Clinical Priorities Advisory Group Summary Report

Agenda item	4.3
Date of Meeting	11.05.2026-13.05.2026
Title of the Proposition	Osilodrostat phosphate for adult patients with endogenous Cushing's syndrome
Unique Reference Number	2331
Programme of Care	Internal Medicine
Clinical Reference Group	Endocrinology
Service/treatment status	delegated

Action requested

Support the adoption of the policy proposition

Recommended its relative prioritisation.

Summary of the proposition:

Cushing's syndrome is an endocrine disorder caused by prolonged exposure to excessive levels of glucocorticoids, a class of hormones that play a crucial role in regulating various bodily functions including controlling the immune system, managing the use of sugars, fats, and proteins, and the stress response. The causes of Cushing's syndrome are either endogenous or exogenous.

Exogenous Cushing's syndrome is caused by exposure to glucocorticoids produced outside of the body, for example in patients prescribed steroids as part of treatment for another medical condition. Exogenous Cushing's syndrome is managed differently and is beyond the scope of this policy.

Endogenous Cushing's syndrome is due to the body excessively producing the main glucocorticoid cortisol. Cortisol is a hormone produced by the adrenal glands, which are walnut-sized endocrine glands that sit on top of the kidneys. Approximately 70% of endogenous Cushing's syndrome cases are caused by an adrenocorticotrophic hormone (ACTH)-secreting adenoma of the pituitary, a pea-sized endocrine gland at the bottom of the brain. This condition is called Cushing's disease and the excessive ACTH production by the pituitary adenoma stimulates the adrenal glands to produce too much cortisol. More rarely, ACTH can be produced by benign or cancerous tumours outside of the pituitary gland, leading to a condition of cortisol excess known as ectopic Cushing's syndrome.

Osilodrostat phosphate is an oral tablet that blocks 11β-hydroxylase, the enzyme involved in the last step of the production of cortisol in the adrenal glands.

Osilodrostat phosphate is licensed for the treatment of adults endogenous Cushing's syndrome, however it has not been reviewed by NICE.

Clinical Panel recommendation:

The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

Assurances

The committee is asked to receive the following assurance:		
1.	The Deputy Director of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of developmental and governance steps.	
2.	The Deputy Director of Acute Programmes confirms the proposition is supported by the following documentation (please tick the box where applicable)	
	Draft Clinical Commissioning policy proposition	☒
	Evidence Review	☒
	Public Health Evidence Report	☒
	Evidence to Decision Making (EtD) Summary	☒
	Equalities and Heath Inequalities Assessment (EHIA)	☒
	Prior Approval Form	☒
	Engagement Report	☒

	13Q Assessment and Patient & Public Voice Assurance	☒
	Clinical Panel Report	☒
	Policy Working Groupmembership	☒
	Other (please state if required)	☐
3.	The Deputy Director of Finance (Specialised Commissioning) confirms that the Impact Assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.	
4.	The Director of Clinical Commissioning (Specialised Commissioning) confirms that the Service and Operational Impact Assessments have been completed.	
5.	The Deputy Director of Quality and Nursing (Specialised Commissioning) confirms that the proposed quality indicators have been adequately defined (where applicable).	

Evidence Review Summary

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[1], after treatment with osilodrostat phosphate in patients with PNCS/EAS. The second retrospective case series measured improvement in Cushing's clinical score[2] 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.

[1] 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.

[2] 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
	Clinical signs of hypercortisolism after treatment, measured using an arbitrary clinical score reflecting Cushing's syndrome severity[2] *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)** Improvement in Cushing's clinical score[3] *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.** **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: Serum cortisol levels *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**

Outcome	Evidence statement
	• 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][3] to 10 ng/mL [range 10 to 528 ng/mL]) in patients with PNCS/EAS. 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)**

[3] 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
	<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 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

Outcome	Evidence statement
	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)** <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[4]. 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>

[4] 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
	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]* • One retrospective case series (Dormoy et al 2023) (n=10 uncontrolled patients)[5] 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

[5] 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
	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 mean UFC levels and serum cortisol levels 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 mean UFC levels and serum cortisol levels 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 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**

Outcome	Evidence statement
	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 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: Systolic blood pressure *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

Outcome	Evidence statement
	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)** Diastolic blood pressure *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 baseline ranged between -33.2% and 9.9%. No statistical measures were reported. **(VERY LOW)** Myopathy *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)** Hypokalaemia *Osilodrostat phosphate vs no comparator* **At unspecified follow-up**

Outcome	Evidence statement
	• 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 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**

Outcome	Evidence statement
	• 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 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)** <u>LDL 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 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)** <u>Triglycerides</u> *Osilodrostat phosphate vs no comparator*

Outcome	Evidence statement
	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.** **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***

Outcome	Evidence statement
	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 Cushing's disease (excluding Cushing's disease). Follow-up timepoints were not stated in the two retrospective case series: Reduction in antihypertensives *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)**

Outcome	Evidence statement
	• 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 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.**

Outcome	Evidence statement
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)** *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

Outcome	Evidence statement
	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[6]. 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. 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:**

[6] 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 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)** • 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[7] 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

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

Outcome	Evidence statement
	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 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**

Outcome	Evidence statement
	and transient adrenal insufficiency after treatment with osilodrostat phosphate. No statistical measures were reported.
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)** • 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*

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

Outcome	Evidence statement
	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 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 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

Outcome	Evidence statement
	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)** • 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[9] 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)**

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

Outcome	Evidence statement
	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 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.**
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 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.

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

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Clinical disease response **Certainty of evidence:** Moderate to very low	This outcome is important to patients because it reflects the clinical improvement that they experience with treatment. In total, one randomised study and one single-arm study provided evidence relating to clinical disease response in people with Cushing's disease. The randomised study reported a range of physical features of hypercortisolism after 48 weeks treatment which included a 12-week randomised period; the single-arm study reported hirsutism in females after up to 72 weeks treatment with osilodrostat phosphate. Facial rubor

Outcome	Evidence statement
	Osilodrostat phosphate vs placebo **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in facial rubor at week 48 in patients randomised to osilodrostat phosphate (n=39); patients randomised to placebo (n=21); and total patients (n=60). Respectively, improvement was reported in 16/39 (41.0%) (95% CI 25.6 to 57.9); 11/21 (52.4%) (95% CI 29.8 to 74.3); 27/60 (45.0%) (95% CI 32.1 to 58.4): no change in 21/39 (53.8%) (95% CI 37.2 to 69.90; 10/21 (47.6%) (95% CI 25.7 to 70.2); 31/60 (51.7%) (95% CI 38.4 to 64.8): and worsening in 2/39 (5.1%) (95% CI 0.6 to 17.3); 0/21 (0%) (95% CI NE); 2/60 (3.3%) (95% CI 0.4 to 11.5). **(MODERATE)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. Osilodrostat phosphate vs no comparator • No evidence was identified for this outcome. <u>Hirsutism</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate):** • One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in hirsutism at week 48 in patients randomised to osilodrostat phosphate (n=33); patients randomised to placebo (n=15); and total patients (n=48). Respectively, improvement was reported in 5/33 (15.2%) (95% CI 5.1 to 31.9); 3/15 (20.0%) (95% CI 4.3 to 48.1); 8/48 (16.7%) (95% CI 7.5 to 30.2): no change in 24/33 (72.7%) (95% CI 95% CI 54.5 to 86.7); 12/15 (80.0%) (95% CI 51.9 to 95.7); 36/48 (75.0%) (95% CI 60.4 to 86.4): and worsening in 4/33 (12.1%) (95% CI 3.4 to 28.2); 0/15 (0%) (95% CI NE); 4/48 (8.3%) (95% CI 2.3 to 20.0). **(MODERATE)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **After up to 72 weeks treatment with osilodrostat phosphate :** • One single-arm study (LINC3, Fleseriu et al 2022b) reported the change in a physician-rated hirsutism score in females with normal and raised testosterone levels. In those with normal testosterone levels the hirsutism score at 12 weeks (n=38); 48 weeks (n=34); 72 weeks (n=38) respectively was reported to be improved in 9/38 (23.7%); 16/34 (47.1%); 7/38 (44.7%): stable in 27/38 (71.1%); 13/34 (38.2%); 16/38 (42.1%): and worsened in 2/38 (5.3%); 5/34 (14.7%); 5/38 (13.2%). In women with raised testosterone level the hirsutism score at 12 weeks (n=48); 48 weeks (n=41); 72 weeks (n=28) respectively was reported to be improved in 3/48 (6.3%); 9/41 (22.0%); 6/28 (21.4%); stable in 41/48 (85.4%); 24/41 (58.5%); 18/28 (64.3%); and worsened in 4/48 (8.3%); 8/41 (19.5%); 4/28 (14.3%). **(VERY LOW)** <u>Supraclavicular fat pad</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in supraclavicular fat pad at week 48 in patients randomised to osilodrostat phosphate (n=39); patients randomised to placebo (n=22); and

