal limit, and if the patient had symptoms suggestive of adrenal insufficiency, a dose	**Biochemical disease response**[39] Follow-up cohort (n=4); expansion cohort (n=15); total (n=19) *Disease response after 10 weeks treatment* Overall response, n (%): 4 (100.0%) (95% CI 39.8% to 100.0%); 13 (86.7%) (95% CI 59.5% to 98.3%); 17 (89.5%) (95% CI 66.9% to 98.7%). Controlled, n (%): 4 (100.0%) (95% CI 39.8% to 100.0%); 12 (80.0%) (95% CI 51.9% to 95.7%); 16 (84.2%) (95% CI 60.4% to 96.6%) Partially controlled, n (%): 0 (0%) (95% CI 0 to 60.2%); 1 (6.7%) (95% CI 0.2% to 32.0%); 1 (5.3%) (95% CI 0.1% to 26.0%) *Disease response after 22 weeks treatment* Overall response, n (%): 3 (75.0%) (95% CI 19.4% to 99.4%); 12 (80.0%) (95% CI 51.9% to 95.7%); 15 (78.9%) (95% CI 54.4% to 94.0%) Controlled, n (%): 3 (75.0%) (95% CI 19.4% to 99.4%); 12 (80.0%) (95% CI 51.9% to 95.7%); 15 (78.9%) (95% CI 54.4% to 94.0%)	6. Yes 7. Yes 8. Yes 9. No 10. Yes **Other comments** This was a non-comparator multicentre phase II study which included patients enrolled in two cohorts. The '*follow-up cohort*' comprised patients who had completed LINC1, a 10-week proof-of-concept study of osilodrostat phosphate in 12 patients with Cushing's disease. They were offered enrolment in LINC2 if their current UFC level was above the upper limit of normal. The patients had been off osilodrostat phosphate treatment for 15 to 19 months before enrolment in LINC2. The '*expansion cohort'* comprised newly enrolled patients who were naive to osilodrostat phosphate. The authors reported that the UFC entry criterion was less strict for the follow-up than the expansion cohort because follow-up patients had already met the criterion of UFC >1.5xULN in LINC1. It was not stated whether recruitment of subjects had been consecutive or complete for the expansion cohort.

[37] Confirmation of a pituitary tumour of ≥6 mm by MRI imaging with a positive dynamic test; history of inferior petrosal sinus gradient >3 after corticotropin-releasing-hormone or desmopressin stimulation; or histological confirmation of an ACTH-producing pituitary tumour in patients with previous pituitary surgery.
[39] Controlled defined as mean UFC ≤ ULN; partially controlled defined as mean UFC > ULN and with ≥50% reduction from baseline; uncontrolled defined as mean UFC>ULN and with <50 % reduction from baseline. Overall response was calculated as the sum of controlled and partially controlled patients.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Expansion cohort: n=15 **Baseline characteristics** Follow-up cohort; expansion cohort; total *Age* Mean age (SD), years: 34.3 (5.5); 37.5 (9.0); 36.8 (8.4) Median age (range), years: 35 (29 to 39); 36 (25 to 52); 36 (25 to 52) *Sex* F:M, n: 3:1; 11:4; 14:5 *Race*, n (%) Caucasian: 4 (100%); 11 (73.3%); 15 (78.9%) Other: 0; 4 (26.7%); 4 (21.1%) *Median time since diagnosis* (range), months 82.5 (57.6 to 100.3); 63.4 (12.2 to 155.2); 70.2 (12.2 to 155.2) *Previous surgery*, n (%) 4 (100%); 13 (86.7%); 17 (89.5%) *Baseline UFC, mean (SD)*	reduction or interruption was considered. **Comparators** No comparator	<u>Partially controlled</u>, n (%): 0 (0%) (95% CI 0 to 60.2%); 0 (0%) (95% CI 0 to 21.8%); 0 (0%) (95% CI 0 to 17.7%) *UFC levels* Mean (SE), nmol/24h Levels at baseline (n=19); week 22 (n=17)[40] Follow-up cohort: 398 (176); 98 (92) Expansion cohort: 1630 (3043); 90 (136) Total: 1371 (2734); 92 (124) *Morning salivary cortisol* Mean (SE), nmol/L[41] Levels at baseline (n=19); week 22 (n=17)[42] Follow-up cohort: 10 (5); 10 (11) Expansion cohort: 28 (46); 4 (3) Total: 24 (41); 5 (6) **Sequelae of Cushing's disease** Mean (SD), change from baseline (SD) [43] Baseline (n=19); week 22 (n=17) *Weight,* kg: 85.1 (24.0); 85.6 (26.2); –1.5 (3.8)	Two patients discontinued prematurely from the study, both from the expansion cohort. One discontinued at week 2 because of a grade 3 AE and one at week 6 because of a non-treatment-related administrative issue. Both patients who discontinued were reported to have had UFC<ULN at that point, but they were classified as non-responders because they were not in the study at weeks 10 or 22. These patients were included in the main efficacy and safety analyses but not in the analyses of other biochemical outcomes. The assessment protocol was described in detail and pharmacodynamic parameters were analysed at one of two central laboratories. Assessors and patients were not reported to be blinded, meaning that there was a risk of bias in the assessment of more subjective outcomes such as adverse events. The authors stated that the original planned analysis was defined by cohort. A pooled analysis of all patients was also carried out which was not pre-specified in the protocol.

[40] Follow-up cohort n=4 at baseline and 22 weeks; extension cohort n=15 at baseline and n=13 at 22 weeks
[41] Normal range, morning salivary cortisol: 1.1–15.5 nmol/L
[42] Follow-up cohort n=4 at baseline and 22 weeks; extension cohort n=15 at baseline and n=13 at 22 weeks
[43] Normal ranges: fasting plasma glucose 70 to 110 mg/dL; HbA1c <6.4 %; total cholesterol 3.9 to 6.5 mmol/L; HDL-cholesterol 1 to 1.7 mmol/L; LDL-cholesterol 0 to 4.2 mmol/L; triglycerides 0.6 to 1.7 mmol/L

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	nmol/24 h[38] 398 (176); 1630 (3043); 1371 (2734) No subgroups reported		*Body mass index*, kg/m^2: 30.7 (7.0); 30.1 (7.9); –0.5 (1.4) *Systolic BP*, mmHg: 132.6 (11.6); 131.9 (17.8); –1.0 (16.2) *Diastolic BP*, mmHg: 85.1 (6.5); 86.0 (8.9); 1.3 (9.7) *Fasting plasma glucose*, mg/dL: 105.6 (49.0); 81.2 (9.0); –14.9 (28.9) *HbA1c*, %: 5.7 (0.7); 5.5 (0.6); –0.2 (0.3) *Total cholesterol*, mmol/L: 5.3 (1.4); 4.6 (0.8); –0.7 (1.4) *HDL-cholesterol*, mmol/L: 1.7 (0.9); 1.3 (0.4); –0.5 (0.8) *LDL-cholesterol*, mmol/L: 3.3 (1.7); 2.8 (0.6); –0.6 (1.6) *Triglycerides*, mmol/L: 1.5 (0.6); 1.3 (0.6); 0 (0.4) **Important outcomes** **Time to improvement** Mean UFC levels decreased from baseline (mean 1371 (SE 2734) nmol/24 h) to within the normal range by week 4 (details at week 4 not reported). **Safety** Safety outcomes were measured up to when the last patient completed 22 weeks of treatment (23 December 2013). *Adverse events* (n=19) [44] Most common AEs (n≥5), n (%)	The paper did not state the study locations where subjects were recruited. Study authors were from four clinical centres in the USA, three in Japan, two in France and one in Italy. **Source of funding** The authors stated that the study was funded by Novartis Pharma AG, and that financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation.

[38] Mean UFC calculated as the mean of 2 or 3 samples. Normal range: 11–138 nmol/24 h

[44] AEs were defined using terminology in the Medical Dictionary for Regulatory Activities (MedDRA; version 13.1), and severity was graded according to the National Cancer Institute Common Toxicity Criteria version 4.03.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Nausea: 6 (31.6%) Diarrhoea: 6 (31.6%) Asthenia: 6 (31.6%) Adrenal insufficiency: 6 (31.6%) Nasopharyngitis: 5 (26.3%) Testosterone increased 5 (26.3) Adrenal precursors increased 7 (36.8%) ACTH increased 6 (31.6) <u>Grade 3-4 AEs:</u> Adrenal insufficiency: 1 (5.3%) Testosterone increased: 1 (5.3%)	
Fleseriu M, Biller BMK, Bertherat J, Young J, Hatipoglu B, Arnaldi G, et al. Long-term efficacy and safety of osilodrostat in Cushing's disease: final results from a Phase II study with an optional extension phase (LINC 2). Pituitary. 2022;25(6):959-70. **(Fleseriu et al 2022a)** **Study location** Multicentre, locations not stated (clinical authors were from the USA, France and Italy). **Study type**	Patients aged 18 to 75 years with a confirmed diagnosis of Cushing's disease **Inclusion criteria** • Initial inclusion criteria as Fleserieu et al 2016. Patients who had received clinical benefit from osilodrostat were eligible for inclusion in the 48-week extension phase. **Exclusion Criteria** • As Fleserieu et al 2016 **Total sample size** n=19 (baseline) n=16 in 70-week extension study	**Interventions** Osilodrostat phosphate orally twice daily Patients were continued on the dose they were on at the end of the 22-week treatment period reported in Fleseriu et al 2016. Dose adjustments were permitted based on individual efficacy and tolerability, up to a maximum dose of 30mg twice daily. Median dose from baseline to the end of the extension was 10.6 mg/day (range 1.1 to 47.9 mg/day, IQR 5.7 to 16.7 mg/day) Median (range) exposure	**Critical outcomes** Outcomes were measured at 70 weeks for the extension study, and at the last observed value (maximum 6.7 years) for other outcomes. **Biochemical disease response**[45] (n=16) *Disease response after 70 weeks treatment,* n (%) (n=16) Overall response: 13 (81.3%) Complete response: 12 (75%) Partial response: 1 (6.3%) *Disease response at last observed value,* n (%) (n=19) Complete response: 12 (63.2%) Partial response: 5 (26.3%) **Sequelae of Cushing's disease** Baseline; last observed value (n=19)	This study was appraised using the JBI checklist for case series. (Where appropriate these responses draw on information presented in Fleseriu et al 2016) 1. Yes 2. Yes 3. Yes 4. No 5. No 6. Unclear 7. Unclear 8. Unclear 9. No 10. No **Other comments** This study included patients recruited to Fleseriu et al 2016. At week 22 patients who had mUFC ≤ ULN or who were considered by the investigator to be receiving clinical

[45] Controlled defined as mean UFC ≤ ULN; partially controlled defined as mean UFC > ULN and with ≥50% reduction from baseline; uncontrolled defined as mean UFC>ULN and with <50 % reduction from baseline. Overall response was calculated as the sum of controlled and partially controlled patients.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Phase II extension study (LINC2) (single-arm study) **Study aim** To report long-term efficacy and safety of osilodrostat. **Study dates** January 2013 to December 2019	**Baseline characteristics** As Fleseriu et al 2016 for original cohort (n=19). Details not reported for extension cohort in Fleseriu et al 2022. No subgroups reported	to osilodrostat phosphate from baseline to study end for all enrolled patients was 5.4 years (0.04 to 6.7). Over half of enrolled patients received osilodrostat phosphate for more than 4.5 years. Patients received concomitant medications (excluding drugs for the treatment of Cushing's disease and drugs known to prolong the QT interval) at the discretion of the investigator. **Comparators** No comparator	*Fasting plasma glucose < 100mg/dL:* 15; 16 *Systolic BP < 130 mmHg:* 10; 13 *Diastolic BP < 90 mm Hg:* 14; 13 *BMI within the normal range (18.5 to 24.9 kg/m^2):* 3; 7 *Mean HbA1c < 5.6%:* 10/18; 13/19 *Blood lipid levels* The authors reported that there were no clear changes in blood lipid levels (cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) from baseline to last observed value but numerical results were not provided. **Safety** *Adverse events (AEs)*[46] All; Grade ≥3 (n=16) Adrenal insufficiency: 7; 1 Arthralgia: 6; 0 Headache: 6; 1 Diarrhoea: 5; 0 Abdominal pain: 4; 1 Hypertension: 3; 3 Lipase increased: 3; 1 Pituitary-dependent Cushing's syndrome: 2; 1 Gastroenteritis: 2; 1 Non-cardiac chest pain: 2; 1 Weight decreased: 2; 1	benefit from osilodrostat phosphate were eligible for inclusion in an additional 48-week extension phase (extension period 1). Of the 17 patients eligible, 16 chose to continue. Following a further 48 weeks of treatment patients who were considered by the study investigator to be achieving clinical benefit from continued treatment with osilodrostat phosphate had the option of entering an additional, open-ended period (week 70 onwards; extension period 2). The study ended when a separate rollover study became available for patients receiving clinical benefit from osilodrostat phosphate or by December 31, 2019, whichever was earlier. Of the 16 patients recruited to extension 1, 14 completed (one discontinued because of AE, and one withdrew consent for reasons not reported). Thirteen continued to extension 2, of whom 8 completed (one discontinued because of AE, one withdrew consent for reasons not reported and three no longer required osilodrostat phosphate). No clinical and demographic details were provided for the subjects included in the extension study.

[46] AEs were defined using terminology in the Medical Dictionary for Regulatory Activities (MedDRA; version 13.1), and severity was graded according to the National Cancer Institute Common Toxicity Criteria version 4.03.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			AEs of special interest during the entire study, n (n=19) All; Grade ≥3 Related to accumulation of adrenal hormone precursors: 12; 4 Related to hypocortisolism: 11; 2 Related to arrhythmogenic potential: 1; 0 Related to QT prolongation: 1; 0	During extension periods 1 and 2, patients attended a scheduled visit monthly for the first 6 months, every 3 months for the next 12 months, and every 6 months thereafter. Patients who discontinued the study for any reason were classed as nonresponders at the subsequent visits up to the furthest study visit that they could have completed at the time of data cut-off in December 2019. The last observed value for these patients was that recorded before study discontinuation. Response and AEs at the end of the extension phase (total 70 weeks) were reported for the 16 patients enrolled in the extension study. Other efficacy and safety outcomes were reported for all enrolled patients who received at least one dose of osilodrostat phosphate, using each patient's last observed value (n=19). Many outcomes in this paper were presented in figures which did not allow numerical data to be extracted. Other outcomes presented, apart from AEs, were taken from narrative text. Assessors and patients were not reported to be blinded, meaning that there was a risk of bias in the assessment of more subjective outcomes such as adverse events. No statistical analyses were reported. The paper did not state the study locations where subjects were

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				recruited. Clinical study authors were from three centres in the USA, two in France and two in Italy. **Source of funding** The authors stated that the study was funded by Novartis Pharma AG, and that financial support for medical editorial assistance was provided by Recordati.
Fleseriu M, Newell-Price J, Pivonello R, Shimatsu A, Auchus RJ, Scaroni C, et al. Long-term outcomes of osilodrostat in Cushing's disease: LINC 3 study extension. European Journal of Endocrinology. 2022;187(4):531-41. **(Fleseriu et al 2022b)** **Study location** As Pivonello et al 2020 **Study type** Phase III extension study (LINC3) (single-arm study) **Study aim** To investigate the long-term efficacy and tolerability of osilodrostat **Study dates**	Patients aged 18 to 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 had refused surgery or were not deemed to be surgical candidates **Inclusion criteria** • Initial inclusion criteria as Pivonello et al 2020. Patients who had benefited from osilodrostat at week 48 in Pivonello et al 2020 could opt to enter the extension study up to at least week 72 of treatment. **Exclusion criteria**	**Interventions** Osilodrostat phosphate orally twice daily Dose started at 2mg twice daily for all patients with dose adjustments as described in Pivonello et al 2020. Dose adjustments could continue to be made throughout this extension phase based on efficacy and safety, up to maximum permitted dose of 30 mg twice daily. Median osilodrostat phosphate dose from the start of the core study reported in Pivonello et al 2020 to the end of the extension reported in this paper was 7.4 mg/day	**Critical outcomes** **Clinical disease response** Outcomes at up to 72 weeks of treatment *Change in physician-rated hirsutism score in females with normal testosterone levels*[47] Change in hirsutism score at 12 weeks (n=38); 48 weeks (n=34); 72 weeks (n=38) Improved: 9/38 (23.7%); 16/34 (47.1%); 7/38 (44.7%) Stable: 27/38 (71.1%); 13/34 (38.2%); 16/38 (42.1%) Worsened: 2/38 (5.3%); 5/34 (14.7%) 5/38 (13.2%) *Change in physician-rated hirsutism score in females with raised testosterone levels*	This study was appraised using the JBI checklist for case series. (Where appropriate these responses draw on information presented in Pivonello et al 2020) 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Unclear 7. Unclear 8. No 9. No 10. No Patients recruited to Pivonello et al 2020 who had benefited from osilodrostat phosphate treatment after 48 weeks were eligible to enter this extension phase of the LINC3 study. Patients continued to receive open-label osilodrostat phosphate during the extension, which ended after all patients completed ≥72

