NHS England Evidence Review:

Osilodrostat phosphate for the treatment of people with endogenous Cushing's syndrome (excluding people with Cushing's disease) requiring pharmacological treatment

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1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of osilodrostat phosphate in people with endogenous Cushing's syndrome (excluding 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 secondary 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. Osilodrostat phosphate for the treatment of people with Cushing's disease requiring pharmacological treatment is 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 syndrome (excluding those with Cushing's disease). Osilodrostat phosphate for the treatment of Cushing's disease is considered in a separate evidence review.

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 ongoing 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 syndrome (excluding people with 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 16 full text papers were obtained and assessed for relevance. Papers relating to osilodrostat phosphate for the treatment of Cushing's disease are included in a separate evidence review.

Four papers were identified for inclusion in this review on Cushing's syndrome; one retrospective cohort study (Detomas et al 2022), one prospective single-arm study that was treated as a case series due to data being mainly described on an individual basis (Tanaka et al 2020), and two retrospective case series (Dormoy et al 2023, Tabarin et al 2022). The retrospective cohort study (Detomas et al 2022) evaluated osilodrostat phosphate (n=8) and metyrapone (n=8) in patients with endogenous Cushing's syndrome, including patients with Cushing's disease. Although patients with Cushing's disease were out of scope for this evidence review (and outcomes were not reported separately for in scope patients with Cushing's syndrome [excluding those with Cushing's disease]), the study was included in this evidence review because a greater proportion of patients had Cushing's syndrome (i.e. 56.25% with Cushing's syndrome [excluding Cushing's disease] compared to 43.75% with Cushing's disease). Outcomes were reported up to 12 weeks after treatment with osilodrostat phosphate and metyrapone.

The prospective single-arm study (Tanaka et al 2020) and two retrospective case series (Dormoy et al 2023, Tabarin et al 2022) provided non-comparative evidence (sample sizes ranged from seven to 33) in patients with different subtypes of Cushing's syndrome (including endogenous Cushing's syndrome other than Cushing's disease, paraneoplastic Cushing's syndrome/ectopic adrenocorticotropin syndrome [PNCS/EAS], or Cushing's syndrome due to adrenocortical carcinomas [ACC]). The prospective single-arm study reported outcomes up to 48 weeks after treatment with osilodrostat, the two retrospective case series did not clearly report follow-up timepoints.

Two of the included studies were conducted in France, one in Germany, and one in Japan. No evidence was identified comparing osilodrostat phosphate versus no adrenal steroidogenesis inhibitors or ketoconazole. No evidence relating to cost effectiveness was identified.

In terms of clinical effectiveness:

- **Clinical disease response (critical outcome)**
  - Osilodrostat phosphate vs metyrapone
    No evidence was identified.
  - Osilodrostat phosphate vs no comparator
    Two retrospective case series provided very low certainty evidence of an improvement in clinical signs of Cushing's syndrome at unspecified durations of follow-up after treatment with osilodrostat phosphate. One of these studies reported a reduction from baseline to an unspecified follow-up duration as measured using an arbitrary clinical score; the difference was statistically significant. The second study reported improvements in Cushing's clinical scores in five of seven patients after treatment with osilodrostat phosphate, but the follow-up duration and statistical measures were not reported.

- **Biochemical disease response (critical outcome)**
  - Osilodrostat phosphate vs metyrapone

    One retrospective cohort study provided very low certainty evidence relating to biochemical disease response. This study showed that although the change in mean urinary free cortisol (UFC) levels and serum cortisol levels compared to baseline were greater after treatment with osilodrostat phosphate than treatment with metyrapone at two and four weeks follow-up, the differences were not statistically significant. By contrast, at 12 weeks follow-up, the change in mean UFC levels and serum cortisol levels compared to baseline were greater after treatment with metyrapone than treatment with osilodrostat phosphate, although the differences were not statistically significant. There was no between group difference for osilodrostat phosphate and metyrapone in the proportion of patients who had a serum cortisol level below 25 µg/dl (normal range 0 to 70 µg/dl); statistical measures were not reported. The same study reported that a greater proportion of patients treated with metyrapone had a normalised UFC level than patients treated with osilodrostat phosphate (66.7% versus 50%, respectively) after 12 weeks, but no statistical measures were reported.

  - Osilodrostat phosphate vs no comparator

    One prospective single-arm study and two retrospective case series provided very low certainty evidence that serum cortisol levels improved after treatment with osilodrostat phosphate at different follow-up timepoints compared to baseline. The two retrospective case series reported the improvements were statistically significant at an unspecified follow-up and at two weeks follow-up. Although the prospective single-arm study also indicated that there were improvements in serum cortisol level from baseline to 12, 24 and 48 weeks follow-up, statistical measures were not reported. One retrospective case series reported a statistically significant improvement in mean UFC levels after treatment with osilodrostat phosphate, but the follow-up duration was not reported. The prospective single-arm study reported a consistent reduction (improvement) in mean UFC levels from baseline at all timepoints from 4 to 48 weeks follow-up. The same study reported that overall response rate was high at week 12 (77.8%), and this was maintained at weeks 24 and 48, but statistical measures were not reported for these outcomes. One retrospective case series reported statistically significant reductions in 24-hour UFC levels compared to baseline regardless of treatment strategy with osilodrostat phosphate (i.e. first-line monotherapy, second-line monotherapy, combination treatment). The same retrospective case series also reported high proportions (67% to 100%) of patients achieving normalisation of 24-hour UFC levels regardless of treatment strategy.

- **Sequelae of Cushing's syndrome (critical outcome)**
  - Osilodrostat phosphate vs metyrapone

    One retrospective cohort study provided very low certainty evidence that there were no statistically significant reductions in **systolic or diastolic blood pressure** from baseline to two weeks follow-up in patients treated with osilodrostat phosphate and patients treated with metyrapone.

  - Osilodrostat phosphate vs no comparator

    One retrospective cohort study, one prospective single-arm study and two retrospective case series provided very low certainty evidence regarding sequelae of Cushing's syndrome. Two retrospective case series reported statistically significant reductions in **systolic blood pressure** after treatment with osilodrostat phosphate compared to baseline, but the follow-up duration was not reported. One of these studies also reported a statistically significant reduction in **diastolic blood pressure** after treatment with osilodrostat phosphate compared to baseline, but the follow-up duration was not reported; it was not clear why diastolic blood pressure was not reported in the other

study. The prospective single-arm study reported *"marginal improvements*" in **systolic and diastolic blood pressure** for most patients after treatment with osilodrostat phosphate, but statistical measures and the follow-up duration were not reported.

One retrospective case series reported that the three patients with **myopathy** prior to treatment with osilodrostat phosphate were able to ambulate and move around independently six months after treatment with osilodrostat phosphate, but statistical measures were not reported. The same study also reported improvements in patients with **hypokalaemia** after treatment with osilodrostat phosphate, but the follow-up duration and statistical measures were not reported. One retrospective case series reported statistically significant reductions in **fasting blood glucose levels** after treatment with osilodrostat phosphate, but the follow-up duration was not reported. One prospective single-arm study reported that *"marginal improvements"* were observed in **fasting blood glucose levels** at 12 weeks after treatment with osilodrostat phosphate , but no further details were reported.

One retrospective case series reported a statistically significant reduction in **HbA1c** compared to baseline after treatment with osilodrostat phosphate, but the follow-up duration was not reported. One prospective single-arm study reported that *"marginal improvements"* were observed in **HbA1c** at 12 weeks after treatment with osilodrostat phosphate, but no further details were reported. One retrospective case series reported that three patients had **diabetes mellitus** and two patients had **glucose intolerance** at baseline, which were no longer evident after treatment with osilodrostat phosphate. No statistical measures were reported and the follow-up duration was not stated.

One retrospective case series reported a statistically significant reduction in **BMI** compared to baseline after treatment with osilodrostat phosphate. One prospective single-arm study reported that only two of seven patients showed a reduction in **BMI** at 12 weeks after treatment with osilodrostat phosphate, but no statistical measures were reported.

One prospective single-arm study reported that *"marginal improvements"* were observed for most patients after 12 weeks treatment with osilodrostat phosphate in **waist circumference**, **total cholesterol**, **high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol** and **triglycerides**, but further details were not reported.

One prospective single-arm study reported that *"no clinically relevant differences"* were observed in the **Becks Depression Inventory-II** at 12 weeks after treatment with osilodrostat phosphate, but no further details were provided.

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

    One retrospective cohort study provided very low certainty evidence of a reduction in the mean number of antihypertensives required at two weeks after treatment with osilodrostat phosphate compared to baseline whilst the requirement for antihypertensive drugs remained comparable at two weeks after treatment with metyrapone compared to baseline (-1.0 and -0.3, respectively).

  - Osilodrostat phosphate vs no comparator

    Two retrospective case series provided very low certainty evidence of a reduction in the number of antihypertensive drugs required by patients after treatment with osilodrostat phosphate compared to baseline, but the follow-up durations were not reported. One of these studies reported that the difference from baseline was statistically significant. The second study reported a reduction in the median number of antihypertensive drugs taken at baseline and after treatment with osilodrostat phosphate, but statistical measures were not reported.

These two retrospective case series also provided very low certainty evidence of a reduction in the potassium supplementation dosage or number of patients requiring potassium supplementation after treatment with osilodrostat phosphate, but statistical measures and follow-up durations were not reported. One of these retrospective case series provided very low certainty evidence of a reduction in the dose of spironolactone after treatment with osilodrostat phosphate, but statistical measures and follow-up durations were not reported. One of these retrospective case series also provided very low certainty evidence of a reduction in the number of patients requiring insulin after treatment with osilodrostat phosphate, but the follow-up duration was not reported.

- **Time to improvement (important outcome)**
  - Osilodrostat phosphate vs metyrapone:
    No evidence was identified.
  - Osilodrostat phosphate vs no comparator:
    Two retrospective case series provided very low certainty evidence relating to control of hypercortisolism. One of these studies reported that control of hypercortisolism was obtained at different timepoints after treatment with osilodrostat, depending on the treatment regimen (i.e. two weeks in patients receiving first-line monotherapy, five weeks in patients receiving second-line monotherapy, and four weeks in patients receiving combination treatment). The second study reported that all seven patients with hypercortisolism at baseline obtained control at variable timepoints after treatment with osilodrostat phosphate (one week, or one, two or three months).
- **Quality of life (QoL) (important outcome)**
  - Osilodrostat phosphate vs metyrapone:
    No evidence was identified.
  - Osilodrostat phosphate vs no comparator:
    One prospective single-arm study provided very low certainty evidence that *"no clinically relevant differences"* were observed in the QoL score measure (i.e. Cushing's QoL) at 12 weeks after treatment with osilodrostat phosphate, but no further details were provided.
- **Activities of daily living (ADLs) (important outcome)**
  - No evidence was identified.

In terms of safety:

- Osilodrostat phosphate vs metyrapone:
  One retrospective cohort study provided very low certainty evidence that more patients treated with osilodrostat phosphate than patients treated with metyrapone required potassium replacement therapy for hypokalaemia (two of eight patients and three of eight patients, respectively) or had a progressive increase of the corrected QT interval (QTc) (one of eight patients and none of eight patients, respectively) at 12 weeks follow-up. The same retrospective cohort study provided very low certainty evidence that one of eight patients treated with osilodrostat phosphate and two of eight patients treated with metyrapone discontinued treatment due to adverse events at 12 weeks follow-up. No statistical measures were reported.
- Osilodrostat phosphate vs no comparator:
  One prospective single-arm study, and two retrospective case series provided very low certainty evidence about the number and type of adverse events of different severity grades after treatment with osilodrostat phosphate. One prospective single-arm study

reported that all nine patients (100%) experienced at least one adverse event at the 30-day safety follow-up (after the last dose of osilodrostat phosphate), six (66.7%) of which were grade 3 (88.9% of which were suspected to be treatment related). The same study reported that 44.4% of patients experienced a serious adverse event at the 30-day safety follow-up (after the last dose of osilodrostat phosphate), 22.2% of which were suspected to be treatment related. The prospective single-arm study also reported that 77.8% patients experienced an adverse event of special interest[1] at the 30-day safety follow-up (after the last dose of osilodrostat phosphate) (66.7% of these were suspected to be treatment related). One retrospective case series reported worsening of hypokalaemia in one of seven patients and that three (42.86%) patients experienced mild and transient adrenal insufficiency after treatment with osilodrostat phosphate. The follow-up duration and statistical measures were not reported.

One retrospective case series reported that 24% of patients experienced a grade 3 or 4 adverse events after treatment with osilodrostat phosphate. The follow-up duration and statistical measures were not reported.

One prospective single-arm study and two retrospective case series also provided very low certainty evidence relating to discontinuation of treatment due to adverse events. The prospective single-arm study reported that 33.3% of patients discontinued treatment with osilodrostat phosphate at 48 weeks, whilst the two retrospective case series reported that 0% of patients discontinued treatment with osilodrostat phosphate due to adverse events. No follow-up durations were reported.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

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

Ongoing schedules/doses used for osilodrostat phosphate:

- One retrospective cohort study reported median doses (mg) of osilodrostat phosphate at two weeks (4.0; range 3.0 to 7.0); at four weeks (6.0; range 4.0 to 20.0); and at 12 weeks (7.0; range 6.0 to 10.0). The same study reported median doses (mg) of metyrapone at two weeks (1,000; range 500 to 2,000); at four weeks (1,250; range 500 to 2,000); and at 12 weeks (1,250; range 1,000 to 2,000).
- One retrospective case series reported a median initial dose of osilodrostat phosphate of 4 mg/day (range 1 to 60) and a maximum dose of 20 mg/day (range 4 to 100); treatment regimens included titration (without combination with hydrocortisone or another glucocorticoid replacement therapy), block and replace, or titration followed by block and replace.
- One prospective single-arm study reported that osilodrostat phosphate during dose titration was 2 to 30 mg twice daily (dose could be down titrated to 1 mg twice daily if required). The same study also reported that the median duration of exposure to osilodrostat phosphate was 12 weeks (range 1.3 to 81.9); the median highest dose was 5 mg/day (range 2 to 10); the median average dose was 2.14 3mg/day (range 1.16 to 7.54); the median dose with longest duration was 2.0 mg/day (range 1 to 10); the median average dose (excluding dose interruption [0 mg/day]) was 2.571 mg/day

[1] Adverse events of special interest were those potentially related to osilodrostat treatment based on the mechanism of action.

(range 1.17 to 7.54); and the median dose with longest duration (excluding dose interruption [0 mg/day]) was 2 mg/day (range 1 to 10).

- One retrospective case series did not report schedules/doses used for osilodrostat phosphate.

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

Limitations:

No randomised controlled trials were identified that provided evidence on any critical or important outcomes. Evidence for the clinical effectiveness and safety of osilodrostat phosphate was available from one retrospective cohort study, one prospective single-arm study, and two retrospective case series. The retrospective cohort study provided evidence on treatment with osilodrostat phosphate or metyrapone for critical outcomes (biochemical disease response and sequelae of Cushing's syndrome) and important outcomes (reduction in treatment for Cushing's syndrome sequelae and safety). The prospective single-arm study and two retrospective case series provided non-comparative evidence for critical outcomes (clinical disease response, biochemical disease response and sequelae of Cushing's syndrome) and important outcomes (reduction in treatment for Cushing's syndrome sequelae, time to improvement, QoL, and safety). No evidence was identified comparing osilodrostat phosphate versus no adrenal steroidogenesis inhibitors or ketoconazole. No studies were identified that reported evidence on ADLs. No studies were identified that reported on relevant subgroups of patients that would benefit more from treatment with osilodrostat phosphate, and no cost effectiveness studies were identified.

Study populations included patients with different Cushing's syndrome subtypes, the retrospective cohort study included a proportion of patients with Cushing's disease (i.e. out of scope patients). Previous and concomitant treatments varied across and within the studies, as did study treatment doses and regimens. Methods used to measure outcomes differed across studies, and statistical measures and follow-up timepoints were not always reported. The certainty in the evidence was very low in all four studies for all outcomes reported. Factors reducing confidence in the outcomes reported include the retrospective design of three of the studies, very serious risk of bias in all four studies (it was unclear whether the recruitment of study participants was consecutive and study methodology was not always clearly described) and serious indirectness due to the lack of a comparator in three of the studies. Further limitations include the small numbers of patients included in the studies and the number of patients lost to follow-up or discontinuing treatment, which reduced the number of patients assessed at longer follow-up durations. One prospective single-arm study reported outcomes in terms of clinical relevance, but no further details were provided. The remaining studies included in this evidence review did not comment on minimally clinically important difference thresholds for the outcomes reported.

Conclusion:

Four studies provided very low certainty evidence on outcomes for treatment with osilodrostat phosphate for Cushing's syndrome.

Comparative evidence for the clinical effectiveness and safety of osilodrostat phosphate was available from one study. This study indicated that improvements in mean UFC levels and serum cortisol levels at two and four weeks follow-up compared to baseline were greater after treatment with osilodrostat phosphate than metyrapone, although the between group differences for osilodrostat phosphate and metyrapone were comparable, as indicated by the lack of statistically significant differences between treatment groups (where reported) or similar

results between treatment groups when statistical tests were not performed. There was a greater improvement after treatment with metyrapone than with osilodrostat phosphate compared to baseline for three outcomes at 12 weeks follow-up (change in mean UFC levels, serum cortisol levels and proportion of patients with normalised UFC), but again, the between group differences for osilodrostat phosphate and metyrapone were comparable.

Three studies provided non-comparative evidence indicating improvements in outcomes relating to clinical disease response, biochemical disease response, sequelae of Cushing's syndrome (with the exception of Becks Depression Inventory-II which showed *"no clinically relevant differences"*), reduction in treatment for Cushing's syndrome sequelae and time to improvement after treatment with osilodrostat phosphate. The three non-comparative studies reported that *"no clinically relevant differences"* were observed in QoL after treatment with osilodrostat phosphate and that most patients experienced an adverse event, with the most common being adrenal insufficiency. The certainty in the evidence was very low in all four studies for all outcomes reported due to very serious risk of bias in all four studies and serious indirectness due to the lack of a comparator in three of the studies. In addition, the number of patients included in the studies was small. No evidence was identified comparing osilodrostat phosphate versus no adrenal steroidogenesis inhibitors or ketoconazole. No evidence was identified regarding ADLs and no evidence was identified for any subgroups of patients that would benefit more from treatment with osilodrostat phosphate. Furthermore, no evidence on cost effectiveness of osilodrostat phosphate was identified.

Given the limitations of the evidence about the clinical effectiveness and safety of osilodrostat phosphate compared to standard care in people with Cushing's syndrome, it is difficult to assess the certainty of the findings.

3. Methodology

Review questions

The review questions for this evidence review are:

1) In people with endogenous Cushing's syndrome (excluding Cushing's disease), what is the clinical effectiveness of osilodrostat phosphate compared to standard care?
2) In people with endogenous Cushing's syndrome (excluding Cushing's disease), what is the safety of osilodrostat phosphate compared to standard care?
3) In people with endogenous Cushing's syndrome (excluding 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 papers were identified for inclusion (Detomas et al 2022, Dormoy et al 2023, Tabarin et al 2022, Tanaka et al 2020). One paper was a retrospective comparative cohort study (Detomas et al 2022), one paper was a non-comparative, prospective single-arm study (Tanaka et al 2020) and two papers were non-comparative case series (Dormoy et al 2023, Tabarin et al 2022).

No evidence was identified comparing osilodrostat phosphate versus no adrenal steroidogenesis inhibitors or ketoconazole. No studies were identified that reported activities of daily living (ADLs). No cost effectiveness studies were identified for inclusion in this review. No studies were identified reporting on relevant subgroups of patients that would benefit more from treatment with osilodrostat phosphate.

Osilodrostat phosphate for the treatment of Cushing's disease is considered in a separate evidence review.

