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Osilodrostat for Cushing Disease and Its Role in Pediatrics

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Abstract
Background: Cushing disease (CD) is a very rare form of hypercortisolism caused by an adrenocorticotropic hormone-secreting pituitary adenoma. Clinical manifestations of CD can include central fat accumulation, arterial hypertension, glucose intolerance, skin atrophy with striae, and hypogonadism. Children are frequently diagnosed due to a growth stunt and excessive weight gain while classic cushingoid signs might be initially absent. Other children-specific presentations of CD are early or delayed puberty and hyperandrogenism in girls. ***Summary:*** We present the main outcomes of clinical trials of osilodrostat (Isturisa®, Recordati) for CD, and its initial development as an aldosterone synthase inhibitor. Osilodrostat is indicated only when the surgical therapy of the pituitary adenoma is not an option or has not been curative; additionally, other steroidogenesis inhibitors were briefly summarized. Clinical trials of osilodrostat in children are lacking and we describe its potential role in the pediatric population. ***Key Messages:*** Osilodrostat is the first adrenal steroidogenesis inhibitor to be European Medicines Agency- and United States Food and Drug Administration-approved (both in 2020) for the treatment of adults with Cushing syndrome/disease. Phase II and III clinical trials have shown its efficacy in normalizing 24-h urinary-free cortisol and a good safety profile. Osilodrostat's pharmacological properties and safety are currently being evaluated in a small Phase II trial (NCT03708900) – the first trial in the pediatric population (<18 years) with an estimated completion date in the year 2023.

Introduction

Cushing disease (CD) is a very rare form of hypercortisolism caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma [1, 2]. Cushing syndrome (CS) is a wider entity that results from an excessive exposure to endogenous or exogenous glucocorticoids. Endogenous production of glucocorticoids can be a result of CD, an ectopic ACTH production by a neuroendocrine tumor or by cortisol-producing tumors of the adrenal glands [3]. It most commonly occurs in

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young- to mid-adulthood women and is an ultrarare disease with an incidence of 2–5 cases per 1 million people per year [4]. Clinical manifestations of CD can include various manifestations, such as central fat accumulation and obesity, arterial hypertension, glucose intolerance, striae, skin atrophy and fungal infections, osteopenia, hypogonadism, and depression [1, 2]. In childhood, CD is even much rarer than in adults and is considered an ultrarare disease – only around 10% of all CD cases are diagnosed in children. While boys and girls are equally affected before and during puberty, girls are more frequently affected after puberty [5]. The classic cushingoid signs/symptoms of CD are usually not the initial presentation seen in children. Most commonly, CD in children manifests with the combination of excessive weight gain and growth failure [6]. Other CD signs, such as early or delayed puberty, and/or signs of hyperandrogenism in girls could be present.

Accurate diagnosis of CD and appropriate treatment selection are warranted for optimal outcomes [1, 2]. Initially, it is important to distinguish ACTH-dependent (CD) from ACTH-independent causes of CS. Transsphenoidal adenomectomy is considered as first-line therapy for CD, enabling remission in up to 80% CD patients. It is also a preferred surgical procedure in children or adolescents with CD [2]. Recurrence rates after the procedure are reported to be in the range of 5–35%, with half of them in the first 5 years. Lifelong monitoring is thus required. In this case, repeated transsphenoidal surgery is recommended mostly in cases where tumor is evident on an MRI scan [2].

In cases of persistent or recurrent CD, when the surgery is contraindicated or refused, or in combination with radiation therapy, medical therapy is indicated to treat hypercortisolism [2]. Adrenal steroidogenesis inhibitors are used as therapeutic agents for CD, inhibiting adrenal enzymes to decrease glucocorticoid and/or adrenal androgen production, but do not target the ACTH-secreting pituitary adenoma. This group includes ketoconazole, metyrapone, mitotane, etomidate, and the recently approved osilodrostat. Other medical therapies are used in cases where adrenal steroidogenesis inhibitors are contraindicated or ineffective. They include pituitary-targeted drugs (cabergoline or pasireotide) or glucocorticoid receptor antagonists (mifepristone) [2, 4, 7, 8]. Unfortunately, there is a lack of trials with direct comparisons of various medical therapies for CD and on the use of combinations of medical therapies [9]. The main medical therapies for CD are further presented in Table 1.