Outcome	Evidence statement
	total patients (n=61). Respectively, improvement was reported in 21/39 (53.8%) (95% CI 37.2 to 69.9); 11/22 (50.0%) (95% CI 28.2 to 71.8); 32/61 (52.5%) (95% CI 39.3 to 65.4): no change in 17/39 (43.6%) (95% CI 27.8 to 60.4); 11/22 (50.0%) (95% CI 28.2 to 71.8); 28/61 (45.9%) (95% CI 33.1 to 59.2): and worsening in 1/39 (2.6%) (95% CI 0.1 to 13.5); 0/22 (0%) (95% CI NE); 1/61 (1.6%) (95% CI 0.0 to 0.8 [sic]). **(MODERATE)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* • No evidence was identified for this outcome. <u>Dorsal fat pad</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in dorsal fat pad at week 48 in patients randomised to osilodrostat phosphate (n=38); patients randomised to placebo (n=22); and total patients (n=60). Respectively, improvement was reported in 20/38 (52.6%) (95% CI 35.8 to 69.0); 10/22 (45.5%) (95% CI 24.4 to 67.8); 30/60 (50.0%) (95% CI 36.8 to 63.2): no change in 16/38 (42.1%) (95% CI 26.3 to 59.2); 10/22 (45.5%) (95% CI 24.4 to 67.8); 26/60 (43.3%) (95% CI 30.6 to 56.8): and worsening in 2/38 (5.3%) (95% CI 0.6 to 17.7); 2/22 (9.1%) (95% CI 1.1 to 29.2); 4/60 (6.7%) (95% CI 1.8 to 16.2). **(MODERATE)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* • No evidence was identified for this outcome. <u>Proximal muscle atrophy</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in proximal muscle atrophy at week 48 in patients randomised to osilodrostat phosphate (n=39); patients randomised to placebo (n=22); and total patients (n=61). Respectively, improvement was reported in 10/39 (25.6%) (95% CI 13.0 to 42.1); 8/22 (36.4%) (95% CI 17.2 to 59.3); 18/61 (29.5%) (95% CI 18.5 to 42.6): no change in 25/39 (64.1%) (95% CI 47.2 to 78.8); 13/22 (59.1%) (95% CI 36.4 to 79.3); 38/61 (62.3%) (95% CI 49.0 to 74.4) : and worsening in 4/39 (10.3%) (95% CI 2.9 to 24.2); 1/22 (4.5%) (95% CI 0.1 to 22.8); 5/61 (8.2%) (95% CI 2.7 to 18.1). **(MODERATE)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* • No evidence was identified for this outcome. <u>Central obesity</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate)**

Outcome	Evidence statement
	• One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in central obesity at week 48 in patients randomised to osilodrostat phosphate (n=39); patients randomised to placebo (n=22); and total patients (n=61). Respectively, improvement was reported in 16/39 (41.0%) (95% CI 25.6 to 57.9); 9/22 (40.9%) (95% CI 20.7 to 63.6); 25/61 (41.0%) (95% CI 28.6 to 54.3): no change in 19/39 (48.7%) (95% CI 32.4 to 65.2); 12/22 (54.5%) (95% CI 32.2 to 75.6); 31/61 (50.8%) (95% CI 37.7 to 63.9): and worsening in 4/39 (10.3%) (95% CI 2.9 to 24.2); 1/22 (4.5%) (95% CI 0.1 to 22.8); 5/61 (8.2%) (95% CI 2.7 to 18.1). **(MODERATE)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* • No evidence was identified for this outcome. <u>Ecchymosis</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomisation and 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) reported the change from baseline in ecchymosis at week 48 in patients randomised to osilodrostat phosphate (n=39); patients randomised to placebo (n=21); and total patients (n=60). Respectively, improvement was reported in 9/39 (23.1%) (95% CI 11.1 to 39.3); 3/21 (14.3%) (95% CI 3.0 to 36.3); 12/60 (20.0%) (95% CI 10.8 to 32.3): no change in 29/39 (74.4%) (95% CI 57.9 to 87.0); 17/21 (81.0%) (95% CI 58.1 to 94.6); 46/60 (76.7%) (95% CI 64.0 to 86.6): and worsening in 1/39 (2.6%) (95% CI 0.1 to 13.5); 1/21 (4.8%) (95% CI 0.1 to 23.8); 2/60 (3.3%) (95% CI 0.4 to 11.5). **(MODERATE)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* • No evidence was identified for this outcome. **Osilodrostat phosphate vs placebo:** **One randomised study (LINC3) provided moderate certainty evidence of improvement or no change in facial rubor, hirsutism, striae, subcutaneous fat pad, dorsal fat pad, proximal muscle atrophy, central obesity and ecchymosis in at least 88% of patients after 48 weeks treatment (consisting of either 48 weeks osilodrostat phosphate or 12 weeks placebo followed by 36 weeks osilodrostat phosphate). There was no statistically significant difference between the treatment groups in the proportion of patients who had improved or not changed with respect to any of the physical features. Physical features with the greatest improvements (reported in at least 40% of all patients) were subcutaneous fat pad, dorsal fat pad, facial rubor and central obesity.** **Osilodrostat phosphate vs metyrapone:** **No evidence was identified for clinical disease response.** **Osilodrostat phosphate vs no comparator:** **One single-arm study (LINC4) provided very low certainty evidence that after 72 weeks treatment with osilodrostat phosphate female hirsutism had improved in 45% and remained stable in 42% of women with normal testosterone, and had improved in 21% and remained stable in 64% of women with raised testosterone. Improvements in female hirsutism were seen in some patients from 12 weeks of treatment onwards.**

Outcome	Evidence statement
Biochemical disease response **Certainty of evidence:** Moderate to very low	This outcome is important to patients because biochemical improvement is a measure of disease response to treatment. In total, two randomised studies and three single-arm studies (reported in six papers) and one retrospective cohort study provided evidence relating to biochemical disease response in people with Cushing's disease. The two randomised studies were conducted during a time-limited randomised double-blind placebo-controlled period within two of the single-arm studies. Patients who took part in the randomised studies also had periods of open label treatment with osilodrostat phosphate which were reported in the single-arm studies. The third single-arm study provided non-comparative evidence only. The randomised studies reported biochemical disease response outcomes after 8 and 12 weeks of randomisation, and the single-arm studies reported biochemical disease response outcomes after between 10 weeks and a median of 5.4 years of osilodrostat phosphate. The retrospective cohort study reported biochemical disease response at the time of best control of hypercortisolism for each patient. <u>Response to treatment (based on mean 24-hour UFC unless otherwise stated)</u> *Osilodrostat phosphate vs placebo* **After 8 weeks randomised treatment** • One randomised study (LINC3, Pivonello et al 2020) (n=71) reported complete response rate (n (%) (95% CI)) in patients randomised to osilodrostat phosphate (n=36) compared to patients randomised to placebo (n=34): randomised to osilodrostat phosphate: 31/36 (86.1%) (95% CI 70.5% to 95.3%); randomised to placebo: 10/34 (29.4%) (95% CI 15.1% to 47.5%). This difference was statistically significant: OR 13.7 (95% CI 3.7 to 53.4), p<0.0001. **(MODERATE)** **After 12 weeks randomised treatment** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported complete response rate (n (%)) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25): randomised to osilodrostat phosphate: 37/48 (77.1%); randomised to placebo: 2/25 (8.0%). This difference was statistically significant: OR 43.4 (95% CI 7.1 to 343.2), p < 0.0001. **(MODERATE)** **After 48 weeks treatment, including 8 weeks randomisation and 40 weeks open label osilodrostat phosphate** • One randomised study (LINC3, Pivonello et al 2020) (n=71) reported overall, complete and partial response rates (n (%) (95% CI)) in patients randomised to osilodrostat phosphate (n=36) compared to patients randomised to placebo (n=35) after a total of 48 weeks treatment (patients randomised to osilodrostat phosphate received 48 weeks osilodrostat phosphate and patients randomised to placebo received placebo between weeks 27 and 34 and osilodrostat phosphate between weeks 1 to 26 and weeks 35 to 48). Randomised to osilodrostat phosphate: overall response 34 (94.4%) (95% CI 81.3% to 99.3%), complete response 32 (88.9%) (95% CI 73.9% to 96.9%), partial response 2 (5.6%) (95% CI 0.7% to 18.7%); randomised to placebo: overall response 31 (88.6%) (95% CI 73.3% to 96.8%), complete response: 27 (77.1%) (95% CI 59.9% to 89.6%), partial response 4 (11.4%) (95% CI 3.2% to 26.7%). The differences between the groups were not statistically significant. **(MODERATE)** *Osilodrostat phosphate vs metyrapone*

Outcome	Evidence statement
	At the point of best control of hypercortisolism • One retrospective cohort study (Bonnet-Serrano et al 2022) (n=33) reported median serum cortisol (nmol/L) ( ) in patients treated with osilodrostat phosphate compared to patients treated with metyrapone: osilodrostat phosphate group, 175 nmol/L (22 to 421); metyrapone group, 307 (68 to 547) nmol/L; p = 0.025. The difference between the two groups was statistically significant. **(VERY LOW)** *Osilodrostat phosphate vs no comparator* **After 10 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported response rates (n (%) (95% CI)) of overall response: 17 (89.5%) (95% CI 66.9% to 98.7%); controlled: 16 (84.2%) (95% CI 60.4% to 96.6%); partially controlled: 1 (5.3%) (95% CI 0.1% to 26.0%). **(VERY LOW)** **After 22 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported response rates (n (%) (95% CI)) of overall response: 15 (78.9%) (95% CI 54.4% to 94.0%); controlled: 15 (78.9%) (95% CI 54.4% to 94.0%); partially controlled: 0 (0%) (95% CI 0% to 17.7%). **(VERY LOW)** **After 24 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported response rates (n (%) (95% CI)) of overall response: 113 (82.5%) (95% CI 75.1% to 88.4%); complete response: 93 (67.9%) (95% CI 59.4% to 75.6%); partial response: 20 (14.6%) (95% CI 9.2% to 21.6%). **(VERY LOW)** **After 36 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported a complete response rate (n (%) (95% CI)) of 59 (80.8%) (95% CI 69.9% to 89.1%). **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported response rates (n (%) (95% CI)) of overall response: 104 (75.9%) (95% CI 67.9% to 82.8%); complete response: 91 (66.4%) (95% CI 57.9% to 74.3%); partial response: 13 (9.5%) (5.2% to 15.7%). **(VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported response rates (n (%)) of overall response: 58 (79.5%); complete response: 50 (68.5%); partial response: 8 (11.0%). **(VERY LOW)** **After 60 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a complete response rate (n (%) (95% CI)) of 86 (81.1%) (95% CI 72.4% to 88.1%). **(VERY LOW)** **After 70 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2022a) (n=16) reported response rates (n (%)) of overall response: 13 (81.3%); complete response: 12 (75%); partial response: 1 (6.3%). **(VERY LOW)** **After 72 weeks treatment**