Table 1 provides a summary of these included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Detomas et al 2022
 	
Retrospective cohort study
 	
Germany
	• Total sample size: N=16
	• Adults with endogenous Cushing's syndrome (Cushing's disease: n=7; Cushing's syndrome: n=9 [ectopic Cushing's syndrome: n=5; cortisol-producing adrenal adenoma: n=2; adrenocortical carcinoma: n=2])
	• Osilodrostat phosphate: n=8
	• Metyrapone: n=8
	• No subgroups reported
		Intervention
		
		Osilodrostat phosphate (dose not reported at baseline)
		
		Median (range) dose (mg) after treatment
		
		• At 2 weeks: 4.0 (3.0 to 7.0)
		• At 4 weeks: 6.0 (4.0 to 20.0)
		• At 12 weeks: 7.0 (6.0 to 10.0)
		• Mean treatment duration: 9.5 (SEM 1.1) weeks
		
		Comparison
		
		Metyrapone (dose not reported at baseline)
		
		Median (range) dose (mg) after treatment
		
		• At 2 weeks: 1,000 (500 to 2,000)
		• At 4 weeks: 1,250 (500 to 2,000)
		• At 12 weeks: 1,250 (1,000 to 2,000)
		• Mean treatment duration: 17.0 (SEM 3.4) weeks
		
		Apart from patients with adrenocortical carcinoma who previously received platinum-based chemotherapy (i.e. etoposide, doxorubicin, cisplatin) alongside mitotane, no other patients had received previous or concomitant pharmacological treatment for hypercortisolism
			Follow-up duration 12 weeks
			
			Critical outcome
			
			• Biochemical disease response
			  ○ Change in serum cortisol levels (µg/dl) from baseline to 2, 4 and 12 weeks after treatment
			  ○ Proportion of patients with serum cortisol levels <25 µg/dl at 4 and 12 weeks after treatment
			  ○ Change in UFC levels (µg/d) from baseline to 2, 4 and 12 weeks after treatment
			  ○ Proportion of patients with normalised mean UFC levels at 4 and 12 weeks after treatment
			• Sequelae of Cushing's syndrome
			  ○ Change in systolic and diastolic blood pressure (mmHg) from baseline to 2 weeks after treatment
			
			Important Outcomes
			
			• Reduction in treatment for Cushing's syndrome sequelae
			  ○ Mean reduction in number of antihypertensives required after treatment
			• Safety
			  ○ Patients requiring potassium replacement therapy for hypokalaemia
			  ○ QTc prolongation
			  ○ Adverse events leading to treatment discontinuation

Dormoy et al 2023	• Total sample size: N=33 • Adults with paraneoplastic Cushing's syndrome/ectopic adrenocorticotropin syndrome • Osilodrostat phosphate: N=33	**Intervention**	Follow-up duration not reported, unless otherwise stated **Critical outcome** • Clinical disease response

Study	Population	Intervention and comparison	Outcomes reported
Retrospective case series Multicentre, France	• Control: none • Some outcomes were reported separately for patients using osilodrostat phosphate as first-line, second-line or as concomitant treatment formed	Osilodrostat phosphate: median initial dose 4 mg/day (range 1 to 60) Maximum dose: 20 mg/day (range 4 to 100) Regimens used, n • Titration (without combination with hydrocortisone or another glucocorticoid replacement therapy): 6 • Block and replace: 16 • Titration followed by block and replace: 11 • At 4 weeks: 6.0 (4.0 to 20.0) • At 12 weeks: 7.0 (6.0 to 10.0) • Mean treatment duration: 9.5 (SEM 1.1) weeks Starting dose (mg/day), median (range) – by treatment regimen • Patients using osilodrostat phosphate as first-line monotherapy (n=11): 10 (2 to 40) • Patients who had prior treatment with other steroidogenesis inhibitor treatments (metyrapone and/or ketoconazole, or cabergoline) before being replaced by osilodrostat phosphate monotherapy as second-line treatment (n=13): 4 (1 to 20) • Patients receiving osilodrostat phosphate in combination with another anticortisolic treatment (metyrapone [with or without cabergoline] and/or ketoconazole) (n=9): 4 (1 to 60) **Comparison** • None	○ Clinical signs of hypercortisolism[a] after treatment • Biochemical disease response ○ Serum cortisol levels (ng/mL) after treatment ○ 24-hour UFC levels (µg/24-hours) after treatment ○ Proportion of patients with normalisation of 24-hour UFC levels after treatment • Sequelae of Cushing's syndrome ○ Systolic and diastolic blood pressure (mmHg) after treatment ○ Proportion of patients with myopathy 3 to 6 months after treatment ○ Proportion of patients with hypokalaemia after treatment ○ Fasting blood glucose levels (g/L) after treatment ○ HbA1c (%) after treatment ○ BMI (kg/m^2) after treatment **Important Outcomes** • Reduction in treatment for Cushing's syndrome sequelae ○ Reduction in number of patients requiring insulin after treatment • Time to improvement ○ Time (weeks) required to normalise 24-hour UFC level • Safety ○ Grade 3 or 4 adverse events ○ Adverse events leading to treatment discontinuation
Tabarin et al 2022 Retrospective case series Multicentre (six centres), France	• Total sample size: N=7 • Adults with cortisol-secreting ACC • Osilodrostat phosphate: N=7 • Control: none • No subgroups reported	**Intervention** Osilodrostat phosphate: starting dose, dose increases, and duration of titration steps were highly variable between patients (no other details provided) **Comparison** • None	Follow-up duration not reported, unless otherwise stated **Critical outcome** • Clinical disease response ○ Improvement in Cushing's clinical score[b] after treatment • Biochemical disease response ○ Decrease in serum cortisol levels (nmol/L) within 2 weeks after treatment ○ UFC levels (x ULN) after treatment • Sequelae of Cushing's syndrome ○ Systolic blood pressure (mmHg) after treatment ○ Proportion of patients with diabetes mellitus and glucose intolerance after treatment **Important Outcomes** • Reduction in treatment for Cushing's syndrome sequelae ○ Reduction in daily antihypertensive drug dosage after treatment ○ Number of patients with increased serum potassium associated with a reduction in potassium supplementation or

Study	Population	Intervention and comparison	Outcomes reported

			spironolactone dosage after treatment
			• Time to improvement
			  ○ Number of patients with fully controlled hypercortisolism within 1 week, 1 month and around 2 months after treatment
			• Safety
			  ○ Adverse events
			  ○ Worsening of hypokalaemia
			  ○ Adverse events leading to treatment discontinuation

Tanaka et al 2020
 	
Prospective single-arm study
 	
Multicentre, Japan
	• Total sample size: N=9 (n=7 [dose titration period, weeks 0 to 12]; n=2 [continued treatment with osilodrostat phosphate, weeks 12 to 48]; n=0 [optional extension period, weeks 48 to 72])
	• Adults with different types of endogenous Cushing's syndrome other than Cushing's disease
	• Osilodrostat phosphate: N=9
	• Control: none
	• No subgroups reported
		Intervention
		
		Osilodrostat phosphate: during dose titration, 2 to 30 mg bid (dose could be down titrated to 1 mg bid if required)
		
		Osilodrostat phosphate dose and duration of exposure (all patients at final cut-off: n=9)
		• Median exposure (range), weeks: 12.00 (1.3 to 81.9)
		• >8 weeks of exposure, n (%): 7 (77.8)
		• >16 weeks of exposure, n (%): 4 (44.4)
		• >48 weeks of exposure, n (%): 2 (22.2)
		• Median highest dose (range), mg/day 5.0 (2 to 10)
		• Median average dose (range), mg/day: 2.143 (1.16 to 7.54)
		  • Median dose with longest duration (range), mg/day: 2.0 (1 to 10)
		  • Median average dose (range) excluding dose interruption (0 mg/day), mg/day: 2.571 (1.17 to 7.54)
		
		Comparison
		
		• None
			Follow-up duration 48 weeks, unless otherwise stated
			
			Critical outcome
			
			• Biochemical disease response
			  ○ Median % change in morning serum cortisol levels (nmol/L) from baseline to 12, 24 and 48 weeks after treatment
			  ○ Median % change in actual mUFC (nmol/24-hours) from baseline to 4, 8, 12, 24 and 48 weeks after treatment
			  ○ Proportion of mUFC responders 12, 24 and 48 weeks after treatment
			• Sequelae of Cushing's syndrome
			  ○ % change in systolic and diastolic blood pressure (mmHg) from baseline to 12 weeks after treatment
			  ○ % change in fasting glucose (mmol/L) from baseline to 12 weeks after treatment
			  ○ % change in HbA1c (%) from baseline to 12 weeks after treatment
			  ○ % change in BMI (kg/m^2) from baseline to 12 weeks after treatment
			  ○ % change in waist circumference (cm) from baseline to 12 weeks after treatment
			  ○ % change in cholesterol (mmol/L) from baseline to 12 weeks after treatment
			  ○ % change in HDL cholesterol (mmol/L) from baseline to 12 weeks after treatment
			  ○ % change in LDL cholesterol (mmol/L) from baseline to 12 weeks after treatment
			  ○ % change in triglycerides (mmol/L) from baseline to 12 weeks after treatment
			  ○ BDI-II score
			
			Important Outcomes
			
			• QoL at 12 weeks
			  ○ Cushing's QoL score
			• Safety (30-day safety follow-up after last dose of osilodrostat phosphate)
			  ○ Adverse events
			  ○ Serious adverse events
			  ○ Adverse events of special interest
			  ○ Adverse events leading to treatment discontinuation

Study	Population	Intervention and comparison	Outcomes reported

Abbreviations

ACC: adrenocortical carcinoma; BDI-II: Beck's Depression Inventory-II; BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; QoL: quality of life; QTc: corrected QT interval; SEM: standard error of the mean; UFC: urinary free cortisol; ULN: upper limit of normal.

a. Measured using an arbitrary clinical score reflecting Cushing's syndrome severity. The score was adapted from Ferriere et al (2017) and included 7 items: obesity of the face and trunk; purple stretch marks; myopathy; supraclavicular fat pad; buffalo hump; facial erythrosis; and facial plethora. In premenopausal women, the score included the same previous items as well as two additional items: hirsutism and amenorrhoea. In postmenopausal women, the same items as previously were used, with the exception of amenorrhea. Each of the clinical items was scored as 0 (absent), 1 (low), or 2 (high), resulting in a total score of 14, 18, and 16, respectively, in men, premenopausal women, and postmenopausal women. To standardise these scores, the value 1.0 corresponded to the maximum in each aforementioned patient category.

b. A decrease in a Cushing score for clinical appearance: 0 reflects lack of symptoms; 2 reflects florid Cushing (as assessed by experienced endocrinologists).

5. Results

In people with endogenous Cushing's syndrome (excluding 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:** Very low	This outcome is important to patients because it reflects the clinical improvement that they experience with treatment. Two retrospective case series provided non-comparative evidence relating to clinical disease response, the follow-up timepoints were not clearly stated in either study. One retrospective case series measured clinical signs of hypercortisolism, using an arbitrary clinical score reflecting Cushing's syndrome severity[2], after treatment with osilodrostat phosphate in patients with PNCS/EAS. The second retrospective case series measured improvement in Cushing's clinical score[3] after treatment with osilodrostat phosphate in patients with Cushing's syndrome associated with ACC. *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. <u>Clinical signs of hypercortisolism after treatment, measured using an arbitrary clinical score reflecting Cushing's syndrome severity[2]</u> *Osilodrostat phosphate vs no comparator* **At unspecified duration of follow-up:** • One retrospective case series (Dormoy et al 2023) (n=33) reported a decrease in the arbitrary clinical score reflecting Cushing's syndrome after treatment with osilodrostat phosphate (from 0.44 to 0.21) in patients with PNCS/EAS. The difference compared to baseline was *statistically significant* (p<0.0001). **(VERY LOW)** <u>Improvement in Cushing's clinical score[3]</u> *Osilodrostat phosphate vs no comparator* **At unspecified duration of follow-up:** • One retrospective case series (Tabarin et al 2022) (n=7) showed an improvement in Cushing's clinical scores in five patients with Cushing's syndrome associated with ACC after treatment with osilodrostat phosphate. Scores were not available for two patients and no statistical measures were reported. **(VERY LOW)** **Osilodrostat phosphate vs metyrapone:** **No evidence was identified for this outcome.**

[2] The score was adapted from Ferriere et al (2017) and included 7 items: obesity of the face and trunk; purple stretch marks; myopathy; supraclavicular fat pad; buffalo hump; facial erythrosis; and facial plethora. In premenopausal women, the score included the same previous items as well as two additional items: hirsutism and amenorrhoea. In postmenopausal women, the same items as previously were used, with the exception of amenorrhea. Each of the clinical items was scored as 0 (absent), 1 (low), or 2 (high), resulting in a total score of 14, 18, and 16, respectively, in men, premenopausal women, and postmenopausal women. To standardise these scores, the value 1.0 corresponded to the maximum in each aforementioned patient category.
[3] A decrease in a Cushing score for clinical appearance: 0 reflects lack of symptoms; 2 reflects florid Cushing (as assessed by experienced endocrinologists).

Outcome	Evidence statement
	Osilodrostat vs no comparator: **Two retrospective case series provided very low certainty evidence that osilodrostat phosphate improves clinical signs of Cushing's syndrome at unspecified durations of follow-up in patients with PNCS/EAS or Cushing's syndrome associated with ACC. One retrospective case series indicated that the difference compared to baseline was *statistically significant*; the second retrospective case series did not report statistical measures.**
Biochemical disease response **Certainty of evidence:** Very low	This outcome is important to patients because biochemical improvement is a measure of disease response to treatment. Four studies (one retrospective cohort study, one prospective single-arm study, two retrospective case series) provided evidence relating to biochemical disease response in patients with different subtypes of Cushing's syndrome. The retrospective cohort study compared outcomes from baseline up to 12 weeks after treatment with osilodrostat phosphate or metyrapone in patients with different subtypes of Cushing's syndrome (including Cushing's disease). One prospective single-arm study and two retrospective case series provided non-comparative evidence in patients with different subtypes of Cushing's disease (excluding Cushing's disease). Outcomes were reported up to 48 weeks in the prospective single-arm study, but follow-up timepoints were not always clearly stated in the two retrospective case series: <u>Serum cortisol levels</u> *Osilodrostat phosphate vs metyrapone* **At two weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=16) reported a greater reduction in mean serum cortisol levels from baseline to two weeks after treatment with osilodrostat phosphate (change –14.4%) than treatment with metyrapone (change –4.9%) in patients with Cushing's syndrome (including Cushing's disease), but the difference was *not statistically significant* (p=0.63). **(VERY LOW)** **At four weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=16) reported a greater reduction in mean cortisol levels from baseline to four weeks after treatment with osilodrostat phosphate (change -17.2%) than treatment with metyrapone (change –4.2%) in patients with Cushing's syndrome (including Cushing's disease), but the difference was *not statistically significant* (p=0.57). **(VERY LOW)** **At 12 weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=16) reported a greater reduction in mean cortisol levels from baseline to 12 weeks after treatment with metyrapone (change –51.1%) than treatment with osilodrostat phosphate (change –25.8%) in patients with Cushing's syndrome (including Cushing's disease), but the difference was *not statistically significant* (p=0.23). **(VERY LOW)** *Osilodrostat phosphate vs no comparator* **At unspecified follow-up duration** • One retrospective case series (Dormoy et al 2023) (n=11) reported a reduction in median serum cortisol levels after treatment with osilodrostat phosphate as first-line monotherapy (from 484 ng/mL [range 141 to 1,350 ng/mL][4] to 10 ng/mL [range 10 to 528 ng/mL]) in patients with PNCS/EAS.

[4] There was a discrepancy between the figures reported in the narrative (median serum cortisol level reported as 484 ng/mL [range 141 to 1,350 ng/mL] and 357 ng/mL (range 141 to 1,150 ng/mL]). We have used the figure that corresponds with the figure reported in the table of clinical and hormonal characteristics of patients at diagnosis (i.e. median serum cortisol level 484 ng/mL [range 141 to 1,350 ng/mL]).

Outcome	Evidence statement
	The difference compared to baseline was *statistically significant* (p<0.001). **(VERY LOW)** **At two weeks follow-up** • One retrospective case series (Tabarin et al 2022) (n=7) reported a reduction in mean serum cortisol levels from baseline to two weeks after treatment with osilodrostat phosphate (from 989 to 330 nmol/L), with a significant decrease observed in six of seven patients with Cushing's syndrome associated with ACC. The difference compared to baseline was *statistically significant* (p=0.02). **(VERY LOW)** **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=7) reported a decrease in median morning serum cortisol levels from baseline to 12 weeks after treatment with osilodrostat phosphate (median % change from baseline of -56.07%) in patients with different subtypes of Cushing's syndrome. No statistical measures were reported. **(VERY LOW)** **At 24 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=3) reported a decrease in median morning serum cortisol levels from baseline to 24 weeks after treatment with osilodrostat phosphate (median % change from baseline of –68.96% in patients with different subtypes of Cushing's syndrome. No statistical measures were reported. **(VERY LOW)** **At 48 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=2) reported a decrease in median morning serum cortisol levels from baseline to 48 weeks after treatment with osilodrostat phosphate (median % change from baseline of –67.39%) in patients with different subtypes of Cushing's syndrome. No statistical measures were reported. **(VERY LOW)** <u>Serum cortisol levels below 25µg/dl (normal range 5 to 25 µg/dl)</u> *Osilodrostat phosphate vs metyrapone* **At four weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=16) reported that the same proportion of patients with Cushing's syndrome (including Cushing's disease) had a serum cortisol level below 25 µg/dl four weeks after treatment with osilodrostat phosphate or metyrapone (62.5% of patients in each treatment arm). Statistical measures were not reported. **(VERY LOW)** **At 12 weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=16) reported that all patients with Cushing's syndrome (including Cushing's disease) had a serum cortisol level below 25 µg/dl 12 weeks after treatment with osilodrostat phosphate or metyrapone (100% of patients in each treatment arm). Statistical measures were not reported. **(VERY LOW)** <u>Urinary free cortisol (UFC) levels</u> *Osilodrostat phosphate vs metyrapone* **At two weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=NR) reported a greater reduction in mean UFC levels from baseline to two weeks after treatment with osilodrostat phosphate (–68.4%) than treatment with metyrapone (–21.3%) in patients with Cushing's syndrome (including

Outcome	Evidence statement
	Cushing's disease). The difference between treatment groups was *not statistically significant* (p=0.15). **(VERY LOW)** **At four weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=13) reported a comparable decrease in mean UFC levels from baseline to four weeks after treatment with osilodrostat phosphate (–50.1%) or metyrapone (–37.3%) in patients with Cushing's syndrome (including Cushing's disease). The difference between treatment groups was *not statistically significant* (p=0.59). **(VERY LOW)** **At 12 weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=7) reported a greater reduction in mUFC levels from baseline to 12 weeks after treatment with metyrapone (–71.5%) than treatment with osilodrostat phosphate (–51.5%) in patients with Cushing's syndrome (including Cushing's disease). The difference between treatment groups was *not statistically significant* (p=0.40). **(VERY LOW)** *Osilodrostat phosphate vs no comparator* **At unspecified follow-up duration** • One retrospective case series (Tabarin et al 2020) (n=7) reported a *statistically significant* decrease in UFC levels (from 10.5 to 0.6 x ULN) after treatment with osilodrostat phosphate in patients with different subtypes of Cushing's syndrome (p=0.03). **(VERY LOW)** **At four weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=8) reported a reduction in actual mUFC levels of –83.32% (range –99.4% to –38.8%) from baseline to four weeks after treatment with osilodrostat phosphate in patients with different subtypes of Cushing's syndrome. No statistical measures were reported. **(VERY LOW)** **At eight weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=8) reported a reduction in actual mUFC levels of –94.37% (range –99.8% to 94.0%) from baseline to eight weeks after treatment with osilodrostat phosphate in patients with different subtypes of Cushing's syndrome. No statistical measures were reported. **(VERY LOW)** **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=7) reported a reduction in actual mUFC levels of –94.47% (range –99.0% to –52.6%) from baseline to 12 weeks after treatment with osilodrostat phosphate in patients with different subtypes of Cushing's syndrome. No statistical measures were reported. **(VERY LOW)** **At 24 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=3) reported a reduction in actual mUFC levels of –91.57% (range –99.5% to –85.2%) from baseline to 24 weeks after treatment with osilodrostat phosphate in patients with different subtypes of Cushing's syndrome. No statistical measures were reported. **(VERY LOW)** **At 48 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=2) reported a reduction in actual mUFC levels of –95.04% (range –99.1% to –91.0%) from baseline to 48 weeks after treatment with osilodrostat phosphate in patients with different subtypes of Cushing's syndrome. No statistical measures were reported. **(VERY LOW)**

Outcome	Evidence statement
	<u>Proportion of mean urinary free cortisol (mUFC) level responders</u> *Osilodrostat phosphate vs no comparator* **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=9) reported that overall response was observed in seven of nine (77.8%) patients with different subtypes of Cushing's syndrome 12 weeks after treatment with osilodrostat phosphate; six were complete responders and one was a partial responder[5]. No statistical measures were reported. **(VERY LOW)** **At 24 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=3) reported that at week 24, two patients with different subtypes of Cushing's syndrome had a complete response and one patient had a partial response after treatment with osilodrostat phosphate. No statistical measures were reported. **(VERY LOW)** **At 48 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=2) reported that one patient with different subtypes of Cushing's syndrome had a complete response and one patient had a partial response after treatment with osilodrostat phosphate. No statistical measures were reported. **(VERY LOW)** <u>Normalised urinary free cortisol (UFC) levels (normal range 0 to 70 µg/d)</u> *Osilodrostat phosphate vs metyrapone* **At four weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=13) reported that a greater proportion of patients with Cushing's syndrome (including Cushing's disease) had a normalised UFC level four weeks after treatment with osilodrostat phosphate than treatment with metyrapone (42.9% versus 0%, respectively). No statistical measures were reported. **(VERY LOW)** **At 12 weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=7) reported that fewer patients with Cushing's syndrome (including Cushing's disease) had a normalised UFC level 12 weeks after treatment with osilodrostat phosphate than metyrapone (50% versus 66.7%, respectively). No statistical measures were reported. **(VERY LOW)** <u>24-hour urinary free cortisol (UFC) levels</u> *Osilodrostat phosphate vs no comparator [patients receiving osilodrostat phosphate as first-line monotherapy]* • One retrospective case series (Dormoy et al 2023) (n=11) reported a decrease in median 24-hour UFC levels after treatment with osilodrostat phosphate as first-line monotherapy (from 1,678 µg/24-hours [range 190 to 32,950 µg/24-hours] to 5 µg/24-hours [range 5 to 743 µg/24-hours]) in patients with PNCS/EAS. The difference compared to baseline was *statistically significant* (p<0.001). **(VERY LOW)** *Osilodrostat phosphate vs no comparator [patients who received prior treatment with other steroidogenesis inhibitor treatments before being replaced by osilodrostat phosphate monotherapy as second-line treatment]*

[5] Two patients discontinued study treatment prior to week 12 and were counted as non-responders for the calculation of response rate at week 12.