Osilodrostat (product code LCI699) is the last among the adrenal steroidogenesis inhibitors that were introduced for medical therapy of CD. Initially, Phase II clinical trials of osilodrostat were conducted for the treatment of hypertension and primary aldosteronism. However, in 2013, Novartis decided to discontinue its development in these indications and to repurpose the drug for the treatment of CD/CS [10]. After completion of clinical trials, in January 2020, European Medicines Agency approved osilodrostat for the treatment of "endogenous CS" in adults [11]. In March 2020, the United States Food and Drug Administration approved osilodrostat for the treatment of CD patients who either cannot undergo pituitary surgery or have undergone pituitary surgery but still have the disease [12]. Prior to that, in 2014, orphan designation (EU/3/14/1345) was granted for osilodrostat for the treatment of CS [13]. Currently, osilodrostat is not approved for pediatric patients with CD. Nonetheless, a pediatric Phase II clinical trial is ongoing with a completion target set for 2023. In this focused review, we aimed to present the main characteristics of the osilodrostat as a therapy for CD, its development timeline and to briefly assess its possible future role in pediatric patients with CD.

Osilodrostat Clinical Trials

Phase I/II

Osilodrostat was initially developed as a selective aldosterone synthase inhibitor that could offer a new approach in the treatment of hypertension, primary aldosteronism, and other conditions with a stimulated renin-angiotensin-aldosterone system. The timeline of osilodrostat development and approval is available in the online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000522054). In 2008 and 2009, four Phase II trials of osilodrostat were conducted: three for the treatment of hypertension and one for primary aldosteronism.

The clinical trial of primary aldosteronism (NCT-00732771) found that low osilodrostat doses (1–2 mg/day) were sufficient at inhibiting aldosterone synthesis and correcting hypokalemia. However, they only mildly reduced blood pressure [14]. In patients with essential hypertension (NCT00758524), different doses (0.25–1 mg/day) of osilodrostat significantly lowered 24-h ambulatory blood pressure compared to a placebo at the end of an 8-week randomized double-blind, double-dummy clinical trial. Blood pressure reductions were similar between osilodrostat 1 mg/day and eplerenone 50 mg twice

Table 1. Main medical therapies used for CD

Name	Type	Route of appl.	Main indications	Efficacy (% at UFC normal.)	Main adverse effects	Approval status (EMA, FDA)	Approved for pediatric use in CD/CS
Osilodrostat [29, 11]	ASI	Oral	If pituitary surgery is not an option or has not been curative (FDA); endogenous CS (EMA)	77% and 86% in maintaining response	Hirsutism, hypertension, hypokalemia, GITD, AI, QTc-p	EMA, FDA	No
Ketoconazole [30]	ASI	Oral	Endogenous CS (EMA)	Approx. 65	GITD, ILE, gynecomastia, skin rash, AI	EMA	Yes, children above 12 years (EMA)
Metyrapone [31, 32]	ASI	Oral	Endogenous CS (EMA)	47–70	Hirsutism, hypertension, hypokalemia, GITD, AI	EMA	Yes (in the UK)
Mitotane [33, 34]	ASI	Oral	Adrenal cancer with endogenous CS (EMA, FDA)	80	GITD, dizziness, cognitive alterations (neurotoxicity), AI; ILE	EMA, FDA	No
Etomidate	ASI	IV	OLO	ND (100% serum cortisol control)	Sedation. AI, myoclonus, nausea, vomiting, dystonic reactions	No	No
Pasireotide [35, 36]	DRA	SC	CD if pituitary surgery is not an option or has not been curative	15–26	Hyperglycemia, diabetes, GITD, cholelithiasis, fatigue, QTc-p	EMA, FDA	No
Cabergoline [37]	DRA	Oral	OLO	40	Headache, nasal congestion, hypotension, depression, dizziness	No	No
Mifepristone [38, 39]	GRB	Oral	Hyperglycemia associated with CS	ND (improvement in glycemia)	GITD, headache, hypokalemia, arthralgia, peripheral edema, hypertension, vaginal bleeding, AI	FDA	No