Outcome	Evidence statement
	• One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a complete response rate (n (%) (95% CI)) of 86 (81.1%) (95% CI 72.4% to 88.1%). **(VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2023) (n=60) reported response rates (n (%)) of overall response: 45 (75%); complete response: 40 (66.7%); partial response: 5 (8.3%). **(VERY LOW)** **Up to the end of treatment (median 87.1 (range 2.0 to 126.6) weeks)** • One single-arm study (LINC4, Gadelha et al 2023) (n=58) reported response rates (n (%)) of overall response: 47 (81%); complete response: 42 (72.4%); partial response: 5 (8.6%). **(VERY LOW)** **At the last observed value (median exposure to osilodrostat phosphate 5.4 (range 0.04 to 6.7) years)** • One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported response rates (n (%) (95% CI)) of complete response 12 (63.2%), partial response 5 (26.3%). **(VERY LOW)** <u>24-hour urinary free cortisol (UFC)</u> *Osilodrostat phosphate vs placebo* **After 12 weeks randomised treatment** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) 24-hour UFC levels (nmol/24h) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25). Randomised to osilodrostat phosphate: baseline 421.4 (291.3), week 12 98.2 (122.5); randomised to placebo: baseline 451.5 (535.1), week 12: 411.3 (389.9). The 12-week result for the osilodrostat phosphate group was within the reference range but the results were not compared statistically. **(LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **After 22 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported a mean (SE) 24-hour UFC (nmol/24h) of 1371 (2734) at baseline and 92 (124) at 22 weeks. **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2023) (n=48) reported a mean (SE) 24-hour UFC (nmol/24h) of 90.5 (122.6). **(VERY LOW)** <u>Serum cortisol</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) serum cortisol levels (nmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25). Randomised to osilodrostat phosphate: baseline 565.8 (169.0), week 12 295.6 (160.4), week

Outcome	Evidence statement
	48 354.0 (114.6); randomised to placebo: baseline 486.1 (198.1), week 12: 560.1 (204.4), week 48 353.7 (145.5). They also reported mean (95% CI) change in serum cortisol levels from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12 −276.0 (95% CI −330.2 to −221.7), week 48 -210.7 (95% CI −261.5 to −159.9); randomised to placebo: week 12: 73.0 (95% CI −5.2 to 151.2), week 48 -131.0 (95% CI −236.1 to −26.0). The change at 12 weeks was statistically significantly greater in the osilodrostat phosphate group. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **After 48 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported (mean (SD)) serum cortisol levels (nmol/L) of 538.1 (182.3) at baseline and 353.9 (124.9) at week 48. Mean change from baseline at week 48 was -182.9 (95% CI -231.5 to -134.3). **(VERY LOW)** **After up to 72 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2023) (n=46 to 73) reported (mean (SD)) serum cortisol levels (nmol/L) of 538.1 (182.3) at baseline (n=73), 353.9 (124.9) at week 48 (n=64) and 319.1 (129.8) at week 72 (n=46). **(VERY LOW)** • One single-arm study (LINC3, Fleseriu et al 2022b) (n not stated) reported that mean serum cortisol levels were within the normal range at week 48 and throughout the extension period (up to 72 weeks). **(VERY LOW)** <u>Early-morning salivary cortisol</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) early-morning salivary cortisol levels (nmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25). Randomised to osilodrostat phosphate: baseline 17.2 (30.0), week 12 5.8 (7.0), week 48 4.7 (2.9); randomised to placebo: baseline 14.1 (12.3), week 12 14.1 (10.0), week 48 6.9 (7.7). They also reported mean (95% CI) change in early-morning salivary cortisol levels from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12 -11.6 (95% CI −20.5 to −2.7), week 48 −11.8 (95% CI −21.8 to −1.8); randomised to placebo: week 12: −0.3 (95% CI −5.1 to 4.4), week 48 −6.0 (95% CI −10.8 to −1.1). The changes at 12 and 48 weeks were not statistically significantly different between the two groups. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **After 22 weeks treatment**

Outcome	Evidence statement
	• One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported mean (SE) morning salivary cortisol levels (nmol/L) of 24 (41) at baseline and 5 (6) at week 22. **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) early-morning salivary cortisol levels (nmol/L) of 16.1 (25.3) at baseline and 5.4 (5.2) at week 48. Mean change from baseline at week 48 was −9.8 (95% CI −16.4 to −3.1). **(VERY LOW)** <u>Late-night salivary cortisol</u> *Osilodrostat phosphate vs placebo* **After 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) late-night salivary cortisol levels (nmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25). Randomised to osilodrostat phosphate: baseline 11.7 (28.7), week 12 3.5 (2.3), week 48 3.5 (2.6); randomised to placebo: baseline 9.0 (6.7), week 12: 10.3 (6.5), week 48 4.0 (2.5). They also reported mean (95% CI) change in late-night salivary cortisol levels from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12 −8.5 (95% CI −17.3 to 0.3), week 48 -9.3 (95% CI −18.5 to −0.2); randomised to placebo: week 12: 1.3 (95% CI −2.4 to 5.1), week 48 −5.0 (95% CI −7.6 to −2.5). The changes at 12 and 48 weeks were not statistically significantly different between the two groups. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **After 48 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported (mean (SD)) late-night salivary cortisol levels (nmol/L) of 10.8 (23.5) at baseline and 3.7 (2.6) at week 48. Mean change from baseline at week 48 was -7.8 (95% CI −13.8 to −1.9). **(VERY LOW)** **After up to 72 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2023) (n=46 to 73) reported (mean (SD)) late-night salivary cortisol levels (nmol/L) of 10.8 (23.5) at baseline (n=73), 3.7 (2.6) at week 48 (n=63) and 3.8 (3.0) at week 72 (n=46). **(VERY LOW)** • One single-arm study (LINC3, Fleseriu et al 2022b) (n not stated) reported that mean (SD) late-night salivary cortisol (nmol/L) was 2.7 (SD 1.6) at week 48 and remained consistently lower than baseline but above the reference range during the extension period (up to 72 weeks). **(VERY LOW)** **Osilodrostat phosphate vs placebo:** **Two randomised studies (LINC3 and LINC4) provided moderate certainty evidence of a statistically significantly better complete response rate (based on mean UFC levels) in patients randomised to osilodrostat phosphate compared to patients randomised to placebo after 8 weeks and 12 weeks treatment. One of the**

Outcome	Evidence statement
	randomised studies (LINC3) provided moderate certainty evidence of no statistically significant differences in overall, complete and partial response rates after 48 weeks treatment in patients randomised to 48 weeks osilodrostat phosphate compared to patients randomised to 8 weeks placebo between weeks 27 and 34 and osilodrostat phosphate between weeks 1 to 26 and weeks 35 to 48. **One randomised study (LINC4) provided low certainty evidence that after 12 weeks treatment mean 24-hour UFC levels fell to within the normal range in patients randomised to osilodrostat phosphate but did not fall in patients randomised to placebo, but the two groups were not compared statistically. The same randomised study provided moderate certainty evidence that after 12 weeks randomised treatment there was a statistically significantly greater fall in mean serum cortisol levels in patients randomised to osilodrostat phosphate than in patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate mean serum cortisol levels had fallen in both groups and there was no statistically significant difference between them in the change in serum cortisol levels.** **One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks randomised treatment the early-morning and late-night salivary cortisol levels had fallen more in patients randomised to osilodrostat phosphate than in patients randomised to placebo, but there was no statistically significant difference between the groups in the change in levels. After a further 36 weeks treatment of both groups with osilodrostat phosphate levels had fallen in both groups and there was no statistically significant difference between them in the change in early-morning or late-night salivary cortisol levels.** **Osilodrostat phosphate vs metyrapone:** **One retrospective cohort study provided very low certainty evidence that patients treated with osilodrostat phosphate had a statistically significantly lower median serum cortisol level than patients treated with metyrapone at the time of best control of hypercortisolism. No evidence was identified for any other biochemical disease response outcomes comparing osilodrostat phosphate to metyrapone.** **Osilodrostat phosphate vs no comparator:** **Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence of overall and complete response rates (based on mean UFC levels) to osilodrostat phosphate of 89.5% and 84.2% respectively after 10 weeks treatment, between 75% and 83% for overall response and between 63% and 81% for complete response at time points between 22 and a median of 87 weeks treatment, and a complete response rate of 63.2% after a median 5.4 years exposure to osilodrostat phosphate.** **Two single-arm studies (LINC2 and LINC4) provided very low certainty evidence that mean 24-hour UFC levels were within the normal range after 22 and 72 weeks treatment with osilodrostat phosphate. They also provided very low certainty evidence that mean serum cortisol levels fell from baseline after 48 and 72 weeks treatment with osilodrostat phosphate, but the levels were within the normal range at all measurement points including baseline.** **Two single-arm studies (LINC2 and LINC4) provided very low certainty evidence that early-morning salivary cortisol levels were above the normal range at baseline and fell to within the normal range after 22 weeks and 48 weeks treatment with osilodrostat phosphate. They also provided very low certainty evidence that late-night salivary cortisol levels fell from baseline after up to 72 weeks treatment with osilodrostat phosphate but remained above the normal range.**