Outcome	Evidence statement
	• One retrospective case series (Dormoy et al 2023) (n=10 uncontrolled patients)[6] reported a decrease in median 24-hour UFC levels after treatment with osilodrostat phosphate as second-line treatment (from 158 µg/24-hours [range 85 to 6,500 µg/24-hours] to 12µg/24-hours [range 5 to 57 µg/24-hours]) in patients with PNCS/EAS. The difference compared to baseline was *statistically significant* (p<0.01). **(VERY LOW)** *Osilodrostat phosphate vs no comparator [patients who received osilodrostat phosphate in combination with another anticortisolic treatment]* • One retrospective case series (Dormoy et al 2023) (n=9) reported a decrease in median 24-hour UFC levels after treatment with osilodrostat phosphate in combination with another anticortisolic treatment (from 588 µg/24-hours [range 20 to 21,448 µg/24-hours] to 28 µg/24-hours [range 5 to 158 µg/24-hours]) in patients with PNCS/EAS. The difference compared to baseline was *statistically significant* (p<0.01). **(VERY LOW)** <u>Normalisation of 24-hour urinary free cortisol (UFC) levels (ULN range 45 to 80 µg/24-hours)</u> *Osilodrostat phosphate vs no comparator [patients receiving osilodrostat phosphate as first-line monotherapy]* • One retrospective case series (Dormoy et al 2023) (n=11) reported normalisation of 24-hour UFC levels in nine of 11 (82%) patients with PNCS/EAS after treatment with osilodrostat phosphate as first-line monotherapy. No statistical measures were reported. **(VERY LOW)** *Osilodrostat phosphate vs no comparator [patients who received prior treatment with other steroidogenesis inhibitor treatments before being replaced by osilodrostat phosphate monotherapy as second-line treatment]* • One retrospective case series (Dormoy et al 2023) (n=13) reported normalisation of 24-hour UFC levels in all 13 patients (100%) with PNCS/EAS after treatment with osilodrostat phosphate as second-line treatment. No statistical measures were reported. **(VERY LOW)** *Osilodrostat phosphate vs no comparator [patients who received osilodrostat phosphate in combination with another anticortisolic treatment]* • One retrospective case series (Dormoy et al 2023) (n=9) reported normalisation of 24-hour UFC levels in six of nine (67%) patients with PNCS/EAS after treatment with osilodrostat phosphate in combination with another anticortisolic treatment. No statistical measures were reported. **(VERY LOW)** **Osilodrostat phosphate vs metyrapone:** **One retrospective cohort study provided very low certainty evidence relating to biochemical disease response. This study showed that although the changes in <u>mean UFC levels and serum cortisol levels</u> compared to baseline were greater in patients with Cushing's syndrome (including Cushing's disease) after treatment with osilodrostat phosphate than treatment with metyrapone at two and four weeks follow-up, the difference was *not statistically significant*. By contrast, at 12 weeks follow-up, the change in <u>mean UFC levels and serum cortisol levels</u> compared to baseline were greater in patients with Cushing's syndrome (including Cushing's disease) after treatment with metyrapone than treatment with osilodrostat phosphate, although the differences were *not statistically significant*. There was no between group difference for osilodrostat phosphate and metyrapone in the**

[6] In the remaining three patients whose 24-hour UFC was normalised at the time of osilodrostat phosphate treatment, UFC levels were maintained [i.e. 24-hour UFC <ULN].

Outcome	Evidence statement
	proportion of patients with Cushing's syndrome (including Cushing's disease) who had a serum cortisol level below 25 µg/dl (normal range 0 to 70 µg/dl); statistical measures were not reported. The same study reported that a greater proportion of patients with Cushing's syndrome (including Cushing's disease) who were treated with metyrapone had a normalised UFC level than patients treated with osilodrostat phosphate (66.7% versus 50%, respectively) after 12 weeks, but no statistical measures were reported. **Osilodrostat phosphate vs no comparator:** **One prospective single-arm study and two retrospective case series provided very low certainty evidence on biochemical disease response. One retrospective case series reported a *statistically significant* decrease in median serum cortisol levels from baseline after first-line osilodrostat phosphate monotherapy in patients with PNCS/EAS, but the follow-up duration was not reported. The second retrospective case series reported a *statistically significant* reduction in serum cortisol levels from baseline to two weeks after treatment with osilodrostat phosphate in patients with Cushing's syndrome associated with ACC. One prospective single-arm study reported a decrease in median morning serum cortisol levels from baseline to weeks 12, 24 and 48 in patients with different subtypes of Cushing's syndrome, but statistical measures were not reported.** **One retrospective case series reported a *statistically significant* decrease in mean UFC levels after treatment with osilodrostat phosphate in patients with different subtypes of Cushing's syndrome, but the follow-up duration was not reported. One prospective single-arm study reported reductions in actual mUFC levels from baseline to weeks four, eight, 12, 24 and 48 after treatment with osilodrostat phosphate, but no statistical measures were reported.** **One prospective single-arm study reported that the proportion of mUFC responders was high in patients with different subtypes of Cushing's syndrome (including Cushing's disease) at 12 weeks after treatment with osilodrostat phosphate and remained high at weeks 24 and 48 in patients who remained on treatment. No statistical measures were reported.** **One retrospective case series reported that median 24-hour UFC levels *statistically significantly* decreased in patients with PNCS/EAS regardless of treatment regimen (i.e. osilodrostat phosphate as first-line monotherapy, osilodrostat phosphate monotherapy as second-line treatment, and osilodrostat phosphate in combination with another anticortisolic treatment).** **One retrospective case series provided very low certainty evidence that 24-hour UFC was normalised (ULN range 45 to 80 µg/24-hours) in 82% patients with PNCS/EAS after treatment with osilodrostat phosphate as first-line monotherapy; 100% patients with PNCS/EAS after treatment with osilodrostat phosphate as second-line treatment; and 67% patients with PNCS/EAS after treatment with osilodrostat phosphate in combination with another anticortisolic treatment. No statistical measures were reported.**
Sequelae of Cushing's syndrome **Certainty of evidence:** Very low	This outcome is important for patients because it measures improvements in the physical health consequences of Cushing's syndrome. 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. Four studies (one retrospective cohort study, one prospective single-arm study, two retrospective case series) provided evidence relating to sequelae of Cushing's syndrome in patients with different Cushing's subtypes. The retrospective cohort study compared outcomes from baseline to two weeks after treatment with osilodrostat phosphate or metyrapone in patients with different Cushing's subtypes (including Cushing's disease). One prospective single-arm study and two retrospective case series provided non-comparative evidence in patients with different subtypes of Cushing's disease (excluding Cushing's disease). Where reported, outcomes were presented at two or 12 weeks after treatment with

Outcome	Evidence statement
	osilodrostat phosphate in the prospective single-arm study, and one outcome was reported at three to six months after treatment with osilodrostat phosphate in one retrospective case series. Follow-up timepoints were not clearly stated in the retrospective cohort study or the two retrospective case series: <u>Systolic blood pressure</u> *Osilodrostat phosphate vs metyrapone* **At two weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=NR) reported that there was *no statistically significant* reduction in systolic blood pressure in patients with Cushing's syndrome (including Cushing's disease) two weeks after treatment with osilodrostat phosphate (p=0.07) or metyrapone (p=0.12). **(VERY LOW)** *Osilodrostat phosphate vs no comparator* **At unspecified follow-up** • One retrospective case series (Dormoy et al 2023) (n=33) reported a decrease in median systolic blood pressure from 143 mmHg (range 102 to 187 mmHg) to 126 mmHg (range 100 to 168 mmHg) after treatment with osilodrostat phosphate in patients with PNCS/EAS. The difference compared to baseline was *statistically significant* (p<0.0001). **(VERY LOW)** • One retrospective case series (Tabarin et al 2022) (n=7) reported a decrease in mean systolic blood pressure from 168 mmHg to 120 mmHg after treatment with osilodrostat phosphate in patients with Cushing's syndrome associated with ACC. The difference compared to baseline was *statistically significant* (p=0.03). **(VERY LOW)** • One prospective single-arm study (Tanaka et al 2020) (n=7) reported that *"marginal improvements"* were observed in systolic blood pressure after treatment with osilodrostat phosphate in most patients (five of seven patients) with different subtypes of Cushing's syndrome. The change from baseline ranged between -31.3% and 9.3%. No statistical measures were reported. **(VERY LOW)** <u>Diastolic blood pressure</u> *Osilodrostat phosphate vs metyrapone* **At two weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=NR) reported that there was *no statistically significant* reduction in diastolic blood pressure in patients with Cushing's syndrome (including Cushing's disease) two weeks after treatment with osilodrostat phosphate (p=0.07) or metyrapone (p=0.35). **(VERY LOW)** *Osilodrostat phosphate vs no comparator* **At unspecified follow-up** • One retrospective case series (Dormoy et al 2023) (n=33) reported a decrease in median diastolic blood pressure from 77 mmHg (range 56 to 101 mmHg) to 69 mmHg (range 49 to 90 mmHg) after treatment with osilodrostat phosphate in patients with PNCS/EAS. The difference compared to baseline was *statistically significant* (p<0.001). **(VERY LOW)** • One prospective single-arm study (Tanaka et al 2020) (n=7) reported that *"marginal improvements"* were observed in diastolic blood pressure after treatment with osilodrostat phosphate in most patients (five of seven patients) with different subtypes of Cushing's syndrome. The change from

Outcome	Evidence statement
	baseline ranged between -33.2% and 9.9%. No statistical measures were reported. **(VERY LOW)** <u>Myopathy</u> *Osilodrostat phosphate vs no comparator* **At three to six months follow-up** • One retrospective case series (Dormoy et al 2023) (n=33) reported that three patients with PNCS/EAS had myopathy prior to treatment with osilodrostat phosphate. All three patients were able to ambulate, move around independently, and were discharged from hospital three to six months after treatment. No statistical measures were reported. **(VERY LOW)** <u>Hypokalaemia</u> *Osilodrostat phosphate vs no comparator* **At unspecified follow-up** • One retrospective case series (Dormoy et al 2023) (n=33) reported that at initiation of treatment with osilodrostat phosphate (i.e. after potassium supplementation and/or spironolactone treatment), 13 (39%) patients with PNCS/EAS were hypokalaemic. After treatment with osilodrostat phosphate, only four of 33 (12%) patients were still hypokalaemic. No statistical measures were reported. **(VERY LOW)** <u>Fasting blood glucose levels</u> *Osilodrostat phosphate vs no comparator* **At unspecified follow-up** • One retrospective case series (Dormoy et al 2023) (n=33) reported that median fasting blood glucose levels decreased from 1.2 g/L (range 0.6 to 3.1 g/L) before treatment with osilodrostat phosphate to 0.9 g/L (range 0.7 to 1.8 g/L) in patients with PNCS/EAS. The difference compared to baseline was *statistically significant* (p<0.0001). **(VERY LOW)** **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=7) reported *"marginal improvements"* in fasting glucose levels after treatment with osilodrostat phosphate in most patients (six of seven patients) with different subtypes of Cushing's syndrome. The percentage change from baseline ranged between -27.2% and 24.2%. No statistical measures were reported. **(VERY LOW)** <u>HbA1c</u> *Osilodrostat phosphate vs no comparator* **At unspecified follow-up** • One retrospective case series (Dormoy et al 2023) (n=33) reported that median HbA1c decreased from 6.7% (range 4.2% to 10.6%) before treatment with osilodrostat phosphate to 6.1% (4.9% to 7.2%) in patients with PNCS/EAS. The difference compared to baseline was *statistically significant* (p<0.05). **(VERY LOW)** **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=7) reported *"marginal improvements"* in HbA1c after treatment with osilodrostat phosphate in most patients (five of seven patients) with different subtypes of Cushing's syndrome. The percentage change from baseline ranged

Outcome	Evidence statement
	between -20.3% and 6.2%. No statistical measures were reported. **(VERY LOW)** <u>Diabetes mellitus and glucose intolerance</u> *Osilodrostat phosphate vs no comparator* **At unspecified follow-up** • One retrospective case series (Tabarin et al 2022) (n=7) reported that in patients with Cushing's syndrome associated with ACC who were treated with osilodrostat phosphate, *"three patients had diabetes mellitus and two had glucose intolerance that disappeared following the control of hypercortisolism"*. No statistical measures were reported. **(VERY LOW)** <u>BMI (kg/m^2)</u> *Osilodrostat phosphate vs no comparator* **At unspecified follow-up** • One retrospective case series (Dormoy et al 2023) (n=33) reported a *statistically significant* decrease in median BMI from 25 kg/m^2 (range 18 to 40 kg/m^2) before treatment to 23.4 kg/m^2 (range 19 to 36 kg/m^2) after treatment with osilodrostat phosphate in patients with PNCS/EAS ($p<0.01$). **(VERY LOW)** **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=7) reported that two of seven patients with different subtypes of Cushing's syndrome showed a reduction in BMI after treatment with osilodrostat phosphate, whilst five patients showed an increase in percentage change from baseline. The percentage change from baseline ranged between -3.1% and 7.4%. No statistical measures were reported. **(VERY LOW)** <u>Waist circumference</u> *Osilodrostat phosphate vs no comparator* **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=7) reported *"marginal improvements"* in waist circumference after treatment with osilodrostat phosphate in most patients (five of seven patients) with different subtypes of Cushing's syndrome. The percentage change from baseline ranged between -4.9% and 2.9%. No statistical measures were reported. **(VERY LOW)** <u>Cholesterol</u> *Osilodrostat phosphate vs no comparator* **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=7) reported *"marginal improvements"* in cholesterol after treatment with osilodrostat phosphate in most patients (six of seven patients) with different subtypes of Cushing's syndrome. The percentage change from baseline ranged between -23% and 23%. No statistical measures were reported. **(VERY LOW)** <u>HDL cholesterol</u> *Osilodrostat phosphate vs no comparator* **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=7) reported *"marginal improvements*" in HDL cholesterol after treatment with

Outcome	Evidence statement
	osilodrostat phosphate in most patients (five of seven patients) with different subtypes of Cushing's syndrome. The percentage change from baseline ranged between -34.4% and 15.5%. No statistical measures were reported. **(VERY LOW)** LDL cholesterol *Osilodrostat phosphate vs no comparator* **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=7) reported *"marginal improvements"* in LDL cholesterol after treatment with osilodrostat phosphate in most patients (five of seven patients) with different subtypes of Cushing's syndrome. The percentage change from baseline ranged between -24.9% and 26.5%. No statistical measures were reported. **(VERY LOW)** Triglycerides *Osilodrostat phosphate vs no comparator* **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=7) reported *"marginal improvements"* in triglycerides after treatment with osilodrostat phosphate in most patients (four of seven patients) with different subtypes of Cushing's syndrome. The percentage change from baseline ranged between -56.7% and 46.8%. No statistical measures were reported. **(VERY LOW)** *Osilodrostat phosphate vs no comparator* **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=9) reported that "*no clinically relevant differences"* were observed in BDI-II scores at 12 weeks follow-up in patients with different subtypes of Cushing's syndrome. **(VERY LOW)** **Osilodrostat phosphate vs metyrapone:** **One retrospective cohort study reported that there were *no statistically significant* reductions in systolic or diastolic blood pressure in patients with Cushing's syndrome (including Cushing's disease) two weeks after treatment with osilodrostat phosphate or metyrapone.** **Osilodrostat phosphate vs no comparator:** **One retrospective cohort study, one prospective single-arm study, and two retrospective case series provided very low certainty evidence relating to sequelae of Cushing's syndrome in patients with different Cushing's subtypes. Two retrospective case series reported a *statistically significant* decrease in systolic blood pressure after treatment with osilodrostat phosphate in patients with PNCS/EAS or patients with Cushing's syndrome associated with ACC, with one of these studies also reporting a *statistically significant* decrease in diastolic blood pressure. The follow-up duration was not reported. One prospective single-arm study reported *"marginal improvements"* in systolic and diastolic blood pressure in most patients with different subtypes of Cushing's syndrome, but statistical measures and the follow-up duration were not reported.** **One retrospective case series reported that three patients with PNCS/EAS who had myopathy prior to treatment with osilodrostat phosphate, were able to ambulate, move around independently, and were discharged from hospital three to six months after treatment. No statistical measures were reported.**

