

Endogenous Hypercortisolemia in Cushing's Syndrome¹



RAPIDLY NORMALIZE¹

CORTISOL

Models are actual patients.

ISTURISA® (osilodrostat) is indicated for the treatment of endogenous hypercortisolemia in adults with Cushing's syndrome for whom surgery is not an option or has not been curative.¹

ISTURISA is an oral therapy¹:

- An FDA-approved therapy that is an inhibitor of the enzyme 11 β -hydroxylase, the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland^{1,2}
- Well-characterized safety profile in clinical trials^{3,4}

FDA, US Food and Drug Administration.

IMPORTANT SAFETY INFORMATION

Hypocortisolism: ISTURISA lowers cortisol levels and can lead to hypocortisolism and sometimes life-threatening adrenal insufficiency. Lowering of cortisol can cause nausea, vomiting, fatigue, abdominal pain, loss of appetite, and dizziness. Significant lowering of serum cortisol may result in hypotension, abnormal electrolyte levels, and hypoglycemia.

Hypocortisolism can occur at any time during ISTURISA treatment. Evaluate patients for precipitating causes of hypocortisolism (infection, physical stress, etc.). Monitor 24-hr urine free cortisol, serum or plasma cortisol, and patient's signs and symptoms periodically during ISTURISA treatment.

Please see IMPORTANT SAFETY INFORMATION throughout and accompanying full PRESCRIBING INFORMATION.

Cushing’s syndrome: Early diagnosis is crucial to improving patient outcomes⁵

As a serious endocrine disease caused by excess cortisol, Cushing’s syndrome (CS) puts patients at risk of life-threatening morbidities⁶⁻⁸



4.3X HIGHER RISK
of stroke 1 year after diagnosis



3.5X HIGHER RISK
of AMI 1 year after diagnosis



17X HIGHER RISK
of VTE 1 year after diagnosis

CARDIOVASCULAR RISK⁹

MORTALITY

3.5-5X HIGHER RISK
than the general population,
if not treated properly^{10,a}

Earlier recognition and diagnosis of CS may help mitigate risks of cardiometabolic comorbidities.⁵

CS is a multisystem condition that can affect many parts of the body⁵

Patients with CS may experience a broad constellation of signs and symptoms across multiple organ systems⁵