Outcome	Evidence statement
Sequelae of Cushing's disease **Certainty of evidence:** Moderate to very low	This outcome is important for patients because it measures improvements in the physical health consequences of Cushing's disease. The associated morbidity is high due to complications such as diabetes, hypertension, metabolic syndrome, low mood, a predisposition to infection and impacts on bone health. In total, one randomised study and three single-arm studies (reported in six papers) provided evidence relating to sequelae of Cushing's disease. The randomised study was conducted during a time-limited randomised double-blind placebo-controlled period within one of the single-arm studies. Patients who took part in the randomised study also had a period of open label treatment with osilodrostat phosphate which was reported in the single-arm studies. Two of the single-arm studies provided non-comparative evidence only. The randomised study reported outcomes relating to sequelae of Cushing's disease after 12 weeks of randomisation, and the single-arm studies reported outcomes relating to sequelae of Cushing's disease after between 22 weeks and a median of 5.4 years of osilodrostat phosphate. <u>Weight, body mass index (BMI) and waist circumference</u> *Osilodrostat phosphate vs placebo* <u>Weight</u> **After up to 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) weight (kg) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 78.8 (17.5), week 12: 78.1 (17.9), week 48: 74.1 (16.6); randomised to placebo: 77.3 (16.9), week 12: 75.7 (15.7), week 48 72.5 (17.4). They also reported mean (95% CI) change in weight from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12 −0.8 (95% CI −1.7 to 0.1), week 48 -3.6 (95% CI −5.7 to −1.6); randomised to placebo: week 12: -3.6 (95% CI −5.7 to −1.6), week 48 −5.5 (95% CI −8.3 to −2.7). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** <u>Waist circumference</u> **After up to 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) waist circumference (cm) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 102.5 (17.0), week 12: 101.4 (17.7), week 48: 97.3 (17.0); randomised to placebo: 103.4 (15.5), week 12: 102.1 (15.1), week 48 97.8 (17.2). They also reported mean (95% CI) change in waist circumference from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12 -1.0 (95% CI −2.3 to 0.3), week 48 −4.1 (95% CI −6.0 to −2.2); randomised to placebo: week 12: −0.5 (95% CI −1.9 to 1.0), week 48 −5.3 (95% CI −7.9 to −2.8). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for these outcomes.

Outcome	Evidence statement
	Osilodrostat phosphate vs no comparator Weight **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) weight (kg): baseline: 85.1 (24.0); week 22: 85.6 (26.2); change from baseline: –1.5 (3.8). **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) weight (kg): baseline: 80.8 (22.4); week 48: 75.5 (20.7); change from baseline: -3.8 (95% CI -4.8 to -2.7). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) weight (kg): baseline: 78.3 (17.2); Week 48: 73.5 (16.8); change from baseline: −4.3 (95% CI −5.9 to −2.6). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in weight (kg) from baseline of -4.7 (6.6). **(VERY LOW)** BMI **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) body mass index (kg/m^2): baseline: 30.7 (7.0); week 22: 30.1 (7.9); change from baseline: –0.5 (1.4). **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) body mass index (kg/m^2): baseline: 30.3 (7.8); Week 48: 28.4 (7.1); change from baseline: -1.4 (95% CI -1.8 to 1.0). (**VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in body mass index (kg/m^2) from baseline of -1.8 (2.5). **(VERY LOW)** **Waist circumference** **After 48 weeks treatment** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) waist circumference (cm): baseline: 102.8 (16.4); week 48: 97.5 (16.9); change from baseline: −4.5 (95% CI −6.0 to −3.0). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in waist circumference (cm) from baseline of -6.2 (8.5). **(VERY LOW)** **Cardiovascular and metabolic outcomes** *Osilodrostat phosphate vs placebo* Systolic BP

Outcome	Evidence statement
	After up to 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate) [10] • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) systolic BP (mm Hg) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 132.4 (19.2), week 12: 125.5 (13.7), week 48: 123.0 (15.4); randomised to placebo: baseline: 130.0 (17.7), week 12: 127.4 (14.9), week 48: 117.0 (16.2). They also reported mean (95% CI) change in systolic BP from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −7.1 (95% CI −12.6 to −1.6), week 48: −9.1 (95% CI −15.2 to −2.9); randomised to placebo: week 12: −0.9 (95% CI −5.8 to 4.1), week 48: −11.0 (−20.8, −1.1). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** <u>Diastolic BP</u> • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) diastolic BP (mm Hg) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 87.2 (12.7), week 12: 125.5 (13.7), week 48: 81.7 (11.0); randomised to placebo: baseline: 88.2 (10.8), week 12: 87.0 (11.2), week 48: 83.5 (10.4). They also reported mean (95% CI) change in diastolic BP from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −4.8 (95% CI −8.2 to −1.5), week 48: −4.4 (95% CI −8.1 to −0.7); randomised to placebo: week 12: −1.4 (95% CI −5.5 to 2.8), week 48: −3.9 (95% CI −9.8 to 2.0). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** <u>Fasting plasma glucose</u> • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) fasting plasma glucose (mg/dl) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 97.3 (18.1), week 12: 92.0 (15.5), week 48: 90.5 (12.9); randomised to placebo: baseline: 91.4 (15.2), week 12: 91.1 (11.2), week 48: 90.7 (13.7). They also reported mean (95% CI) change in fasting plasma glucose from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −4.3 (95% CI −8.9 to 0.2), week 48: −5.6 (95% CI −10.1 to −1.1); randomised to placebo: week 12: −1.7 (95% CI −6.3 to 2.9), week 48: 1.8 (95% CI −4.5 to 8.1). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups and levels were within the normal range in both groups at all time points. **(MODERATE/LOW)** <u>HbA1c</u> • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) HbA1c (%) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 6.0 (0.9), week 12: 5.7 (0.7), week 48: 5.8 (0.6); randomised to placebo: baseline: 5.7 (0.6), week 12: 5.6 (0.6), week 48: 5.7 (0.5). They also reported mean (95% CI) change in HbA1c

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

Outcome	Evidence statement
	from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −0.2 (95% CI −0.4 to −0.1), week 48: −0.2 (95% CI −0.4 to 0.0); randomised to placebo: week 12: 0.0 (95% CI −0.2 to 0.1), week 48: 0.1 (95% CI −0.1 to 0.2). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups and levels were within the normal range in both groups at all time points. **(MODERATE/LOW)** <u>Total cholesterol</u> • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) total cholesterol (mmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 5.7 (1.3), week 12: 4.9 (1.2), week 48: 5.1 (1.3); randomised to placebo: baseline: 5.3 (1.2), week 12: 5.3 (1.3), week 48: 4.9 (1.2). They also reported mean (95% CI) change in total cholesterol from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −0.8 (95% CI −1.1 to −0.5), week 48: −0.6 (95% CI −1.0 to −0.1); randomised to placebo: week 12: 0.0 (95% CI −0.2 to 0.3), week 48: -0.4 (95% CI −0.9 to 0.1). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups; levels were above the normal range in both groups at baseline and in the placebo group at week 12 but within the normal range at all other timepoints. **(MODERATE/LOW)** <u>LDL cholesterol</u> • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) LDL cholesterol (mmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 3.4 (1.1), week 12: 3.0 (1.0), week 48: 3.0 (1.0); randomised to placebo: baseline: 3.0 (1.1), week 12: 3.1 (1.1), week 48: 2.8 (1.1). They also reported mean (95% CI) change in LDL cholesterol from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −0.5 (95% CI −0.7 to −0.2), week 48: −0.5 (95% CI −0.8 to −0.2); randomised to placebo: week 12: 0.1 (95% CI −0.1 to 0.3), week 48: −0.2 (95% CI −0.6 to 0.2). The fall in LDL cholesterol was *statistically significantly greater* in the osilodrostat phosphate group at week 12 but not at week 48, but levels remained within the normal range in both groups at all time points. **(MODERATE/LOW)** <u>HDL cholesterol</u> • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) HDL cholesterol (mmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 1.6 (0.4), week 12: 1.3 (0.3), week 48: 1.4 (0.3); randomised to placebo: 1.5 (0.4), week 12: 1.5 (0.5), week 48: 1.4 (0.4). They also reported mean (95% CI) change in HDL cholesterol from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −0.3 (95% CI −0.4 to −0.2), week 48: −0.2 (95% CI −0.3 to −0.1); randomised to placebo: week 12: 0.0 (95% CI −0.1 to 0.1), week 48: −0.1 (95% CI −0.3 to 0.0). There was a *statistically significant fall* in HDL cholesterol in the osilodrostat phosphate group but not in the placebo group, but levels remained within the normal range in both groups at all time points. **(MODERATE/LOW)** <u>Triglycerides</u> • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) triglycerides (mmol/L) in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and