Outcome	Evidence statement
	One retrospective case series reported that after treatment with osilodrostat phosphate, four of 13 patients with PNCS/EAS still had hypokalaemia. No statistical measures were reported. **One retrospective case series reported a *statistically significant* reduction in median fasting blood glucose levels in patients with PNCS/EAS after treatment with osilodrostat phosphate. One prospective single-arm study provided very low certainty evidence of *"marginal improvements"* in fasting blood glucose levels 12 weeks after treatment with osilodrostat phosphate in most patients with different subtypes of Cushing's syndrome. No statistical measures were reported.** **One retrospective case series reported a *statistically significant* reduction in HbA1c after treatment with osilodrostat phosphate in patients with PNCS/EAS. One prospective single-arm study provided very low certainty evidence of *"marginal improvements"* in HbA1c 12 weeks after treatment with osilodrostat phosphate in most patients with different subtypes of Cushing's syndrome. No statistical measures were reported.** **One retrospective case series reported that in patients with Cushing's syndrome associated with ACC who were treated with osilodrostat phosphate, *"three patients had diabetes mellitus and two had glucose intolerance that disappeared following the control of hypercortisolism."* No statistical measures were reported.** **One retrospective case series reported a *statistically significant* decrease in BMI after treatment with osilodrostat phosphate in patients with PNCS/EAS. One prospective single-arm study provided very low certainty evidence that only two of seven patients with different subtypes of Cushing's syndrome showed a reduction in BMI 12 weeks after treatment with osilodrostat phosphate. No statistical measures were reported.** **One prospective single-arm study reported that *"marginal improvements"* were observed in waist circumference in most patients with different subtypes of Cushing's syndrome 12 weeks after treatment with osilodrostat phosphate, but no statistical measures were reported.** **One prospective single-arm study provided very low certainty evidence that "*marginal improvements"* were observed in cholesterol, HDL and LDL cholesterol, and triglycerides in most patients with different subtypes of Cushing's syndrome 12 weeks after treatment with osilodrostat phosphate. No statistical measures were reported.** **One prospective single-arm study reported that "*no clinically relevant differences"* were observed in the BDI-II score at 12 weeks follow-up in patients with different subtypes of Cushing's syndrome, but no further details were provided.**
Important outcomes	
Reduction in treatment for Cushing's syndrome 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 syndrome, for example improvement in diabetes or hypertension. It may also provide them benefit as it reduces their medication burden. Three studies (one retrospective cohort study, two retrospective case series) provided evidence relating to reduction in treatment for Cushing's syndrome sequelae in patients with different subtypes of Cushing's syndrome. The retrospective cohort study compared outcomes from baseline to two weeks after treatment with osilodrostat phosphate or metyrapone in patients with different Cushing's subtypes (including Cushing's disease). The two retrospective case series provided non-comparative evidence in patients with different subtypes of

Outcome	Evidence statement
	Cushing's disease (excluding Cushing's disease). Follow-up timepoints were not stated in the two retrospective case series: <u>Reduction in antihypertensives</u> *Osilodrostat phosphate vs metyrapone* **At two weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=16) reported a reduction in the mean number of antihypertensives required by patients with Cushing's syndrome (including Cushing's disease) two weeks after treatment with osilodrostat phosphate (-1.0) whilst the number of antihypertensive drugs remained comparable after treatment with metyrapone (-0.3). No statistical measures were reported. **(VERY LOW)** *Osilodrostat phosphate vs no comparator* **At unspecified follow-up** • One retrospective case series (Dormoy et al 2023) (n=33) reported that in patients with PNCS/EAS the number of antihypertensive drugs reduced after treatment with osilodrostat phosphate (from a median of two antihypertensive before treatment to one after treatment). No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Tabarin et al 2022) (n=7) reported a *statistically significant* reduction in daily antihypertensive drug dosage after treatment with osilodrostat phosphate in patients with Cushing's syndrome associated with ACC (p=0.03). **(VERY LOW)** <u>Reduction in insulin</u> *Osilodrostat phosphate vs no comparator* **At unspecified follow-up** • One retrospective case series (Dormoy et al 2023) (n=33) reported that in patients with PNCS/EAS *"the number of patients requiring insulin reduced from 11 to eight due to improvement in fasting blood glucose and HbA1c"* after treatment with osilodrostat phosphate. No statistical measures were reported. **(VERY LOW)** <u>Reduction in potassium supplementation or spironolactone dosage</u> *Osilodrostat phosphate vs no comparator* **At unspecified follow-up** • One retrospective case series (Tabarin et al 2022) (n=7) reported that six of seven patients with Cushing's syndrome associated with ACC achieved a reduction in potassium supplementation (associated with an increase in serum potassium) after treatment with osilodrostat phosphate. No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Dormoy et al 2023) (n=33) reported that in patients with PNCS/EAS the median dose of spironolactone reduced from 25 mg/d to 0 mg/d after treatment with osilodrostat phosphate. No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Dormoy et al 2023) (n=33) reported that in patients with PNCS/EAS the median dose of potassium supplementation reduced from 3.3 g/d to 0 g/d after treatment with osilodrostat phosphate. No statistical measures were reported. **(VERY LOW)** **Osilodrostat phosphate vs metyrapone:** **One retrospective cohort study provided very low certainty evidence that there was a reduction in the mean number of antihypertensives required by**

Outcome	Evidence statement
	patients with Cushing's syndrome (including Cushing's disease) two weeks after treatment with osilodrostat phosphate (-1.0) whilst the number of antihypertensive drugs remained comparable after treatment with metyrapone (-0.3). No statistical measures were reported. **Osilodrostat phosphate vs no comparator:** **Two retrospective case series provided very low certainty evidence of a reduction in the number of antihypertensive drugs required after treatment with osilodrostat phosphate in patients with PNCS/EAS or Cushing's syndrome associated with ACC. One of these retrospective case series reported that the difference from baseline was *statistically significant*. One retrospective case series provided very low certainty evidence that there was a reduction in the number of patients with PNCS/EAS who required insulin after treatment with osilodrostat phosphate, but statistical measures and follow-up duration were not reported. Two retrospective case series provided very low certainty evidence that there was a reduction in the dose or number of patients with Cushing's syndrome associated with ACC or PNCS/EAS who required potassium supplementation or spironolactone after treatment with osilodrostat phosphate. Statistical measures and follow-up durations were not reported.**
Time to improvement **Certainty of evidence:** Very low	This is important to patients because current medicine for Cushing's syndrome 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 syndrome developing. Two retrospective case series provided non-comparative evidence relating to time to improvement in patients with PNCS/EAS or Cushing's syndrome associated with ACC. One retrospective case series provided evidence on time required to normalise 24-hour UFC in patients receiving different lines of treatment with osilodrostat phosphate. The second retrospective case series provided evidence on the number of patients with fully controlled hypercortisolism within one week, one month, around two months, and three months after treatment with osilodrostat phosphate: *Osilodrostat phosphate vs metyrapone* No evidence was identified for this outcome. <u>Time (weeks) required to normalise 24-hour urinary free cortisol (UFC) levels</u> *Osilodrostat phosphate vs no comparator* *Osilodrostat phosphate vs no comparator [patients receiving osilodrostat phosphate as first-line monotherapy]* • One retrospective case series (Dormoy et al 2023) (n=11) reported that the median time required to normalise 24-hour UFC was two weeks (range 1 to 56) in patients with PNCS/EAS after treatment with osilodrostat phosphate as first-line monotherapy. No statistical measures were reported. **(VERY LOW)** *Osilodrostat phosphate vs no comparator [patients who received prior treatment with other steroidogenesis inhibitor treatments before being replaced by osilodrostat phosphate monotherapy as second-line treatment]* • One retrospective case series (Dormoy et al 2023) (n=13) reported that the median time required to normalise 24-hour UFC levels was five weeks (range 1 to 41) in patients with PNCS/EAS after treatment with osilodrostat phosphate as second-line treatment. No statistical measures were reported. **(VERY LOW)**

Outcome	Evidence statement
	Osilodrostat phosphate vs no comparator [patients who received osilodrostat phosphate in combination with another anticortisolic treatment] • One retrospective case series (Dormoy et al 2023) (n=9) reported that the median time to normalise 24-hour UFC levels was four weeks (range 1 to 22) in patients with PNCS/EAS after treatment with osilodrostat phosphate in combination with another anticortisolic treatment. No statistical measures were reported. **(VERY LOW)** <u>Patients with fully controlled hypercortisolism</u> *Osilodrostat phosphate vs no comparator* **Within one week follow-up** • One retrospective case series (Tabarin et al 2022) (n=7) reported that control of hypercortisolism was obtained within one week of treatment with osilodrostat phosphate in two of seven patients with Cushing's syndrome associated with ACC. No statistical measures were reported. **(VERY LOW)** **Within one month follow-up** • One retrospective case series (Tabarin et al 2022) (n=7) reported that control of hypercortisolism was obtained within one month of treatment with osilodrostat phosphate in one of seven patients with Cushing's syndrome associated with ACC. No statistical measures were reported. **(VERY LOW)** **Around two months follow-up** • One retrospective case series (Tabarin et al 2022) (n=7) reported that control of hypercortisolism was obtained after two months of treatment with osilodrostat phosphate in two of seven patients with Cushing's syndrome associated with ACC. No statistical measures were reported. **(VERY LOW)** **After three months follow-up** • One retrospective case series (Tabarin et al 2022) (n=7) reported that control of hypercortisolism was obtained after three months of treatment with osilodrostat phosphate in two of seven patients with Cushing's syndrome associated with ACC. No statistical measures were reported. **(VERY LOW)** **Osilodrostat phosphate vs metyrapone:** **No evidence was identified for this outcome.** **Osilodrostat phosphate vs no comparator:** **Two retrospective case series provided very low certainty evidence relating to time to improvement after treatment with osilodrostat phosphate. One retrospective case series reported median time to normalise 24-hour UFC levels in patients with PNCS/EAS; two weeks after treatment with first-line osilodrostat phosphate monotherapy, five weeks after treatment with second-line osilodrostat monotherapy, and four weeks in osilodrostat phosphate combination treatment. One retrospective case series reported that control of hypercortisolism was obtained in all seven patients with Cushing's syndrome associated with ACC across variable timepoints[7]. No statistical measures were reported.**
Quality of life **Certainty of evidence:** 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.

[7] There was a discrepancy in the number of patients reported to have obtained control of hypercortisolism after treatment with osilodrostat phosphate and we have reported seven rather than eight patients as only seven patients were included in the study.

Outcome	Evidence statement
	One prospective single-arm study reported very limited evidence on QoL (measured using the Cushing's QoL) in patients with different subtypes of Cushing's syndrome: *Osilodrostat phosphate vs metyrapone* No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **At 12 weeks follow-up** • One prospective single-arm study (Tanaka et al 2020) (n=9) reported that "*no clinically relevant differences"* were observed in the Cushing's QoL score at 12 weeks follow-up in patients with different subtypes of Cushing's syndrome. **(VERY LOW)** **Osilodrostat phosphate vs metyrapone:** **No evidence was identified for this outcome.** **Osilodrostat phosphate vs no comparator:** **One prospective single-arm study reported that "*no clinically relevant differences"* were observed in the Cushing's QoL score at 12 weeks follow-up, but no further details were provided.**
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	
Frequency of adverse events **Certainty of evidence:** 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, four studies (one retrospective cohort study, one prospective single-arm study, two retrospective case series) provided evidence relating to the number of patients with different Cushing's subtypes experiencing adverse events. The retrospective cohort study compared outcomes from baseline to 12 weeks after treatment with osilodrostat phosphate or metyrapone in patients with different Cushing's subtypes (including Cushing's disease). One prospective single-arm study and two retrospective case series provided non-comparative evidence in patients with different subtypes of Cushing's disease (excluding Cushing's disease). Follow-up duration in the prospective single-arm study was 30 days after the last dose of osilodrostat, but follow-up timepoints were not stated in the two retrospective case series: <u>Number of patients with adverse events</u> *Osilodrostat phosphate vs no comparator* **30-day safety follow-up after last dose of osilodrostat phosphate** • One prospective single-arm study (Tanaka et al 2020) (n=9) reported that all nine (100%) patients with different subtypes of Cushing's syndrome experienced at least one adverse event at 30-day safety follow-up after last dose of osilodrostat phosphate. Six (66.7%) were grade 3 adverse events, and eight (88.9%) were suspected to be treatment related. No statistical measures were reported. **(VERY LOW)**

Outcome	Evidence statement
	• One prospective single-arm study (Tanaka et al 2020) (n=9) reported that four (44.4%) patients with different subtypes of Cushing's syndrome experienced a serious adverse event[8] at 30-day safety follow-up after last dose of osilodrostat phosphate. Two (22.2%) were suspected to be treatment related. No statistical measures were reported. **(VERY LOW)** <u>Number of patients with adverse events of special interest</u> *Osilodrostat phosphate vs metyrapone* **At 12 weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=16) reported that two patients with Cushing's syndrome (including Cushing's disease) required potassium replacement therapy for hypokalaemia after treatment with osilodrostat phosphate and three patients required potassium replacement therapy for hypokalaemia after treatment with metyrapone. No statistical measures were reported. **(VERY LOW)** • One retrospective cohort study (Detomas et al 2022) (n=16) reported that one patient with Cushing's syndrome (including Cushing's disease) had a progressive increase of the QTc interval after treatment with osilodrostat phosphate and zero patients had a progressive increase of the QTc interval after treatment with metyrapone. No statistical measures were reported. **(VERY LOW)** *Osilodrostat phosphate vs no comparator* **30-day safety follow-up after last dose of osilodrostat phosphate** • One prospective single-arm study (Tanaka et al 2020) (n=9) reported adverse events of special interest at 30-day safety follow-up after last dose of osilodrostat phosphate were observed in seven (77.8%) patients with different subtypes of Cushing's syndrome: two (22.2%) patients experienced hypokalaemia (one [1.11%] was a grade 3 adverse event); one (11.1%) patient experienced weight increase (this was not a grade 3 adverse event); 7 (77.8%) patients experienced adrenal insufficiency (two [22.2%] were grade 3 adverse events); one (1.11%) patient experienced steroid withdrawal syndrome (this was a grade 3 adverse event). Of the adverse events of special interest, six (66.7%) were suspected to be treatment related (of which 2 [22.2%] were grade 3 adverse events). No statistical measures were reported. **(VERY LOW)** **At unspecified follow-up** • One retrospective case series (Tabarin et al 2022) (n=7) reported that one patient with Cushing's syndrome associated with ACC had worsening of hypokalaemia (from 3.2 to 2.8 mmol/L) during concomitant treatment with osilodrostat phosphate (60mg/day) and cabozantinib. No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Tabarin et al 2022) (n=7) reported that three (42.86%) patients with Cushing's syndrome associated with ACC experienced mild and transient adrenal insufficiency after treatment with osilodrostat phosphate. No statistical measures were reported. **(VERY LOW)** **Osilodrostat phosphate vs metyrapone:** **One retrospective cohort study provided very low certainty evidence relating to adverse events of special interest in patients with Cushing's syndrome (including Cushing's disease). Potassium replacement therapy for hypokalaemia was required by two patients after treatment with osilodrostat phosphate and three patients after treatment with metyrapone. One patient had a progressive increase of the QTc interval after treatment with**

[8] All serious adverse events were grade 3; no grade 4 adverse events or serious events were observed.

Outcome	Evidence statement
	osilodrostat phosphate and zero patients who were treated with metyrapone. No statistical measures were reported. **Osilodrostat phosphate vs no comparator:** **One prospective single-arm study provided very low certainty evidence about the number and type of adverse events of different severity grades at 30-day safety follow-up after the last dose of osilodrostat phosphate. Grade 3 adverse events were experienced by 66.7% of patients with different subtypes of Cushing's syndrome and 88.9% were suspected to be treatment related. The prospective single-arm study also provided very low certainty evidence reported that 77.8% patients with different subtypes of Cushing's syndrome experienced an adverse event of special interest at 30-day safety follow-up after the last dose of osilodrostat phosphate. Of the adverse events of special interest, 66.7% were suspected to be treatment related (of which 2 [22.2%] were grade 3 adverse events). One retrospective case series reported worsening of hypokalaemia in one patient with Cushing's syndrome associated with ACC after treatment with osilodrostat phosphate and cabozantinib, and 42.86% patients experienced mild and transient adrenal insufficiency after treatment with osilodrostat phosphate. No statistical measures were reported.**
Frequency of grade 3 or 4 adverse events **Certainty of evidence:** 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, one retrospective case series provided evidence relating to frequency of grade 3 or 4 adverse events. The retrospective case series provided non-comparative evidence in patients with paraneoplastic Cushing's syndrome/ectopic adrenocorticotropin syndrome. The follow-up duration was not clearly stated: *Osilodrostat phosphate vs metyrapone* No evidence was identified for this outcome. <u>Frequency of grade 3 or 4 adverse events</u> *Osilodrostat phosphate vs no comparator* **At unspecified follow-up** • One retrospective case series (Dormoy et al 2023) (n=33) reported that eight (24%) patients with PNCS/EAS experienced a grade 3 or 4 adverse event after treatment with osilodrostat phosphate. No statistical measures were reported. **(VERY LOW)** **Osilodrostat phosphate vs metyrapone:** **No evidence was identified for this outcome.** **Osilodrostat phosphate vs no comparator:** **One retrospective case series provided very low certainty evidence that 24% of patients with PNCS/EAS experienced a grade 3 or 4 adverse event after treatment with osilodrostat phosphate. No statistical measures were reported.**
Adverse events leading to discontinuation **Certainty of evidence:** 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, four studies (one retrospective cohort study, one prospective single-arm study, two retrospective case series) provided evidence relating to the number of patients with different subtypes of Cushing's disease (excluding Cushing's disease)

Outcome	Evidence statement
	discontinuing treatment due to adverse events. The retrospective cohort study compared outcomes from baseline to 12 weeks after treatment with osilodrostat phosphate or metyrapone. The prospective single-arm study and two retrospective case series provided non-comparative evidence. The prospective single-arm study reported outcomes at 48 weeks follow-up, but follow-up timepoints were not clearly stated in the two retrospective case series: <u>Number of patients with adverse events leading to treatment discontinuation</u> *Osilodrostat phosphate vs metyrapone* **At 12 weeks follow-up** • One retrospective cohort study (Detomas et al 2022) (n=16) reported that one patient with Cushing's syndrome (including Cushing's disease) discontinued treatment with osilodrostat phosphate and two patients discontinued treatment with metyrapone due to adverse events at 12 weeks follow-up. No statistical measures were reported. **(VERY LOW)** *Osilodrostat phosphate vs no comparator* **30-day safety follow-up after last dose of osilodrostat phosphate** • One prospective single-arm study (Tanaka et al 2020) (n=9) reported the number of patients with different subtypes of Cushing's syndrome who discontinued treatment with osilodrostat phosphate due to adverse events at 30-day safety follow-up after the last dose of osilodrostat phosphate: three (33.3%) patients discontinued treatment due to all grades of adverse events; one (1.11%) was a grade 3 adverse event. No statistical measures were reported. **(VERY LOW)** **At unspecified follow-up** • One retrospective case series (Dormoy et al 2023) (n=33) reported that zero (0%) patients with PNCS/EAS discontinued treatment with osilodrostat phosphate due to adverse events (liver function abnormalities or alteration in corrected QT interval). No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Tabarin et al 2022) (n=7) reported that zero (0%) patients with Cushing's syndrome associated with ACC discontinued treatment with osilodrostat phosphate due to adverse events. No statistical measures were reported. **(VERY LOW)** **Osilodrostat phosphate vs metyrapone:** **One retrospective cohort study provided very low certainty evidence on the number of patients with Cushing's syndrome (including Cushing's disease) discontinuing treatment due to adverse events at 12 weeks follow-up: one patient treated with osilodrostat phosphate and two patients treated with metyrapone. No statistical measures were reported.** **Osilodrostat phosphate vs no comparator:** **One prospective single-arm study and two retrospective case series provided very low certainty evidence relating to discontinuation of treatment due to adverse events. The prospective single-arm study reported discontinuation of treatment with osilodrostat phosphate at 30-day safety follow-up after last dose of osilodrostat phosphate in 33.3% of patients with different subtypes of Cushing's syndrome; 1.11% was a grade 3 adverse event. Two retrospective case series reported that 0% of patients with PNCS/EAS or Cushing's syndrome associated with ACC discontinued treatment with osilodrostat phosphate due to adverse events. Statistical measures and follow-up durations were not reported.**

Outcome	Evidence statement
Abbreviations ACC: adrenocortical carcinoma; BDI-II: Beck's Depression Inventory-II; BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; NR: not reported; PNCS/EAS: paraneoplastic Cushing's syndrome/ectopic adrenocorticotropin syndrome; QoL: quality of life; UFC: urinary free cortisol; ULN: upper limit of normal.	