[47] Assessment of physical features was based on review of photographs by the investigator (unblinded); features were rated subjectively on a semi-quantitative scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe),

Study details	Population	Interventions	Study outcomes	Appraisal and funding
October 2014 to December 2019	• As Pivonello et al 2020 **Total sample size** n=137 For extension period (weeks 48 to 72): n= 106 **Baseline characteristics** As Pivonello et al 2020 for original cohort (n=137). Baseline characteristics for n=106 included in this extension study not reported. **Additional baseline characteristics reported in this paper** (n=137) *Most common (≥15%) comorbidities, n (%)* Hypertension: 93 (67.9%) Obesity: 41 (29.9%) Osteoporosis: 38 (27.7%) Diabetes mellitus: 30 (21.9%) Depression: 27 (19.7%) Hypothyroidism: 25 (18.2%) *Physical manifestations of hypercortisolism, n (%)* Central obesity: 63 (86.3%) Supraclavicular fat pad: 61 (83.6%) Dorsal fat pad: 56 (76.7%) Facial rubor: 46 (63.0%)	(range 0.8–46.6, interquartile range (IQR) 3.5– 13.6. **Comparators** No comparator	Change in hirsutism score at 12 weeks (n=48); 48 weeks (n=41); 72 weeks (n=28) Improved: 3/48 (6.3%); 9/41 (22.0%); 6/28 (21.4%) Stable: 41/48 (85.4%); 24/41 (58.5%); 18/28 (64.3%) Worsened: 4/48 (8.3%); 8/41 (19.5%); 4/28 (14.3%) **Biochemical disease response**[48] Outcomes at up to 72 weeks of treatment *Response to treatment* n (%) (95% CI) Complete response at the end of the core period (week 48) (n=137) 91/137 (66.4%) (95% CI 57.9% to 74.3%) Complete response at week 60 (n=106) 86/106 (81.1%) (95% CI 72.4% to 88.1%) Complete response at week 72 (n=106) 86/106 (81.1%) (95% CI 72.4% to 88.1%) *Morning serum cortisol* Mean morning serum cortisol levels were reported to be within the normal	weeks of treatment or had discontinued. Of 137 patients enrolled in the core study, 113 completed the core phase and 106 (77.4%) opted to enter the extension phase; 98 (71.5%) completed 72 weeks of treatment. All 137 patients were included in outcomes reported at 48 weeks and 106 in outcomes reported at 72 weeks, apart from AEs in which all patients were included. No clinical and demographic details were provided for the subjects included in the extension study. Subjects in the original study had been recruited from 66 sites in 19 countries, which included locations in the UK; it was not stated which sites subjects in this extension study had been recruited from. Limited statistical analyses were reported and some outcomes (including physical manifestations of Cushing's disease) were only presented in figures, meaning that data could not be extracted to report in this review. As in Pivonello et al 2020, the MCIDs for the Cushing QoL and the BDI-II scores were defined as a 10.1-point increase from baseline and a 17.5% reduction from baseline respectively.

[48] Complete response was defined as mean UFC ≤ ULN. Partial response was defined as mean UFC > ULN but with a ≥ 50% reduction from baseline. Uncontrolled was defined as neither a complete nor partial response, having discontinued, or having had a missing mean UFC at the given time point.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Proximal muscle atrophy: 36 (49.3%) Hirsutism (females only, n=61): 29 (47.5%) Striae: 30 (41.1% Ecchymoses: 19 (26.0%) No subgroups reported		range at week 48 and throughout the extension period. *Late night salivary cortisol (LNSC)*[49] Week 48: mean LNSC 2.7 (SD 1.6) nmol/L During extension: LNSC remained consistently lower than baseline but above ULN **Sequelae of Cushing's disease** [50] Mean (SD) Baseline (n=137); change from baseline at week 48 (n=137); change from baseline at week 72 (n=106) *Weight, kg*: 80.8 (22.4); −3.8 (5.7); −4.7 (6.6) *BMI, kg/m²*: 30.3 (7.8); −1.4 (2.2); −1.8 (2.5) *Waist circumference, cm:* 103.5 (19.3); −4.7 (7.8); −6.2 (8.5) *Systolic BP, mm Hg:* 132.2 (15.1); −9.8 (15.5); −10.1 (18.1) *Diastolic BP, mm Hg:* 85.3 (10.6); −6.3 (11.1); −5.8 (11.3) *Fasting plasma glucose, mmol/L;* 5.5 (1.7); −0.5 (1.3); −0.3 (1.1) *HbA1c, %:* 6.0 (1.0); −0.4 (0.7); −0.4 (0.6) *Total cholesterol, mmol/L:* 5.3 (1.2); −0.5 (0.9); −0.4 (0.9) *Triglycerides, mmol/L:* 1.5 (1.3); −0.1 (0.9); −0.1 (0.6)	Outcome assessors were not blinded beyond the 48-week point, increasing the risk of bias in the assessment of more subjective outcomes. **Source of funding** The authors stated that the study was funded by Novartis Pharma AG, and that financial support for medical editorial assistance was provided by Recordati.

[49] LNSC ULN: 2.5 nmol/L

[50] Normal ranges: plasma glucose, 3.9–5.5 mmol/L; HbA1c, ≤6.4%; total cholesterol, ≤4.4 mmol/L in people aged <19 years and ≤5.2 mmol/L in people aged ≥20 years; triglycerides, ≤2.2 mmol/L.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			BDI-II score[51]*:* 16.8 (10.6); −5.8 (9.5); −6.7 (10.7) **Important outcomes** **Reduction in treatment for Cushing's disease sequelae** n (%) *Change in use of hypertensive medications from baseline to week 48 (n=85 taking hypertensive medications at baseline)* Increase in dose or number of medications: 34/85 (40%) Decrease in dose or stopped medication: 34/85 (40%) *Change in use of diabetic medications from baseline to week 48 (n=43 taking diabetic medications at baseline)* Increase in dose or number of medications: 10/43 (23%) Decrease in dose or stopped medication: 21/43 (49%) **Quality of life** *Cushing QoL score* [52] Mean (SD) Baseline (n=137); change from baseline at week 48 (n=137); change from baseline at week 72 (n=106)	

[51] BDI-II: Beck depression inventory 2, a self-scored questionnaire which indicates possible mood disturbance or depression. Decrease in BDI-II score indicates improvement. No further details were provided in this paper. The % change in score was not reported in this paper but the authors reported that it exceeded to 17.5% MCID.
[52] Cushing QoL score: a health-related quality of life questionnaire developed and validated for use in people with Cushing's disease. Increases in Cushing QoL score indicate improvement. No further details were provided in this paper.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Cushing QoL total score 42.2 (19.1); 14.0 (16.8); 15.1 (19.4) Physical problems subscore 38.9 (23.7); 18.3 (22.0); 19.3 (22.9) Psychosocial issues subscore 43.3 (20.4); 12.7 (17.4); 13.6 (20.1) **Safety** *Adverse events (AEs)* (n=137) n (%) All grades; grade 3-4 Any AE: 137 (100%); 83 (60.6%) AEs leading to discontinuation: 25 (18.2%); 17 (12.4%) AEs requiring dose adjustment/ interruption: 110 (80.3%); 42 (30.7%) AEs requiring additional therapy: 132 (96.4%); 61 (44.5%) *Selected most common AEs* (n=137) n (%) All grades; grade 3-4 Nausea: 62 (45.3%); 3 (2.2%) Headache: 50 (36.5%); 6 (4.4%) Fatigue: 45 (32.8%); 3 (2.2%) Adrenal insufficiency: 40 (29.2%); 6 (4.4%) Vomiting: 34 (24.8%); 5 (3.6%) Nasopharyngitis: 33 (24.1%); 1 (0.7%) Glucocorticoid deficiency[53]: 28 (20.4%); 5 (3.6%)	

[53] Glucocorticoid deficiency includes 'hypocortisolism', 'symptoms of hypocortisolism', 'relative hypocortisolism', 'suspicion of hypocortisolism', 'asymptomatic/symptomatic hypocortisolism', and 'subjective symptoms of hypocortisolism'.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Hypertension: 24 (17.5%); 16 (11.7%) AEs potentially related to arrhythmogenic potential and QT prolongation were reported to be infrequent but actual numbers were not reported.	
Gadelha M, Bex M, Feelders RA, Heaney AP, Auchus RJ, Gilis-Januszewska A, et al. Randomized Trial of Osilodrostat for the Treatment of Cushing Disease. Journal of Clinical Endocrinology & Metabolism. 2022;107(7):e2882-e95. **Study location** Forty centres in 14 countries (Belgium, Brazil, Canada, China, Costa Rica, Greece, Poland, Portugal, Russia, Spain, Switzerland, Thailand, Turkey, USA) **Study type**	Patients aged 18 to 75 years with a confirmed diagnosis of persistent/recurrent Cushing disease after pituitary surgery and/or irradiation or de novo disease **Inclusion criteria** • Mean 24-hour UFC >1.3 x ULN[54] : • Morning plasma ACTH level above the lower limit of normal (LLN)[55] • Evidence of a pituitary origin for the excess ACTH[56] Patients receiving other medical therapies for Cushing's disease could be	**Interventions** Osilodrostat phosphate orally twice daily Dose was started at 2mg twice daily for all patients with dose adjustments approximately every 3 weeks during the placebo-controlled phase (weeks 1 to 12). During the open label phase (weeks 13 to 48) all patients restarted on osilodrostat phosphate 2 mg twice daily unless they were on a lower dose at week 12, when they continued to receive the lower dose. Dose adjustments were made as	**Critical outcomes** Outcomes at up to 48 weeks from start of treatment[57] **Clinical disease response** *Change from baseline in physical features of hypercortisolism at week 48[58]* Randomised to osilodrostat phosphate (n=33 to 39); randomised to placebo (n=15 to 22); total (n=48 to 61) *Facial rubor* Improvement: 16/39 (41.0%) (95% CI 25.6 to 57.9); 11/21 (52.4%) (95% CI 29.8 to 74.3); 27/60 (45.0%) (95% CI 32.1 to 58.4) No change: 21/39 (53.8%) (95% CI 37.2 to 69.90; 10/21 (47.6%) (95% CI	The single-arm phase of this study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Unclear 4. Unclear 5. Unclear 6. Yes 7. Yes 8. No 9. No 10. Yes The randomised phase of this study was appraised using the JBI checklist for RCTs. 1. Yes 2. Yes 3. Unclear 4. Yes 5. No

[54] Mean UFC calculated as the mean of 3 samples, with ≥2 values >1.3 × ULN. ULN: 138 nmol/24 h or 50 µg/24 h. Mean UFC reference range 11-138 nmol/24 hours (4-50 µg/24 hours).
[55] LLN: 1.6 pmol/ (males) and 1.1 pmol/L (females)
[56] Confirmation of a pituitary tumour of ≥6 mm by MRI imaging; central-to-peripheral bilateral inferior petrosal sinus sampling gradient of >2 pre-stimulation or >3 post-stimulation with either corticotropin-releasing-hormone or desmopressin stimulation; or histopathological and immunohistochemical confirmation of an ACTH-producing pituitary tumour in patients with previous pituitary surgery.
[57] At week 48, patients randomised to placebo had received 12 weeks of placebo followed by 36 weeks of osilodrostat phosphate treatment; patients randomised to osilodrostat phosphate had received 48 weeks of osilodrostat phosphate.
[58] Physical features were reported to have been assessed using a semi-quantitative Likert scale; no further details were provided and it was not stated who they were assessed by

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Phase III study (LINC4) (randomised study followed by single-arm study) **Study aim** To evaluate the safety and efficacy of osilodrostat compared with placebo in patients with Cushing disease **Study dates** November 2016 to February 2020	included after a suitable washout period **Exclusion Criteria** • Stereotactic radiosurgery in the last 2 years • Conventional radiotherapy in the past 3 years • Pituitary surgery in the past 3 months • Receipt of glucocorticoid replacement therapy after surgery within the past week or five half-lives (whichever was longer) • Treatment with other investigational drugs within 30 days or five half-lives (whichever was longer) • History of hypersensitivity to osilodrostat or therapies of a similar chemical class • Presence or high risk of compression of optic chiasm **Total sample size** n=73 **Number in each treatment group**	during the placebo-controlled period. Median osilodrostat phosphate dose from baseline to data cutoff was 5.0 (IQR 3.8 to 9.2) mg/day. At week 48, 84% of patients with normal mean UFC were receiving doses of ≤10 mg/day (≤4 mg/day, n = 28 (56.0%); >4 to 10 mg/day, n = 14 (28.0%); >10 to 20 mg/day, n = 2 (4.0%); >20 mg/day, n = 6 (12.0%)). **Comparators** Placebo Patients also received concomitant medications as required.	25.7 to 70.2); 31/60 (51.7%) (95% CI 38.4 to 64.8) Worsening: 2/39 (5.1%) (95% CI 0.6 to 17.3); 0/21 (0%) (95% CI NE); 2/60 (3.3%) (95% CI 0.4 to 11.5) *Hirsutism* Improvement: 5/33 (15.2%) (95% CI 5.1 to 31.9); 3/15 (20.0%) (95% CI 4.3 to 48.1); 8/48 (16.7%) (95% CI 7.5 to 30.2) No change: 24/33 (72.7%) (95% CI 95% CI 54.5 to 86.7); 12/15 (80.0%) (95% CI 51.9 to 95.7); 36/48 (75.0%) (95% CI 60.4 to 86.4) Worsening: 4/33 (12.1%) (95% CI 3.4 to 28.2); 0/15 (0%) (95% CI NE); 4/48 (8.3%) (95% CI 2.3 to 20.0) *Striae* Improvement: 11/38 (28.9%) (95% CI 15.4 to 45.9); 4/21 (19.0%) (95% CI 5.4 to 41.9); 15/59 (25.4%) (95% CI 15.0 to 38.4) No change: 27/38 (71.1%) (95% CI 54.1 to 84.6); 17/21(81.0%) (95% CI 58.1 to 94.6); 44/59 (74.6%) (95% CI 61.6 to 85.0) Worsening: 0/38 (0%) (95% CI NE); 0/21 (0%) (95% CI NE); 0/59 (0%) (95% CI NE) *Supraclavicular fat pad* Improvement: 21/39 (53.8%) (95% CI 37.2 to 69.9); 11/22 (50.0%) (95% CI 28.2 to 71.8); 32/61 (52.5%) (95% CI 39.3 to 65.4) No change: 17/39 (43.6%) (95% CI 27.8 to 60.4); 11/22 (50.0%) (95% CI	6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Unclear 12. No 13. Yes **Other comments** This study comprised a 12-week randomised double-blind placebo-controlled period followed by a 36-week open-label osilodrostat phosphate treatment period. Enrolled patients were randomly assigned 2:1 to osilodrostat phosphate or matching placebo, stratified by prior pituitary irradiation. The study was reported to be based at 40 centres in 14 countries (not including the UK) but it was not stated how many subjects were recruited at each. It was not clear whether groups were similar at baseline; there appeared to be differences eg. the placebo group had more males, more people of Asian origin and lower median UFC levels but no statistical tests comparing the two groups were reported so it is not possible to say whether these differences were statistically significant. Patients, investigators, and study sponsor were reported to be blinded to treatment assignment and, during the placebo-controlled period, to