Outcome	Evidence statement
	week 48. Randomised to osilodrostat phosphate: baseline: 1.5 (0.8), week 12: 1.5 (0.8), week 48: 1.5 (1.0); randomised to placebo: baseline: 1.7 (0.9), week 12: 1.5 (0.8), week 48: 1.5 (0.8). They also reported mean (95% CI) change in triglycerides from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: 0.0 (95% CI −0.1 to 0.2), week 48: 0.1 (95% CI −0.2 to 0.4); randomised to placebo: week 12: −0.2 (95% CI −0.4 to 0.0), week 48: −0.2 (95% CI −0.5 to 0.0). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups and levels were within the normal range in both groups at all time points. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for these outcomes. *Osilodrostat phosphate vs no comparator* <u>Systolic BP</u> **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) systolic BP (mm Hg): baseline: 132.6 (11.6); week 22: 131.9 (17.8); change from baseline: –1.0 (16.2). **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) systolic BP (mm Hg): baseline: 132.2 (15.1); week 48: 121.7 (13.7); change from baseline: -9.8 (95% CI -12.7 to -6.9). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) systolic BP (mm Hg): baseline: 131.5 (18.6); week 48: 120.9 (15.8); change from baseline: −9.7 (95% CI −14.9 to −4.6). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in systolic BP (mm Hg) from baseline of -10.1 (18.1). **(VERY LOW)** <u>Diastolic BP</u> **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) diastolic BP (mm Hg): baseline: 85.1 (6.5); week 22: 86.0 (8.9); change from baseline: 1.3 (9.7). **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) diastolic BP (mm Hg): baseline: 85.3 (10.6); week 48: 78.9 (10.1); change from baseline: -6.3 (95% CI -8.4 to -4.2). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) diastolic BP (mm Hg): baseline: 87.5 (12.0); week 48: 82.3 (10.8); change from baseline: −4.2 (95% CI −7.3 to −1.2). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in diastolic BP (mm Hg) from baseline of -5.8 (11.3). **(VERY LOW)** <u>Fasting plasma glucose</u> **After 22 weeks treatment**

Outcome	Evidence statement
	• One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) fasting plasma glucose (mg/dl) [11]: baseline: 105.6 (49.0); week 22: 81.2 (9.0); change from baseline: -14.9 (28.9). **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) fasting plasma glucose (mg/dl) [12]: baseline: 99.2 (29.8); week 48: 87.2 (18.9); change from baseline: -9.5 (95% CI -14.3 to -4.8). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) fasting plasma glucose (mg/dl)[13]: baseline: 95.3 (17.3); week 48: 90.6 (13.1); change from baseline: −3.1 (95% CI −6.8 to 0.6). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in fasting plasma glucose (mmol/L)[14] from baseline of -0.3 (1.1). **(VERY LOW)** <u>HbA1c</u> **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) HbA1c (%)[15]: baseline: 5.7 (0.7); week 22: 5.5 (0.6); change from baseline: -0.2 (0.3). **(VERY LOW)** **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) HbA1c (%): baseline: 6.0 (1.0); week 48: 5.6 (0.8); change from baseline: -0.4 (95% CI -0.5 to -0.2). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) HbA1c (%): baseline: 5.9 (0.2); week 48: 5.7 (0.5); change from baseline: −0.1 (95% CI −0.2 to 0.0). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in HbA1c (%) from baseline of -0.4 (0.6). **(VERY LOW)** <u>Total cholesterol</u> **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) total cholesterol (mmol/L)[16]: baseline: 5.3 (1.4); week 22: 4.6 (0.8); change from baseline: -0.7 (1.4). **(VERY LOW)** **After 48 weeks treatment** [17] • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) total cholesterol (mmol/L): baseline: 5.3 (1.2); week 48: 4.8 (1.0); change from baseline: -0.5 (95% CI -0.7 to -0.3). (**VERY LOW)**

[11] Normal range Fleseriu et al 2016: fasting plasma glucose 70 to 110 mg/dL
[12] Reference range Pivonello et al 2020: plasma glucose 70 to 125 mg/dL
[13] Reference range Gadelha et al 2022: fasting plasma glucose, 70–115 mg/dL
[14] Reference range Fleseriu et al 2022b: plasma glucose, 3.9–5.5 mmol/L
[15] Reference range in all studies: HbA1c ≤6.4%
[16] Normal range Fleseriu et al 2016: total cholesterol 3.9 to 6.5 mmol/L
[17] Reference range Pivonello et al 2020 and Gadelha et al 2022: total cholesterol 0 to 5.2 mmol/L

Outcome	Evidence statement
	• One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) total cholesterol (mmol/L): baseline: 5.5 (1.3); week 48: 5.0 (1.3); change from baseline: −0.5 (95% CI −0.8 to -0.2). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in total cholesterol (mmol/L)[18] from baseline of -0.4 (0.9). **(VERY LOW)** <u>HDL cholesterol</u> **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) HDL cholesterol (mmol/L)[19]: baseline: 1.7 (0.9); week 22: 1.3 (0.4); change from baseline: -0.5 (0.8). **(VERY LOW)** **After 48 weeks treatment [20]** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) HDL cholesterol (mmol/L): baseline: 1.6 (0.5); week 48: 1.3 (0.3); change from baseline: -0.3 (95% CI -0.3 to -0.2). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) HDL cholesterol (mmol/L): baseline: 1.6 (0.4); week 48: 1.4 (0.4); change from baseline: −0.2 (95% CI −0.3 to -0.1). **(VERY LOW)** <u>LDL cholesterol</u> **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) LDL cholesterol (mmol/L) [21]: baseline: 3.3 (1.7); week 22: 2.8 (0.6); change from baseline: -0.6 (1.6). **(VERY LOW)** **After 48 weeks treatment [22]** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) LDL cholesterol (mmol/L): baseline: 3.0 (1.0); week 48: 2.8 (1.0); change from baseline: -0.2 (95% CI -0.4 to -0.1). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) LDL cholesterol (mmol/L): baseline: 3.3 (1.1); week 48: 2.9 (1.1); change from baseline: −0.4 (95% CI −0.6 to -0.1). **(VERY LOW)** <u>Triglycerides</u> **After 22 weeks treatment** • One single-arm study (LINC2, Fleseriu et al 2016) (n=17) reported mean (SD) triglycerides (mmol/L)[23]: baseline: 1.5 (0.6); week 22: 1.3 (0.6); change from baseline: -0.7 (1.4). **(VERY LOW)** **After 48 weeks treatment [24]** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) triglycerides (mmol/L): baseline: 1.5 (1.3); week 48: 1.4 (0.9); change from baseline: -0.1 (95% CI -0.2 to 0.1). (**VERY LOW)**

[18] Normal ranges Fleseriu et al 2022b: total cholesterol, ≤4.4 mmol/L in people aged <19 years and ≤5.2 mmol/L in people aged ≥20 years
[19] Normal range Fleseriu et al 2016: HDL-cholesterol 1 to 1.7 mmol/L
[20] Reference range Pivonello et al 2020 and Gadelha et al 2022: HDL cholesterol >0.89 mmol/L
[21] Normal range Fleseriu et al 2016: LDL-cholesterol 0 to 4.2 mmol/L
[22] Reference range Pivonello et al 2020 and Gadelha et al 2022: LDL cholesterol 0 to 3.4 mmol/L
[23] Normal range Fleseriu et al 2016: triglycerides 0.6 to 1.7 mmol/L
[24] Reference range Pivonello et al 2020, Gadelha et al 2022 and Fleseriu et al 2022b: triglycerides 0 to 2.2 mmol/L

Outcome	Evidence statement
	• One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) triglycerides (mmol/L): baseline: 1.6 (0.8); week 48: 1.5 (0.9); change from baseline: 0 (95% CI −0.2 to 0.2). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in triglycerides (mmol/L) from baseline of -0.1 (0.6). **(VERY LOW)** Beck depression inventory II (BDI-II) score [25] *Osilodrostat phosphate vs placebo* **After up to 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) BDI-II score in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 12.2 (10.2), week 12: 10.3 (8.5), week 48: 6.7 (6.7); randomised to placebo: baseline: 8.4 (7.8), week 12: 4.7 (6.1), week 48: 4.1 (7.5). They also reported mean (95% CI) change in BDI-II score from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: −1.4 (95% CI −3.7 to 1.0), week 48: −4.3 (95% CI −6.7 to −2.0); randomised to placebo: week 12: −3.9 (95% CI −6.2 to −1.6); week 48: −4.0 (95% CI −7.5 to −0.6). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) BDI-II score: baseline: 16.8 (10.6); week 48: 10.7 (10.7); change from baseline: -5.8 (95% CI -7.6 to -4.1); mean % change from baseline: -31.8% (95% CI -44.3% to -19.3%). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) BDI-II score: baseline: 10.9 (9.6); week 48: 5.8 (7.9); change from baseline: -4.2 (95% CI −6.1 to -2.3). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in BDI-II score from baseline of -6.7 (10.7). **(VERY LOW)** **Up to the end of treatment (median 87.1 (range 2.0 to 126.6 weeks))** • One single-arm study (LINC4, Gadelha et al 2023) (n=48 at week 72, n=13 at the end of treatment) reported a mean (SD) BDI-II score of 6.5 (7.0), mean change from baseline -4.1 (9.3) at week 72, and 6.2 (7.1), mean change from baseline -4.5 (7.9) at the end of treatment. **(VERY LOW)** **Osilodrostat phosphate vs placebo:** **One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks randomised treatment there was no statistically significant difference**