In people with endogenous Cushing's syndrome (excluding 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 for subgroups of patients.**

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

Outcome	Evidence statement
Osilodrostat phosphate regimens	One retrospective cohort study (Detomas et al 2022) provided details on the median doses (mg) of osilodrostat phosphate at two weeks (4.0 [range 3.0 to 7.0]); at four weeks (6.0 [range 4.0 to 20.0]); and at 12 weeks (7.0 [range 6.0 to 10.0]). The same study provided details on the median doses (mg) of metyrapone at two weeks (1,000 [range 500 to 2,000]); at four weeks (1,250 [range 500 to 2,000]); and at 12 weeks (1,250 [range 1,000 to 2,000]). One retrospective case series (Dormoy et al 2023) provided details on the median initial dose of osilodrostat phosphate: 4 mg/day (range 1 to 60) and a maximum dose of osilodrostat phosphate: 20 mg/day (range 4 to 100). This study also provided details on the starting dose (mg/day) for osilodrostat phosphate, depending on treatment regimens: osilodrostat phosphate as first-line monotherapy (n=11): 10 (2 to 40) [maximum dose 20 (10 to 100)]; osilodrostat phosphate monotherapy as second-line treatment (n=13): 4 (1 to 20) [maximum dose 25 (4 to 60)]; and osilodrostat phosphate in combination with another anticortisolic treatment (n=9): 4 (1 to 60) [maximum dose 40 (4 to 80)]. Treatment regimens included titration (without combination with hydrocortisone or another glucocorticoid replacement therapy), block and replace, or titration followed by block and replace. One prospective single-arm study (Tanaka et al 2020) reported that osilodrostat phosphate during dose titration was 2 to 30 mg twice daily (dose could be down titrated to 1 mg twice daily if required). The same study also reported that the median duration of exposure to osilodrostat phosphate was 12 weeks (range 1.3 to 81.9): >8 weeks of exposure (n=7 [77.8%]); >16 weeks of exposure (n=4 [44.4%]); >48 weeks of exposure (n=2 [22.2%]). This study also reported the median highest dose was 5 mg/day (range 2 to 10); the median average dose was 2.143 mg/day (range 1.16 to 7.54); the median dose with longest duration was 2.0 mg/day (range 1 to 10); the median average dose (excluding dose interruption [0 mg/day]) was

Outcome	Evidence statement
	2.571 mg/day (range 1.17 to 7.54); and the median dose with longest duration (excluding dose interruption [0 mg/day]) was 2 mg/day (range 1 to 10). One retrospective case series (Tabarin et al 2022) did not report schedules/doses used for osilodrostat phosphate.

6. Discussion

This review examined the clinical effectiveness, safety and cost effectiveness of osilodrostat phosphate compared to standard care in patients with endogenous Cushing's syndrome (excluding those with Cushing's disease). The critical outcomes of interest were total clinical disease response, biochemical disease response, and sequelae of Cushing's syndrome. The important outcomes of interest were reduction in treatment for Cushing's syndrome, time to improvement, quality of life (QoL), activities of daily living (ADLs), and safety.

No randomised controlled trials were identified that provided evidence on any critical or important outcomes. Evidence for the clinical effectiveness of osilodrostat phosphate and safety was available from one retrospective cohort study (Detomas et al 2022), one prospective single-arm study (Tanaka et al 2020) and two retrospective case series (Tabarin et al 2022, Tanaka et al 2020). The retrospective cohort study (Detomas et al 2022) provided comparative evidence (osilodrostat phosphate and metyrapone) for critical outcomes (biochemical disease response and sequelae of Cushing's syndrome) and important outcomes (reduction in treatment for Cushing's syndrome sequelae and safety). The prospective single-arm study (Tanaka et al 2020) and two retrospective case series (Tabarin et al 2022, Tanaka et al 2020) provided non-comparative evidence for critical outcomes (clinical disease response, biochemical disease response and sequelae of Cushing's syndrome) and important outcomes (reduction in treatment for Cushing's syndrome sequelae, time to improvement, QoL, and safety). No evidence was identified comparing osilodrostat phosphate versus no adrenal steroidogenesis inhibitors or ketoconazole. No studies were identified that reported evidence on ADLs. No studies were identified that reported on relevant subgroups of patients that would benefit more from treatment with osilodrostat phosphate, and no cost effectiveness studies were identified.

The retrospective cohort study, prospective single-arm study and two retrospective case series included in this evidence review were all undertaken in adults (sample sizes ranged from seven to 33 patients). The studies were conducted in France (two studies), Germany or Japan. The two studies conducted in France were undertaken in some of the same centres and by some of the same authors but included different patients. The included study populations were in patients with different types of Cushing's syndrome, and these varied across and within the included studies, as did the baseline intensity of the hypercortisolism. The retrospective cohort study (Detomas et al 2022) included both in scope patients with Cushing's syndrome (ectopic Cushing's syndrome, cortisol-producing adrenal adenoma, or adrenocortical carcinoma [ACC]), and out of scope patients with Cushing's disease. The Cushing's syndrome subtypes differed across treatment arms, mainly in relation to the proportion of patients with Cushing's disease (i.e. 62.5% receiving osilodrostat phosphate and 25% receiving metyrapone) or ectopic Cushing's syndrome (i.e. 12.5% receiving osilodrostat phosphate and 50% receiving metyrapone). As this study included a greater proportion of in scope patients with Cushing's syndrome compared to patients with Cushing's disease, the evidence was included in this evidence review. The prospective single-arm study (Tanaka et al 2020) included patients with different subtypes of endogenous Cushing's syndrome (other than Cushing's disease), including adrenal adenoma, ectopic corticotropin syndrome, or adrenocorticotropic hormone (ACTH)-independent macronodular adrenal hyperplasia (AIMAH. One retrospective case series (Dormoy et al 2023) included patients with paraneoplastic Cushing's syndrome/ectopic adrenocorticotropin syndrome (PNCS/EAS), of which the primary tumours differed, and some had metastasised. The second retrospective case series (Tabarin et al 2022) included patients with Cushing's syndrome associated with adrenocortical carcinomas (ACC). Follow-up assessments were performed up to 12 weeks in the retrospective cohort study and up to 48 weeks in the prospective single-arm study, but timepoints were not always clearly stated in the two retrospective case series.

The retrospective cohort study (Detomas et al 2022), including 16 patients with endogenous Cushing's syndrome, included patients receiving osilodrostat phosphate monotherapy or metyrapone monotherapy. Baseline characteristics in terms of sex, age and biochemical measures were similar across both treatment arms. The mean duration of treatment was statistically significantly longer in patients receiving metyrapone than patients receiving osilodrostat phosphate (17 weeks versus 9.5 weeks; p<0.0001, respectively). The prospective single-arm study (Tanaka et al 2020) provided non-comparative evidence for nine patients with different subtypes of endogenous Cushing's syndrome. The study comprised two study periods (dose titration period from weeks 0 to 12 and treatment period from weeks 12 to 48) and an optional extension period (weeks 48 to 72). Seven patients completed the dose titration period, two patients completed the treatment period, and no patients completed the optional extension period. The main reasons for study discontinuation were reported to be due to adverse events or patient/guardian decision. The median duration of exposure to osilodrostat phosphate was 12 weeks at final cut-off.

The two retrospective case series (Dormoy et al 2023, Tabarin et al 2022) were both multicentre studies conducted in France. Although the centres and authors were similar across the two studies, the patient populations differed. The initial and maximum doses varied in one retrospective case series (Dormoy et al 2023) dependent on treatment regimen (i.e. first-line or second-line osilodrostat phosphate monotherapy or combined treatment). The treatment strategy also varied across patients in this retrospective case series, including titration (without combination with hydrocortisone or another glucocorticoid replacement therapy), a block and replace regimen upfront, or initial titration followed by block and replace secondarily. The authors acknowledged the variability in daily dosage of osilodrostat phosphate and differences in prescribing practices between centres in hypercortisolism of similar intensity. The second retrospective case series (Tabarin et al 2022) did not provide details in relation to osilodrostat phosphate regimens, other than stating that they were *"highly variable between patients in terms of starting dose, dose increases and duration of titration steps"*. It is unclear what impact the differences in doses and regimens may have had on the outcomes.

Previous and concomitant treatments also varied across and within the studies. For patients in the retrospective cohort study (Detomas et al 2022), except for two patients with ACC who were previously treated with chemotherapy and mitotane, the remaining 14 patients had not previously received drug therapy and were not receiving concomitant drug therapy for hypercortisolism. The prospective single-arm study (Tanaka et al 2020) included four patients with adrenal adenoma who had not received any prior treatment for Cushing's syndrome, whilst five patients had received prior metyrapone, of which, one patient with ectopic corticotropin syndrome had received cisplatin, irinotecan, and amrubicin in addition to metyrapone and had also undergone prior surgery. Previous and concomitant treatment also varied across patients included in the two retrospective case series (Dormoy et al 2023, Tabarin et al 2022). Dormoy et al (2023) included 11 patients receiving osilodrostat phosphate monotherapy as first-line treatment, 13 patients previously treated with other anticortisolic treatments and subsequently receiving osilodrostat phosphate monotherapy as second-line treatment, and nine patients who were treated with osilodrostat phosphate in combination with another anticortisolic treatment. Tabarin et al (2022) included three patients who had not previously received treatments prior to osilodrostat phosphate (but one of these patients received an anti-neoplastic treatment in combination with osilodrostat phosphate) and four patients who had previously received surgery and mitotane, and radiotherapy or chemotherapy (three of whom received mitotane or cabozantinib in combination with osilodrostat phosphate).

Comparative evidence was available for biochemical disease response, sequelae of Cushing's syndrome, reduction in treatment for Cushing's syndrome sequelae, and safety. Where statistical measures were reported, these indicated that outcomes were comparable between patients treated with osilodrostat phosphate or metyrapone (i.e. not statistically significantly

different). Non-comparative evidence was available for clinical disease response, biochemical disease response, sequelae of Cushing's syndrome, reduction in treatment for Cushing's syndrome sequelae, time to improvement, QoL, and safety. The evidence indicated improvements in hypercortisolism and sequelae of Cushing's syndrome (with the exception of Becks Depression Inventory-II which showed *"no clinically relevant differences"*) after treatment with osilodrostat phosphate. Statistical measures were not reported for all outcomes, but where they were reported, improvements were shown to be statistically significant compared to baseline. The non-comparative evidence showed that *"no clinically relevant differences"* were observed in QoL, and that most patients experienced an adverse event, with the most common being adrenal insufficiency. Methods used to measure outcomes differed across studies or were not clearly reported and it is unclear whether the use of different methods may have had an impact on the findings. For example, one study measured serum and urinary cortisol levels using various immunoassays or liquid chromatography-mass spectrometry assays. One study reported evidence on QoL, but it was limited narrative information stating that *"no clinically relevant differences"* were observed in the Cushing's QoL score measure.

The certainty in the evidence was very low in all four studies for all outcomes reported. Factors reducing confidence in the outcomes reported include the retrospective design of three of the studies very serious risk of bias in all four studies (it was unclear whether the recruitment of study participants was consecutive and study methodology was not always clearly described) and serious indirectness due to the lack of a comparator in three of the studies. Further limitations include the small numbers of patients included in the studies and the number of patients lost to follow-up or discontinuing treatment, which reduced the number of patients assessed at longer follow-up durations. One prospective single-arm study reported outcomes in terms of clinical relevance, but no further details were provided. The remaining studies included in this evidence review did not comment on minimally clinically important difference thresholds for the outcomes reported.

7. Conclusion

This review examined the clinical effectiveness, safety and cost effectiveness of osilodrostat phosphate compared to standard care in patients with endogenous Cushing's syndrome (excluding those with Cushing's disease). The critical outcomes of interest were total clinical disease response, biochemical disease response, and sequelae of Cushing's syndrome. The important outcomes of interest were reduction in treatment for Cushing's syndrome, time to improvement, quality of life (QoL), activities of daily living (ADLs), and safety. No evidence was identified comparing osilodrostat phosphate versus no adrenal steroidogenesis inhibitors or ketoconazole. No evidence was available for one important clinical effectiveness outcome (ADLs) and no evidence was available on cost effectiveness. No evidence was identified regarding any subgroups of patients that would benefit more from treatment with osilodrostat phosphate.

Evidence for the clinical effectiveness of osilodrostat phosphate and safety was available from one retrospective cohort study reporting comparative evidence for osilodrostat phosphate versus metyrapone, and three studies (one prospective single-arm study, and two retrospective case series) providing non-comparative evidence. The studies differed in terms of the population, treatment doses and regimens, and previous or concomitant treatments. The certainty in the evidence was very low in all four studies for all outcomes reported. Factors reducing confidence in the outcomes reported include the retrospective design of three of the studies very serious risk of bias in all four studies (it was unclear whether the recruitment of study participants was consecutive and study methodology was not always clearly described) and serious indirectness due to the lack of a comparator in three of the studies. Further limitations include the small numbers of patients included in the studies and the number of patients lost to follow-up or discontinuing treatment, which reduced the number of patients assessed at longer follow-up durations.

Given the limitations of the evidence about the clinical effectiveness and safety of osilodrostat phosphate compared to standard care in patients with Cushing's syndrome, it is difficult to assess the certainty of the findings.

Appendix A PICO document

The review questions for this evidence review are:

1) In people with endogenous Cushing's syndrome (excluding Cushing's disease), what is the clinical effectiveness of osilodrostat phosphate compared to standard care?
2) In people with endogenous Cushing's syndrome (excluding Cushing's disease), what is the safety of osilodrostat phosphate compared to standard care?
3) In people with endogenous Cushing's syndrome (excluding 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 endogenous Cushing's syndrome (excluding Cushing's disease) requiring pharmacological treatments, who are either waiting for, not suitable for, or not responding to interventions including surgery.[9] [Endogenous Cushing's syndrome can be either ACTH-dependent or ACTH-independent. Aetiologies of endogenous Cushing's syndrome that might be referred to in literature include, but are not restricted to: 1) Non-pituitary ACTH-dependent causes (ectopic Cushing's syndrome): • Neuroendocrine tumours • Small-cell lung carcinomas 2) ACTH-independent causes: • Adrenal adenomas • Adrenocortical carcinomas • Nodular hyperplasia of the adrenal gland] [Pituitary ACTH-dependent aetiologies causing Cushing's disease are not relevant here] [Reasons for requiring pharmacological therapy could include: • Optimisation pre-surgery or radiotherapy • Response to surgery is inadequate e.g., persistent hypercortisolism post-surgery • Contraindications to surgery due to co-morbidities resulting in unsuitability for surgery • Patient wish/need to delay intervention including surgery • Patient refusal of surgery or radiotherapy] [Pharmacological bridging may be given prior to radiotherapy or whilst awaiting surgery]
I-Intervention	Oral osilodrostat phosphate

[9] A PICO amendment was agreed on the 1st November 2023 to reflect that people with endogenous Cushing's syndrome (excluding Cushing's disease) could have received previous pharmacological treatment for Cushing's syndrome.

	[Patients may be receiving supportive care to treat the physical sequelae of Cushing's syndrome such as treatment for diabetes, hypertension, hyperlipidaemia]
C-Comparator	Standard care which is: • No adrenal steroidogenesis inhibitors • Ketoconazole • Metyrapone [Patients may be receiving supportive care.] [Osilodrostat phosphate is an adrenal steroidogenesis inhibitor. No adrenal steroidogenesis inhibitor could therefore include patients receiving placebo or supportive care alone]
O-Outcomes	**<u>Clinical Effectiveness</u>** Minimally clinically important differences (MCIDs) are not known unless stated. Outcomes measured at 3 – 6 months are of particular interest. <u>Critical to decision-making:</u> • **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 syndrome** *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.] <u>Important to decision-making:</u> • **Reduction in treatment for Cushing's syndrome sequelae**

	This is important to patients because they may be getting symptomatic relief with improvement in their physical health consequences of Cushing's syndrome, 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 antihypertensives, reduction in need for statin.] • **Time to improvement** *This is important to patients because current medicine for Cushing's syndrome 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 syndrome 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: o Timed task completion (e.g., timed repeatable test such as dressing, meal preparation or patient specific ADL goal) o ADLs assessment using a tool (e.g., Barthel Index (BI) or Independence in Activities of Daily Living (ADL) o 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: o Toxicity o Frequency of adverse events o Frequency of grade 3 or 4 adverse events o 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 syndrome 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.

One 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

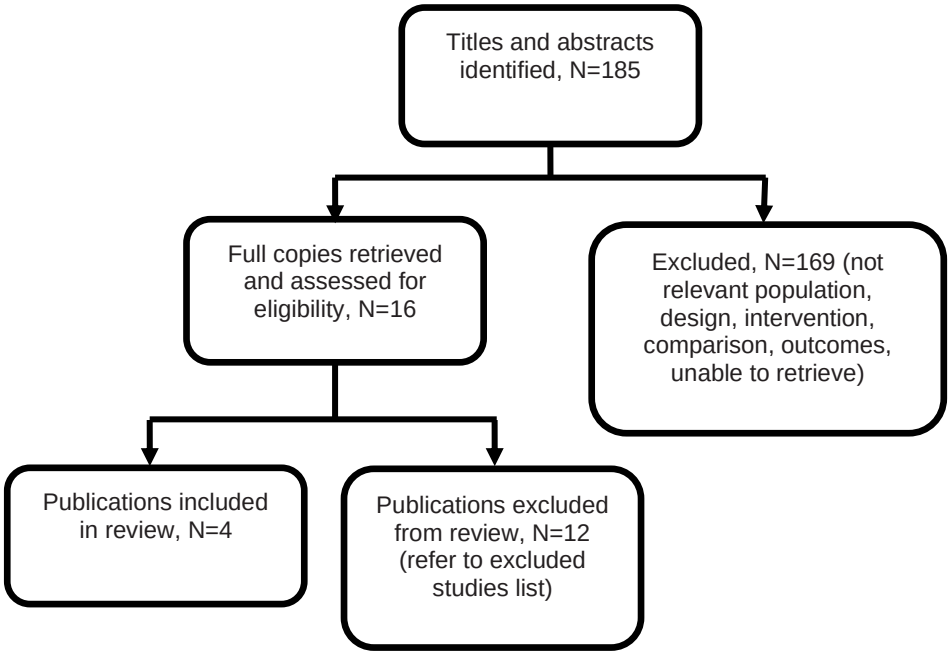
1	Cushing Syndrome/
2	cushing*.ti,ab,kf.
3	hypercortisolism.ti,ab,kf.
4	Pituitary ACTH Hypersecretion/
5	(acth adj (dependent or independent or hypersecret* or secret*)).ti,ab,kf.
6	1 or 2 or 3 or 4 or 5
7	(osilodrostat or isturisa or cy11b1).ti,ab,kf.
8	6 and 7
9	exp animals/ not humans/
10	8 not 9
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 16 references were obtained in full text and assessed for relevance. Of these, four references 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 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.	The study population does not meet PICO criteria because the 137 patients included in the study were adult patients with confirmed persistent or recurrent Cushing's disease.
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.	The study population does not meet PICO criteria because the 106 patients included in the LINC 3 extension study were adult patients with confirmed persistent or recurrent Cushing's disease.
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.	The study population does not meet PICO criteria because the 73 patients included in the study were adult patients with confirmed Cushing's disease.

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) RCT included in the Cushing's Disease evidence review; corrections have been implemented in the full text paper.
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.	The study population does not meet the PICO criteria because most patients were treated for Cushing's disease (29 of 33 patients).
Dougherty JA, Desai DS, Herrera JB. Osilodrostat: A Novel Steroidogenesis Inhibitor to Treat Cushing's Disease. Annals of Pharmacotherapy. 2021;55(8):1050-60.	Not a systematic review of Cushing's Disease; relevant studies included in this review have been returned by the search and will be considered separately.
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.	The study population does not meet the PICO criteria; the 16 patients included in the extension study had Cushing's disease.
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.	Not a systematic review of Cushing's Syndrome and Disease; relevant studies included in this review have been returned by the search and will be considered separately.
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.	The study population does not meet the PICO criteria; the 86 patients included in the RCT extension study were treated for Cushing's disease.
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 in Cushing's disease. Pituitary. 2016;19(2):138-48.	The study population does not meet the PICO criteria; the two cohorts included patients with Cushing's disease.
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.	The study population does not meet the PICO criteria; the 73 patients included in the RCT were treated for confirmed Cushing's disease.
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.	The study population does not meet the PICO criteria; the 60 patients included in the RCT were treated for Cushing's disease.
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.	The study population does not meet the PICO criteria; the 137 patients included in the RCT were treated for Cushing's disease.
Simoes Correa Galendi J, Correa Neto ANS, Demetres M, Boguszewski CL, Nogueira V. Effectiveness of Medical Treatment of Cushing's Disease: A Systematic	Systematic review of Cushing's Disease; relevant studies included in this review have been returned by the search and will be considered separately.