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Osilodrostat phosphate: n=48 Placebo: n=25 **Baseline characteristics** Osilodrostat phosphate; Placebo; Total *Age, years* Median (range) 41.0 (21.0 to 67.0); 37.0 (19.0 to 63.0); 39.0 (19.0 to 67.0) *Sex*, n (%) Female: 43 (89.6%); 18 (72.0%); 61 (83.6%) Male: 5 (10.4%); 7 (28.0%); 12 (16.4%) *Race*, n (%) White: 34 (70.8%); 15 (60.0%); 49 (67.1%) Asian: 9 (18.8%); 8 (32.0%); 17 (23.3%) Black/African American: 2 (4.2%); 0; 2 (2.7%) Other: 1 (2.1%); 1 (4.0%); 2 (2.7%) Unknown: 2 (4.2%); 1 (4.0%); 3 (4.1%) *Time since diagnosis, months* Median (IQR) 69.9 (22.9 to 92.0); 65.0 (30.4 to 103.8); 67.4 (26.4 to 93.8)		28.2 to 71.8); 28/61 (45.9%) (95% CI 33.1 to 59.2) Worsening: 1/39 (2.6%) (95% CI 0.1 to 13.5); 0/22 (0%) (95% CI NE); 1/61 (1.6%) (95% CI 0.0 to 0.8 [sic]) *Dorsal fat pad* Improvement: 20/38 (52.6%) (95% CI 35.8 to 69.0); 10/22 (45.5%) (95% CI 24.4 to 67.8); 30/60 (50.0%) (95% CI 36.8 to 63.2) No change: 16/38 (42.1%) (95% CI 26.3 to 59.2); 10/22 (45.5%) (95% CI 24.4 to 67.8); 26/60 (43.3%) (95% CI 30.6 to 56.8) Worsening: 2/38 (5.3%) (95% CI 0.6 to 17.7); 2/22 (9.1%) (95% CI 1.1 to 29.2); 4/60 (6.7%) (95% CI 1.8 to 16.2) *Proximal muscle atrophy* Improvement: 10/39 (25.6%) (95% CI 13.0 to 42.1); 8/22 (36.4%) (95% CI 17.2 to 59.3); 18/61 (29.5%) (95% CI 18.5 to 42.6) No change: 25/39 (64.1%) (95% CI 47.2 to 78.8); 13/22 (59.1%) (95% CI 36.4 to 79.3); 38/61 (62.3%) (95% CI 49.0 to 74.4) Worsening: 4/39 (10.3%) (95% CI 2.9 to 24.2); 1/22 (4.5%) (95% CI 0.1 to 22.8); 5/61 (8.2%) (95% CI 2.7 to 18.1) *Central obesity* Improvement: 16/39 (41.0%) (95% CI 25.6 to 57.9); 9/22 (40.9%) (95% CI 20.7 to 63.6); 25/61 (41.0%) (95% CI 28.6 to 54.3)	laboratory results that could disclose treatment assignment. During weeks 1 to 12 independent endocrinologists were unblinded to treatment assignment and laboratory data and made dose adjustments as required based on efficacy and tolerability. During the open-label period dose adjustments were determined by the investigators using the same guidelines as for weeks 1 to 12. During the 12-week randomised period three patients discontinued (all osilodrostat phosphate); one due to AE and two a patient/guardian decision. During the open-label period five discontinued; two due to AE and three a patient/guardian decision. Safety analyses for the whole study period used all data from the first patient's visit until data cutoff when the last patient completed or discontinued the core study (February 25, 2020). The assessment protocol was described and laboratory investigations were assessed centrally. Validated self-report tools were used to measure QoL and depression. A semi-quantitative Likert scale was used to assess physical features of hypercortisolism; no further details about the assessment of these outcomes were provided. A number of disease response outcomes were reported in figures

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Previous pituitary surgery, n (%) 41 (85.4%); 23 (92.0%); 64 (87.7%) *Previous medical therapy for Cushing's disease*, n (%) 26 (54.2%); 19 (76.0%); 45 (61.6%) *Previous pituitary irradiation*, n (%) 6 (12.5%); 3 (12.0%); 9 (12.3%) *UFC, nmol/24 hours* Mean (SD) 421.4 (291.3); 451.5 (535.1); 431.7 (388.6) Median (IQR) 342.2 (252.6–519.9); 297.6 (211.2–518.8); 340.3 (221.3–518.8)		No change: 19/39 (48.7%) (95% CI 32.4 to 65.2); 12/22 (54.5%) (95% CI 32.2 to 75.6); 31/61 (50.8%) (95% CI 37.7 to 63.9) Worsening: 4/39 (10.3%) (95% CI 2.9 to 24.2); 1/22 (4.5%) (95% CI 0.1 to 22.8); 5/61 (8.2%) (95% CI 2.7 to 18.1) *Ecchymosis* Improvement: 9/39 (23.1%) (95% CI 11.1 to 39.3); 3/21 (14.3%) (95% CI 3.0 to 36.3); 12/60 (20.0%) (95% CI 10.8 to 32.3) No change: 29/39 (74.4%) (95% CI 57.9 to 87.0); 17/21 (81.0%) (95% CI 58.1 to 94.6); 46/60 (76.7%) (95% CI 64.0 to 86.6) Worsening: 1/39 (2.6%) (95% CI 0.1 to 13.5); 1/21 (4.8%) (95% CI 0.1 to 23.8); 2/60 (3.3%) (95% CI 0.4 to 11.5) **Biochemical disease response** n=73 *Complete response at week 12* [59]*, n (%)* Randomised to osilodrostat phosphate: 37/48 (77.1%) Randomised to placebo: 2/25 (8.0%) OR 43.4 (95% CI 7.1 to 343.2) p < 0.0001 *Complete response at week 36, n (%) (95% CI)*	from which data could not be extracted to report in this review; results for complete and partial response and mean UFC are taken from narrative text so in some cases are incompletely reported. Limited statistical analyses were presented, particularly with respect to comparisons between the randomised groups (although some comparisons were presented in figures). **Source of funding** The authors stated that the study was funded by Novartis Pharma AG who contributed to study design, data collection, data analysis, data interpretation, and writing of the manuscript. The asset holder (Recordati) contributed to data interpretation, writing of the manuscript, and the decision to submit the report for publication. The services of professional medical writers were funded by Recordati.

[59] Complete response was defined as mean UFC≤ULN, partial response was defined as mean UFC>ULN but ≥ 50% reduction from baseline. Overall response = complete response + partial response

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			59/73 (80.8%) (95% CI 69.9 to 89.1) *Response at week 48, n (%)*[60] Overall response: 58/73 (79.5%) Complete response: (68.5%) Partial response: (11.0%) *Mean 24-hour UFC* Randomised to osilodrostat phosphate (n=48); randomised to placebo (n=25) Mean (SD), nmol/24h Baseline: 421.4 (291.3); 451.5 (535.1) Week 12: 98.2 (122.5) 411.3 (389.9) *Serum and salivary cortisol* Randomised to osilodrostat phosphate (n=48); randomised to placebo (n=25); total (n=73) *Serum cortisol*[61] Mean (SD), nmol/L Baseline 565.8 (169.0); 486.1 (198.1); 538.1 (182.3) Week 12: 295.6 (160.4); 560.1 (204.4); nr (nr) Week 48; 354.0 (114.6); 353.7 (145.5); 353.9 (124.9) *Change in serum cortisol from baseline* Mean (95% CI), nmol/L	

[60] n not stated for complete or partial response
[61] Serum cortisol reference range, male and female, ≥18 years old: 127–567 nmol/L

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Week 12: −276.0 (95% CI −330.2 to −221.7); 73.0 (95% CI −5.2 to 151.2); nr (nr) Week 48: −210.7 (95% CI −261.5 to −159.9); −131.0 (95% CI −236.1 to −26.0); −182.9 (95% CI −231.5 to −134.3) *Early-morning salivary cortisol*[62] Mean (SD), nmol/L Baseline: 17.2 (30.0); 14.1 (12.3); 16.1 (25.3) Week 12: 5.8 (7.0); 14.1 (10.0); nr (nr) Week 48: 4.7 (2.9); 6.9 (7.7); 5.4 (5.2) *Change in early-morning salivary cortisol from baseline* Mean (95% CI), nmol/L Week 12: −11.6 (95% CI −20.5 to −2.7); −0.3 (95% CI −5.1 to 4.4); nr (nr) Week 48: −11.8 (95% CI −21.8 to −1.8); −6.0 (95% CI −10.8 to −1.1); −9.8 (95% CI −16.4 to −3.1) *Late-night salivary cortisol*[63] Mean (SD), nmol/L Baseline: 11.7 (28.7); 9.0 (6.7); 10.8 (23.5) Week 12: 3.5 (2.3); 10.3 (6.5); nr (nr) Week 48: 3.5 (2.6); 4.0 (2.5); 3.7 (2.6)	

[62] Early-morning (07:00–09:00) salivary cortisol reference range, male and female, ≥18 years old: 1.1–15.5 nmol/L
[63] Late-night (22:00–23:00) salivary cortisol reference range, male and female, ≥18 years old: ≤2.5 nmol/L.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Change in late-night salivary cortisol from baseline Mean (95% CI), nmol/L Week 12: −8.5 (95% CI −17.3 to 0.3); 1.3 (95% CI −2.4 to 5.1); nr (nr) Week 48: −9.3 (95% CI −18.5 to −0.2); −5.0 (95% CI −7.6 to −2.5); −7.8 (95% CI −13.8 to −1.9) **Sequelae of Cushing's disease** [64] Randomised to osilodrostat phosphate (n=48); randomised to placebo (n=25); total (n=73) *Weight, kg* Mean (SD) Baseline: 78.8 (17.5); 77.3 (16.9); 78.3 (17.2) Week 12: 78.1 (17.9); 75.7 (15.7); nr (nr) Week 48: 74.1 (16.6); 72.5 (17.4); 73.5 (16.8) *Change in weight from baseline, kg* Mean (95% CI) Week 12: −0.8 (95% CI −1.7 to 0.1); −0.1 (95% CI −1.0 to 0.8); nr (nr) Week 48: −3.6 (95% CI −5.7 to −1.6); −5.5 (95% CI −8.3 to −2.7); −4.3 (95% CI −5.9 to −2.6) *Waist circumference, cm* Mean (SD)	

[64] Reference ranges: fasting plasma glucose, 70–115 mg/dL (13–49 years), 70–125 mg/dL (≥50 years); HbA1c, ≤6.4%; total cholesterol, 0–5.2 mmol/L (≥20 years); HDL cholesterol, >0.89 mmol/L; LDL cholesterol, 0–3.4 mmol/L (≥20 years); triglycerides, 0–2.2 mmol/L. Decrease in BDI-II score indicates improvement

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Baseline: 102.5 (17.0); 103.4 (15.5); 102.8 (16.4) Week 12: 101.4 (17.7); 102.1 (15.1); nr (nr) Week 48: 97.3 (17.0); 97.8 (17.2); 97.5 (16.9) *Change in waist circumference from baseline, cm* Mean (95% CI) Week 12: −1.0 (95% CI −2.3 to 0.3); −0.5 (95% CI −1.9 to 1.0); nr (nr) Week 48: −4.1 (95% CI −6.0 to −2.2); −5.3 (95% CI −7.9 to −2.8); −4.5 (95% CI −6.0 to −3.0) *Systolic BP, mm Hg* Mean (SD) Baseline: 132.4 (19.2); 130.0 (17.7); 131.5 (18.6) Week 12: 125.5 (13.7), 127.4 (14.9); nr (nr) Week 48: 123.0 (15.4); 117.0 (16.2); 120.9 (15.8) *Change in systolic BP from baseline, mm Hg* Mean (95% CI) Week 12: −7.1 (95% CI −12.6 to −1.6); −0.9 (95% CI −5.8 to 4.1); nr (nr) Week 48: −9.1 (95% CI −15.2 to −2.9); −11.0 (95% CI −20.8 to −1.1); −9.7 (95% CI −14.9 to −4.6) *Diastolic BP, mm Hg* Mean (SD) Baseline: 87.2 (12.7); 88.2 (10.8); 87.5 (12.0)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Week 12: 81.8 (10.7); 87.0 (11.2), nr (nr) Week 48: 81.7 (11.0); 83.5 (10.4); 82.3 (10.8) *Change in diastolic BP from baseline, mm Hg* Mean (95% CI) Week 12: −4.8 (95% CI −8.2 to −1.5); −1.4 (95% CI −5.5 to 2.8); nr (nr) Week 48: −4.4 (95% CI −8.1 to −0.7); −3.9 (95% CI −9.8 to 2.0); −4.2 (95% CI −7.3 to −1.2) *Fasting plasma glucose, mg/dL* Mean (SD) Baseline: 97.3 (18.1); 91.4 (15.2); 95.3 (17.3) Week 12: 92.0 (15.5); 91.1 (11.2); nr (nr) Week 48: 90.5 (12.9); 90.7 (13.7); 90.6 (13.1) *Change in fasting plasma glucose from baseline, mg/dL* Mean (95% CI) Week 12: −4.3 (95% CI −8.9 to 0.2); −1.7 (95% CI −6.3 to 2.9); nr (nr) Week 48: −5.6 (95% CI −10.1 to −1.1); 1.8 (95% CI −4.5 to 8.1); −3.1 (95% CI −6.8 to 0.6) *HbA1c, %* Mean (SD) Baseline: 6.0 (0.9); 5.7 (0.6); 5.9 (0.8) Week 12: 5.7 (0.7); 5.6 (0.6); nr (nr) Week 48: 5.8 (0.6); 5.7 (0.5); 5.7 (0.5) *Change in HbA1c % from baseline*	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Mean (95% CI) Week 12: −0.2 (95% CI −0.4 to −0.1); 0.0 (95% CI −0.2 to 0.1); nr (nr) Week 48: −0.2 (95% CI −0.4 to 0.0); 0.1 (95% CI −0.1 to 0.2); −0.1 (95% CI −0.2 to 0.0) *Total cholesterol, mmol/L* Mean (SD) Baseline: 5.7 (1.3); 5.3 (1.2); 5.5 (1.3) Week 12: 4.9 (1.2); 5.3 (1.3); nr (nr) Week 48: 5.1 (1.3); 4.9 (1.2); 5.0 (1.3) *Change in total cholesterol from baseline, mmol/L* Mean (95% CI) Week 12: −0.8 (95% CI −1.1 to −0.5); 0.0 (95% CI −0.2 to 0.3); nr (nr) Week 48: −0.6 (95% CI −1.0 to −0.1); −0.4 (95% CI −0.9 to 0.1); −0.5 (95% CI −0.8 to −0.2) *LDL cholesterol, mmol/L* Mean (SD) Baseline: 3.4 (1.1); 3.0 (1.1); 3.3 (1.1) Week 12: 3.0 (1.0); 3.1 (1.1); nr (nr) Week 48: 3.0 (1.0); 2.8 (1.1); 2.9 (1.1) *Change in LDL cholesterol from baseline, mmol/L* Mean (95% CI) Week 12: −0.5 (95% CI −0.7 to −0.2); 0.1 (95% CI −0.1 to 0.3); nr (nr) Week 48: −0.5 (95% CI −0.8 to −0.2); −0.2 (95% CI −0.6 to 0.2); −0.4 (95% CI −0.6 to −0.1) *HDL cholesterol, mmol/L* Mean (SD)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Baseline: 1.6 (0.4); 1.5 (0.4); 1.6 (0.4) Week 12: 1.3 (0.3); 1.5 (0.5); nr (nr) Week 48: 1.4 (0.3); 1.4 (0.4); 1.4 (0.4) *Change in HDL cholesterol from baseline, mmol/L* Mean (95% CI) Week 12: −0.3 (95% CI −0.4 to −0.2); 0.0 (95% CI −0.1 to 0.1); nr (nr) Week 48: −0.2 (95% CI −0.3 to −0.1); −0.1 (95% CI −0.3 to 0.0); −0.2 (95% CI −0.3 to −0.1) *Triglycerides, mmol/L* Mean (SD) Baseline: 1.5 (0.8); 1.7 (0.9); 1.6 (0.8) Week 12: 1.5 (0.8); 1.5 (0.8); nr (nr) Week 48: 1.5 (1.0); 1.5 (0.8); 1.5 (0.9) *Change in triglycerides from baseline, mmol/L* Mean (95% CI) Week 12: 0.0 (95% CI −0.1 to 0.2); −0.2 (95% CI −0.4 to 0.0), nr (nr) Week 48: 0.1 (95% CI −0.2 to 0.4); −0.2 (95% CI −0.5 to 0.0); 0.0 (95% CI −0.2 to 0.2) *BDI-II score* Mean (SD) Baseline: 12.2 (10.2); 8.4 (7.8); 10.9 (9.6) Week 12: 10.3 (8.5); 4.7 (6.1); nr (nr) Week 48: 6.7 (6.7); 4.1 (7.5); 5.8 (7.0) *Change in BDI-II score from baseline* Mean (95% CI) Week 12: −1.4 (95% CI −3.7 to 1.0); −3.9 (95% CI −6.2 to −1.6); nr (nr)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Week 48: −4.3 (95% CI −6.7 to −2.0); −4.0 (95% CI −7.5 to −0.6); −4.2 (95% CI −6.1 to −2.3) **Important outcomes** **Time to improvement** *Median time to first controlled mean UFC response* For patients randomised to osilodrostat phosphate: 35 days (95% CI 34.0 to 52.0 days) For patients randomised to placebo: not reached For patients randomised to placebo once they had crossed over to osilodrostat phosphate: 35 days **Quality of life** Randomised to osilodrostat phosphate (n=48); randomised to placebo (n=25); total (n=73) *Cushing QoL score* Mean (SD) Baseline: 49.1 (19.6); 56.9 (19.0); 51.8 (19.6) Week 12: 56.1 (22.1);65.6 (17.6); nr (nr) Week 48: 62.8 (22.2); 69.9 (16.9); 65.3 (20.7) *Change in Cushing QoL score compared to baseline*[65] Mean (95% CI)	