[25] Decrease in BDI-II score indicates benefit

Outcome	Evidence statement
	in the change in mean weight or waist circumference between patients randomised to osilodrostat phosphate and patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate there remained no statistically significant difference in the change in weight or waist circumference between the two groups. **One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks randomised treatment there was a statistically significantly greater fall in mean LDL cholesterol and HDL cholesterol in patients randomised to osilodrostat phosphate compared to patients randomised to placebo, but values remained within the normal ranges in both groups at all time points. There was no statistically significant difference at 12 weeks in the change in mean systolic BP, diastolic BP, fasting plasma glucose, HbA1c, total cholesterol or triglycerides between patients randomised to osilodrostat phosphate and patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate there were no statistically significant differences in the changes in any of these measures between the groups. Total cholesterol values were above the normal range in both groups at baseline and fell to within the normal range in the osilodrostat phosphate group by 12 weeks and in the group which had been randomised to placebo by 48 weeks. For all other measures values were within the normal range (where specified) in both groups at all time points.** **One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks randomised treatment there was no statistically significant difference in the change in BDI-II score between patients randomised to osilodrostat phosphate and patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate there remained no statistically significant difference in the change in BDI-II score between the two groups.** **Osilodrostat phosphate vs metyrapone:** **No evidence was identified for sequelae of Cushing's disease.** **Osilodrostat phosphate vs no comparator:** **Two single-arm studies (LINC2 and LINC3) provided very low certainty evidence of a fall in mean weight from baseline after up to 72 weeks treatment with osilodrostat phosphate. Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence of a fall in mean body mass index and two single-arm studies provided very low certainty evidence of a fall in mean waist circumference from baseline after up to 72 weeks treatment with osilodrostat phosphate.** **Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence of a fall in mean systolic BP, diastolic BP, fasting plasma glucose, HbA1c, total cholesterol and triglycerides after between 22 and 72 weeks treatment with osilodrostat phosphate. The three single-arm studies also provided very low certainty evidence of a fall in mean HDL and LDL cholesterol after between 22 and 48 weeks treatment with osilodrostat phosphate.** **Two single-arm studies (LINC3 and LINC4) provided very low certainty evidence of a fall (improvement) in mean BDI-II score after between 48 and a median of 87.1 weeks treatment with osilodrostat phosphate. One single-arm study (LINC3) provided very low certainty evidence that the percentage fall in BDI-II score at 48 weeks exceeded the MCID[26].**
Important outcomes	

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

Outcome	Evidence statement
Reduction in treatment for Cushing's disease sequelae **Certainty of evidence:** Very low	This is important to patients because they may be getting symptomatic relief with improvement in their physical health consequences of Cushing's disease, for example improvement in diabetes or hypertension. It may also provide them benefit as it reduces their medication burden. In total, one single-arm study provided evidence relating to reduction in treatment for Cushing's disease sequelae. *Osilodrostat phosphate vs placebo* • No evidence was identified for this outcome. *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome. *Osilodrostat phosphate vs no comparator* **At 48 weeks follow-up[27]:** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=85 taking hypertensive medication at baseline) reported that compared to baseline 34/85 (40%) had increased their dose or number of medications and 34/85 (40%) had decreased their dose or stopped the medication. (**VERY LOW)** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=43 taking diabetic medication at baseline) reported that compared to baseline 10/43 (23%) had increased their dose or number of medications and 21/43 (49%) had decreased their dose or stopped the medication. (**VERY LOW)** **Osilodrostat phosphate vs placebo:** **No evidence was identified for reduction in treatment for Cushing's disease sequelae.** **Osilodrostat phosphate vs metyrapone:** **No evidence was identified for reduction in treatment for Cushing's disease sequelae.** **Osilodrostat phosphate vs no comparator:** **One single-arm study (LINC3) provided very low certainty evidence that after 48 weeks treatment with osilodrostat phosphate, of the patients taking hypertensive medication at baseline 40% had an increase and 40% had a decrease in their medication, and of the patients taking diabetic medication at baseline 23% had an increase and 49% had a decrease in their medication.**
Time to improvement **Certainty of evidence:** Low to very low	This is important to patients because current medicine for Cushing's disease differ with regards to their mechanism of action and time course of pharmacological effect. A treatment that works more quickly is more likely to reduce the risk of subsequent sequelae of Cushing's disease developing. In total, one randomised study and two single-arm studies (reported in three papers) provided evidence relating to time to improvement. Patients in the randomised study who were initially randomised to placebo later crossed over to open-label treatment with osilodrostat phosphate. *Osilodrostat phosphate vs placebo* **After an unspecified duration of follow-up**

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

Outcome	Evidence statement
	• One randomised study (LINC4, Gadelha et al 2022) (n=73) reported median time to first controlled UFC response of 35 (95% CI 34.0 to 52.0) days in patients randomised to osilodrostat phosphate (n=48), and not reached in patients randomised to placebo (n=25). They also reported that the median time to first controlled UFC response was 35 days in patients randomised to placebo once they had crossed over to osilodrostat phosphate. **(LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome *Osilodrostat phosphate vs no comparator* **After an unspecified duration of follow-up** • One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported that the mean (SE) 24-hour UFC was 1371 at baseline and fell to within the normal range by week 4. **(VERY LOW)** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported that the median time to first complete response was 41.0 days (IQR 27.0 to 56.0 days). (**VERY LOW)** **Osilodrostat phosphate vs placebo** **One randomised study (LINC4) provided moderate certainty evidence that the median time to first controlled UFC response for patients treated with osilodrostat phosphate was 35 days.** **Osilodrostat phosphate vs metyrapone** **No evidence was identified for time to improvement.** **Osilodrostat phosphate vs no comparator:** **One single-arm study (LINC2) provided very low certainty evidence that mean UFC fell to within the normal range at a mean of 4 weeks. One single-arm study (LINC3) provided very low certainty evidence that the median time to first complete response was 41.0 days.**
Quality of life **Certainty of evidence:** Moderate to very low	Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making. In total, one randomised study and two single-arm studies (reported in four papers) provided evidence relating to quality of life. Patients in the randomised study who were randomised to osilodrostat phosphate received 48 weeks osilodrostat phosphate, while those randomised to placebo received 12 weeks placebo followed by 36 weeks osilodrostat phosphate. The randomised study reported outcomes relating to quality of life after 12 and 48 weeks treatment, and the single-arm studies reported outcomes relating to quality of life after between 48 weeks and a median of 87.1 weeks treatment with osilodrostat phosphate. *Osilodrostat phosphate vs placebo* **After up to 48 weeks treatment (12 weeks randomised followed by 36 weeks open label osilodrostat phosphate)** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) Cushing quality of life score in patients randomised to osilodrostat phosphate (n=48) compared to patients randomised to placebo (n=25) at baseline, week 12 and week 48. Randomised to osilodrostat phosphate: baseline: 49.1 (19.6),

Outcome	Evidence statement
	week 12: 56.1 (22.1), week 48: 62.8 (22.2); randomised to placebo: baseline: 56.9 (19.0), week 12: 65.6 (17.6), week 48: 69.9 (16.9). They also reported mean (95% CI) change in Cushing quality of life score from baseline at 12 weeks and 48 weeks: randomised to osilodrostat phosphate: week 12: 6.2 (95% CI 1.7 to 10.6), week 48: 11.7 (95% CI 6.6 to 16.7); randomised to placebo: week 12: 8.6 (95% CI 3.5 to 13.7); week 48: 12.8 (95% CI 6.5 to 19.1). The changes at 12 and 48 weeks were *not statistically significantly different* between the two groups. **(MODERATE/LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for this outcome *Osilodrostat phosphate vs no comparator* **After 48 weeks treatment** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported mean (SD) Cushing quality of life score: baseline: 42.2 (19.1); week 48: 58.3 (21.3); change from baseline: 14.1 (95% CI 10.9 to 17.3). (**VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported mean (SD) Cushing quality of life score: baseline: 51.8 (19.6); week 48: 65.3 (20.7); change from baseline: 12.0 (95% CI 8.2 to 15.9). **(VERY LOW)** **After 72 weeks treatment** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=106) reported a mean (SD) change in Cushing quality of life score from baseline of 15.1 (19.4). **(VERY LOW)** **Up to the end of treatment (median 87.1 (range 2.0 to 126.6 weeks))** • One single-arm study (LINC4, Gadelha et al 2023) (n=48 at week 72, n=13 at the end of treatment) reported a mean (SD) Cushing quality of life score of 66.4 (19.6), mean change from baseline 15.2 (19.0) at week 72, and 69.0 (20.9), mean change from baseline 17.1 (17.1) at the end of treatment. **(VERY LOW)** **Osilodrostat phosphate vs placebo** **One randomised study (LINC4) provided moderate certainty evidence that after 12 weeks treatment there was no statistically significant difference in the change in mean Cushing QoL score between patients randomised to osilodrostat phosphate and patients randomised to placebo. After a further 36 weeks treatment of both groups with osilodrostat phosphate there remained no statistically significant difference in the change in mean Cushing QoL score between the two groups.** **Osilodrostat phosphate vs metyrapone** **No evidence was identified for QoL.** **Osilodrostat phosphate vs no comparator** **Two single-arm studies (LINC3 and LINC4) provided very low certainty evidence of an increase (improvement) in mean Cushing QoL score after between 48 and a median of 87.1 weeks treatment with osilodrostat phosphate. They also provided very low certainty evidence that the change from baseline exceeded the MCID at all timepoints[28].**
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