Study reference	Reason for exclusion
Review and Meta-Analysis. Frontiers in Endocrinology. 2021;12:732240.	
Tritos NA. Adrenally Directed Medical Therapies for Cushing Syndrome. Journal of Clinical Endocrinology & Metabolism. 2021;106(1):16-25.	Not a systematic review of Cushing's Syndrome (narrative review discussing current treatments); relevant studies included in this review have been returned by the search and will be considered separately.

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
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. Front. Endocrinol. 2022;13:903545. **Study location** Germany **Study type** Retrospective cohort study **Study aim** To compare the efficacy of short-term treatment with metyrapone versus osilodrostat phosphate on cortisol levels in patients with endogenous Cushing's syndrome **Study dates** December 2017 to December 2021	**Inclusion criteria** Patients with endogenous Cushing's syndrome who were treated with metyrapone or osilodrostat phosphate as monotherapy for at least four weeks **Exclusion Criteria** Not stated **Total sample size** N=16 **No. of participants in each treatment group** Osilodrostat phosphate: n=8 Metyrapone: n=8 **Baseline characteristics** Age (years), mean (SEM) Osilodrostat phosphate: 50.1 (4.1) Metyrapone: 52.1 (3.8) Sex, female (n, %) Osilodrostat phosphate: 7 (87.5)	**Interventions** Osilodrostat phosphate: dose not reported at baseline Median (range) dose (mg) after treatment At 2 weeks: 4.0 (3.0 to 7.0) At 4 weeks: 6.0 (4.0 to 20.0) At 12 weeks: 7.0 (6.0 to 10.0) **Comparators** Metyrapone dose not reported at baseline Median (range) dose (mg) after treatment At 2 weeks: 1,000 (500 to 2,000) At 4 weeks: 1,250 (500 to 2,000) At 12 weeks: 1,250 (1,000 to 2,000)	**Critical outcomes** **Biochemical disease response** Defined as serum cortisol level (µg/dl), mean (SEM) Osilodrostat phosphate: Week 2 (n=8): 21.1 (6.4); vs baseline p=0.99 Week 4 (n=8): 18.7 (4.3); vs baseline p=0.82 Week 12 (n=4): 13 (1.6); vs baseline p= 0.44 Metyrapone: Week 2 (n=8): 21 (3.8); vs baseline p=0.61 Week 4 (n=8): 22.3 (2); vs baseline p=0.67 Week 12 (n=5): 8.3 (2.5); vs baseline p= 0.007 *Change[10] from baseline to follow-up:* *Week 2: osilodrostat phosphate: -14.4% vs metyrapone -4.9% (p=0.63)*	This study was appraised using the JBI checklist for cohort studies 1. Yes 2. Not applicable 3. Yes 4. No 5. No 6. No 7. Unclear 8. Unclear 9. No 10. No 11. Yes Other comments: This study included patients with Cushing's syndrome (n=9) and patients with Cushing's disease (n=7). As a greater proportion of patients had Cushing's syndrome, it was agreed that the study should be included in the Cushing's syndrome evidence review. This was a retrospective cohort study and patients in the two

[10] The delta (change) percentage from baseline to a subsequent study timepoint was calculated to assess the alteration of a parameter during pharmacological treatment with osilodrostat phosphate or metyrapone.

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	Metyrapone: 3 (37.5) Cushing's subtype, n (%) Cushing's disease: 7 (43.75% Cushing's syndrome: 9 (56.25%) (ectopic Cushing's syndrome: 5; cortisol-producing adrenal adenoma: 2; adrenocortical carcinoma: 2) Treatment by Cushing's subtype, n (%) Cushing's disease: Osilodrostat phosphate: 5 (62.5); Metyrapone 2 (25) Ectopic Cushing's syndrome: Osilodrostat phosphate 1 (12.5); Metyrapone 4 (50) Cortisol-producing adrenal adenoma: Osilodrostat phosphate 1 (12.5); Metyrapone 1 (12.5) Adrenocortical carcinoma: Osilodrostat phosphate 1 (12.5); Metyrapone 1 (12.5) Biochemical analysis, mean (SEM) Basal serum cortisol (µg/dl): Osilodrostat phosphate 22.8 (3.5); Metyrapone 27.8 (5.5) Urinary free cortisol (µg/d): Osilodrostat phosphate 817 (644); Metyrapone 758 (309)		*Week 4: osilodrostat phosphate: -17.2% vs metyrapone -4.2% (p=0.57)* *Week 12: osilodrostat phosphate: -25.8% vs metyrapone -51.1% (p=0.23)* Defined as serum cortisol level below 25 µg/dl (normal range 5 to 25 µg/dl), n (%) At week 4 Osilodrostat phosphate (n=8): 5 (62.5) Metyrapone (n=8): 5 (62.5) At week 12 Osilodrostat phosphate (n=4): 4 (100) Metyrapone (n=5): 5 (100) Defined as mean UFC (µg/d) (SEM) Osilodrostat phosphate: Week 2 (n=NR): 74 (36); vs baseline p=0.44 Week 4 (n=7): 117 (34); vs baseline p=0.41 Week 12 (n=4): 131 (55); vs baseline p= 0.55 Metyrapone: Week 2 (n=NR): 748 (434); vs baseline p=0.99	treatment arms were recruited from the same University Hospital over the same time period. Cushing's syndrome was diagnosed according to established criteria and the authors acknowledged the differences between treatment groups in terms of Cushing's syndrome subtypes and clinical characteristics. No attempts were made to identify confounding factors or implement strategies to deal with them. The authors reported procedures used to perform hormonal and electrocardiogram analysis, but no further details were provided on measures of reliability (i.e. inter- or intra-observer reliability). Follow-up assessments were performed at weeks 2, 4 and 12. Outcomes were not always reported for all patients, but reasons for discontinuation or loss to follow up were described: two patients discontinued metyrapone after four weeks due to adverse events; one patient receiving metyrapone was lost to follow-up before week 12; osilodrostat phosphate was discontinued in one patient at week 4 due to adverse events and in two patients after tumour resection, one patient receiving osilodrostat phosphate was lost to follow-up at week 12. Apart from patients with ACC who previously received platinum-based chemotherapy (i.e. etoposide,

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	Late-night salivary: Osilodrostat phosphate 0.9 (0.5); Metyrapone 2.3 (1.1) <u>Blood pressure (mmHg), mean (SEM)</u> Systolic blood pressure: Osilodrostat phosphate: 139.4 (4.8); Metyrapone: 142.0 (7.6) Diastolic blood pressure: Osilodrostat phosphate: 83.7 (4.1); Metyrapone: 83.5 (4.6)		Week 4 (n=6): 281 (87); vs baseline p=0.73 Week 12 (n=3): 53 (25); vs baseline p= 0.62 *Change[10] from baseline to follow-up:* *Week 2: osilodrostat phosphate: -68.4% vs metyrapone –21.3% (p=0.15)* *Week 4: osilodrostat phosphate: -50.1% vs metyrapone -37.3% (p=0.59)* *Week 12: osilodrostat phosphate: -51.5% vs metyrapone -71.5% (p=0.40)* <u>Defined as normalised mean UFC (normal range 0 to 70 µg/d), n (%)</u> <u>At week 4</u> Osilodrostat phosphate (n=7): 3 (42.9) Metyrapone (n=6): 0 <u>At week 12</u> Osilodrostat phosphate (n=4): 2 (50) Metyrapone (n=3): 2 (66.7) **Sequelae of Cushing's syndrome** <u>Defined as systolic and diastolic blood pressure (mmHg) - change[10] from baseline to week 2</u>	doxorubicin, cisplatin) plus mitotane, no other patients had received previous or concomitant pharmacological treatment for hypercortisolism. Three patients treated with osilodrostat phosphate and wo patients treated with metyrapone had undergone previous surgery and one patient treated with metyrapone had undergone prior radiotherapy. Mean (SEM) treatment duration was 9.5 (1.1) weeks in the osilodrostat phosphate group and 17.0 (3.4) weeks in the metyrapone group (p<0.0001). Source of funding: DFG German Research Foundation and the European Reference Network on Rare Endocrine Conditions (Endo-ERN).

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			Osilodrostat phosphate: systolic (n=NR): -3.7% (mean 134.2 [SEM 5.7]; p=0.07); diastolic: -16.2% (mean 69.2 [SEM 6.6]; p=0.07) Metyrapone: systolic (n=NR): +0.5% (mean 142.5 [SEM 6.9]; p=0.12); diastolic: +4.9% (mean 88.7 [SEM 4.2]; p=0.35) **Important outcomes** **Reduction in treatment for Cushing's syndrome sequelae** Defined as reduction in number of antihypertensives required, mean Osilodrostat phosphate (n=NR): -1.0 Metyrapone (n=NR): -0.3 **Safety** Defined as number of patients requiring potassium replacement therapy for hypokalaemia, n Osilodrostat phosphate (n=8): 2 Metyrapone (n=8): 3 Defined as QTc prolongation, n Osilodrostat phosphate (n=8): 1[11] Metyrapone (n=8): 0	

[11] One patient receiving osilodrostat phosphate had their treatment discontinued at week 12 due to a QTc of 503 ms.

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			Defined as adverse events leading to treatment discontinuation, n Osilodrostat phosphate (n=8): 1 patient with Cushing's disease (adverse events were depression, asthenia, and nausea) Metyrapone (n=8): 2 patients with endogenous Cushing's syndrome (adverse events were asthenia and dizziness)	
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. **Study location** France **Study type** Retrospective case series **Study aim**	**Inclusion criteria** Patients with poor initial clinical status due to intense hypercortisolism and/or severe comorbidities related to underlying PNCS/EAS **Exclusion Criteria** Not stated **Total sample size** N=33 **No. of participants in each treatment group** Osilodrostat phosphate: N=33 Control: None	**Interventions** Osilodrostat phosphate: median initial dose 4 mg/day (range 1 to 60) Maximum dose: 20 mg/day (range 4 to 100) Starting dose (mg/day), median (range) – subgroups of patients Osilodrostat phosphate as first-line monotherapy (n=11): 10 (2 to 40) [maximum dose 20 (10 to 100)] Prior treatment with other steroidogenesis inhibitor treatments (metyrapone	Follow-up durations not reported, unless otherwise stated **Critical outcomes** **Clinical disease response** Defined as clinical signs of hypercortisolism, measured using an arbitrary clinical score reflecting Cushing's syndrome severity[15] After treatment with osilodrostat phosphate: 0.21 *Difference compared to baseline: p<0.0001* **Biochemical disease response** Defined as serum cortisol (ng/mL), median (range)	This study was appraised using the JBI checklist for case series 1. No 2. Unclear 3. Unclear 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes

[15] The score was adapted from Ferriere et al (2017) and included 7 items: obesity of the face and trunk; purple stretch marks; myopathy; supraclavicular fat pad; buffalo hump; facial erythrosis; and facial plethora. In premenopausal women, the score included the same previous items as well as two additional items: hirsutism and amenorrhea. In postmenopausal women, the same items as previously were used, with the exception of amenorrhea. Each of the clinical items was scored as 0 (absent), 1 (low), or 2 (high), resulting in a total score of 14, 18, and 16, respectively, in men, premenopausal women, and postmenopausal women. To standardise these scores, the value 1.0 corresponded to the maximum in each aforementioned patient category.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
To assess the efficacy and safety of osilodrostat phosphate for the treatment of patients with paraneoplastic Cushing's syndrome/ectopic adrenocorticotropin syndrome **Study dates** May 2019 to March 2022	**Baseline characteristics – all participants** Age, years (median, range): 65 (24 to 85) Sex, male (n): 18 BMI (kg/m^2), median (range): 25 (18 to 40) Systolic blood pressure (mmHg), median (range): 143 (102 to 187) Diastolic blood pressure (mmHg), median (range): 77 (56 to 101) Underlying ACTH-secreting NETs, n Gastrointestinal NETs: 4 Small-cell lung neuroendocrine carcinoma: 8 Bronchial carcinoid tumours/well-differentiated NETs located in the bronchi: 7 Pancreatic well-differentiated NETs: 5 Ear, nose, throat NETs: 1 Parotid NETs: 1 Occult tumours: 2 NETs of unknown origin: 2 Medullary thyroid carcinoma: 2	and/or ketoconazole, or cabergoline) before being replaced by osilodrostat phosphate monotherapy as second-line treatment (n=13): 4 (1 to 20) [maximum dose 25 (4 to 60)] Osilodrostat phosphate in combination with another anticortisolic treatment (metyrapone [with or without cabergoline] and/or ketoconazole) (n=9): 4 (1 to 60) [maximum dose 40 (4 to 80)] Regimens used, n Titration (without combination with hydrocortisone or another glucocorticoid replacement therapy): 6 Block and replace: 16 Titration followed by block and replace: 11 **Comparators** None	Osilodrostat phosphate first-line monotherapy (n=11): 10 (10 to 528) [27.6 nmol/L (range 27.6 to 1,457 nmol/L)] *Difference compared to baseline: p<0.001* Defined as 24-hour UFC (ug/24-hours), median (range) Osilodrostat phosphate first-line monotherapy (n=11): 5 (5 to 743) [13.8 nmol/24-hours (range 13.8 to 2,050 nmol/24-hours)] *Difference compared to baseline: p<0.001* Prior treatment with other steroidogenesis inhibitor treatments before being replaced by osilodrostat phosphate monotherapy as second-line treatment ((n=10 uncontrolled patients, i.e. 24-hour UFC >ULN): 12 (5 to 57) [33 nmol/24-hours (range 13.8 to 157 nmol/24-hours)] *Difference compared to baseline: p<0.01* (In the remaining 3 patients whose 24-hour UFC was normalised at the time of osilodrostat phosphate treatment, UFC levels were maintained [i.e. 24-hour UFC <ULN]) Osilodrostat phosphate in combination with another anticortisolic treatment (n=9): 28	Other comments: This was a retrospective case series including 'data from 33 patients with PNCS/EAS treated with osilodrostat phosphate from May 2019 and March 2022'. Clinical assessment of Cushing's syndrome was evaluated using data collected from medical charts and forms using an adapted semi-quantitative arbitrary clinical score. Although valid methods were used to measure serum and urinary cortisol levels, various immunoassays or liquid chromatography-mass spectrometry assays were used at different study centres. Detailed baseline characteristics were reported for all patients and some baseline characteristics and outcomes were reported for subgroups of patients, depending on their treatment line and regimen (i.e. osilodrostat phosphate first-line monotherapy, osilodrostat phosphate second-line monotherapy, osilodrostat phosphate in combination with metyrapone and/or ketoconazole). Follow-up duration was not clearly stated. This study appears to have been conducted in some of the same centres and by some of the same authors as those mentioned by Tabarin et al 2022, but the two retrospective case series appear to

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Neuroendocrine prostate cancer: 1 Clinical signs of hypercortisolism, measured using an arbitrary clinical score reflecting Cushing's syndrome severity[15] 0.44 UFC (µg/24-hours), median (range) 1,867 (80 to 32,950) (5,152 nmol/24-hours [220 to 90,942 nmol/24-hours]) Serum cortisol (ng/mL), median (range) 484 (141 to 1,350) (1,335 nmol/L [389 to 3,726 nmol/L])[12] Comorbidities/hypercortisolism-related complications[13], n Hypokalaemia (kalaemia ≤3.5 mmol/L): 30 (91%) [median kalaemia 2.5 mmol/L; minimum 1.5 mmol/L] Diabetes: 21 (64%) Hypertension: 30 (91%)[14] Myopathy: 3		(5 to 158) [77 nmol/24-hours (range 13.8 to 436 nmol/24-hours)] *Difference compared to baseline: p<0.01* Defined as number of patients with normalisation of 24-hour UFC (ULN range 45 to 80 µg/24-hours), n (%) Osilodrostat phosphate first-line monotherapy (n=11): 9 (82) (median delay of 2 weeks [range 1 to 56 weeks]) Prior treatment with other steroidogenesis inhibitor treatments before being replaced by osilodrostat phosphate monotherapy as second-line treatment (n=13): 13 (100) Osilodrostat phosphate in combination with another anticortisolic treatment (n=9): 6 (67) **Sequelae of Cushing's syndrome** Defined as systolic and diastolic blood pressure (mmHg) after treatment with osilodrostat phosphate, median (range)	include different patient populations. Thirty of 33 patients (91%) had intense hypercortisolism at diagnosis (defined as an increase in 24-hour UFC >5 times the ULN). Twenty five of 33 patients (76%) had very intense hypercortisolism with 24-hour UFC ≥10 times ULN. All patients were hospitalised and received symptomatic treatment for comorbidities, including potassium supplementation, antimineralocorticoid spironolactone, anti-hypertensives, and oral antidiabetic drugs or insulin. Previous treatments were discontinued for various reasons, including drug intolerance, lack of efficacy or partial efficacy, or shortage of drug supply. Conversion factor for UFC: 1 µg/24-hours=2.76 nmol/24 hours. Conversion factor for serum cortisol: 1 ng/mL=2.76 nmol/L. Eighteen of 22 patients with metastatic disease died during study follow-up, between 0.4 and 140 months after initial diagnosis.