[65] Increases in Cushing QoL score indicate improvement

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Week 12: 6.2 (95% CI 1.7 to 10.6); 8.6 (95% CI 3.5 to 13.7); nr (nr) Week 48: 11.7 (95% CI 6.6 to 16.7); 12.8 (95% CI 6.5 to 19.1); 12.0 (95% CI 8.2 to 15.9) **Safety** *Adverse events (AEs) in the randomised groups* Osilodrostat phosphate (n=48); placebo (n=25) n (%) <u>AEs occurring up to week 12</u> Any AE: 46 (95.8%); 23 (92.0%) Serious AE: 2 (4.2%); 1 (4.0%) AE leading to discontinuation: 1 (2.1%); 0 Grade 1–2 AEs: 36 (75.0%) 18 (72.0%) Grade 3–4 AEs: 10 (20.8%); 5 (20.0%) <u>Most common AEs</u> Decreased appetite: 18 (37.5%); 4 (16.0%) Arthralgia: 17 (35.4%) 2 (8.0%) Fatigue: 12 (25.0%) 4 (16.0%) Nausea: 15 (31.3%) 3 (12.0%) Hypertension: 8 (16.7%) 7 (28.0%) *AEs over the whole study period (n=73)*[66] n (%) Any AE: 73 (100%)	

[66] Excludes data from patients receiving placebo during the 12-week randomised period

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Serious AE: 8 (11.0%) AE leading to discontinuation: 8 (11.0%) Grade 1–2 AE: 45 (61.6%) Grade 3–4 AE: 28 (38.4%) <u>Most common AEs</u> Decreased appetite: 33 (45.2%) Arthralgia: 33 (45.2%) Fatigue: 28 (38.4%) Nausea: 27 (37.0%) Headache: 24 (32.9%) Myalgia: 19 (26.0%) Dizziness: 19 (26.0%) Adrenal insufficiency: 18 (24.7%) Increased blood testosterone: 18 (24.7%) Diarrhoea: 17 (23.3%) Hypertension: 16 (21.9%) Asthenia: 15 (20.5%) Upper respiratory tract infection: 15 (20.5%)	
Gadelha M, Snyder PJ, Witek P, Bex M, Belaya Z, Turcu AF, et al. Long-term efficacy and safety of osilodrostat in patients with Cushing's disease: results from the LINC 4 study extension. Frontiers in Endocrinology. 2023;14:1236465. **Study location** As Gadelha et al 2022	Patients aged 18 to 75 years with a confirmed diagnosis of persistent/recurrent Cushing's disease after pituitary surgery and/or irradiation or de novo disease **Inclusion criteria** • Initial inclusion criteria as Gadelha et al 2022. Patients who were	**Interventions** Osilodrostat phosphate orally twice daily Dose was started at the established effective dose from the core phase (Gadelha et al 2022). Dose adjustments were permitted based on efficacy and tolerability; the maximum permitted dose was 30 mg twice daily.	**Critical outcomes** Outcomes reported at up to 96 weeks from the start of treatment **Biochemical response to treatment** *Response at week 48 (n=73[67]), n (%)* Overall response: 58/73 (79.5%) Complete response: 50/73 (68.5%) Partial response: 8/73 (11.0%) No response: 15/73 *Response at week 72 (n=60), n (%)* Overall response: 45/60 (75%)	This study was appraised using the JBI checklist for case series. (Where appropriate these responses draw on information presented in Gadelha et al 2022) 1. Yes 2. Yes 3. Unclear 4. Unclear 5. Unclear 6. Unclear 7. Unclear 8. No

[67] Patients who had discontinued were classed as non-responders

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study type Phase III study (LINC4) (single-arm study) **Study aim** To evaluate the long-term efficacy and safety of osilodrostat in patients with Cushing disease **Study dates** November 2016 to December 2020	receiving clinical benefit at week 48 could enter the optional open-label extension. **Exclusion Criteria** • As Gadelha et al 2022 **Total sample size** n=73 For extension period (week 48 on): n= 60 **Baseline characteristics** As Gadelha et al 2022 for original cohort (n=73). Baseline characteristics for n=60 included in this extension study not reported. **Additional baseline characteristics reported in this paper** (n=73) *Most common comorbidities, n (%)* Hypertension: 45 (61.6% Diabetes mellitus: 21 (28.8% Osteoporosis: 19 (26.0% Vitamin D deficiency: 18 (24.7%) Dyslipidemia: 15 (20.5%	Median osilodrostat phosphate dose received during the overall study period was 4.6 (IQR 3.7 to 9.2) mg/day. Median osilodrostat phosphate exposure was 87.1 (range 2.0 to 126.6) weeks. **Comparators** No comparator	Complete response: 40/60 (66.7%) Partial response: 5/60 (8.3%) *Response at extension end of treatment (n=58), n (%)* Overall response: 47/58 (81%) Complete response: 42/58 (72.4%) Partial response: 5/58 (8.6%) *24-hour UFC at week 72,* mean (SD)[68] (n=48) 90.5 (122.6) nmol/24 h *Serum cortisol*[69] Mean (SD), nmol/L Baseline (n=73): 538.1 (182.3) Week 48 (n=64): 353.9 (124.9) Week 72 (n=46): 319.1 (129.8) *Late-night salivary cortisol*[70] Mean (SD), nmol/L Baseline (n=73): 10.8 (23.5) Week 48 (n=63): 3.7 (2.6) Week 72 (n=46): 3.8 (3.0) **Sequelae of Cushings disease** *BDI-II score*[71] Mean (SD) score; mean (SD) change from baseline Week 72 (n=48): 6.5 (7.0); −4.1 (9.3) End of treatment (n=13): 6.2 (7.1); −4.5 (7.9)	9. No 10. No This study included patients recruited to Gadelha et al 2022. Patients who were receiving clinical benefit at week 48 could enter an optional open-label extension. Of the 73 patients in Gadelha et al 2022, 65 completed the core phase and 60 then entered the extension phase and 53 completed it. The extension phase was initially planned to run for an additional 48 weeks, to week 96 for the last patient enrolled. However a subsequent protocol amendment resulted in approximately half of the patients completing the extension phase between weeks 72 and 96, at which point they either transitioned to a long-term safety follow-up study or had discontinued from the study. Baseline demographic and clinical data were only reported for the original cohort of n=73, not for the extension cohort. For biochemical response to treatment, the numbers and %s for response presented in text and in figures in the paper appeared

[68] Mean 24-hour UFC ULN: 138 nmol/24 h
[69] Serum cortisol range for males and females ≥18 years old: 127–567 nmol/L
[70] Reference LNSC (22:00–23:00) range for males and females ≥18 years old: ≤2.5 nmol/L
[71] Decreases in BDI-II score indicate improvement

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Hypothyroidism: 15 (20.5%) Fatigue *Physical manifestations of hypercortisolism, n (%)* Central obesity: 63 (86.3%) Supraclavicular fat pad: 61 (83.6%) Dorsal fat pad: 56 (76.7%) Facial rubor: 46 (63.0%) Proximal muscle atrophy: 36 (49.3%) Hirsutism (females only, n=61): 29 (47.5%) Striae: 30 (41.1% Ecchymoses: 19 (26.0%) No subgroups reported		**Important outcomes** **Quality of life** *Cushing QoL score*[72] Mean (SD) standardized Cushing QoL score; mean (SD) change from baseline Week 72 (n=48): 66.4 (19.6); 15.2 (19.0) End of treatment (n=13): 69.0 (20.9); 17.1 (17.1) **Safety** *Adverse events (AE)s over the whole study period (*n=73), n (%) All grades; grade 3-4 Any AE: 72 (98.6%); 29 (39.7%) Serious AE: 10 (13.7%); 9 (12.3%) ≥1 AE leading to discontinuation: 9 (12.3%); 2 (2.7%) ≥1 AE leading to dose adjustment/interruption: 42 (57.5%); 13 (17.8%) ≥1 AE requiring additional therapy: 67 (91.8%); 22 (30.1%) <u>Most common AEs</u> Decreased appetite: 34 (46.6%); 1 (1.4%) Arthralgia: 33 (45.2%); 2 (2.7%) Fatigue: 29 (39.7%); 3 (4.1%) Nausea: 27 (37.0%); 1 (1.4%) Headache: 25 (34.2%); 1 (1.4%)	inconsistent. The data reported here are taken from the text. The authors reported that improvements in most cardiovascular and metabolic-related parameters and physical features of hypercortisolism continued or were maintained during the extension phase but these outcomes were only presented in figures and numerical data were not reported. No statistical tests were performed. **Source of funding** This study was funded by Novartis Pharma AG. Financial support for medical editorial assistance was provided by Recordati.

[72] Increases in Cushing QoL score indicate improvement

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Dizziness: 22 (30.1%); 0 Adrenal insufficiency: 19 (26.0%); 3 (4.1%) Increased blood testosterone: 18 (24.7%); 0 Myalgia: 18 (24.7%); 5 (6.8%) Asthenia: 17 (23.3%); 2 (2.7%) Diarrhoea: 17 (23.3%); 0 Hypertension: 16 (21.9%); 9 (12.3%) Upper respiratory tract infection: 16 (21.9%); 0 <u>AEs of special interest, %</u> Weeks 1-12 (n=48); weeks 12-24 (n=71); weeks 24-36 (n=69); weeks 36-48 (n=68); weeks 48-60 (n=64); weeks 60 onwards (n=59) AEs related to hypocortisolism: 14.6%; 12.7%; 7.2%; 5.9%; 0; 8.5% AEs related to arrhythmogenic potential and QT prolongation: 0; 1.4%; 1.4%; 1.5%; 0; 0	
Pivonello R, Fleseriu M, Newell-Price J, Bertagna X, Findling J, Shimatsu A, et al. 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. The	Patients aged 18 to 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 had refused surgery or were not	**Interventions** Osilodrostat phosphate orally twice daily Dose started at 2mg twice daily for all patients with dose adjustments every 2 weeks based on efficacy and tolerability.	**Critical outcomes** Outcomes reported at up to 48 weeks from the start of treatment **Biochemical disease response** *Response to treatment at week 34 (end of the 8-week randomised withdrawal period) (n=70)*[76] n (%) (95% CI)	The single-arm phase of this study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes

[76] Response was defined as having maintained a complete response (ie. mean 24-h UFC concentration ≤ULN) to osilodrostat phosphate therapy or matching placebo at week 34 (the end of the 8-week randomised withdrawal period)

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Lancet Diabetes & Endocrinology. 2020;8(9):748-61. **Study location** Multicentre, in 66 hospital sites and private clinical practices across 19 countries **Study type** Prospective, multicentre, open-label, phase III study with a double-blind randomised withdrawal period (LINC 3) (single- arm study and randomised study) **Study aim** To identify an effective osilodrostat dose within a narrow therapeutic window and to assess osilodrostat against a placebo while minimising the duration of placebo treatment **Study dates** November 2014 to February 2018	deemed to be surgical candidates **Inclusion criteria** • Mean 24-hour UFC >1.5 x ULN[73] : • Morning plasma ACTH level above the lower limit of normal (LLN)[74] • Evidence of a pituitary origin for the excess ACTH[75] Patients receiving other medical therapies for Cushing's disease could be included after a suitable washout period. **Exclusion Criteria** • Stereotactic radiosurgery in the last 2 years • Conventional radiotherapy in the past 3 years • Pituitary surgery in the past 29 days • Receipt of glucocorticoid	Dose range 1 to 30 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 (SD 13.6). During the randomised withdrawal phase (week 26 to 34) mean dose was 10.0 mg per day (SD 9.6). Median exposure to osilodrostat phosphate was 74.7 weeks (IQR 48.1 to 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 either completed the core period of the study or discontinued early. **Comparators** Placebo	*Osilodrostat phosphate*: 31/36 (86.1%) (95% CI 70.5% to 95.3%) *Placebo:* 10/34[77] (29.4%) (95% CI 15.1% to 47.5%) OR 13.7 (95% CI 3.7 to 53.4), p<0.0001 *Response to treatment after 24 weeks (pre-randomisation) (n=137)*[78] (Randomised to osilodrostat phosphate n=36; randomised to placebo n=35; not randomised n=66; all patients n=137) Overall response; complete response; partial response; n (%) (95% CI) *Osilodrostat phosphate*: 36 (100%) (95% CI 90.3% to 100%); 36 (100%) (95% CI 90.3% to 100%); 0 (95% CI 0 to 9.7%) *Placebo*: 34 (97.1%) (95% CI 85.1% to 99.9%); 34 (97.1%); (95% CI 85.1% to 99.9%); 0 (95% CI 0 to 10.0%) *Not randomised*: 43 (65.2%) (95% CI 52.4% to 76.5%); 23 (34.8%) (95% CI 23.5% to 47.6%); 20 (30.3%) (95% CI 19.6% to 42.9%)	8. Yes 9. No 10. Yes The randomised phase of this study was appraised using the JBI checklist for RCTs. 1. Yes 2. Yes 3. Unclear 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes 12. Yes 13. Yes The study had four stages: Period 1 (weeks 1 to 12): all participants initiated open-label oral osilodrostat phosphate 2 mg twice daily with dose adjustments every 2 weeks (range 1 to 30 mg twice a day) based on efficacy (mean 24-h UFC) and tolerability.

[73] Mean UFC calculated as the mean of 2 or 3 samples. ULN: 138 nmol/24 h or 50 µg/24 h
[74] LLN: 1.6 pmol/ (males) and 1.1 pmol/L (females)
[75] Confirmation of a pituitary tumour of ≥6 mm by MRI imaging; central-to-peripheral bilateral inferior petrosal sinus sampling gradient of more than 2 pre-stimulation or more than 3 post-stimulation with either corticotropin-releasing-hormone or desmopressin stimulation; or histopathological and immunohistochemical confirmation of an ACTH-producing pituitary tumour in patients with previous pituitary surgery.
[77] One patient allocated to placebo did not receive the allocated treatment because of an adverse event (glucocorticoid deficiency) which required drug interruption. They were not included in the biochemical disease response outcome comparing the two groups but were included in other outcomes
[78] Complete response was defined as having a mean 24-h UFC concentration ≤ULN; partial response was defined as having a mean 24-h UFC concentration >ULN but with ≥50% reduction from baseline

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	replacement therapy after surgery within the past week or five half-lives (whichever was longer) • Treatment with other investigational drugs within 30 days or five half-lives (whichever was longer) • History of hypersensitivity to osilodrostat or therapies of a similar chemical class • Presence or high risk of compression of optic chiasm **Total sample size** n=137 Number in each treatment group: Osilodrostat phosphate: n=36 Placebo: n=35 Not randomised: n=66 **Baseline characteristics** Osilodrostat phosphate; placebo; not randomised; total *Age, years*	All enrolled patients also received concomitant medications and clinically relevant non-drug therapies during the study.	*All patients*: 113 (82.5%) (95% CI 75.1% to 88.4%); 93 (67.9%) (95% CI 59.4% to 75.6%); 20 (14.6%) (95% CI 9.2% to 21.6%) *Response to treatment after 48 weeks (n=137)*[79] (Randomised to osilodrostat phosphate n=36; randomised to placebo n=35; not randomised n=66; all patients n=137) Overall response; complete response; partial response; n (%) (95% CI) *Osilodrostat phosphate:* 34 (94.4%) (95% CI 81.3% to 99.3%); 32 (88.9%) (95% CI 73.9% to 96.9%); 2 (5.6%) (95% CI 0.7% to 18.7%) *Placebo:* 31 (88.6%) (95% CI 73.3% to 96.8%); 27 (77.1%) (95% CI 59.9% to 89.6%); 4 (11.4%) (95% CI 3.2% to 26.7%) *Not randomised:* 39 (59.1) (95% CI 46.3% to 71.1%); 32 (48.5%) (95% CI 36.0% to 61.1%); 7 (10.6%) (95% CI 4.4% to 20.6%) *All patients:* 104 (75.9%) (95% CI 67.9% to 82.8%); 91 (66.4%) (95% CI 57.9% to 74.3%); 13 (9.5%) (5.2% to 15.7%) **Sequelae of Cushing's disease (**n=137)	Period 2: (weeks 13 to 26): osilodrostat phosphate was continued at the therapeutic dose determined during study period 1. If mean UFC increased >ULN the dose was increased. Period 3 (week 27-34): eligible participants were randomly assigned (1:1), in a double-blind manner, to continue osilodrostat phosphate at the same therapeutic dose or to receive matching placebo for 8 weeks. Patients were eligible for this phase if they had mean 24-h UFC concentrations ≤ULN at week 24 without a dose increase after week 12. Participants who were not eligible for randomisation continued open-label osilodrostat phosphate. Period 4: (weeks 35 to 48): all participants received open-label osilodrostat phosphate. Throughout the study, dose was reduced if indicated by 24-h UFC concentration. Subjects were recruited from 66 sites in 19 countries; study locations included sites in the UK but it was not stated how many subjects were recruited from each location. The randomisation process was clearly described. Randomisation was stratified by osilodrostat phosphate dose at week 24 (≤5 mg or >5 mg