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

Outcome	Evidence statement
Certainty of evidence: Not applicable	recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. **No evidence was identified for this outcome.**
Safety	
Adverse events **Certainty of evidence:** Low to very low	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. In total, two randomised studies and three single-arm studies (reported in six papers) provided evidence relating to adverse events in people with Cushing's disease. The two randomised studies were conducted during a time-limited randomised double-blind placebo-controlled period within two of the single-arm studies. The randomised studies reported adverse events during the randomised treatment periods (8 and 12 weeks in the two studies), and the single-arm studies reported adverse events after between 22 weeks and a median of 5.4 years of osilodrostat phosphate. *Osilodrostat phosphate vs placebo* <u>Any adverse event</u> **During the 8-week randomised treatment period** • One randomised study (LINC3, Pivonello et al 2020) (n=71) reported that in patients randomised to osilodrostat phosphate (n=35) and those randomised to placebo (n=35) the incidence of any AE (all grades) was 26 (72%) and 23 (66%), and of grade 3-4 AEs was 2 (6%) and 3 (9%) respectively. The incidence of any serious AE (all grades) was 2 (6%) and 1 (3%), and of any serious grade 3-4 AE was 1 (3%) and 1 (3%) respectively. **(LOW)** **During the 12-week randomised treatment period** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported that in patients randomised to osilodrostat phosphate (n=48) and those randomised to placebo (n=25) respectively the incidence of any AE was 46 (95.8%) and 23 (92.0%), of any serious AE was 2 (4.2%) and 1 (4.0%), of AEs leading to discontinuation was 1 (2.1%) and 0, of grade 1–2 AEs was 36 (75.0%) and 18 (72.0%) and of grade 3–4 AEs was 10 (20.8%) and 5 (20.0%). **(LOW)** <u>Most common adverse events</u> **During the 8-week randomised treatment period** • One randomised study (LINC3, Pivonello et al 2020) (n=71) reported that in patients randomised to osilodrostat phosphate (n=35) and those randomised to placebo respectively (n=35) the most common AEs were: nausea, 4 (11%) and 0; anaemia, 3 (8%) and 3 (9%) and fatigue, 2 (6%) and 3 (9%). **(LOW)** **During the 12-week randomised treatment period** • One randomised study (LINC4, Gadelha et al 2022) (n=73) reported that in patients randomised to osilodrostat phosphate (n=48) and those randomised to placebo (n=25) respectively the most common AEs were: decreased appetite, 18 (37.5%) and 4 (16.0%); arthralgia, 17 (35.4%) and 2 (8.0%); fatigue, 12 (25.0%) 4 (16.0%); nausea, 15 (31.3%) and 3 (12.0%) and hypertension, 8 (16.7%) and 7 (28.0%). **(LOW)** <u>Adverse events of special interest</u> **During the 8-week randomised treatment period**

Outcome	Evidence statement
	• One randomised study (LINC3, Pivonello et al 2020) (n=71) reported that in patients randomised to osilodrostat phosphate (n=35) and those randomised to placebo (n=35) respectively the incidence of AEs of special interest was: related to adrenal hormone precursor accumulation, 2 (6%) and 1 (3%); related to hypocortisolism, 3 (8%) and 1 (3%). No incidences were reported of AEs related to pituitary tumour enlargement, QT interval prolongation or arrhythmogenic potential on ECG. **(LOW)** *Osilodrostat phosphate vs metyrapone* • No evidence was identified for adverse events. *Osilodrostat phosphate vs no comparator* <u>Any adverse event</u> **After up to 48 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported that the incidence of any AE of all grades was 100%, and of any grade 3-4 AE was 56.9%. The incidence of any serious AE was 36.5% and any serious grade 3-4 AE was 28.5%. AEs requiring dose interruption and/or change occurred in 77.4% (all grades) and 28.5% (grade 3-4). One death was reported. **(VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported that the incidence of any AE of all grades was 100%, and of any grade 3-4 AE was 38.4%. The incidence of any serious AE was 11.0% and of AEs leading to discontinuation was 11.0%. **(VERY LOW)** **After up to 72 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=137) reported that the incidence of any AE of all grades was 100%, and of any grade 3-4 AE was **60.6%.** AEs leading to discontinuation occurred in 18.2% (all grades) and 12.4% (grades 3-4). AEs requiring dose adjustment or interruption occurred in 80.3% (all grades) and 30.7% (grades 3-4). **(VERY LOW)** **After a median 87.1 weeks exposure to osilodrostat phosphate** • One single-arm study (LINC4, Gadelha et al 2023) (n=73) reported that incidence of any AE of all grades was 98.6% and of any grade 3-4 AE was 39.7%. The incidence of any serious AE was 13.7% and any serious grade 3-4 AE was 12.3%. AEs leading to discontinuation occurred in 12.3% (all grades) and 2.7% (grade 3-4); AEs leading to dose adjustment or interruption occurred in 57.5% (all grades) and 17.8% (grades 3-4). AEs requiring additional therapy occurred in 91.8% (all grades) and 30.1% (grade 3-4). **(VERY LOW)** <u>Most common adverse events</u> **After up to 22 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC2, Fleseriu et al 2016) (n=19) reported that the most common AEs of all grades (between 5 (26.3%) and 7 (36.8%) reported of each) were nausea, diarrhoea, asthenia, adrenal insufficiency, nasopharyngitis, increased testosterone, increased adrenal precursors and increased ACTH. Grade 3-4 AEs reported (1 (5.3%) of each reported) were adrenal insufficiency and increased testosterone. **(VERY LOW)** **After up to 48 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported that the most common AEs of all grades (between 30 (21.9%) and 57 (41.6%) reported) were nausea, headache, fatigue, adrenal insufficiency, nasopharyngitis and vomiting. The most common grade 3-4 AEs (n, (%)) were adrenal insufficiency;

Outcome	Evidence statement
	6 (4.4%); headache, 4 (2.9%); vomiting, 4 (2.9%); nausea, 3 (2.2%), fatigue, 3 (2.2%). **(VERY LOW)** • One single-arm study (LINC4, Gadelha et al 2022) (n=73) reported that the most common AEs of all grades (between 15 (20.5%) and 33 (45.2%) reported) were decreased appetite, arthralgia, fatigue, nausea, headache, myalgia, dizziness, adrenal insufficiency, increased blood testosterone, diarrhoea, hypertension, asthenia and upper respiratory tract infection. **(VERY LOW)** **After up to 70 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC2, Fleseriu et al 2022a) (n=16) reported that the most common AEs of all grades (between 4 and 7 reported of each) were adrenal insufficiency, arthralgia, headache and diarrhoea. Grade 3-4 AEs (1 of each reported) were adrenal insufficiency, headache, abdominal pain, increased lipase, pituitary-dependant Cushing's syndrome, gastroenteritis, non-cardiac chest pain and decreased weight. **(VERY LOW)** **After up to 72 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC3, Fleseriu et al 2022b) (n=137) reported that the most common AEs of all grades (between 28 (20.4%) and 50 (36.5%) each) were nausea, headache, fatigue, adrenal insufficiency, vomiting, nasopharyngitis and glucocorticoid deficiency. The most common grade 3-4 AEs (n, (%)) were hypertension, 16 (11.7%); headache, 6 (4.4%); adrenal insufficiency, 6 (4.4%); glucocorticoid deficiency, 5 (3.6%); vomiting, 5 (3.6%); fatigue, 3 (2.2%); nausea, 3 (2.2%). **(VERY LOW)** **After a median 87.1 weeks exposure to osilodrostat phosphate:** • One single-arm study (LINC4, Gadelha et al 2023) (n=73) reported that the most common AEs of all grades (between 16 (21.9%) and 34 (46.6%) reported) were decreased appetite, arthralgia, fatigue, nausea, headache, dizziness, adrenal insufficiency, increased blood testosterone, myalgia, asthenia, diarrhoea, hypertension, upper respiratory tract infection. The most common grade 3-4 AEs (n, (%)) were hypertension, 9 (12.3%); myalgia, 5 (6.8%); adrenal insufficiency,3 (4.1%); fatigue, 3 (4.1%); arthralgia, 2 (2.7%); asthenia, 2 (2.7%). **(VERY LOW)** <u>Adverse events of special interest</u> **After up to 48 weeks treatment with osilodrostat phosphate** • One single-arm study (LINC3, Pivonello et al 2020) (n=137) reported that the AEs of special interest of all grades (n, (%)) were adrenal hormone precursor accumulation related, 58 (42.3%); hypocortisolism related, 70 (51.1%); pituitary tumour enlargement related, 3 (2.2%); QT prolongation related, 5 (3.6%); arrhythmogenic potential, 1 (0.7%). Grade 3-4 AEs of special interest (n, (%)) were adrenal hormone precursor accumulation related, 22 (16.1%); hypocortisolism related, 14 (10.2%); QT prolongation related, 1 (0.7%); arrhythmogenic potential, 1 (0.7%). **(VERY LOW)** **After a median 87.1 weeks exposure to osilodrostat phosphate:** • One single-arm study (LINC4, Gadelha et al 2023) reported the incidence of AEs of special interest (%) at weeks 1-12 (n=48), weeks 12-24 (n=71), weeks 24-36 (n=69), weeks 36-48 (n=68), weeks 48-60 (n=64) and weeks 60 onwards (n=59). The incidence of AEs related to hypocortisolism during these time periods was 14.6%, 12.7%, 7.2%, 5.9%, 0 and 8.5% respectively. The incidence of AEs related to arrhythmogenic potential and QT prolongation during these time periods was 0, 1.4%, 1.4%, 1.5%, 0 and 0, respectively. **(VERY LOW)** **After median 5.4 years exposure to osilodrostat phosphate** • One single-arm study (LINC2, Fleseriu et al 2022a) (n=19) reported that the most common AEs of special interest of all grades (n) were related to accumulation of adrenal hormone precursors, 12; related to hypocortisolism, 11;