[12] There was a discrepancy between the figures reported in the narrative and we have used the figure that corresponds to that also reported in the table of clinical and hormonal characteristics of patients at diagnosis (i.e. median serum cortisol level 484 ng/mL [range 141 to 1,350 ng/mL] rather than 357 ng/mL (range 141 to 1,150 ng/mL]).
[13] Patients may have experienced more than one comorbidity/hypercortisolism-related complication.
[14] There was a discrepancy in the number of patients reported to have hypertension (reported as 29 patients in the description of baseline characteristics and as 30 patients in the results section and clinical characteristics table); we have presented the figure reported in the table and results section (i.e. n=30).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Other severe PNCS/EAS-related comorbidity (DVT, fracture, heart failure, psychiatric disorders, sepsis): 20 (61) **Baseline characteristics – subgroups of patients** 24-hour UFC (ug/24-hours), median (range) Osilodrostat phosphate first-line monotherapy (n=11): 1,678 (190 to 32,950) [4,631 nmol/24-hours (range 524 to 90,942 nmol/24 hours)] Prior treatment with other steroidogenesis inhibitor treatments before being replaced by osilodrostat phosphate monotherapy as second-line treatment (n=10 uncontrolled patients, i.e. 24-hour UFC >ULN): 158 (85 to 6,500) [436 nmol/24-hours (range 234 to 17,940 nmol/24 hours)]; n=3 patients had normalised 24-hour UFC Osilodrostat phosphate in combination with another anticortisolic treatment (n=9): 588 (20 to 21,448) [1,622 nmol/L (range 55 to 59,196 nmol/L)] Serum cortisol (ng/mL), median (range) Osilodrostat phosphate first-line monotherapy (n=11): 357		Systolic: 125 (100 to 168) *Difference compared to baseline: p<0.0001* Diastolic: 69 (49 to 90) *Difference compared to baseline: p<0.001* Defined as patients with myopathy 3 to 6 months after treatment with osilodrostat phosphate After treatment with osilodrostat phosphate, the 3 patients with myopathy were able to ambulate, move around independently, and were discharged from hospital Defined as number of patients with hypokalaemia, n (%) At osilodrostat phosphate treatment initiation (after potassium supplementation and/or spironolactone treatment): 13 (39) [median 3.8 mmol/L (range 2.6 to 4.9 mmol/L)] After osilodrostat phosphate treatment: 4 (12) [median 4.2 mmol/L (range 3.1 to 5.0 mmol/L)] Defined as fasting blood glucose levels (g/L) after treatment with osilodrostat phosphate, median (range) 0.9 (0.7 to 1.8)	All but one patient died of metastatic disease progression. One patient died after control of hypercortisolism - although the diagnosis of acute adrenal insufficiency was not identified and appropriate treatment was not administered, the authors stated that the clinical features prior to death suggested a probable acute adrenal crisis. Source of funding: The French Association of Patients with Adrenal Diseases, Novartis and Recordati Pharma.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	(141 to 1,150) [985 nmol/L (range 389 to 3,174 nmol/L)]		*Difference compared to baseline: p<0.0001* Defined as HbA1c (%) after treatment with osilodrostat phosphate, median (range) 6.1 (4.9 to 7.2) *Difference compared to baseline: p<0.05* Defined as BMI (kg/m^2), median (range) After treatment with osilodrostat phosphate: 23.4 (19 to 36) *Difference compared to baseline: p<0.01* **Important outcomes** **Reduction in treatment for Cushing's syndrome sequelae** Defined as reduction in number of patients requiring insulin, n The number of patients requiring insulin reduced from 11 to 8 due to improvement in fasting blood glucose and HbA1c Defined as number of antihypertensive drugs, median Before treatment with osilodrostat phosphate: 2 After treatment with osilodrostat phosphate: 1 Defined as spironolactone (mg/d), median	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Before treatment with osilodrostat phosphate: 25 After treatment with osilodrostat phosphate: 0 Defined as potassium supplementation (g/d), median Before treatment with osilodrostat phosphate: 3.3 After treatment with osilodrostat phosphate: 0 **Time to improvement** Defined as time (week) required to normalise 24-hour UFC, median (range) Osilodrostat phosphate first-line monotherapy (n=11): 2 (1 to 56) Prior treatment with other steroidogenesis inhibitor treatments before being replaced by osilodrostat phosphate monotherapy as second-line treatment (n=13): 5 (1 to 41) Osilodrostat phosphate in combination with another anticortisolic treatment (n=9): 4 (1 to 22) **Safety** Defined as frequency of grade 3 or 4 adverse events after treatment with osilodrostat phosphate, n (%) Adrenal insufficiency: 8 (24)	

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			Defined as adverse events leading to discontinuation of osilodrostat phosphate, n (%) Liver function abnormalities: 0 (0) Alteration in corrected QT interval: 0 (0)	
Tabarin A, Haissaguerre M, Lassole H, Jannin A, Paepegaey AC, Chabre O, Young J. Efficacy and tolerance of osilodrostat in patients with Cushing's syndrome due to adrenocortical carcinomas. Eur J Endocrinol. 2022;186(2):K1-K4. **Study location** France (six centres) **Study type** Retrospective case series **Study aim** To evaluate the efficacy and safety of osilodrostat phosphate for the treatment of patients with Cushing's syndrome associated with ACC **Study dates**	**Inclusion criteria** Patients with cortisol-secreting ACC **Exclusion Criteria** Not stated **Total sample size** N=7 **No. of participants in each treatment group** Osilodrostat phosphate: n=7 Control: None **Baseline characteristics** Age, years (range): 29 to 86 Sex, female (n): 4 ACC ENSAT tumour grade (n) Stage IV: 5 Stage III: 1 Stage II: 1	**Interventions** Osilodrostat phosphate: starting dose, dose increases, and duration of titration steps were highly variable between patients (no other details provided) **Comparators** None	Follow-up durations were not clearly stated **Critical outcomes** **Clinical disease response** Defined as improvement in Cushing's clinical score after treatment with osilodrostat phosphate, n/N[16] Score of 0: 2/7 Score of 1: 3/7 Not applicable:[17] 2/7 **Biochemical disease response** Defined as decrease in serum cortisol level (nmol/L) within 2 weeks of treatment with osilodrostat phosphate, mean[18] 330 (47) *Difference compared to baseline: p=0.02* Defined as mean UFC (x ULN) after treatment with osilodrostat phosphate, mean[18]	This study was appraised using the JBI checklist for case series 1. No 2. Unclear 3. Unclear 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. Unclear 10. Unclear Other comments: This was a retrospective case series; limited details were reported on study methods and how patients were recruited. All patients had clinical features of Cushing's syndrome associated with an increase in UFC and clinical characteristics were

[16] A decrease in a Cushing score for clinical appearance: 0 reflects lack of symptoms; 2 reflects florid Cushing (as assessed by experienced endocrinologists).
[17] One patient experienced COVID-19 infection and one patients was lost to follow-up.
[18] The variance in the reported data was not stated and it was therefore unclear whether the figures reflect the standard deviation or the standard error of the mean.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Not stated	Cushing clinical score, n[16] Score of 1: 1 Score of 2: 6 Serum cortisol level (nmol/L), mean[18] 989 (159) UFC (x ULN), mean[18] 10.5 (5.0) Blood pressure (mmHg), mean[18] Systolic: 168 (8) Daily anti-hypertensive drug dosage (no details provided on measure), mean[18] 4.0 (1.4)		0.6 (0.1) *Difference compared to baseline: p=0.03* **Sequelae of Cushing's syndrome** Defined as blood pressure (mmHg) after treatment with osilodrostat phosphate, mean[18] Systolic: 120 (7) *Difference compared to baseline: p=0.03* Defined as number of patients with diabetes mellitus and glucose intolerance after treatment with osilodrostat phosphate, n The authors stated that "*Three patients had diabetes mellitus and two had glucose intolerance that disappeared following the control of hypercortisolism."* **Important outcomes** **Reduction in treatment for Cushing's syndrome sequelae** Defined as reduction in daily antihypertensive drug dosage after treatment with osilodrostat phosphate (no details provided on measure), mean[18] 1.9 (1.1)	reported for all patients. Limited statistical analyses were performed and details on methods used were not provided, including which statistical variance was reported for outcomes. Reasons for loss to follow-up were described. This study appears to have been conducted in some of the same centres and by some of the same authors as those mentioned by Dormoy et al 2023, but the two retrospective case series appear to include different patient populations. Four patients had recurrence or tumour progression of a previously treated ACC (treated with surgery, mitotane, and radiotherapy or chemotherapy. Three patients were diagnosed with ACC during the workup of Cushing's syndrome. Three patients previously diagnosed with ACC and one newly diagnosed patient received other anti-neoplastic treatments (mitotane or cabozantinib) in addition to osilodrostat phosphate. Five of seven patients had intense hypercortisolism (defined by an increase in UFC ≥5.0× ULN and/or the mean of several daily serum cortisol concentrations ≥1000 nmol/L). The authors stated that osilodrostat phosphate fully controlled hypercortisolism in all seven patients at daily doses of 4

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			Difference compared to baseline: p=0.03 Defined as an increase in serum potassium associated with a reduction in potassium supplementation or spironolactone dosage after treatment with osilodrostat phosphate, n/N 6/7 **Time to improvement** Defined as number of patients with fully controlled hypercortisolism after treatment with osilodrostat phosphate, n/N Within 1 week: 2/7 Within 1 month: 1/7 Around 2 months: 2/7 3 months: 2/7 **Safety** Defined as number of patients with adverse events, n Mild and transient adrenal insufficiency: 3 Defined as worsening of hypokalaemia, n/N One patient had worsening of hypokalaemia (from 3.2 to 2.8 mmol/L) during concomitant treatment with osilodrostat	mg (n=1), 8 mg (n=1), 10 mg (n=1), 20 mg (n=1) and 40 mg (n=3). The authors reported that no treatment escape was observed; but its duration was limited to 13.7 (4.2) weeks (range: 1 to 29) due to death following progression of ACC (n=4 patients), COVID-19 infection (n=1 patient), being lost to follow-up (n=1 patient) or the resolution of Cushing's syndrome after surgical removal of peritoneal metastasis (n=1 patient). Source of funding: None

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			phosphate (60mg/day) and cabozantinib Defined as adverse events leading to discontinuation of osilodrostat phosphate, n/N 0/7	
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. **Study location** Japan **Study type** Prospective phase II, single-arm, multicentre study **Study aim** To evaluate the efficacy, safety and tolerability of osilodrostat phosphate for the treatment of Japanese patients with different types of endogenous Cushing's syndrome other than Cushing's disease	**Inclusion criteria** Adults aged 18 to 85 years with confirmed Cushing's syndrome, including: ectopic corticotropin syndrome, adrenal adenoma, adrenal carcinoma, AIMAH/PMAH, or PPNAD. Patients were expected to have remained in a stable condition for at least 5 months prior to the study entry; patients on medical treatment for hypercortisolism due to Cushing's syndrome were required to complete appropriate washout periods **Exclusion Criteria** Patients with Cushing's disease or hypersensitivity to osilodrostat phosphate or drugs of similar chemical classes **Total sample size** N=9 patients enrolled; n=7 (dose titration period, weeks 0 to 12); n=2 (continued treatment with osilodrostat phosphate, weeks 12 to 48);	**Interventions** Osilodrostat phosphate: during dose titration, 2 to 30 mg bid (dose could be down titrated to 1 mg bid if required) Osilodrostat phosphate dose and duration of exposure (all patients at final cut-off: n=9) Median exposure (range), weeks: 12.00 (1.3 to 81.9) >8 weeks of exposure, n (%): 7 (77.8) >16 weeks of exposure, n (%): 4 (44.4) >48 weeks of exposure, n (%): 2 (22.2) Median highest dose (range), mg/day 5.0 (2 to 10) Median average dose (range), mg/day: 2.143 (1.16 to 7.54)	Follow-up duration: 48 weeks **Critical outcomes** **Biochemical disease response** Defined as reduction in morning serum cortisol level (nmol/L) after treatment with osilodrostat phosphate, median Week 12 (n=7): 235 *Median % change from baseline: –56.07* Week 24 (n=3): *median % change from baseline: –68.96* Week 48 (n=2): *median % change from baseline: –67.39* Defined as actual mUFC (nmol/24-hours) after treatment with osilodrostat phosphate, median (range) Week 4 (n=8): 185.70 (26.1 to 635.8) *Median (range) % change from baseline: –83.32 (–99.4 to –38.8)* Week 8 (n=8): 72.60 (–9.0 to 723.5)	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 8. Yes 9. No 10. Unclear Other comments: This was a prospective, multicentre, single-arm study. It was unclear whether patients were recruited consecutively. Confirmed Cushing's syndrome was evidenced by an mUFC level >1.3 × ULN and as per other specific eligibility criteria for the study for each type of Cushing's syndrome. Due to the limited number of patients, with various disease types, data were mainly

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study dates Data cut-off date: October 2018	n=0 (optional extension period, weeks 48 to 72) Safety analysis set: N=9 **No. of participants in each treatment group** Osilodrostat phosphate: N=9 Control: None **Baseline characteristics** Age (years), median (range): 46 (20 to 75) Age ≥65 years, n (%): 3 (33.3) Sex (female, n (%): 7 (77.8) Ethnicity, n (%): Japanese: 9 (100) BMI (kg/m^2), median (range): 23.88 (19.31 to 38.19) Type of disease, n (%) AIMAH: 1 (11.1) Adrenal adenoma: 5 (55.6) Ectopic corticotropin syndrome: 3 (33.3) Previous treatment, n (%)[19] Surgery: 1 (11.1)	Median dose with longest duration (range), mg/day: 2.0 (1 to 10) Median average dose (range) excluding dose interruption (0 mg/day), mg/day: 2.571 (1.17 to 7.54) Median dose with longest duration (range) excluding dose interruption (0 mg/day), mg/day: 2.0 (1 to 10) **Comparators** None	*Median (range) % change from baseline: –94.37 (–99.8 to 94.0)* Week 12 (n=7): 77.10 (6.2 to 141.2) *Median (range) % change from baseline: –94.47 (–99.0 to –52.6)* Week 24 (n=3): 63.90 (40.9 to 893.6) *Median (range) % change from baseline: –91.57 (–99.5 to –85.2)* Week 48 (n=2): 511.30 (67.5 to 955.1) *Median (range) % change from baseline: –95.04 (–99.1 to –91.0)* Defined as the proportion of mUFC responders after treatment with osilodrostat phosphate, n (%) [95% CI] *Week 12 (n=9)* Complete response: 6 (66.7) [29.9 to 92.5] Partial response: 1 (11.1) [0.3 to 48.2] Overall response: 7 (77.8) [40.0 to 97.2] *Week 24 (n=3)* Complete response: 2 (66.7) [9.4 to 99.2]	described on an individual basis or by disease type and is therefore assessed as a case series. Some outcomes were reported for patients with different disease types or separately in patients who had or had not received prior metyrapone. These populations were not specified as subgroups of interest for this evidence review and outcomes are therefore not presented for these subgroups. Appropriate washout periods for patients on medical treatment for hypercortisolism due to Cushing's syndrome were: 1 week for steroidogenesis inhibitors (metyrapone, trilostane, ketoconazole); 6 months for mitotane; 4 weeks for mifepristone, and at least 5 half-lives or 30 days, whichever was longer, for other investigational therapies. All patients had a 30-day safety follow-up after the last dose of osilodrostat phosphate. Six patients discontinued study treatment; n=4 due to adverse events (of which, one patient discontinued due to grade 3 hypokalaemia that started before treatment with osilodrostat phosphate), n=2 due to patient/guardian decision. There were no on-treatment deaths.

[19] Four patients with adrenal adenoma were naïve to any treatment for Cushing's syndrome.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Medication: 5 (55.6)[20] Radiotherapy: 0 (0.0) Morning serum cortisol level (nmol/L), median All patients (n=9): 535.0 Actual mUFC value (nmol/24-hours), median (range) All patients (n=9): 841.80 (277.9 to 10,595.6)		Partial response: 1 (33.3) [0.8 to 90.6] Overall response: 3 (100) [29.2 to 100.0] *Week 48 (n=2)* Complete response: 1 (50.0) [1.3 to 98.7] Partial response: 1 (50.0) [1.3 to 98.7] Overall response: 2 (100) [15.8 to 100.0] **Sequelae of Cushing's syndrome** Defined as % change in blood pressure (mmHg) from baseline to 12 weeks after treatment with osilodrostat phosphate, range Systolic (n=7): -31.3 to 9.3 Diastolic (n=7): -33.2 to 9.9 Defined as % change in fasting glucose (mmol/L) from baseline to 12 weeks after treatment with osilodrostat phosphate, range n=7: -27.2 to 24.2[21] Defined as % change in HbA1c (%) from baseline to 12 weeks	The authors reported that, overall, *"no clinically relevant differences"* were observed in any of the quality of life scores evaluated (Cushing's QoL and BDI-II) at week 12, but no further details were provided. Source of funding: Novartis

[20] All five patients received metyrapone, of which, three had a complete response and one patient each had a partial response and no response as the best response to metyrapone [last regimen prior to washout before entering study]). One patient with ectopic corticotropin syndrome (received cisplatin, irinotecan, and amrubicin in addition to metyrapone and had prior surgery.

[21] The normal range for fasting glucose was 3.89 to 6.05 mmol/L in 4 patients and 4.05 to 6.05 in 3 patients.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			after treatment with osilodrostat phosphate, range n=7: -20.3 to 6.2[22] Defined as % change in BMI (kg/m^2) from baseline to 12 weeks after treatment with osilodrostat phosphate, range n=7: -3.1 to 7.4 Defined as % change in waist circumference (cm) from baseline to 12 weeks after treatment with osilodrostat phosphate, range n=7: -4.9 to 2.9 Defined as % change in cholesterol (mmol/L) from baseline to 12 weeks after treatment with osilodrostat phosphate, range n=7: -23 to 23[23] Defined as % change in HDL cholesterol (mmol/L) from baseline to 12 weeks after treatment with osilodrostat phosphate, range n=7: -34.4 to 15.5[24] Defined as % change in LDL cholesterol (mmol/L) from baseline to 12 weeks after	

[22] The normal range for HbA1c was 4.6 to 6.2 in 5 patients, 4.9 to 6 in one patient, and NA to 6.4 in one patient.
[23] The normal range for cholesterol was 3.23 to 5.66 in 5 patients, NA to 5.66 in one patient, and 3.36 to 5.69 or NA to 5.66 in one patient.
[24] The normal range for HDL cholesterol was 1.03 to NA in all 7 patients.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			treatment with osilodrostat phosphate, range n=7: -24.9 to 26.5[25] Defined as % change in triglycerides (mmol/L) from baseline to 12 weeks after treatment with osilodrostat phosphate, range n=7: -56.7 to 46.8[26] Defined as BDI-II score The authors stated that *"no clinically relevant differences*" were observed in BDI-II scores at week 12 **Important outcomes** **QoL** Measured using Cushing's QoL The authors stated that overall, *"no clinically relevant differences*" were observed in the QoL score evaluated using Cushing's QoL at week 12 **Safety (n=9)** Defined as number of patients experiencing at least one adverse event, n (%) All grades: 9 (100) Grade 3: 6 (66.7)	

[25] The normal range for LDL cholesterol was NA to 3.59 in 5 patients and NA to 3.62 in 2 patients.
[26] The normal range for triglycerides was 0.4 to 1.68 in 5 patients, 0.34 to 1.69 in one patient, and NA to 1.68 in one patient.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Suspected to be treatment related: All grades: 8 (88.9) Grade 3: 4 (44.4) <u>Defined as number of patients experiencing serious adverse events, n (%)</u> All grades: 4 (44.4)[27] Suspected to be treatment-related: All grades: 2 (22.2) Grade 3: 2 (22.2) <u>Defined as number of patients experiencing adverse events of special interest, n (%)</u> <u>Adrenal hormone precursor accumulation-related adverse events</u> *Hypokalaemia* All grades: 2 (22.2) Grade 3: 1 (11.1) *Weight increase* All grades: 1 (11.1) Grade 3: 0 (0) <u>Hypocortisolism-related adverse events</u>	

[27] All serious adverse events were grade 3; no grade 4 adverse events or serious events were observed.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Adrenal insufficiency[28] All grades: 7 (77.8) Grade 3: 2 (22.2) *Steroid withdrawal syndrome*[29] All grades: 1 (11.1) Grade 3: 1 (11.1) Suspected to be treatment related: All grades: 6 (66.7) Grade 3: 2 (22.2) Defined as number of patients discontinuing osilodrostat phosphate due to adverse events, n (%)[30] All grades: 3 (33.3) Grade 3: 1 (11.1)	

Abbreviations

ACC: adrenocortical carcinoma; ACTH: adrenocorticotropic hormone; AIMAH/PMAH: ACTH-independent macronodular adrenal hyperplasia/primary macronodular adrenal hyperplasia; BDI-II: Beck's Depression Inventory-II; bid: twice daily; CI: confidence interval; DVT: deep vein thrombosis; HDL: high density lipoprotein; LDL: low density lipoprotein; NETs: neuroendocrine tumours; NR: not reported; PNCS/EAS: paraneoplastic Cushing's syndrome/ectopic adrenocorticotropin syndrome; PPNAD: primary pigmented nodular adrenal dysplasia; QoL: quality of life; SEM: standard error of the mean; UFC: urinary free cortisol; ULN: upper limit of normal.

[28] Adrenal insufficiency includes the reported terms of adrenal insufficiency, hypoadrenalism and adrenal gland hypofunction.
[29] Steroid withdrawal syndrome includes the reported term of glucocorticoid withdrawal syndrome.
[30] One patient had grade 3 hypokalaemia leading to discontinuation that started at day –1 (i.e., before treatment with osilodrostat phosphate) and was not counted in any adverse event.

Appendix F Quality appraisal checklists

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 endogenous Cushing's syndrome (excluding Cushing's disease), what is the clinical effectiveness of osilodrostat phosphate compared to standard care?