[79] Complete response was defined as having a mean 24-h UFC concentration ≤ULN; partial response was defined as having a mean 24-h UFC concentration >ULN but with ≥50% reduction from baseline

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Median (IQR) (range) 41.0 (37.5 to 51.5) (20.0 to 69.0); 40.0 (31.0 to 55.0) (19.0 to 68.0); 37.5 (28.0 to 47.0) (19.0 to 70.0); 40.0 (31.0 to 49.0) (19.0 to 70.0) *Sex*, n (%) Male: 6 (17%); 13 (37%); 12 (18%); 31 (23%) Female: 30 (83%); 22 (63%): 54 (82%): 106 (77%) *Race* Caucasian: 27 (75%); 23 (66%); 39 (59%); 89 (65%) Black: 0; 3 (9%); 1 (2%); 4 (3%) Asian: 7 (19%); 7 (20%); 25 (38%); 39 (28%) Other: 2 (6%); 2 (6%); 1 (2%); 5 (4%) *Time since diagnosis*, months Median (IQR) 53.6 (25.9 to 94.3); 76.8 (39.3 to 133.7); 34.7 (14.1 to 65.7); 47.2 (19.0 to 88.3) *Previous pituitary surgery*, n (%)		Value at baseline (mean (SD)); value at week 48 (mean ((SD)); mean change from baseline (95% CI) [80] *Weight, kg:* 80.8 (22.4); 75.5 (20.7); -3.8 ((95% CI -4.8 to -2.7) *BMI, kg/m²*: 30.3 (7.8); 28.4 (7.1); -1.4 (95% CI -1.8 to 1.0) *Systolic BP, mm Hg*: 132.2 (15.1) 121.7 (13.7); -9.8 (95% CI -12.7 to -6.9) *Diastolic BP, mmHg:* 85.3 (10.6); 78.9 (10.1); -6.3 (95% CI -8.4 to -4.2) *Fasting plasma glucose, mg/dL:* 99.2 (29.8); 87.2 (18.9); -9.5 (95% CI -14.3 to -4.8) *HbA1c, %:* 6.0 (1.0); 5.6 (0.8); -0.4 (95% CI -0.5 to -0.2) *Total cholesterol, mmol/L:* 5.3 (1.2); 4.8 (1.0); -0.5 (95% CI -0.7 to -0.3) *LDL cholesterol, mmol/L:* 3.0 (1.0); 2.8 (1.0); -0.2 (95% CI -0.4 to -0.1) *HDL cholesterol, mmol/L:* 1.6 (0.5); 1.3 (0.3); -0.3 (95% CI -0.3 to -0.2) *Triglycerides, mmol/L*: 1.5 (1.3); 1.4 (0.9); -0.1 (95% CI -0.2 to 0.1) *BDI score:* 16.8 (10.6); 10.7 (10.7); -5.8 (95% CI -7.6 to -4.1) (mean % change from baseline -31.8% (95% CI -44.3% to -19.3%)) **Important outcomes** **Time to improvement** (n=137)	twice a day) and history of pituitary irradiation (yes or no). Investigators, assessors and patients were blinded to treatment allocation from the time of random assignment until week 48. Assessors were not blinded before week 26. The groups appeared similar on most measures at baseline except that there were more males in the placebo group and the placebo group had a longer time since diagnosis. The mean 24-h UFC was higher in the osilodrostat phosphate group than the placebo group at baseline but the levels were similar at week 26 when randomisation took place (osilodrostat phosphate group 57.6 nmol/24 h (IQR 44.2 to 87.5); placebo group 57.0 nmol/24 h (IQR 40.5 to 96.6)). As no statistical tests comparing the two groups were reported it is not possible to say whether these differences were statistically significant. One patient randomly assigned to the placebo group did not receive treatment because of an adverse event (glucocorticoid deficiency), which required drug interruption. They were not included in biochemical disease response outcomes comparing the two groups but were included in other outcomes. Outcomes were defined and validated measures were used for QoL and

[80] Reference ranges: plasma glucose 70 to 125 mg/dL; HbA1c ≤6.4%; total cholesterol 0 to 5.2 mmol/L; HDL cholesterol >0.89 mmol/L; LDL cholesterol 0 to 3.4 mmol/L; triglycerides 0 to 2.2 mmol/L

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	32 (89%); 33 (94%); 55 (83%); 120 (88%) *Previous medical therapy for Cushing's disease*, n (%) 26 (72%); 24 (69%); 52 (79%); 102 (74%) *Previous pituitary irradiation*, n (%) 6 (17%); 5 (14%); 11 (17%); 22 (16%) *24h UFC, nmol/24h* Mean (SD) 890 (1276); 560 (549); 1306 (2012); 1006 (1590) *24h UFC, nmol/24h* Median (IQR) 457 (268 to 777); 358 (210 to 652); 557 (348 to 1246); 476 (314 to 919)		Median time to first complete response: 41.0 days (IQR 27.0 to 56.0). **Quality of life** *Cushing QoL score (n=137)* Mean (SD) Baseline: 42.2 (19.1) Week 48: 58.3 (21.3) Mean change from baseline: 14.1 (95% CI 10.9 to 17.3) **Safety** **Adverse events (AEs) in the randomised groups during the randomised withdrawal phase** Osilodrostat phosphate (n=36); placebo (n=35) *AEs and serious AEs,* n (%) Any AE, all grades: 26 (72%); 23 (66%) Any AE, Grade 3-4: 2 (6%); 3 (9%) Any serious AE, all grades: 2 (6%); 1 (3%) Any serious AE, grades 3-4: 1 (3%); 1 (3%) AE requiring dose adjustment, all grades: 7 (19%); 5 (14%) *AEs of special interest,* n (%) Related to adrenal hormone precursor accumulation: 2 (6%); 1 (3%) Related to hypocortisolism: 3 (8%); 1 (3%)	depression (the Cushing QoL score and the BDI-II). MCIDs were defined for these two measures: for the Cushing QoL score this was defined as 10.1 (based on a 0.5 SD unit change using baseline data), and for the BDI score it was defined as a 17.5% reduction in score from baseline. **Source of funding** The authors stated that the study was funded by Novartis Pharma AG, who 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.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			No incidences were reported of AEs related to pituitary tumour enlargement, QT interval prolongation or arrhythmogenic potential on ECG *Most common AEs (all grades)* n (%) Nausea: 4 (11%); 0 Anaemia: 3 (8%); 3 (9%) Fatigue: 2 (6%); 3 (9%) **Adverse events in all patients** (n=137) All grades; Grade 3/4, n (%) Any AE: 137 (100%); 78 (56.9%) Any serious AE: 50 (36.5%); 39 (28.5%) AEs requiring dose interruption and/or change: 106 (77.4%); 39 (28.5%) Death: 1 (0.7%); 1 (0.7%) *Most common AEs* Nausea: 57 (41.6%); 3 (2.2%) Headache: 46 (33.6%); 4 (2.9%) Fatigue: 39 (28.5%); 3 (2.2%) Adrenal insufficiency: 38 (27.7%); 6 (4.4%) Nasopharyngitis: 31 (22.6%); 1 (0.7%) Vomiting: 30 (21.9%) 4 (2.9%) *AEs of special interest* Adrenal hormone precursor accumulation related: 58 (42.3%); 22 (16.1%) Hypocortisolism related: 70 (51.1%); 14 (10.2%)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Pituitary tumour enlargement related: 3 (2.2%); 0 QT prolongation related: 5 (3.6%); 1 (0.7%) Arrythmogenic potential: 1 (0.7%); 1 (0.7%)	

Abbreviations

ACTH: adrenocorticotropic hormone; AE: adverse event; BDI-II: Beck's Depression Inventory-II; bid: twice daily; BP: blood pressure; CI: confidence interval; DM: diabetes mellitus; HbA1c: glycated haemoglobin; HDL: high density lipoprotein; IQR: interquartile range; LDL: low density lipoprotein; LNSC: late-night salivary cortisol; MCID: minimal clinically important difference; mUFC: mean 24-hour urinary free cortisol; N/A: not applicable; NE: not evaluable; nr: not reported; QoL: quality of life; QTcF: prolonged QT interval using Fridericia's correction formula; SD: Standard deviation; SE: standard error; UFC: urinary free cortisol; ULN: upper limit of normal; UPLC-MS/MS: ultra-high-performance liquid chromatography-mass spectrometry

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for RCTs

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blinded to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomised?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisations, parallel groups) accounted for in the conduct and analysis of the trial

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?

2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

In people with Cushing's disease, what is the clinical effectiveness and safety of osilodrostat phosphate compared to standard care?

Table 3: Osilodrostat phosphate vs placebo

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Osilodrostat phosphate	Placebo	Result		
Clinical disease response (1 randomised study)									
Change from baseline in facial rubor at week 48, n (%) (95% CI)									
1 randomised study (LINC4) Gadelha et al 2022 [a]	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	39	21	Randomised to osilodrostat phosphate; randomised to placebo; total Improvement: 16/39 (41.0%) (95% CI 25.6 to 57.9); 11/21 (52.4%) (95% CI 29.8 to 74.3); 27/60 (45.0%) (95% CI 32.1 to 58.4) No change: 21/39 (53.8%) (95% CI 37.2 to 69.90; 10/21 (47.6%) (95% CI 25.7 to 70.2); 31/60 (51.7%) (95% CI 38.4 to 64.8) Worsening: 2/39 (5.1%) (95% CI 0.6 to 17.3); 0/21 (0%) (95% CI NE); 2/60 (3.3%) (95% CI 0.4 to 11.5)	Critical	Moderate
Change from baseline in hirsutism at week 48, n (%) (95% CI)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	33	15	Randomised to osilodrostat phosphate; randomised to placebo; total Improvement: 5/33 (15.2%) (95% CI 5.1 to 31.9); 3/15 (20.0%) (95% CI 4.3 to 48.1); 8/48 (16.7%) (95% CI 7.5 to 30.2) No change: 24/33 (72.7%) (95% CI 95% CI 54.5 to 86.7); 12/15 (80.0%) (95% CI 51.9 to 95.7);	Critical	Moderate

							36/48 (75.0%) (95% CI 60.4 to 86.4) Worsening: 4/33 (12.1%) (95% CI 3.4 to 28.2); 0/15 (0%) (95% CI NE); 4/48 (8.3%) (95% CI 2.3 to 20.0)		
Change from baseline in striae at week 48, n (%) (95% CI)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	38	21	Randomised to osilodrostat phosphate; randomised to placebo; total Improvement: 11/38 (28.9%) (95% CI 15.4 to 45.9); 4/21 (19.0%) (95% CI 5.4 to 41.9); 15/59 (25.4%) (95% CI 15.0 to 38.4) No change: 27/38 (71.1%) (95% CI 54.1 to 84.6); 17/21 (81.0%) (95% CI 58.1 to 94.6); 44/59 (74.6%) (95% CI 61.6 to 85.0) Worsening: 0/38 (0%) (95% CI NE); 0/21 (0%) (95% CI NE); 0/59 (0%) (95% CI NE)	Critical	Moderate
Change from baseline in supraclavicular fat pad at week 48, n (%) (95% CI)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	39	22	Randomised to osilodrostat phosphate; randomised to placebo; total Improvement: 21/39 (53.8%) (95% CI 37.2 to 69.9); 11/22 (50.0%) (95% CI 28.2 to 71.8); 32/61 (52.5%) (95% CI 39.3 to 65.4) No change: 17/39 (43.6%) (95% CI 27.8 to 60.4); 11/22 (50.0%) (95% CI 28.2 to 71.8); 28/61 (45.9%) (95% CI 33.1 to 59.2) Worsening: 1/39 (2.6%) (95% CI 0.1 to 13.5); 0/22 (0%) (95% CI NE); 1/61 (1.6%) (95% CI 0.0 to 0.8 [sic])	Critical	Moderate
Change from baseline in dorsal fat pad at week 48, n (%) (95% CI)									
1 randomised study (LINC4)	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	38	22	Randomised to osilodrostat phosphate; randomised to placebo; total	Critical	Moderate

Gadelha et al 2022							Improvement: 20/38 (52.6%) (95% CI 35.8 to 69.0); 10/22 (45.5%) (95% CI 24.4 to 67.8); 30/60 (50.0%) (95% CI 36.8 to 63.2) No change: 16/38 (42.1%) (95% CI 26.3 to 59.2); 10/22 (45.5%) (95% CI 24.4 to 67.8); 26/60 (43.3%) (95% CI 30.6 to 56.8) Worsening: 2/38 (5.3%) (95% CI 0.6 to 17.7); 2/22 (9.1%) (95% CI 1.1 to 29.2); 4/60 (6.7%) (95% CI 1.8 to 16.2)		
Change from baseline in proximal muscle atrophy at week 48, n (%) (95% CI)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	39	22	Randomised to osilodrostat phosphate; randomised to placebo; total Improvement: 10/39 (25.6%) (95% CI 13.0 to 42.1); 8/22 (36.4%) (95% CI 17.2 to 59.3); 18/61 (29.5%) (95% CI 18.5 to 42.6) No change: 25/39 (64.1%) (95% CI 47.2 to 78.8); 13/22 (59.1%) (95% CI 36.4 to 79.3); 38/61 (62.3%) (95% CI 49.0 to 74.4) Worsening: 4/39 (10.3%) (95% CI 2.9 to 24.2); 1/22 (4.5%) (95% CI 0.1 to 22.8); 5/61 (8.2%) (95% CI 2.7 to 18.1)	Critical	Moderate
Change from baseline in central obesity at week 48, n (%) (95% CI)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	39	22	Randomised to osilodrostat phosphate; randomised to placebo; total Improvement: 16/39 (41.0%) (95% CI 25.6 to 57.9); 9/22 (40.9%) (95% CI 20.7 to 63.6); 25/61 (41.0%) (95% CI 28.6 to 54.3) No change: 19/39 (48.7%) (95% CI 32.4 to 65.2); 12/22 (54.5%) (95% CI 32.2 to 75.6); 31/61 (50.8%) (95% CI 37.7 to 63.9) Worsening: 4/39 (10.3%) (95% CI 2.9 to 24.2); 1/22 (4.5%) (95% CI	Critical	Moderate

							0.1 to 22.8); 5/61 (8.2%) (95% CI 2.7 to 18.1)		
Change from baseline in ecchymosis at week 48, n (%) (95% CI)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	39	21	Randomised to osilodrostat phosphate; randomised to placebo; total Improvement: 9/39 (23.1%) (95% CI 11.1 to 39.3); 3/21 (14.3%) (95% CI 3.0 to 36.3); 12/60 (20.0%) (95% CI 10.8 to 32.3) No change: 29/39 (74.4%) (95% CI 57.9 to 87.0); 17/21 (81.0%) (95% CI 58.1 to 94.6); 46/60 (76.7%) (95% CI 64.0 to 86.6) Worsening: 1/39 (2.6%) (95% CI 0.1 to 13.5); 1/21 (4.8%) (95% CI 0.1 to 23.8); 2/60 (3.3%) (95% CI 0.4 to 11.5)	Critical	Moderate
Biochemical disease response (2 randomised studies)									
Complete response after 8 weeks of randomisation (at week 34) [A], n (%) (95% CI)									
1 randomised study (LINC3) Pivonello et al 2020 [b]	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	36	34	Randomised to osilodrostat phosphate: 31 (86.1%) (95% CI 70.5% to 95.3%) Randomised to placebo: 10 (29.4%) (95% CI 15.1% to 47.5%) OR 13.7 (95% CI 3.7 to 53.4), p<0.0001	Critical	Moderate
Complete response after 12 weeks randomisation [B], n (%)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate: 37 (77.1%) Randomised to placebo: 2 (8.0%) OR 43.4 (95% CI 7.1 to 343.2) p < 0.0001	Critical	Moderate
Response to treatment at 48 weeks (including randomisation during weeks 27-34), n (%) (95% CI)									
1 randomised study (LINC3)	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	36	35	Randomised to osilodrostat phosphate; randomised to placebo Overall response:	Critical	Moderate