The table was partially adapted from the data presented in Table 2 in an article by Fleseriu et al. [2]. Approval status was verified on the official websites of the EMA and US FDA. AI, adrenal insufficiency; appl., application; Approx., approximately; ASI, adrenal steroidogenesis inhibitor; CD, Cushing disease; CS, Cushing syndrome; DRA, dopamine receptor agonist; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; GITD, gastrointestinal disturbances; GRB, glucocorticoid receptor blocker; ILE, increased liver enzymes; IV, intravenous; ND, no data; normal., normalization; OLO, off-label use only; QTc-p, QTc-prolongation; SC, subcutaneous; UFC, urinary-free cortisol.

daily. ACTH stimulation test revealed that 20% of patients receiving osilodrostat 1 mg daily had a blunted cortisol response [15]. The results of the latter study were confirmed by another clinical trial (NCT00817414) in 63 patients with hypertension. This proved the nonselectivity of osilodrostat for aldosterone synthase as a dose-dependent inhibition was observed at an ACTH stimulation test [16]. Moreover, osilodrostat as an add-on therapy, administered in 0.5–2-mg doses, was not associated with statistically significant blood pressure reductions when compared to a placebo in a study of patients with resistant hypertension (NCT00817635) [17]. All four clinical trials showed that osilodrostat is well tolerated in patients, but had a modest blood pressure-lowering effect, probably due to an accumulation of aldosterone precursors. Additionally, higher doses led to an impaired cortisol production. These findings drove the repurposing of osilodrostat away from the treatment of hypertension and to the treatment of endogenous hypercortisolism [18].

After repurposing, the first proof of concept clinical trial for the treatment of CD (NCT01331239) was started in 2011. It consisted of two parts: LINC-1 (LCI699 IN Cushing-1) and LINC-2. Thirty-one patients with CD and urinary-free cortisol (UFC) levels >1.5 upper limit of normal (ULN) were enrolled and introduced to osilodrostat for 10 weeks (LINC-1) and 22 weeks (LINC-2).

Twelve patients included in LINC-1 started with 4 mg/day of osilodrostat. The dose increased every 2 weeks according to UFC. The primary endpoint was defined as UFC ≤ULN or ≥50% UFC reduction from baseline levels at week 10. All 12 patients had a ≥50% UFC reduction from baseline, while 11 patients (92%) had UFC ≤ULN at week 10, thus proving the concept and demonstrating the efficacy of osilodrostat in lowering cortisol levels. UFC rose above ULN 2 weeks after discontinuation of osilodrostat [19].

LINC-2 trial enrolled 19 patients, four of whom had been included in LINC-1 and were reenrolled if UFC >ULN. Osilodrostat was introduced at the maximum efficacious and tolerable dose from LINC-1 for reenrolled patients and at 4 mg/day for osilodrostat-naive patients (or 10 mg/day if baseline UFC >3 × ULN). Dosage was increased every 2 weeks if UFC remained below ULN. LINC-2 confirmed the findings from LINC-1, since UFC decreased from baseline and normal UFC levels were observed in all patients. At week 22, 15/17 patients had UFC <ULN at week 22 and two had experienced a roughly 50% decrease of UFC. One patient discontinued the trial due to an administrative reason and one due to an osilodrostat-related papular rash [20]. Another Phase II trial (NCT02468193) evaluated the efficacy and safety of osilodrostat in a small cohort ($N = 9$) of patients with CS except CD in short (up to 12 weeks) and long term (up to 48 weeks). It showed similar results to LINC-1 and LINC-2 that only enrolled patients with CD [21].

Two Phase I trials were conducted for osilodrostat in a single 30 mg dose. The first (NCT02399202) found no significant differences in exposure to osilodrostat between individuals with normal kidney function, severe function impairment, and end-stage renal disease [11, 22]. On the other hand, hepatic function impairment had a significant effect on its pharmacokinetics (NCT02372084). Patients with severe (Child-Pugh C) and moderate (Child-Pugh B) hepatic impairment had higher systemic exposure (AUC 1.4- and 2.7-times higher) and osilodrostat half-life was increased by 1.8- and 3.7-times compared to individuals with normal liver function. No significant differences in exposure parameters were seen at a Child-Pugh A stage [11, 23].