Table 2: Osilodrostat phosphate or 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									
Serum cortisol level (µg/dl), change from baseline to 2 weeks follow-up [benefit indicated by greater reduction]									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	8	8	Osilodrostat phosphate: -14.4%; metyrapone -4.9% (p=0.63)	Critical	VERY LOW
Serum cortisol level (µg/dl), change from baseline to 4 weeks follow-up [benefit indicated by greater reduction]									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	8	8	Osilodrostat phosphate: -17.2%; metyrapone -4.2% (p=0.57)	Critical	VERY LOW
Serum cortisol level (µg/dl), change from baseline to 12 weeks follow-up [benefit indicated by greater reduction]									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	8	8	Osilodrostat phosphate: -25.8%; metyrapone -51.1% (p=0.23)	Critical	VERY LOW
Serum cortisol level below 25 µg/dl (normal range 5 to 25 µg/dl), n (%) at 4 weeks follow-up									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	8	8	Osilodrostat phosphate: 5 (62.5) Metyrapone: 5 (62.5)	Critical	VERY LOW

Serum cortisol level below 25 µg/dl (normal range 5 to 25 µg/dl), n (%) at 12 weeks follow-up									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	4	5	Osilodrostat phosphate: 4 (100) Metyrapone: 5 (100)	Critical	VERY LOW
mUFC level (µg/d), change from baseline to 2 weeks follow-up [benefit indicated by greater reduction]									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	NR	NR	Osilodrostat phosphate: -68.4%; metyrapone - 21.3% (p=0.15)	Critical	VERY LOW
mUFC level (µg/d), change from baseline to 4 weeks follow-up [benefit indicated by greater reduction]									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	7	6	Osilodrostat phosphate: -50.1%; metyrapone -37.3% (p=0.59)	Critical	VERY LOW
mUFC level (µg/d), change from baseline to 12 weeks follow-up [benefit indicated by greater reduction]									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	4	3	Osilodrostat phosphate: -51.5%; metyrapone -71.5% (p=0.40)	Critical	VERY LOW
Normalised mUFC level (normal range 0 to 70 µg/d), n (%) at 4 weeks follow-up									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Serious imprecision[3]	7	6	Osilodrostat phosphate: 3 (42.9) Metyrapone: 0	Critical	VERY LOW
Normalised mUFC level (normal range 0 to 70 µg/d), n (%) at 12 weeks follow-up									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	4	3	Osilodrostat phosphate: 2 (50) Metyrapone: 2 (66.7)	Critical	VERY LOW

Sequelae of Cushing's syndrome – 1 retrospective cohort study									
Systolic blood pressure (mmHg), change from baseline to 2 weeks follow-up [benefit indicated by greater reduction]									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	NR	NR	Osilodrostat: -3.7% (mean 134.2 [SEM 5.7]; p=0.07) Metyrapone: +0.5% (mean 142.5 [SEM 6.9]; p=0.12)	Critical	VERY LOW
Diastolic blood pressure (mmHg), change from baseline to 2 weeks follow-up [benefit indicated by greater reduction]									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	NR	NR	Osilodrostat: -16.2% (mean 69.2 [SEM 6.6]; p=0.07) Metyrapone: +4.9% (mean 88.7 [SEM 4.2]; p=0.35)	Critical	VERY LOW
Reduction in treatment for Cushing's syndrome sequelae – 1 retrospective cohort study									
Reduction in number of antihypertensives required after two weeks, mean [benefit indicated by greater reduction]									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	NR	NR	Osilodrostat: -1.0 Metyrapone: -0.3	Important	VERY LOW
Safety – 1 retrospective cohort study									
Number of patients requiring potassium replacement therapy for hypokalaemia at 12 weeks follow-up, n									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	8	8	Osilodrostat phosphate: 2 Metyrapone: 3	Important	VERY LOW
Number of patients with QTc prolongation at 12 weeks follow-up, n									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Serious imprecision[3]	8	8	Osilodrostat phosphate: 1[a] Metyrapone: 0	Important	VERY LOW

Adverse events leading to treatment discontinuation at 12 weeks follow-up, n									
1 retrospective cohort study Detomas et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	8	8	Osilodrostat phosphate: 1 Metyrapone: 2	Important	VERY LOW

Abbreviations

mUFC – mean urinary free cortisol; NR – not reported.

1 Risk of bias: Very serious limitations due to unclear measures of reliability (i.e. inter- or intra-observer reliability) and lack of identification of and adjustment for potential confounding factors.
2 Indirectness: Very serious indirectness due to the inclusion of seven of 16 out of scope patients (i.e. patients with Cushing's disease).
3 Imprecision: Serious imprecision due to 0 events in the comparator treatment arm.

a One patient receiving osilodrostat phosphate had their treatment discontinued at week 12 due to a QTc of 503 ms.

Table 3: Osilodrostat phosphate (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 – 2 retrospective case series									
Clinical signs of hypercortisolism after treatment, measured using an arbitrary clinical score reflecting Cushing's syndrome severity[a] [benefit indicated by lower score]									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	0.21 *Difference compared to baseline score: p<0.0001*	Critical	VERY LOW
Improvement in Cushing's clinical score after treatment, n[b] [benefit indicated by lower score]									
1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	Score of 0: 2 Score of 1: 3 Not applicable: 2	Critical	VERY LOW

Biochemical disease response – 2 retrospective case series, 1 prospective single-arm study									
Serum cortisol level (ng/mL), median (range) [patients receiving osilodrostat phosphate as first-line monotherapy]									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	11	None	10 (10 to 528) [27.6 nmol/L (range 27.6 to 1,457 nmol/L)] *Difference compared to baseline: p<0.001*	Critical	VERY LOW
Serum cortisol level (nmol/L) 2 weeks after treatment, mean (variance not stated)									
1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	330 (47) *Difference compared to baseline: p=0.02*	Critical	VERY LOW
Morning serum cortisol level 12 weeks after treatment, median % change from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	7	None	*Median % change from baseline: -56.07*	Critical	VERY LOW
Serum cortisol level 24 weeks after treatment, median % change from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	3	None	*Median % change from baseline: -68.96*	Critical	VERY LOW
Serum cortisol level 48 weeks after treatment, median % change from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	2	None	*Median % change from baseline: -67.39*	Critical	VERY LOW
UFC (x ULN) after treatment, (variance not stated)									
1 retrospective case series	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	0.6 (0.1) x ULN *Difference compared to baseline: p=0.03*	Critical	VERY LOW

Tabarin et al 2022									
Actual mUFC (nmol/24-hours) 4 weeks after treatment, median (range) % change from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	8	None	185.70 (26.1 to 635.8) *Median (range) % change from baseline: –83.32 (–99.4 to –38.8)*	Critical	VERY LOW
Actual mUFC (nmol/24-hours) 8 weeks after treatment, median (range) % change from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	8	None	72.60 (–9.0 to 723.5) *Median (range) % change from baseline: –94.37 (–99.8 to 94.0)*	Critical	VERY LOW
Actual mUFC (nmol/24-hours) 12 weeks after treatment, median (range) % change from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	7	None	77.10 (6.2 to 141.2) *Median (range) % change from baseline: –94.47 (–99.0 to –52.6)*	Critical	VERY LOW
Actual mUFC (nmol/24-hours) 24 weeks after treatment, median (range) % change from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	3	None	63.90 (40.9 to 893.6) *Median (range) % change from baseline: –91.57 (–99.5 to –85.2)*	Critical	VERY LOW
Actual mUFC (nmol/24-hours) 48 weeks after treatment, median (range) % change from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	2	None	511.30 (67.5 to 955.1) *Median (range) % change from baseline: –95.04 (–99.1 to –91.0)*	Critical	VERY LOW
Proportion of mUFC responders 12 weeks after treatment, n (%) [95% CI]									
1 prospective single-arm study	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	9	None	Complete response: 6 (66.7) [29.9 to 92.5] Partial response: 1 (11.1) [0.3 to 48.2]	Critical	VERY LOW

Tanaka et al 2020							Overall response: 7 (77.8) [40.0 to 97.2]		
Proportion of mUFC responders 24 weeks after treatment, n (%) [95% CI]									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	3	None	Complete response: 2 (66.7) [9.4 to 99.2] Partial response: 1 (33.3) [0.8 to 90.6] Overall response: 3 (100) [29.2 to 100.0]	Critical	VERY LOW
Proportion of mUFC responders 48 weeks after treatment, n (%) [95% CI]									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	2	None	Complete response: 1 (50.0) [1.3 to 98.7] Partial response: 1 (50.0) [1.3 to 98.7] Overall response: 2 (100) [15.8 to 100.0]	Critical	VERY LOW
24-hour UFC level (µg/24-hours), median (range) [patients receiving osilodrostat phosphate as first-line monotherapy]									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	11	None	5 (5 to 743) [13.8 nmol/24-hours (range 13.8 to 2,050 nmol/24-hours)] *Difference compared to baseline: p<0.001*	Critical	VERY LOW
24-hour UFC level (µg/24-hours), median (range) [patients who received prior treatment with other steroidogenesis inhibitor treatments before being replaced by osilodrostat phosphate monotherapy as second-line treatment]									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	10 uncontrolled patients[c]	None	12 (5 to 57) [33 nmol/24-hours (range 13.8 to 157 nmol/24-hours)] *Difference compared to baseline: p<0.01*	Critical	VERY LOW
24-hour UFC level (µg/24-hours), median (range) [patients who received osilodrostat phosphate in combination with another anticortisolic treatment]									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9	None	28 (5 to 158) [77 nmol/24-hours (range 13.8 to 436 nmol/24-hours)] *Difference compared to baseline: p<0.01*	Critical	VERY LOW

Normalisation of 24-hour UFC level (ULN range 45 to 80 µg/24-hours), n (%) [patients receiving osilodrostat phosphate as first-line monotherapy]									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	11	None	9 (82)	Critical	VERY LOW
Normalisation of 24-hour UFC level (ULN range 45 to 80 µg/24-hours), n (%) [patients who received prior treatment with other steroidogenesis inhibitor treatments before being replaced by osilodrostat phosphate monotherapy as second-line treatment]									
1 retrospective cohort study Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	13	None	13 (100)	Critical	VERY LOW
Normalisation of 24-hour UFC level (ULN range 45 to 80 µg/24-hours), n (%) [patients who received osilodrostat phosphate in combination with another anticortisolic treatment]									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9	None	6 (67)	Critical	VERY LOW
Sequelae of Cushing's syndrome – 2 retrospective case series, 1 prospective single-arm study									
Systolic blood pressure (mmHg), median (range)									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	125 (100 to 168) *Difference compared to baseline: p<0.0001*	Critical	VERY LOW
Systolic blood pressure (mmHg), mean (the variance statistic was not stated and it was therefore unclear whether the figures reflect the SD or the SE of the mean)									
1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	120 (7) *Difference compared to baseline: p=0.03*	Critical	VERY LOW
Systolic blood pressure (mmHg), % change (range) from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	7	None	-31.3 to 9.3	Critical	VERY LOW

Diastolic blood pressure (mmHg), median (range)									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	69 (49 to 90) *Difference compared to baseline: p<0.001*	Critical	VERY LOW
Diastolic blood pressure (mmHg), % change (range) from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	7	None	-33.2 to 9.9	Critical	VERY LOW
Myopathy 3 to 6 months after treatment									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	3 of 33 patients had myopathy before treatment with osilodrostat phosphate; all 3 were able to ambulate, move around independently, and were discharged from hospital after treatment	Critical	VERY LOW
Hypokalaemia, n (%)									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	At osilodrostat phosphate treatment initiation[d]: 13 (39)] After osilodrostat phosphate treatment: 4 (12)	Critical	VERY LOW
Fasting blood glucose levels (g/L), median (range)									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	0.9 (0.7 to 1.8) *Difference compared to baseline: p<0.0001*	Critical	VERY LOW
Fasting glucose (mmol/L) 12 weeks after treatment, % change (range) from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	7	None	-27.2 to 24.2[e]	Critical	VERY LOW

HbA1c %, median (range)									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	6.1 (4.9 to 7.2) *Difference compared to baseline: p<0.05*	Critical	VERY LOW
HbA1c 12 weeks after treatment, % change (range) from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	7	None	-20.3 to 6.2[f]	Critical	VERY LOW
Number of patients with diabetes mellitus and glucose intolerance after treatment, n									
1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	*"Three patients had diabetes mellitus and two had glucose intolerance that disappeared following the control of hypercortisolism"*	Critical	VERY LOW
BMI (kg/m^2), median (range)									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	23.4 (19 to 36) *Difference compared to baseline: p<0.01*	Critical	VERY LOW
BMI (kg/m^2) 12 weeks after treatment, % change (range) from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	7	None	-3.1 to 7.4	Critical	VERY LOW
Waist circumference (cm) 12 weeks after treatment, % change (range) from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	7	None	-4.9 to 2.9	Critical	VERY LOW

Cholesterol (mmol/L) 12 weeks after treatment, % change (range) from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	7	None	-23 to 23[g]	Critical	VERY LOW
HDL cholesterol (mmol/L) 12 weeks after treatment, % change (range) from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	7	None	-34.4 to 15.5[h]	Critical	VERY LOW
LDL cholesterol (mmol/L) 12 weeks after treatment, % change (range) from baseline									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	7	None	-24.9 to 26.5[i]	Critical	VERY LOW
Triglycerides (mmol/L) 12 weeks after treatment, % change (range) from baseline									
1 prospective, single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	7	None	-56.7 to 46.8[j]	Critical	VERY LOW
Reduction in treatment for Cushing's syndrome sequelae – 2 retrospective case series									
Reduction in daily antihypertensive drug dosage after treatment (no further details provided on dosage), mean (variance not stated)									
1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	1.9 (1.1) *Difference compared to baseline: p=0.03*	Important	VERY LOW
Number of antihypertensive drugs after treatment, median									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	Before treatment with osilodrostat phosphate: 2 After treatment with osilodrostat phosphate: 1	Important	VERY LOW
Reduction in number of patients requiring insulin after treatment, n									

1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	11	None	The number of patients requiring insulin reduced from 11 to 8 due to improvement in fasting blood glucose and HbA1c	Important	VERY LOW
Reduction in potassium supplementation or spironolactone dosage (associated with an increase in serum potassium) after treatment, n									
1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	6	Important	VERY LOW
Spironolactone dosage (mg/d) after treatment, median									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	Before treatment with osilodrostat phosphate: 25 After treatment with osilodrostat phosphate: 0	Important	VERY LOW
Potassium supplementation dosage (g/d) after treatment, median									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	Before treatment with osilodrostat phosphate: 3.3 After treatment with osilodrostat phosphate: 0	Important	VERY LOW
Time to improvement – 2 retrospective case series									
Time (weeks) required to normalise 24-hour UFC, median (range) [patients receiving osilodrostat phosphate as first-line monotherapy]									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	11	None	2 (1 to 56)	Important	VERY LOW
Time (weeks) required to normalise 24-hour UFC, median (range) [patients who received prior treatment with other steroidogenesis inhibitor treatments before being replaced by osilodrostat phosphate monotherapy as second-line treatment]									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	13	None	5 (1 to 41)	Important	VERY LOW
Time (weeks) required to normalise 24-hour UFC, median (range) [patients who received prior treatment with other steroidogenesis inhibitor treatments before being replaced by osilodrostat phosphate monotherapy as second-line treatment]									

1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9	None	4 (1 to 22)	Important	VERY LOW
Patients with control of hypercortisolism within 1 week of treatment, n[k]									
1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	2	Important	VERY LOW
Patients with control of hypercortisolism within 1 month of treatment, n[k]									
1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	1	Important	VERY LOW
Patients with control of hypercortisolism around 2 months of treatment, n[k]									
1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	2	Important	VERY LOW
Patients with control of hypercortisolism after 3 months of treatment, n[k]									
1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	2	Important	VERY LOW
Safety – 2 retrospective case series, 1 prospective single-arm study									
Number of patients with at least 1 adverse event at 48 weeks follow-up, n (%)									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	9	None	All grades: 9 (100) Grade 3: 6 (66.7) *Suspected to be treatment related:* All grades: 8 (88.9) Grade 3: 4 (44.4)	Important	VERY LOW

Number of patients with serious adverse events at 48 weeks follow-up, n (%)									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	9	None	All grades: 4 (44.4)[l] *Suspected to be treatment-related:* All grades: 2 (22.2) Grade 3: 2 (22.2)	Important	VERY LOW
Adverse events of special interest – follow-up not reported unless otherwise stated									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	9	None	<u>Adrenal hormone precursor accumulation-related adverse events at 48 weeks follow-up, n (%)</u> *Hypokalaemia* All grades: 2 (22.2) Grade 3: 1 (11.1) *Weight increase* All grades: 1 (11.1) Grade 3: 0 (0) <u>Hypercortisolism-related adverse events at 48 weeks follow-up, n (%)</u> <u>Adrenal insufficiency</u>[m] All grades: 7 (77.8) Grade 3: 2 (22.2) <u>Steroid withdrawal syndrome</u>[n] All grades: 1 (11.1) Grade 3: 1 (11.1) *Suspected to be treatment related:* All grades: 6 (66.7) Grade 3: 2 (22.2)	Important	VERY LOW
1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	One patient had worsening of hypokalaemia (from 3.2 to 2.8 mmol/L) during concomitant treatment with osilodrostat phosphate (60mg/day) and cabozantinib	Important	VERY LOW

1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	3 patients experienced mild and transient adrenal insufficiency	Important	VERY LOW
Frequency of grade 3 or 4 adverse events – adrenal insufficiency, n (%)									
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	8 (24)	Important	VERY LOW
Adverse events leading to treatment discontinuation – follow-up not reported unless otherwise stated, n (%)									
1 prospective single-arm study Tanaka et al 2020	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	9	None	At 48 weeks follow-up All grades: 3 (33.3)[o] Grade 3: 1 (11.1)	Important	VERY LOW
1 retrospective case series Dormoy et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	None	Liver function abnormalities: 0 (0) Alteration in corrected QT interval: 0 (0)	Important	VERY LOW
1 retrospective case series Tabarin et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	0 (0)	Important	VERY LOW

Abbreviations

BMI: body mass index; CI: confidence interval; mUFC: mean urinary free cortisol; NA: not applicable; SD: standard deviation; SE: standard error; UFC: urinary free cortisol; ULN: upper limit of normal.

1 Risk of bias: Very serious limitations due to unclear recruitment and study methodology, and unclear follow-up durations.
2 Indirectness: Serious indirectness due to lack of a comparator group.
3 Risk of bias: Very serious limitations due to unclear recruitment and study methodology, limited statistical analyses and unclear follow-up durations.
4 Risk of bias: Very serious limitations due to unclear recruitment methods and limited statistical analyses.

a The score was adapted from Ferriere et al (2017) and included 7 items: obesity of the face and trunk; purple stretch marks; myopathy; supraclavicular fat pad; buffalo hump; facial erythrosis; and facial plethora. In premenopausal women, the score included the same previous items as well as two additional items: hirsutism and amenorrhoea. In postmenopausal

women, the same items as previously were used, except for amenorrhea. Each of the clinical items was scored as 0 (absent), 1 (low), or 2 (high), resulting in a total score of 14, 18, and 16, respectively, in men, premenopausal women, and postmenopausal women. To standardise these scores, the value 1.0 corresponded to the maximum in each aforementioned patient category.
b A decrease in a Cushing score for clinical appearance: 0 reflects lack of symptoms; 2 reflects florid Cushing (as assessed by experienced endocrinologists).
c In the remaining three patients whose 24-hour UFC was normalised at the time of osilodrostat phosphate treatment, UFC levels were maintained [i.e. 24-hour UFC <ULN].
d After potassium supplementation and/or spironolactone treatment.
e The normal range for fasting glucose was 3.89 to 6.05 mmol/L in 4 patients and 4.05 to 6.05 in 3 patients.
f The normal range for HbA1c was 4.6 to 6.2 in 5 patients, 4.9 to 6 in one patient, and NA to 6.4 in one patient.
g The normal range for cholesterol was 3.23 to 5.66 in 5 patients, NA to 5.66 in one patient, and 3.36 to 5.69 or NA to 5.66 in one patient.
h The normal range for HDL cholesterol was 1.03 to NA in all 7 patients.
i The normal range for LDL cholesterol was NA to 3.59 in 5 patients and NA to 3.62 in 2 patients.
j The normal range for triglycerides was 0.4 to 1.68 in 5 patients, 0.34 to 1.69 in one patient, and NA to 1.68 in one patient.
k There was a discrepancy in the number of patients reported to have obtained control of hypercortisolism after treatment with osilodrostat phosphate and we have reported seven rather than eight patients.
l The patient was receiving osilodrostat phosphate plus cabozantinib.
m Adrenal insufficiency includes the reported terms of adrenal insufficiency, hypoadrenalism and adrenal gland hypofunction.
n Steroid withdrawal syndrome includes the reported term of glucocorticoid withdrawal syndrome.
o One patient had grade 3 hypokalaemia leading to discontinuation that started at day –1 (i.e. before treatment with osilodrostat phosphate) and was not counted in any adverse event.

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.
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.
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.
Reliability	The ability to get the same or similar result each time a study is repeated with a different population or group.
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.

References

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