Pivonello et al 2020							34 (94.4%) (95% CI 81.3% to 99.3%); 31 (88.6%) (95% CI 73.3% to 96.8%); Complete response: 32 (88.9%) (95% CI 73.9% to 96.9%); 27 (77.1%) (95% CI 59.9% to 89.6%); Partial response: 2 (5.6%) (95% CI 0.7% to 18.7%); 4 (11.4%) (95% CI 3.2% to 26.7%)		
24-hour UFC at week 12, nmol/24h, mean (SD) (value within reference range indicates benefit) [C]									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 421.4 (291.3); 451.5 (535.1) Week 12: 98.2 (122.5) 411.3 (389.9)	Critical	Low
Serum cortisol at up to 48 weeks (including randomisation during weeks 1-12), nmol/L, mean (SD), (value within reference range indicates benefit) [D]									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 565.8 (169.0); 486.1 (198.1) Week 12: 295.6 (160.4); 560.1 (204.4) Week 48: 354.0 (114.6); 353.7 (145.5)	Critical	Low
Change in serum cortisol from baseline at up to 48 weeks, nmol/L, mean (95% CI), (greater negative change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −276.0 (95% CI −330.2 to −221.7); 73.0 (95% CI −5.2 to 151.2) Week 48:	Critical	Moderate

							−210.7 (95% CI −261.5 to −159.9); −131.0 (95% CI −236.1 to −26.0)		
Early-morning salivary cortisol at up to 48 weeks (including randomisation during weeks 1-12), nmol/L, mean (SD) (value within reference range indicates benefit) [E]									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo; Baseline: 17.2 (30.0); 14.1 (12.3) Week 12: 5.8 (7.0); 14.1 (10.0) Week 48: 4.7 (2.9); 6.9 (7.7)	Critical	Low
Change in early-morning salivary cortisol from baseline at up to 48 weeks, nmol/L, mean (95% CI) (greater negative change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −11.6 (95% CI −20.5 to −2.7); −0.3 (95% CI −5.1 to 4.4) Week 48: −11.8 (95% CI −21.8 to −1.8); −6.0 (95% CI −10.8 to −1.1)	Critical	Moderate
Late-night salivary cortisol at up to 48 weeks (including randomisation during weeks 1-12), nmol/L, mean (SD), (value within reference range indicates benefit) [F]									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 11.7 (28.7); 9.0 (6.7) Week 12: 3.5 (2.3); 10.3 (6.5) Week 48: 3.5 (2.6); 4.0 (2.5)	Critical	Low
Change in late-night salivary cortisol from baseline at up to 48 weeks, nmol/L, mean (95% CI), (greater negative change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −8.5 (95% CI −17.3 to 0.3); 1.3 (95% CI −2.4 to 5.1) Week 48: −9.3 (95% CI −18.5 to −0.2); −5.0 (95% CI −7.6 to −2.5)	Critical	Moderate

Sequelae of Cushing's disease (2 RCTs)									
Weight at up to 48 weeks (including randomisation during weeks 1-12), kg, mean (SD), (lower weight indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 78.8 (17.5); 77.3 (16.9) Week 12: 78.1 (17.9); 75.7 (15.7) Week 48: 74.1 (16.6); 72.5 (17.4)	Critical	Low
Change in weight from baseline at up to 48 weeks, kg, mean (95% C), (greater negative change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable		48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −0.8 (95% CI −1.7 to 0.1); −0.1 (95% CI −1.0 to 0.8) Week 48: −3.6 (95% CI −5.7 to −1.6); −5.5 (95% CI −8.3 to −2.7)	Critical	Moderate
Waist circumference at up to 48 weeks (including randomisation during weeks 1-12), cm, mean (SD) (smaller circumference indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 102.5 (17.0); 103.4 (15.5) Week 12: 101.4 (17.7); 102.1 (15.1) Week 48: 97.3 (17.0); 97.8 (17.2)	Critical	Low
Change in waist circumference from baseline at up to 48 weeks, cm, mean (95% CI) (greater negative change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable		48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −1.0 (95% CI −2.3 to 0.3); −0.5 (95% CI −1.9 to 1.0) Week 48:	Critical	Moderate

							−4.1 (95% CI −6.0 to −2.2); −5.3 (95% CI −7.9 to −2.8)		
Systolic BP at up to 48 weeks (including randomisation during weeks 1-12), mm Hg, mean (SD) (lower BP indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 132.4 (19.2); 130.0 (17.7) Week 12: 125.5 (13.7), 127.4 (14.9) Week 48: 123.0 (15.4); 117.0 (16.2)	Critical	Low
Change in systolic BP from baseline at up to 48 weeks, mm Hg, mean (95% CI) (greater negative change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable		48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −7.1 (95% CI −12.6 to −1.6); −0.9 (95% CI −5.8 to 4.1) Week 48: −9.1 (95% CI −15.2 to −2.9); −11.0 (−20.8, −1.1)	Critical	Moderate
Diastolic BP at up to 48 weeks (including randomisation during weeks 1-12), mm Hg, mean (SD) (lower BP indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 87.2 (12.7); 88.2 (10.8) Week 12: 81.8 (10.7); 87.0 (11.2) Week 48: 81.7 (11.0); 83.5 (10.4)	Critical	Low
Change in diastolic BP from baseline at up to 48 weeks, mm Hg, mean (95% CI) (greater negative change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable		48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −4.8 (95% CI −8.2 to −1.5); −1.4 (95% CI −5.5 to 2.8) Week 48: −4.4 (95% CI −8.1 to −0.7); −3.9 (95% CI −9.8 to 2.0)	Critical	Moderate

Fasting plasma glucose at up to 48 weeks (including randomisation during weeks 1-12), mg/dl, mean (SD) (lower value indicates greater benefit) [G]									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 97.3 (18.1); 91.4 (15.2) Week 12: 92.0 (15.5); 91.1 (11.2) Week 48: 90.5 (12.9); 90.7 (13.7)	Critical	Low
Change in fasting plasma glucose from baseline at up to 48 weeks, mg/dl, mean (95% CI) (greater negative change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable		48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −4.3 (95% CI −8.9 to 0.2); −1.7 (95% CI −6.3 to 2.9) Week 48: −5.6 (95% CI −10.1 to −1.1); -1.8 (95% CI −4.5 to 8.1)	Critical	Moderate
HbA1c at up to 48 weeks (including randomisation during weeks 1-12), %, mean (SD), (lower value indicates greater benefit) [H]									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 6.0 (0.9); 5.7 (0.6) Week 12: 5.7 (0.7); 5.6 (0.6) Week 48: 5.8 (0.6); 5.7 (0.5)	Critical	Low
Change in HbA1c from baseline at up to 48 weeks, %, mean (95% CI) (greater negative change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable		48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −0.2 (95% CI −0.4 to −0.1); 0.0 (95% CI −0.2 to 0.1) Week 48: −0.2 (95% CI −0.4 to 0.0); 0.1 (95% CI −0.1 to 0.2)	Critical	Moderate
Total cholesterol at up to 48 weeks (including randomisation during weeks 1-12), mmol/L, mean (SD) (lower value indicates greater benefit) [J]									
1 randomised study (LINC4)	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo	Critical	Low

Gadelha et al 2022							Baseline: 5.7 (1.3); 5.3 (1.2) Week 12: 4.9 (1.2); 5.3 (1.3) Week 48: 5.1 (1.3); 4.9 (1.2)		
Change in total cholesterol from baseline at up to 48 weeks, mmol/L, mean (95% CI) (greater negative change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable		48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −0.8 (95% CI −1.1 to −0.5); 0.0 (95% CI −0.2 to 0.3) Week 48: −0.6 (95% CI −1.0 to −0.1); −0.4 (95% CI −0.9 to 0.1)	Critical	Moderate
LDL cholesterol at up to 48 weeks (including randomisation during weeks 1-12), mmol/L, mean (SD) (lower value indicates greater benefit) [K]									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 3.4 (1.1); 3.0 (1.1) Week 12: 3.0 (1.0); 3.1 (1.1) Week 48: 3.0 (1.0); 2.8 (1.1)	Critical	Low
Change in LDL cholesterol from baseline at up to 48 weeks, mmol/L, mean (95% CI) (greater negative change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable		48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −0.5 (95% CI −0.7 to −0.2); 0.1 (95% CI −0.1 to 0.3) Week 48: −0.5 (95% CI −0.8 to −0.2); −0.2 (95% CI −0.6 to 0.2)	Critical	Moderate
HDL cholesterol at up to 48 weeks (including randomisation during weeks 1-12), mmol/L, mean (SD) (lower valueindicates greater benefit) [L]									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 1.6 (0.4); 1.5 (0.4) Week 12: 1.3 (0.3); 1.5 (0.5) Week 48: 1.4 (0.3); 1.4 (0.4)	Critical	Low
Change in HDL cholesterol from baseline at up to 48 weeks, mmol/L, mean (95% CI) (greater negative change indicates greater benefit)									

1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable		48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −0.3 (95% CI −0.4 to −0.2); 0.0 (95% CI −0.1 to 0.1) Week 48: −0.2 (95% CI −0.3 to −0.1); −0.1 (95% CI −0.3 to 0.0)	Critical	Moderate
Triglycerides at up to 48 weeks (including randomisation during weeks 1-12), mmol/L, mean (SD) (lower value indicates greater benefit) [M]									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 1.5 (0.8); 1.7 (0.9) Week 12: 1.5 (0.8); 1.5 (0.8) Week 48: 1.5 (1.0); 1.5 (0.8)	Critical	Low
Change in triglycerides from baseline at up to 48 weeks, mmol/L, mean (95% CI) (greater negative change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: 0.0 (95% CI −0.1 to 0.2); −0.2 (95% CI −0.4 to 0.0) Week 48: 0.1 (95% CI −0.2 to 0.4); −0.2 (95% CI −0.5 to 0.0)	Critical	Moderate
BDI-II score at up to 48 weeks (including randomisation during weeks 1-12), mean (SD) (lower score indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 12.2 (10.2); 8.4 (7.8) Week 12: 10.3 (8.5); 4.7 (6.1) Week 48: 6.7 (6.7); 4.1 (7.5)	Critical	Low
Change in BDI-II score from baseline at up to 48 weeks, mean (95% CI) (greater negative change indicates greater benefit)									
1 randomised study (LINC4)	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: −1.4 (95% CI −3.7 to 1.0);	Critical	Moderate

Gadelha et al 2022							−3.9 (95% CI −6.2 to −1.6) Week 48: −4.3 (95% CI −6.7 to −2.0); −4.0 (95% CI −7.5 to −0.6)		
Time to improvement (1 RCT)									
Median time to first controlled UFC response, days (shorter time indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No indirectness	Not applicable	Not calculable	48	25	Patients randomised to osilodrostat phosphate: 35 days (95% CI 34.0 to 52.0 days) Patients randomised to placebo: not reached Patients randomised to placebo once they had crossed over to osilodrostat phosphate: 35 days	Important	Low
Quality of life (1 RCT)									
Cushing QoL score at up to 48 weeks (including randomisation during weeks 1-12), mean (SD) (higher score indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Baseline: 49.1 (19.6); 56.9 (19.0) Week 12: 56.1 (22.1);65.6 (17.6) Week 48: 62.8 (22.2); 69.9 (16.9)	Important	Low
Change in Cushing QoL score from baseline at up to 48 weeks, mean (95% CI) (greater positive change indicates greater benefit)									
1 randomised study (LINC4) Gadelha et al 2022	Serious limitations [1]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Week 12: 6.2 (95% CI 1.7 to 10.6); 8.6 (95% CI 3.5 to 13.7) Week 48: 11.7 (95% CI 6.6 to 16.7); 12.8 (95% CI 6.5 to 19.1)	Important	Low
Adverse events (2 RCTs)									
Any adverse event during the randomised treatment period, n (%)									
1 randomised study (LINC3)	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	36	35	Randomised to osilodrostat phosphate; randomised to placebo Any AE, all grades: 26 (72%); 23 (66%)	Important	Low

Pivonello et al 2020							Any AE, grades 3-4: 2 (6%); 3 (9%) Any serious AE, all grades: 2 (6%); 1 (3%) Any serious AE, grades 3-4: 1 (3%); 1 (3%) AE requiring dose adjustment, all grades: 7 (19%); 5 (14%)		
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Any AE: 46 (95.8%); 23 (92.0%) Serious AE: 2 (4.2%); 1 (4.0%) AE leading to discontinuation: 1 (2.1%); 0 Grade 1–2 AEs: 36 (75.0%) 18 (72.0%) Grade 3–4 AEs: 10 (20.8%); 5 (20.0%)	Important	Low
Most common adverse events during the randomised treatment period, n (%)									
1 randomised study (LINC3) Pivonello et al 2020	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	36	35	Randomised to osilodrostat phosphate; randomised to placebo Nausea: 4 (11%); 0 Anaemia: 3 (8%); 3 (9%) Fatigue: 2 (6%); 3 (9%)		Low
1 randomised study (LINC4) Gadelha et al 2022	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	48	25	Randomised to osilodrostat phosphate; randomised to placebo Decreased appetite: 18 (37.5%); 4 (16.0%) Arthralgia: 17 (35.4%) 2 (8.0%) Fatigue: 12 (25.0%) 4 (16.0%) Nausea: 15 (31.3%) 3 (12.0%) Hypertension: 8 (16.7%) 7 (28.0%)	Important	Low
Adverse events of special interest during the randomised treatment period, n (%)									
1 randomised study (LINC3)	Very serious limitations [2]	No serious indirectness	Not applicable	Not calculable	36	35	Randomised to osilodrostat phosphate; randomised to placebo	Important	Low

Pivonello et al 2020							Related to adrenal hormone precursor accumulation: 2 (6%); 1 (3%) Related to hypocortisolism: 3 (8%); 1 (3%) No incidences were reported of AEs related to pituitary tumour enlargement, QT interval prolongation or arrhythmogenic potential on ECG		

Abbreviations
AE: adverse event; BDI-II: Beck's Depression Inventory-II; BP: blood pressure; CI: confidence interval; HbA1c: glycated haemoglobin; HDL: high density lipoprotein; IQR: interquartile range; LDL: low density lipoprotein; MCID: minimal clinically important difference; mm Hg: millimeters of mercury; nr: not reported; QoL: quality of life; SD: standard deviation; SE: standard error; UFC: urinary free cortisol; ULN: upper limit of normal

1 Risk of bias: serious limitations as it was unclear whether the groups were similar at baseline
2 Risk of bias: very serious limitations as it was unclear whether the groups were similar at baseline and there was no statistical analysis

a In Gadelha et al 2022, in weeks 1 to 12 the osilodrostat phosphate group received osilodrostat phosphate and the placebo group received placebo, and in weeks 13 to 48 all subjects received osilodrostat phosphate
b In Pivonello et al 2020, in weeks 1 to 26 all subjects received osilodrostat phosphate, in weeks 27 to 34 the osilodrostat phosphate group received osilodrostat phosphate and the placebo group received placebo, and in weeks 35 to 48 all subjects received osilodrostat phosphate

A In Pivonello et al 2020 complete response was defined as having a mean 24-h UFC concentration ≤ULN; partial response was defined as having a mean 24-h UFC concentration >ULN but with ≥50% reduction from baseline; overall response = complete response + partial response
B In Gadelha et al 2022 complete response was defined as mean UFC≤ULN, partial response was defined as mean UFC>ULN but ≥ 50% reduction from baseline. Overall response = complete response + partial response
C Mean 24-hour UFC reference range: 11-138 nmol/24 hours
D Serum cortisol reference range, male and female, ≥18 years old: 127–567 nmol/L
E Early-morning (07:00–09:00) salivary cortisol reference range, male and female, ≥18 years old: 1.1–15.5 nmol/L
F Late-night (22:00–23:00) salivary cortisol reference range, male and female, ≥18 years old: ≤2.5 nmol/L.
G Fasting plasma glucose reference range: 70–115 mg/dL (13–49 years), 70–125 mg/dL (≥50 years)
H HbA1c reference range: ≤6.4%
J Total cholesterol reference range: 0–5.2 mmol/L (≥20 years)
K LDL cholesterol reference range: 0–3.4 mmol/L (≥20 years)
L HDL cholesterol reference range: >0.89 mmol/L
M Triglycerides reference range: 0–2.2 mmol/L

Table 4: Osilodrostat phosphate vs metyrapone

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Osilodrostat phosphate**	**Metyrapone**	**Result**		
Biochemical disease response (1 retrospective cohort study)									
Median serum cortisol level at the time of best control of hypercortisolism, nmol/L [A] (lower value indicates greater benefit)									
1 Retrospective cohort study Bonnet-Serrano et al 2022	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	25	14	Osilodrostat phosphate group: 175 (22 to 421) nmol/L Metyrapone group: 307 (68 to 547) nmol/L p = 0.025	Critical	Very low

1 Risk of bias: very serious limitations as it was unclear whether the groups were similar at baseline, six patients were included in both comparator groups and confounders were not identified or adjusted for
2 Indirectness: serious indirectness as the analysis included some patients with Cushing's syndrome

A Figures within brackets appear to be the range; this would be consistent with some other reporting in this paper but was not stated for these outcomes.