Phase III/IV

LINC-3 and LINC-4 trials (NCT02180217 and NCT02697734) included 137 and 73 adults with CD that had UFC >1.5 × ULN and elevated morning ACTH levels (LINC-3) or UFC >1.3 ULN (LINC-4). LINC-3 was the first study that included a double-blind placebo-controlled withdrawal phase. It showed that 86% of patients on a fixed osilodrostat dose (mean dose 10 mg/day) maintained a complete response (UFC ≤ULN) during 8 weeks compared to only 29% on placebo. All patients included in this phase were complete responders before randomization to osilodrostat or placebo [24]. In the second Phase III study LINC-4, patients enrolled started a 12-week double-blind placebo-controlled phase with dose adjustments according to efficacy and tolerability. In the osilodrostat group, 77% of individuals achieved UFC ≤ULN while only 8% in the placebo group at the end of this phase. Osilodrostat recipients maintained the response until week 36 [25]. Moreover, patients on osilodrostat experienced improvements in clinical parameters of hypercortisolism: reduction of body weight, blood pressure, cholesterol, fasting glucose, and HbA1c concentrations, along with an improved quality of life and psychological state [24].

Ongoing Clinical Trials

Currently, two ongoing Phase II clinical trials (NCT03606408 and NCT03708900) are registered at clinicaltrials.gov. The first is an open-label study and aims to investigate long-term adverse events and clinical