Outcome	Evidence statement
	related to arrhythmogenic potential, 1; related to QT prolongation, 1. Grade 3-4 AEs reported were related to accumulation of adrenal hormone precursors, 4; and related to hypocortisolism, 2**. (VERY LOW)** **Osilodrostat phosphate vs placebo** **Two randomised studies (LINC3 and LINC4) provided low certainty evidence that the incidence of any AE was 72-96% in the osilodrostat phosphate group and 66-92% in the placebo group. The incidence of grade 3-4 AEs was 6-21% and 9-20% respectively, and of any serious AE (all grades) was 4.2-6% and 3-4% respectively. One of the randomised studies (LINC3) provided low certainty evidence that AEs related to adrenal hormone precursor accumulation occurred in 6% and 3% respectively, and AEs related to hypocortisolism occurred in 8% and 3% respectively. There were no statistical comparisons between the two groups.** **Osilodrostat phosphate vs metyrapone** **No evidence was identified for adverse events.** **Osilodrostat phosphate vs no comparator** **Two single-arm studies(LINC3 and LINC4) provided very low certainty evidence that 98.6 to 100% of patients experienced at least one AE of any grade, and that between 38.4% and 60.0% experienced at least one grade 3-4 AE. The incidence of any serious AE was 11.0% to 36.5% and any serious grade 3-4 AE was 12.3% to 28.5%. AEs requiring dose interruption and/or change occurred in 57.5% to 80.3% (all grades) and 17.8% to 30.7% (grade 3-4), and AEs leading to discontinuation occurred in 11.0% to 12.3%. One single-arm study (LINC3) reported one death.** **Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence that the most commonly reported AEs of any grade were nausea, headache, fatigue, adrenal insufficiency, arthralgia, nasopharyngitis, increased blood testosterone and asthenia. The most commonly reported grade 3-4 AEs were adrenal insufficiency, hypertension, headache, vomiting, fatigue and nausea.** **Three single-arm studies (LINC2, LINC3 and LINC4) provided very low certainty evidence on AEs of special interest. Two studies (LINC2 and LINC3) reported that the AEs of special interest of all grades were adrenal hormone precursor accumulation in 42.3% to 63.1%, hypocortisolism related in 51.1% to 57.9%, QT prolongation related in 3.6% to 5.3%, arrhythmogenic potential in 0.7% to 5.3% and pituitary tumour enlargement related in 0 to 2.2%. Two studies also reported that Grade 3-4 AEs of special interest were adrenal hormone precursor accumulation related in 16.1% to 21.1%, hypocortisolism related in 10.2% to 10.5%, QT prolongation related in 0 to 0.7% and arrhythmogenic potential in 0 to 0.7%.**
Abbreviations ACTH: adrenocorticotrophic hormone; AE: adverse event; BDI-II: Beck's Depression Inventory-II; BP: blood pressure; CI: confidence interval; HbA1c: glycated haemoglobin; HDL: high density lipoprotein; IQR: interquartile range; LDL: low density lipoprotein; MCID: minimal clinically important difference; NE: not evaluable; OR: odds ratio; SD: standard deviation; SE: standard error; UFC: urinary free cortisol.	

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

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

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

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

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

Outcome	Evidence statement
Osilodrostat phosphate schedules and doses	All studies used osilodrostat phosphate orally twice daily. Bonnet-Serrano et al 2022 Median dose 10mg/day (range 2 to 40mg). No further details were provided. **LINC2** Fleseriu et al 2016 *Follow-up cohort*: osilodrostat phosphate was initiated at the penultimate dose that was efficacious and tolerable in LINC 1 (starting dose: 4 mg/day, n = 1; 20 mg/day, n = 3) *Expansion cohort*: osilodrostat phosphate was initiated at 4 mg/day if baseline UFC was >1.5 to ≤3 x ULN (n=9), and 10 mg/day if baseline UFC was >3 x ULN (n=6). For both cohorts, dose was escalated every 2 weeks according to the escalation sequence 10, 20, 40, and 60 mg/day until UFC was ≤ULN. Titration was continued up to week 10 as needed based on efficacy and tolerability. Treatment was then continued at the same dose from week 10 for a further 12 weeks. If UFC was in the lower normal range or below the lower normal limit, and if the patient had symptoms suggestive of adrenal insufficiency, a dose reduction or interruption was considered. Fleseriu et al 2022a Patients were continued on the dose they were on at the end of the 22-week treatment period reported in Fleseriu et al 2016. Dose adjustments were permitted based on individual efficacy and tolerability, up to a maximum dose of 30mg twice daily. Median dose from baseline to the end of the study 10.6 mg/day (range 1.1 to 47.9 mg/day, IQR 5.7 to 16.7 mg/day). **LINC3** Pivonello et al 2020 Dose started at 2mg twice daily for all patients with dose adjustments every 2 weeks based on efficacy and tolerability. The dose range was 1 to 30 mg twice a day. During the first 26 weeks the mean dose received was 10.0 mg per day (SD 7.3), and mean highest dose was 17.8 mg per day (SD 13.6). During the randomised withdrawal phase (week 26 to 34) mean dose was 10.0 mg per day (SD 9.6). Fleseriu et al 2022b Dose started at 2mg twice daily for all patients with dose adjustments as described in Pivonello et al 2020, up to a maximum permitted dose of 30 mg twice daily. Median osilodrostat phosphate dose from the start of the core study reported in Pivonello et al 2020 to the end of the extension reported in this paper was 7.4 mg/day (range 0.8–46.6, IQR 3.5– 13.6). **LINC4**

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

Patient Impact assessment

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients have moderate problems in walking about
- **ability to provide self-care:** Patients have moderate problems in washing or dressing
- **undertaking usual activities:** Patients have moderate problems in doing their usual activities
- **experience of pain/discomfort:** Patients have moderate pain or discomfort
- **experience of anxiety/depression:** Patients are moderately anxious or depressed

Further details of impact upon patients:
Cushing's syndrome negatively impacts quality of life. Patients experience many symptoms, including fatigue, weight gain, muscle weakness, thinning of the skin and large stretch marks. The physical changes can negatively impact patients' self-esteem and confidence. Cushing's syndrome can also impact mood, causing depression or cognitive impairment, further worsening quality of life. Cushing's syndrome can have detrimental impact on neurocognition, emotional control and executive function. Patients report levels of guilt that they are not able to do the activities they want to do with families and loved ones, particularly when they are looking after young children. Consequences of Cushing's syndrome can be difficult for patients, as it can cause long term conditions such as high blood pressure, type 2 diabetes and osteoporosis. These problems result in multiple health consequences for patients and lead to a higher morbidity and mortality. These associated health conditions also result in a high tablet burden and increased frequency of medical appointments. Furthermore, complications associated with either the condition or treatments can also have both a physical and psychological impact on the patient.

Further details of impact upon carers: Looking after those with Cushing's syndrome can be a significant burden on carers. Many of the symptoms' patients with Cushing's report are difficult to see, such as low mood, fatigue and myalgia. This can sometimes make the relationship between patients and carers difficult. The multiple health complications associated with Cushing's syndrome result in a high burden of medical appointments, which may be hugely time consuming for both patients and their carers. The high mortality and morbidity associated with Cushing's syndrome is also a psychological burden for carers, as they help patients navigate their increasing care needs and uncertainty about the future.

Considerations

Equality and Health Inequalities Impact Assessment (EHIA)	
Summary of any potential impacts of the proposal	The introduction of osilodrostat phosphate would increase health equity for all patients with Cushing's syndrome compared to standard care for groups who face health inequalities as highlighted in the EHIA. The subset of patients with Cushing's syndrome who have Cushing's disease are more commonly women between the ages of 25-40 years. In women, osilodrostat phosphate will be of particular benefit, as this treatment produces much lower levels of the hormones 11-deoxycortisol, androstenedione and testosterone compared with current standard therapy, metyrapone. This means that less androgens are produced as a result of osilodrostat compared with metyrapone, and women are less likely to suffer from side effects they might find distressing such as excess hair. Malignant causes of Cushing's syndrome are more common in older people, and this will increase health equity by providing this group with another treatment option whilst waiting for more definitive surgery. If they are not suitable for more definitive surgery, then it provides them a pharmacological option to treat some of their side effects.
13Q Assessment	
PPVAG outcome	No consultation required

Were PPVAG assured of the level of stakeholder testing?	Yes

Rare Disease Advisory Group

Not Applicable

Pharmaceutical

Yes

This clinical commissioning policy proposition is for the use osilodrostat phosphate for adult patients with endogenous Cushing's Syndrome. The recommendations are aligned to the marketing authorisation for osilodrostat phosphate. Osilodrostat phosphate may be used in post-pubescent children by application of the NHS England's Policy 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children). Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined, using separate prior approval forms for registration of adults and children.

Osilodrostat phosphate is included on the NHS Payment Scheme Annex A, so is a high-cost drug.

National Programme of Care

The proposal received the full support of the Internal Medicine National Programme of Care.