Table 5: Osilodrostat phosphate vs no comparator

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Osilodrostat phosphate**	**Comparator**	**Result**		
Clinical disease response (1 single-arm study)									
Change in physician-rated hirsutism score in females with normal testosterone levels, n (%)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	38 (12 weeks) 34 (48 weeks) 38 (72 weeks)	0	Change in hirsutism score at 12 weeks; 48 weeks; 72 weeks Improved: 9/38 (23.7%); 16/34 (47.1%); 7/38 (44.7%) Stable: 27/38 (71.1%); 13/34 (38.2%); 16/38 (42.1%)	Critical	Very low

							Worsened: 2/38 (5.3%); 5/34 (14.7%) 5/38 (13.2%)		
Change in physician-rated hirsutism score in females with raised testosterone levels, n (%)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	48 (12 weeks) 41 (48 weeks) 28 (72 weeks)	0	Change in hirsutism score at 12 weeks; 48 weeks; 72 weeks Improved: 3/48 (6.3%); 9/41 (22.0%); 6/28 (21.4%) Stable: 41/48 (85.4%); 24/41 (58.5%); 18/28 (64.3%) Worsened: 4/48 (8.3%); 8/41 (19.5%); 4/28 (14.3%)	Critical	Very low
Biochemical disease response (3 single-arm studies)									
Disease response after 10 weeks treatment [A], n (%) (95% CI)									
1 single-arm study (LINC2) Fleseriu et al 2016	Serious limitations [3]	Serious indirectness [2]	Not applicable	Not calculable	19	0	Overall response: 17 (89.5%) (95% CI 66.9% to 98.7%) Controlled: 16 (84.2%) (95% CI 60.4% to 96.6%) Partially controlled: 1 (5.3%) (95% CI 0.1% to 26.0%)	Critical	Very low
Disease response after 22 weeks treatment, n (%) (95% CI)									
1 single-arm study (LINC2) Fleseriu et al 2016	Serious limitations [3]	Serious indirectness [2]	Not applicable	Not calculable	19	0	Overall response: 15 (78.9%) (95% CI 54.4% to 94.0%) Controlled: 15 (78.9%) (95% CI 54.4% to 94.0%) Partially controlled: 0 (0%) (95% CI 0% to 17.7%)	Critical	Very low
Disease response after 24 weeks treatment [B], n (%) (95% CI)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Overall response: 113 (82.5%) (95% CI 75.1% to 88.4%) Complete response: 93 (67.9%) (95% CI 59.4% to 75.6%) Partial response: 20 (14.6%) (95% CI 9.2% to 21.6%)	Critical	Very low
Disease response after 36 weeks treatment (including randomisation during weeks 1-12) [C], n (%) (95% CI)									
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Complete response: 59 (80.8%) (95% CI 69.9% to 89.1%)	Critical	Very low

Disease response after 48 weeks treatment (including randomisation during weeks 27-34 in Pivonello et al 2020, and during weeks 1-12 in Gadelha et al 2022), n (%) (95% CI)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Overall response: 104 (75.9%) (95% CI 67.9% to 82.8%) Complete response: 91 (66.4%) (95% CI 57.9% to 74.3%) Partial response: 13 (9.5%) (95% CI 5.2% to 15.7%)	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2023	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Overall response: 58 (79.5%) Complete response: 50 (68.5%) Partial response: 8 (11.0%)	Critical	Very low
Disease response after 60 weeks treatment (including randomisation during weeks 27-34), n (%) (95% CI)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	106	0	Complete response: 86 (81.1%) (95% CI 72.4% to 88.1%)	Critical	Very low
Disease response after 70 weeks treatment, n (%)									
1 single-arm study (LINC2) Fleseriu et al 2022a	Very serious limitations [6]	Serious indirectness [2]	Not applicable	Not calculable	16	0	Overall response: 13 (81.3%) Complete response: 12 (75%) Partial response: 1 (6.3%)	Critical	Very low
Disease response after 72 weeks treatment (including randomisation during weeks 27-34 in Fleseriu et al 2022b, and during weeks 1-12 in Gadelha et al 2023), n (%)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	106	0	Complete response: 86 (81.1%) (95% CI 72.4% to 88.1%)	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2023	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	60	0	Overall response: 45/60 (75%) Complete response: 40/60 (66.7%) Partial response: 5/60 (8.3%)	Critical	Very low

Disease response up to the end of treatment (median 87.1 (range 2.0 to 126.6) weeks), n (%)									
1 single-arm study (LINC4) Gadelha et al 2023	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	58	0	Overall response: 47/58 (81%) Complete response: 42/58 (72.4%) Partial response: 5/58 (8.6%)	Critical	Very low
Disease response at last observed value (median exposure to osilodrostat phosphate 5.4 years (range 0.04 to 6.7)), n									
1 single-arm study (LINC2) Fleseriu et al 2022a	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	19	0	Complete response: 12 (63.2%) Partial response: 5 (26.3%)	Critical	Very low
Mean 24-hour UFC at 22 weeks, nmol/24h, mean (SE) (value within reference range indicates benefit) [D]									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	19	0	Baseline: 1371 (2734) 22 weeks: 92 (124)	Critical	Very low
Mean 24-hour UFC at 72 weeks, nmol/24h, mean (SE) (value within reference range indicates benefit) [D]									
1 single-arm study (LINC4) Gadelha et al 2023	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	48	0	90.5 (122.6)	Critical	Very low
Serum cortisol at 48+ weeks, nmol/L, mean (SD) (value within reference range indicates benefit) [E]									
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 538.1 (182.3) Week 48: 353.9 (124.9) Change from baseline at week 48: −182.9 (95% CI −231.5 to −134.3)	Critical	Very low
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [8]	Serious indirectness [2]	Not applicable	Not calculable	Not stated	0	Mean morning serum cortisol levels were reported to be within the normal range at week 48 and throughout the extension period (72 weeks).	Critical	Very low

1 single-arm study (LINC4) Gadelha et al 2023	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	46 to 73	0	Baseline (n=73): 538.1 (182.3) Week 48 (n=64): 353.9 (124.9) Week 72 (n=46): 319.1 (129.8)	Critical	Very low
Morning salivary cortisol at 22 weeks, nmol/L, mean (SE) (value within reference range indicates benefit) [F]									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	19 (baseline) 17 (22 weeks)	0	Baseline: 24 (41) Week 22: 5 (6)	Critical	Very low
Morning salivary cortisol at 48 weeks, nmol/L, mean (SD) (value within reference range indicates benefit) [F]									
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 16.1 (25.3) Week 48: 5.4 (5.2) Change from baseline at week 48: −9.8 (95% CI −16.4 to −3.1)	Critical	Very low
Late night salivary cortisol at 48+ weeks, nmol/L, mean (SD) (value within reference range indicates benefit) [G]									
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 10.8 (23.5) Week 48: 3.7 (2.6) Change from baseline at week 48: −7.8 (95% CI −13.8 to −1.9)	Critical	Very low
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [8]	Serious indirectness [2]	Not applicable	Not calculable	Not stated	0	Week 48: mean LNSC 2.7 (SD 1.6) nmol/L During extension (72 weeks): LNSC remained consistently lower than baseline but above the reference range	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2023	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	46 to 73	0	Baseline (n=73): 10.8 (23.5) Week 48 (n=63): 3.7 (2.6) Week 72 (n=46): 3.8 (3.0)	Critical	Very low

Sequelae of Cushing's disease (3 single-arm studies)									
Weight at 22 weeks, kg, mean (SD), change from baseline, mean (SD) (lower weight and greater negative change indicate greater benefit)									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	Baseline n=19 Week 22 n=17	0	Baseline: 85.1 (24.0) Week 22: 85.6 (26.2) Change from baseline: –1.5 (3.8)	Critical	Very low
Weight at 48 weeks, kg, mean (SD), change from baseline, mean (95% CI) (lower weight and greater negative change indicate greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Baseline: 80.8 (22.4) Week 48: 75.5 (20.7) Change from baseline: -3.8 (95% CI -4.8 to -2.7)	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 78.3 (17.2) Week 48: 73.5 (16.8) Change from baseline: −4.3 (95% CI −5.9 to −2.6)	Critical	Very low
Change in weight from baseline at 72 weeks, kg, mean (SD) (greater negative change indicates greater benefit)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Baseline: n=137 Week 72: n=106	0	Week 72: −4.7 (6.6)	Critical	Very low
Body mass index at 22 weeks, kg/m^2, mean (SD), change from baseline, mean (SD) (lower BMI and greater negative change indicate greater benefit)									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	Baseline n=19 Week 22 n=17	0	Baseline: 30.7 (7.0) Week 22: 30.1 (7.9) Change from baseline: –0.5 (1.4)	Critical	Very low
Body mass index at 48 weeks, kg/m^2, mean (SD), change from baseline, mean (95% CI) (lower BMI and greater negative change indicate greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Baseline: 30.3 (7.8) Week 48: 28.4 (7.1) Change from baseline: -1.4 (95% CI -1.8 to 1.0)	Critical	Very low

Change in body mass index from baseline at 72 weeks, kg/m^2, mean (SD), mean (SD) (greater negative change indicates greater benefit)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Baseline: n=137 Week 72: n=106	0	Week 72: −1.8 (2.5)	Critical	Very low
Waist circumference at 48 weeks, cm, mean (SD), change from baseline, mean (95% CI) (smaller circumference and greater negative change indicate greater benefit)									
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 102.8 (16.4) Week 48: 97.5 (16.9) Change from baseline: −4.5 (95% CI −6.0 to −3.0)	Critical	Very low
Change in waist circumference from baseline at 72 weeks, cm, mean (SD) (greater negative change indicates greater benefit)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Baseline: n=137 Week 72: n=106	0	−6.2 (8.5)	Critical	Very low
Systolic BP at 22 weeks, mm Hg, mean (SD), change from baseline, mean (SD) (lower BP and greater negative change indicate greater benefit)									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	Baseline n=19 Week 22 n=17	0	Baseline: 132.6 (11.6) Week 22: 131.9 (17.8) Change from baseline: –1.0 (16.2)	Critical	Very low
Systolic BP at 48 weeks, mm Hg, mean (SD), change from baseline, mean (95% CI) (lower BP and greater negative change indicate greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Baseline: 132.2 (15.1) Week 48: 121.7 (13.7) Change from baseline: -9.8 (95% CI -12.7 to -6.9)	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 131.5 (18.6) Week 48: 120.9 (15.8) Change from baseline: −9.7 (95% CI −14.9 to −4.6)	Critical	Very low

Change in systolic BP from baseline at 72 weeks, mm Hg, mean (SD) (greater negative change indicates greater benefit)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Baseline: n=137 Week 72: n=106	0	−10.1 (18.1)	Critical	Very low
Diastolic BP at 22 weeks, mm Hg, mean (SD), change from baseline, mean (SD) (lower BP and greater negative change indicate greater benefit)									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	Baseline n=19 Week 22 n=17	0	Baseline: 85.1 (6.5) Week 22: 86.0 (8.9) Change from baseline: 1.3 (9.7)	Critical	Very low
Diastolic BP at 48 weeks, mm Hg, mean (SD), change from baseline, mean (95% CI), (lower BP and greater negative change indicate greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Baseline: 85.3 (10.6) Week 48: 78.9 (10.1) Change from baseline: -6.3 (95% CI -8.4 to -4.2)	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 87.5 (12.0) Week 48: 82.3 (10.8) Change from baseline: −4.2 (95% CI −7.3 to −1.2)	Critical	Very low
Change in diastolic BP from baseline at 72 weeks, mm Hg, mean (SD) (greater negative change indicates greater benefit)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Baseline: n=137 Week 72: n=106	0	−5.8 (11.3)	Critical	Very low
Fasting plasma glucose [H] at 22 weeks, mg/dl, mean (SD), change from baseline, mean (SD) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	Baseline n=19 Week 22 n=17	0	Baseline: 105.6 (49.0) Week 22: 81.2 (9.0) Change from baseline: –14.9 (28.9)	Critical	Very low

Fasting plasma glucose [J] at 48 weeks, mg/dl, mean (SD), change from baseline, mean (95% CI) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Baseline: 99.2 (29.8) Week 48: 87.2 (18.9) Change from baseline: -9.5 (95% CI -14.3 to -4.8)	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 95.3 (17.3) Week 48: 90.6 (13.1) Change from baseline: −3.1 (95% CI −6.8 to 0.6)	Critical	Very low
Change in fasting plasma glucose[K] from baseline at 72 weeks, mmol/L, mean (SD) (greater negative change indicates greater benefit)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Baseline: n=137 Week 72: n=106	0	−0.3 (1.1)	Critical	Very low
Hb A1c [L] at 22 weeks, %, mean (SD), change from baseline, mean (SD) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	Baseline n=19 Week 22 n=17	0	Baseline: 5.7 (0.7) Week 22: 5.5 (0.6) Change from baseline: –0.2 (0.3)	Critical	Very low
Hb A1c [L] at 48 weeks, %, mean (SD), change from baseline, mean (95% CI) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Baseline: 6.0 (1.0) Week 48: 5.6 (0.8) Change from baseline: -0.4 (95% CI -0.5 to -0.2)	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 5.9 (0.8) Week 48: 5.7 (0.5) Change from baseline: −0.1 (95% CI −0.2 to 0.0	Critical	Very low

Change in Hb A1c from baseline at 72 weeks, %, mean (SD), (greater negative change indicates greater benefit)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Baseline: n=137 Week 72: n=106	0	−0.4 (0.6)	Critical	Very low
Total cholesterol at 22 weeks [M], mmol/L, mean (SD), change from baseline, mean (SD) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	Baseline n=19 Week 22 n=17	0	Baseline: 5.3 (1.4) Week 22: 4.6 (0.8) Change from baseline: –0.7 (1.4)	Critical	Very low
Total cholesterol at 48 weeks [N], mmol/L, mean (SD), change from baseline, mean (95% CI) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Baseline: 5.3 (1.2) Week 48: 4.8 (1.0) Change from baseline: -0.5 (95% CI -0.7 to -0.3)	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 5.5 (1.3) Week 48: 5.0 (1.3) Change from baseline: −0.5 (95% CI −0.8 to −0.2)	Critical	Very low
Change in total cholesterol from baseline at 72 weeks, mmol/L, mean (SD) (greater negative change indicates greater benefit)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Baseline: n=137 Week 72: n=106	0	−0.4 (0.9)	Critical	Very low
HDL-cholesterol at 22 weeks [P], mmol/L, mean (SD), change from baseline, mean (SD) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	Baseline n=19 Week 22 n=17	0	Baseline: 1.7 (0.9) Week 22: 1.3 (0.4) Change from baseline: –0.5 (0.8)	Critical	Very low

HDL-cholesterol at 48 weeks [Q], mmol/L, mean (SD), change from baseline, mean (95% CI) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Baseline: 1.6 (0.5) Week 48: 1.3 (0.3) Change from baseline: -0.3 (95% CI -0.3 to -0.2)	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 1.6 (0.4) Week 48: 1.4 (0.4) Change from baseline: −0.2 (95% CI −0.3 to −0.1)	Critical	Very low
LDL-cholesterol at 22 weeks [R], mmol/L, mean (SD), change from baseline, mean (SD) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	Baseline n=19 Week 22 n=17	0	Baseline: 3.3 (1.7) Week 22: 2.8 (0.6) Change from baseline: –0.6 (1.6)	Critical	Very low
LDL-cholesterol at 48 weeks [S], mmol/L, mean (SD), change from baseline, mean (95% CI) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Baseline: 3.0 (1.0) Week 48: 2.8 (1.0) Change from baseline: -0.2 (95% CI -0.4 to -0.1)	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 3.3 (1.1) Week 48: 2.9 (1.1) Change from baseline: −0.4 (95% CI −0.6 to −0.1)	Critical	Very low
Triglycerides at 22 weeks [T], mmol/L, mean (SD), change from baseline, mean (SD) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	Baseline n=19 Week 22 n=17	0	Baseline: 1.5 (0.6) Week 22: 1.3 (0.6) Change from baseline: 0 (0.4)	Critical	Very low

Triglycerides at 48 weeks [U], mmol/L, mean (SD), change from baseline, mean (95% CI) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Baseline: 1.5 (1.3) Week 48: 1.4 (0.9) Change from baseline: -0.1 (95% CI -0.2 to 0.1)	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 1.6 (0.8) Week 48: 1.5 (0.9) Change from baseline: 0.0 (95% CI −0.2 to 0.2)	Critical	Very low
Change in triglycerides from baseline at 72 weeks, mmol/L, mean (SD) (greater negative change indicates greater benefit)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Baseline: n=137 Week 72: n=106	0	−0.1 (0.6)	Critical	Very low
BDI-II score at 48 weeks, mean (SD), change from baseline, mean (95% CI) (lower value and greater negative change indicate greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Baseline: 16.8 (10.6) Week 48:10.7 (10.7) Change from baseline: -5.8 (95% CI -7.6 to -4.1) Mean % change from baseline: -31.8% (95% CI -44.3% to -19.3%)	Critical	Very low
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 10.9 (9.6) Week 48: 5.8 (7.0) Change from baseline: −4.2 (95% CI −6.1 to −2.3)	Critical	Very low
Change in BDI-II score from baseline at 72 weeks, mean (SD) (greater negative change indicates greater benefit)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Baseline: n=137 Week 72: n=106	0	−6.7 (10.7)	Critical	Very low