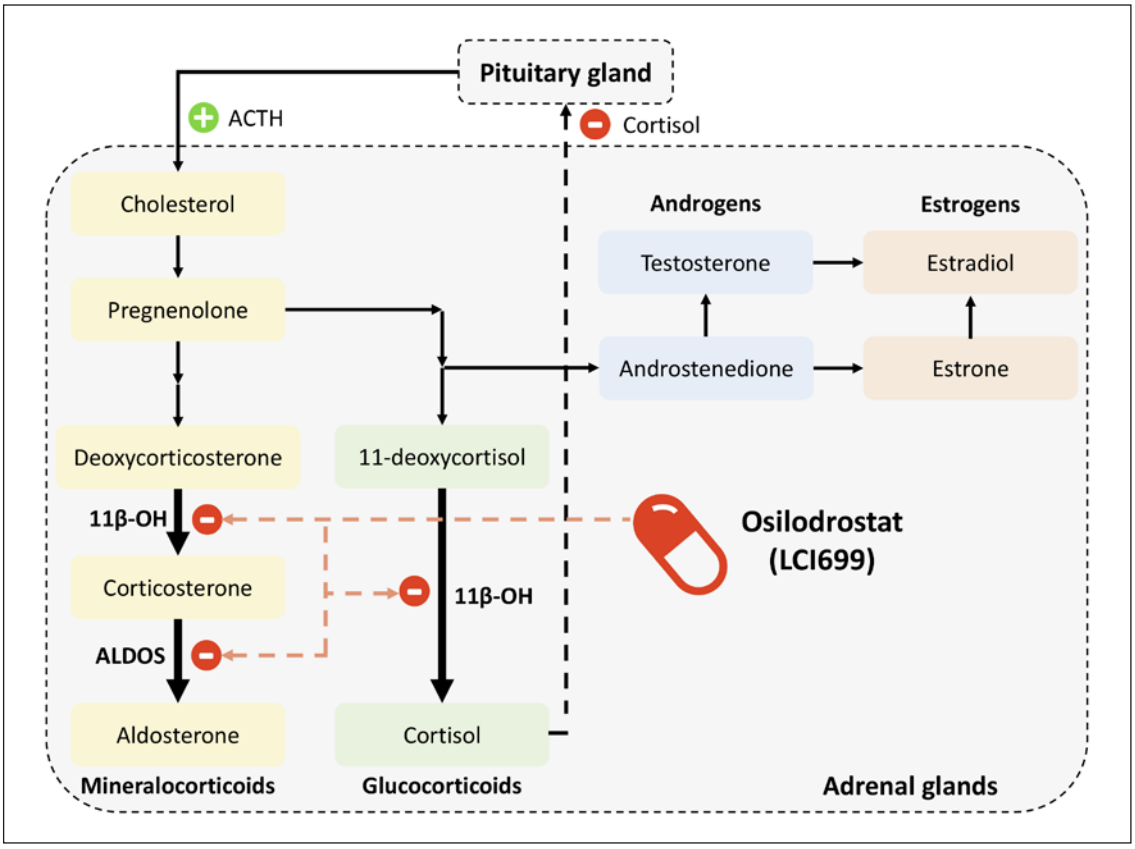

Fig. 1. Mechanism of action of osilodrostat (LCI699). Osilodrostat blocks the last enzymes in both glucocorticoid and mineralocorticoid synthesis pathways, thereby halting the production of both cortisol and aldosterone. The pituitary responds by an increased production of ACTH to low cortisol levels. By blocking ALDOS and 11β-OH, upstream metabolites, including androgens, start to accumulate in the cortex of adrenal glands [10]. ACTH, adrenocorticotropic hormone; 11β-OH, 11β-hydroxylase; ALDOS, aldosterone synthase.

benefits in adult patients with endogenous CS that were included in a previously completed osilodrostat trial and benefited from the drug. All included patients will be receiving the predetermined efficacious osilodrostat dose in a prior trial.

The other ongoing trial (NCT03708900) will be the first to include a small cohort of pediatric patients (<18 years) with CD. Its goal is to evaluate the pharmacokinetics, pharmacodynamics, and tolerability of osilodrostat. The expected completion date is in 2023.

In summary, osilodrostat proved to be an efficacious treatment for CS and CD. Due to its oral administration and good tolerance, osilodrostat could help patients suffering from hypercortisolism. Nonetheless, to prevent adverse events, they should be regularly monitored for timely dose adjustments.

Pharmacology

Mechanisms of Action

The production of corticosteroids in the adrenal glands is closely regulated by two endocrine systems: the renin-angiotensin-aldosterone system and the hypothalamus-pituitary-adrenal axis. Aldosterone and cortisol, the main mineralocorticoid and glucocorticoid hormone, are produced from cholesterol and share some of the same precursors (shown in Fig. 1). An enzyme 11β-hydroxylase (CYP11B1) catalyzes the last step in the synthesis of cortisol while CYP11B2, also known as aldosterone synthase, is responsible for the conversion of deoxycorticosterone to aldosterone [18]. While osilodrostat inhibits both enzymes, it has a greater potency for inhibition of CYP11B1 [26], thereby reducing the synthesis of aldosterone and cortisol. Low cortisol levels stimulate the hypothalamus-

pituitary-adrenal axis and ACTH from the pituitary which in the end stimulates steroidogenesis and the production of glucocorticoids, mineralocorticoids, and adrenal androgens [18].

Pharmacokinetics

Osilodrostat is designed to be taken orally due to its rapid absorption ($t_{max} \cong 1$ h) in the gastrointestinal tract and minor first-pass metabolism. Administration of osilodrostat with food slightly reduces its bioavailability (11% reduction of AUC compared to a fasting state). It has a high volume (≈100 L) of distribution, which indicates good penetration into tissues where no significant accumulation is observed. The majority of osilodrostat is metabolized by cytochromes P450 and UDP-glucuronosyltransferases and excreted by kidneys. Only around 20% of the dose is excreted in the unchanged form [11, 27].

Adverse Effects, Drug Interactions, and Use in Pregnancy and during Lactation

Osilodrostat proved to be tolerable by patients in the completed Phase II and III trials; however, a minority of patients discontinued participation in the studies due to an osilodrostat-related adverse event which were in general mild and nonspecific. The most frequent by relative frequency in the largest Phase III trial (LINC-3) that included 137 patients were nausea (42%), headache (34%), fatigue (28%), and adrenal insufficiency (28%). In the randomized double-blind withdrawal phase, the overall frequency of adverse events was similar in the osilodrostat-receiving group and placebo-receiving group. Hypocortisolism and related adverse events occurred in 70% and 42% of patients, most commonly observed in the dose titration phase. They were manageable by dose adjustments or glucocorticoid supplementation [24, 28]. Patients taking osilodrostat in the double-blind placebo-controlled LINC-4 trial reported decreased appetite (38% vs. 16% placebo), arthralgia (35% vs. 8%), nausea (31% vs. 12%), hypocortisolism-related adverse events (15% vs. 0%), all of which were mild (grade 1–2) and manageable as previously mentioned [25].