BDI-II score up to the end of treatment (median 87.1 (range 2.0 to 126.6) weeks), mean (SD), change from baseline, mean (SD) (lower score and greater negative change indicate greater benefit)									
1 single-arm study (LINC4) Gadelha et al 2023	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Week 72: n=48 End of treatment: n=13	0	Week 72: 6.5 (7.0) Change from baseline: −4.1 (9.3) End of treatment: 6.2 (7.1) Change from baseline: −4.5 (7.9)	Critical	Very low
Reduction in treatment for Cushing's disease sequelae (1 single-arm study)									
Change in use of hypertensive medications from baseline to week 48, n (%) (reduction in use indicates greater benefit)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	85	0	Increase in dose or number of medications: 34/85 (40%) Decrease in dose or stopped medication: 34/85 (40%)	Important	Very low
Change in use of diabetic medications from baseline to week 48, n (%) (reduction in use indicates greater benefit)									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	43	0	Increase in dose or number of medications: 10/43 (23%) Decrease in dose or stopped medication: 21/43 (49%)	Important	Very low
Quality of life (3 single-arm studies)									
Cushing quality of life score at 48 weeks, (mean (SD), change from baseline, mean (95% CI) (higher score and greater positive change indicate greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	137	0	Baseline: 42.2 (19.1) Week 48: 58.3 (21.3) Change from baseline: 14.1 (95% CI 10.9 to 17.3)	Important	Very low
1 single-arm study (LINC4) Gadelha et al 2022	Serious limitations [4]	Serious indirectness [2]	Not applicable	Not calculable	73	0	Baseline: 51.8 (19.6) Week 48: 65.3 (20.7) Change from baseline: 12.0 (95% CI 8.2 to 15.9)	Important	Very low
Cushing quality of life score change from baseline at 72 weeks, mean (SD) (greater positive change indicates greater benefit)									
1 single-arm study (LINC3)	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Baseline: n=137 Week 72: n=106	0	Baseline: 42.2 (19.1) Change from baseline at week 72: 15.1 (19.4)	Important	Very low

Fleseriu et al 2022b									
Cushing quality of life score up to the end of treatment (median 87.1 (range 2.0 to 126.6) weeks), mean (SD), change from baseline, mean (SD) (higher score and greater positive change indicate greater benefit)									
1 single-arm study (LINC4) Gadelha et al 2023	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	Week 72: n=48 End of treatment: n=13	0	Week 72: 66.4 (19.6) Change from baseline at week 72: 15.2 (19.0) End of treatment: 69.0 (20.9) Change from baseline at end of treatment: 17.1 (17.1)	Important	Very low
Time to improvement in mean UFC levels (nmol/24h), weeks (shorter time indicates greater benefit)									
1 single-arm study (LINC2) Fleseriu et al 2016	Very serious limitations [9]	Serious indirectness [2]	Not applicable	Not calculable	19	0	Baseline: mean 1371 (SE 2734) Week 4: mean within the normal range (details at week 4 not reported).	Important	Very low
Time to improvement, days, median (IQR) time to first complete response (shorter time indicates greater benefit)									
1 single-arm study (LINC3) Pivonello et al 2020	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	137	0	41.0 days (IQR 27.0 to 56.0).	Important	Very low
Safety (3 single-arm studies)									
Most common adverse events, n (%) after up to 22 weeks treatment									
1 single-arm study (LINC2) Fleseriu et al 2016 [a]	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	19	0	*All grades; Grade 3/4* Nausea: 6 (31.6%); 0 Diarrhoea: 6 (31.6%); 0 Asthenia: 6 (31.6%); 0 Adrenal insufficiency: 6 (31.6%); 1 (5.3%) Nasopharyngitis: 5 (26.3%); 0 Testosterone increased: 5 (26.3%); 1 (5.3%) Adrenal precursors increased: 7 (36.8); 0 ACTH increased: 6 (31.6%); 0	Important	Very low
Most common adverse events, n (%) after up to 48 weeks treatment									
1 single-arm study (LINC3)	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	137	0	*All grades; Grade 3/4* Nausea: 57 (41.6%); 3 (2.2%) Headache: 46 (33.6%); 4 (2.9%)	**Important**	**Very low**

Pivonello et al 2020							Fatigue: 39 (28.5%); 3 (2.2%) Adrenal insufficiency: 38 (27.7%); 6 (4.4%) Nasopharyngitis: 31 (22.6%); 1 (0.7%) Vomiting: 30 (21.9%) 4 (2.9%)		
1 single-arm study (LINC4) Gadelha et al 2022	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	73 [U]	0	Decreased appetite: 33 (45.2%) Arthralgia: 33 (45.2%) Fatigue: 28 (38.4%) Nausea: 27 (37.0%) Headache: 24 (32.9%) Myalgia: 19 (26.0%) Dizziness: 19 (26.0%) Adrenal insufficiency: 18 (24.7%) Increased blood testosterone: 18 (24.7%) Diarrhoea: 17 (23.3%) Hypertension: 16 (21.9%) Asthenia: 15 (20.5%) Upper respiratory tract infection: 15 (20.5%)	Important	Very low
Most common adverse events, n, after up to 70 weeks treatment									
1 single-arm study (LINC2) Fleseriu et al 2022a	Very serious limitations [6]	Serious indirectness [2]	Not applicable	Not calculable	16	0	*All grades; Grade ≥3* Adrenal insufficiency: 7; 1 Arthralgia: 6; 0 Headache: 6; 1 Diarrhoea: 5; 0 Abdominal pain: 4; 1 Hypertension: 3; 3 Lipase increased: 3; 1 Pituitary-dependent Cushing's syndrome: 2; 1 Gastroenteritis: 2; 1 Non-cardiac chest pain: 2; 1 Weight decreased: 2; 1	Important	Very low
Most common adverse events, n (%) after up to 72 weeks treatment									
1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	137	0	*All grades; grade 3-4* Nausea: 62 (45.3%); 3 (2.2%) Headache: 50 (36.5%); 6 (4.4%) Fatigue: 45 (32.8%); 3 (2.2%) Adrenal insufficiency: 40 (29.2%); 6 (4.4%) Vomiting: 34 (24.8%); 5 (3.6%) Nasopharyngitis: 33 (24.1%); 1 (0.7%)	Important	Very low

							Glucocorticoid deficiency: 28 (20.4%); 5 (3.6%) [b] Hypertension: 24 (17.5%); 16 (11.7%)		
Most common adverse events, n (%) after median 87.1 weeks exposure to osilodrostat phosphate									
1 single-arm study (LINC4) Gadelha et al 2023	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	73	0	*All grades; grade 3-4* Decreased appetite: 34 (46.6%); 1 (1.4%) Arthralgia: 33 (45.2%); 2 (2.7%) Fatigue: 29 (39.7%); 3 (4.1%) Nausea: 27 (37.0%); 1 (1.4%) Headache: 25 (34.2%); 1 (1.4%) Dizziness: 22 (30.1%); 0 Adrenal insufficiency: 19 (26.0%); 3 (4.1%) Increased blood testosterone: 18 (24.7%); 0 Myalgia: 18 (24.7%); 5 (6.8%) Asthenia: 17 (23.3%); 2 (2.7%) Diarrhoea: 17 (23.3%); 0 Hypertension: 16 (21.9%); 9 (12.3%) Upper respiratory tract infection: 16 (21.9%); 0	Important	Very low
Any adverse event (2 single-arm studies)									
Any adverse event, n (%) after up to 48 weeks treatment									
1 single-arm study (LINC3) Pivonello et al 2020	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	137	0	*All grades; grade 3-4* Any AE: 137 (100%); 78 (56.9%) Any serious AE: 50 (36.5%); 39 (28.5%) AEs requiring dose interruption and/or change: 106 (77.4%); 39 (28.5%) Death: 1 (0.7%); 1 (0.7%)	Important	Very low
1 single-arm study (LINC4) Gadelha et al 2022	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	73 [U]	0	Any AE: 73 (100%) Serious AE: 8 (11.0%) AE leading to discontinuation: 8 (11.0%) Grade 1–2 AE: 45 (61.6%) Grade 3–4 AE: 28 (38.4%)	Important	Very low
Any adverse event, n (%) after up to 72 weeks treatment									

1 single-arm study (LINC3) Fleseriu et al 2022b	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	137	0	*All grades; grade 3-4* Any AE: 137 (100%); 83 (60.6%) AEs leading to discontinuation: 25 (18.2%); 17 (12.4%) AEs requiring dose adjustment/ interruption: 110 (80.3%); 42 (30.7%) AEs requiring additional therapy: 132 (96.4%); 61 (44.5%)	Important	Very low
Any adverse event, n (%) after median 87.1 weeks exposure to osilodrostat phosphate									
1 single-arm study (LINC4) Gadelha et al 2023	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	73	0	*All grades; grade 3-4* Any AE: 72 (98.6%); 29 (39.7%) Serious AE: 10 (13.7%); 9 (12.3%) ≥1 AE leading to discontinuation: 9 (12.3%); 2 (2.7%) ≥1 AE leading to dose adjustment/interruption: 42 (57.5%); 13 (17.8%) ≥1 AE requiring additional therapy: 67 (91.8%); 22 (30.1%)	Important	Very low
Adverse events of special interest (3 single-arm studies)									
Adverse events of special interest, n (%) after up to 48 weeks treatment									
1 single-arm study (LINC3) Pivonello et al 2020	Very serious limitations [5]	Serious indirectness [2]	Not applicable	Not calculable	137	0	*All grades; Grade 3-4* Adrenal hormone precursor accumulation related: 58 (42.3%); 22 (16.1%) Hypocortisolism related: 70 (51.1%); 14 (10.2%) Pituitary tumour enlargement related: 3 (2.2%); 0 QT prolongation related: 5 (3.6%); 1 (0.7%) Arrhythmogenic potential: 1 (0.7%); 1 (0.7%)	Important	Very low
Adverse events of special interest, n (%) after median 87.1 weeks exposure to osilodrostat phosphate									
1 single-arm study (LINC4) Gadelha et al 2023	Very serious limitations [1]	Serious indirectness [2]	Not applicable	Not calculable	weeks 1-12: n=48 weeks 12-24: n=71 weeks 24-36: n=69 weeks 36-48: n=68	0	Weeks 1-12; weeks 12-24; weeks 24-36; weeks 36-48; weeks 48-60; weeks 60 onwards AEs related to hypocortisolism: 14.6%; 12.7%; 7.2%; 5.9%; 0; 8.5%	Important	Very low

					weeks 48-60: n=64 weeks 60 onwards: n=59		AEs related to arrhythmogenic potential and QT prolongation 0; 1.4%; 1.4%; 1.5%; 0; 0		
Adverse events of special interest, n, after median 5.4 years exposure to osilodrostat phosphate									
1 single-arm study (LINC2) Fleseriu et al 2022a [a]	Very serious limitations [7]	Serious indirectness [2]	Not applicable	Not calculable	19	0	*All grades; Grade 3-4* Related to accumulation of adrenal hormone precursors: 12; 4 Related to hypocortisolism: 11; 2 Related to arrhythmogenic potential: 1; 0 Related to QT prolongation: 1; 0	Important	Very low

Abbreviations

AE: adverse event; BDI-II: Beck's Depression Inventory-II; BP: blood pressure; CI: confidence interval; HbA1c: glycated haemoglobin; HDL: high density lipoprotein; IQR: interquartile range; LDL: low density lipoprotein; MCID - minimal clinically important difference; mm Hg: millimeters of mercury; nr: not reported; QoL: quality of life; SD: Standard deviation; SE: standard error; UFC: urinary free cortisol; ULN: upper limit of normal.

1 Risk of bias: very serious limitations as it was unclear whether recruitment of study subjects was consecutive or complete, there was no reporting of clinical or demographic information for the included subjects and there were no statistical analyses
2 Indirectness: serious indirectness due to lack of comparator group
3 Risk of bias: serious limitations as recruitment of study subjects was not consecutive or complete
4 Risk of bias: serious limitations as it was unclear whether recruitment of study subjects was consecutive or complete
5 Risk of bias: very serious limitations as it was unclear whether recruitment of study subjects was consecutive or complete and there were no statistical analyses
6 Risk of bias: very serious limitations as recruitment of study subjects was not consecutive or complete, there was no reporting of clinical or demographic information for the included subjects and there were no statistical analyses
7 Risk of bias: very serious limitations as recruitment of study subjects was not consecutive or complete and there were no statistical analyses
8 Risk of bias: very serious limitations as it was unclear whether recruitment of study subjects was consecutive or complete, the number of subjects included in the outcome was not reported and there were no statistical analyses
9 Risk of bias: very serious limitations as recruitment of subjects was not consecutive or complete, there were no statistical analyses and the outcome was not clearly defined

a AEs were defined using terminology in the Medical Dictionary for Regulatory Activities (MedDRA; version 13.1), and severity was graded according to the National Cancer Institute Common Toxicity Criteria version 4.03.
b Glucocorticoid deficiency includes 'hypocortisolism', 'symptoms of hypocortisolism', 'relative hypocortisolism', 'suspicion of hypocortisolism', 'asymptomatic/symptomatic hypocortisolism', and 'subjective symptoms of hypocortisolism'.

A In Fleseriu et al 2016 and Fleseriu et al 2022a, controlled defined as mean UFC ≤ ULN; partially controlled defined as mean UFC > ULN and with ≥50% reduction from baseline; uncontrolled defined as mean UFC>ULN and with <50 % reduction from baseline. Overall response was calculated as the sum of controlled and partially controlled patients.
B In Pivonello et al 2020 and Fleseriu et al 2022b, complete response was defined as having a mean 24-h UFC concentration ≤ULN; partial response was defined as having a mean 24-h UFC concentration >ULN but with ≥50% reduction from baseline. Overall response = complete response + partial response
C In Gadelha et al 2022 and Gadelha et al 2023, complete response was defined as having a mean 24-h UFC concentration ≤ULN; partial response was defined as having a mean 24-h UFC concentration >ULN but with ≥50% reduction from baseline. Overall response = complete response + partial response

D Mean 24-hour UFC reference range: 11-138 nmol/24 hours. Mean calculated as the mean of 2 or 3 samples
E Serum cortisol reference range, male and female, ≥18 years old: 127–567 nmol/L
F Morning salivary cortisol reference range: 1.1–15.5 nmol/L
G Late-night (22:00–23:00) salivary cortisol reference range, male and female, ≥18 years old: ≤2.5 nmol/L
H Fasting plasma glucose reference range: 70 to 110 mg/dl (Fleseriu et al 2016)
J Fasting plasma glucose reference range: 70 to 125 mg/dl (Pivonello et al 2020); 70-115 mg/dl (Gadelha et al 2022)
K Fasting plasma glucose normal range: 3.9–5.5 mmol/L
L HbA1c reference range: ≤6.4%
M Total cholesterol reference range: 3.9-6.5 mmol/L (Fleseriu et al 2016)
N Total cholesterol reference range: 0-5.2 mmol/L (Pivonello et al 2020 and Gadelha et al 2022)
P HDL cholesterol reference range: 1-1.7 mmol/L (Fleseriu et al 2016)
Q HDL cholesterol reference range: >0.89 mmol/ L (Pivonello et al 2020 and Gadelha et al 2022)
R LDL cholesterol reference range: 0-4.2 mmol/L(Fleseriu et al 2016)
S LDL cholesterol reference range: 0-3.4 mmol/L (Pivonello et al 2020 and Gadelha et al 2022)
T Triglycerides reference range: 0.6-1.7 mmol/L (Fleseriu et al 2016)
U Triglycerides reference range: 0-2.2 mmol/L (Pivonello et al 2020 and Gadelha et al 2022)

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Comparator	The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care).
Cost effectiveness analysis	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully adhered to the treatment or switched to an alternative treatment. ITT analyses are often used to assess clinical effectiveness because they mirror actual practice, when not everyone adheres to the treatment, and the treatment people have may be changed according to how their condition responds to it. Studies of drug treatments often use a modified ITT analysis, which includes only the people who have taken at least one dose of a study drug.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Odds ratio	Compares the odds of something happening in 1 group with the odds of it happening in another. An odds ratio of 1 shows that the odds of the event happening (for example, a person developing a disease or a treatment working) is the same for both groups. An odds ratio of greater than 1 means that the event is more likely in the first group than the second. An odds ratio
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.

Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Single-arm trial	A clinical trial in which all participants receive the experimental intervention of interest. This is especially common in phase I and II trials.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

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