Aldosterone and cortisol production inhibition by osilodrostat can result in a cortisol withdrawal syndrome or adrenal insufficiency. It is therefore advised to monitor serum cortisol in patients taking osilodrostat and intervene with dose reductions or glucocorticoid supplementation if cortisol levels fall below the lower limit of normal [11]. Hypokalemia and hypertension can occur as a consequence of the accumulation of biologically active aldosterone precursors. With this in mind, potassium levels should be determined prior to the introduction of osilodrostat and in regular intervals afterwards [9, 11]. The follow-up of these patients should also include an electrocardiogram since a dose-dependent QTc interval prolongation has been reported in patients taking osilodrostat [11, 27]. Female patients in the LINC-3 trial had adverse events related to androgen and estrogen increase and reported mild hirsutism (11%) and acne (11%) [24].

Osilodrostat should be cautiously used with drugs that cause QTc-prolongation, such as certain antibiotics and antidepressants, and hypokalemia. Prior to excretion, the majority of the drug is metabolized by cytochromes P450. Furthermore, certain cytochromes can be inhibited or induced by osilodrostat. Thus, a clinician prescribing osilodrostat should be cautious at its initiation or at introducing a new drug in a patient already receiving osilodrostat [11].

Preclinical data in animals indicated that osilodrostat could have a toxic effect on the fetus and should not be prescribed to pregnant women or to women in the childbearing period who are not using contraception. Due to a lack of data on the effect of osilodrostat on newborns/infants, it is also advised to avoid breastfeeding for at least 1 week after discontinuing treatment [11].

Dosage and Administration

Osilodrostat comes in the form of film-coated tablets for oral use and can be taken with or without food. The starting dose for adults with CS is 2 mg daily and is gradually titrated (maximum dose 30 mg twice daily) to achieve UFC <ULN while taking the patient's tolerability into account. Dose adjustments should be made in patients with severe (Child-Pugh C) and moderate (Child-Pugh B) liver impairment, but not for those with kidney function impairment. Response to the drug should be monitored every 1–2 weeks with 24-h UFC and serum cortisol measurements [11].

Potential Role of Osilodrostat for Pediatric Patients

CD is extremely rare in children and adolescents, which is also reflected in scarce data on clinical management and the lack of clinical trials available on pediatric CD. Transsphenoidal adenomectomy is considered a first-line therapy for CD in children and adolescents. If CD persists or recurs, or when the surgery is contraindicated or refused, medical therapy is indicated [2]. Adrenal steroidogenesis inhibitors, mostly ketoconazole and me-

tyrapone (but not pasireotide), are the first-line medical therapy for pediatric CD [2]. Osilodrostat has not yet been approved for pediatric patients but is currently being evaluated in a small Phase II trial (NCT03708900), which is expected to be completed in 2023. However, most of the current medical therapies for CD in children and adolescents were not tested in pediatric patients and are currently used off-label. Based on current evidence indicating a superior efficacy and safety profile of osilodrostat over other adrenal steroidogenesis inhibitors, it might already be considered for off-label use in selected pediatric patients. However, we find it reasonable that pediatric patients with CD that are candidates for medical therapy participate in the ongoing clinical trial on pediatric patients. In addition, children with CD should be referred to multidisciplinary tertiary centers with pediatric endocrinologists, experts in managing disorders of the pituitary, and with specialized neurosurgery units [2].

Conclusions

Osilodrostat is the first adrenal steroidogenesis inhibitor to be European Medicines Agency- and United States Food and Drug Administration-approved (both in 2020) for the treatment of adults with CD, when surgical resection of the pituitary adenoma is not indicated, desired, or effective. Thus far, other steroidogenesis inhibitors have been used off-label in pediatric patients for this indication. Phase II and III clinical trials have shown osilodrostat's efficacy in normalizing the 24-h UFC and a good safety profile [19, 20, 24, 25]. Osilodrostat has not yet been approved for pediatric patients, but is currently being evaluated in a small Phase II trial (NCT03708900), which is expected to bring more answers on its pharmacological properties and safety.

Conflict of Interest Statement

T.B. (PI) and U.G. (sub-I) are currently involved in a pediatric trial of osilodrostat (NCT03708900). J.S. declares no conflicts of interest.

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Author Contributions

Urh Groselj: investigation, conceptualization, and writing – original draft; Jaka Sikonja: investigation, writing – original draft, and visualization; and Tadej Battelino: investigation and writing – original draft.

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