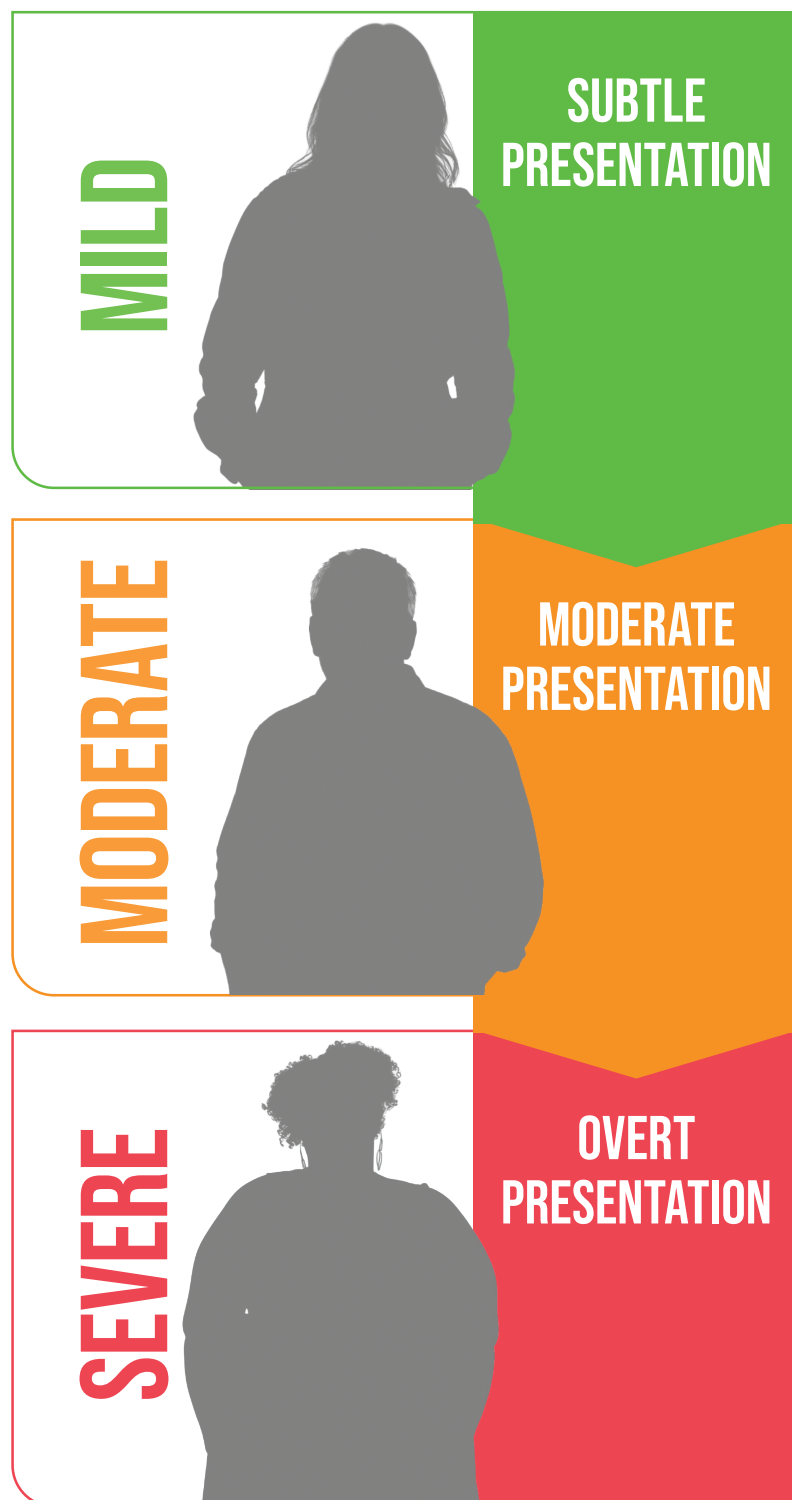
METABOLIC AND CARDIOVASCULAR ^{5,6}	• Difficult-to-treat type 2 diabetes • Dyslipidemia • Resistant hypertension • Weight gain and central obesity
COGNITIVE/ PSYCHIATRIC ^{5,11}	• Anxiety and depression • Irritability or mood swings • Memory problems and difficulty concentrating (“brain fog”) • Sleep disruptions, including insomnia
MUSCULOSKELETAL ⁶	• Increased risk of fractures • Proximal muscle weakness • Osteoporosis or bone loss
REPRODUCTIVE ⁶	• Decreased libido • Erectile dysfunction • Hirsutism in women • Menstrual irregularities in women • Reduced fertility
DERMATOLOGIC ⁶	• Acne • Easy bruising • Facial plethora (facial redness) • Thin skin • Poor wound healing • Purple or red striae
PHYSICAL ^{11,12}	• Central/truncal obesity • Dorsocervical fat pad (“buffalo hump”) • Facial rounding (“moon face”)

AMI, acute myocardial infarction; VTE, venous thromboembolism.

^aMortality rates vary depending on disease etiology.

CS, Cushing’s syndrome.

CS can present differently in every patient⁵



Models are not actual patients.

Who is more likely to be affected by CS?

- Average age of diagnosis: **30-60 years**⁶
- CS is approximately **2-4x more common in women than in men**^{6,13}
- Patients with resistant or difficult-to-treat **cardiometabolic conditions**⁵

In the CATALYST study¹⁴

24% of patients with **difficult-to-treat type 2 diabetes**^a also had hypercortisolism

In the MOMENTUM study¹⁵

27% of patients with **resistant hypertension**^b also had hypercortisolism

CS is not a one-size-fits-all disease⁵

- Clinical burden can exist anywhere along the spectrum
- Physical, emotional, and metabolic effects may not always align with outward appearance alone

BP, blood pressure; CS, Cushing's syndrome; HbA_{1c}, hemoglobin A_{1c}; SBP, systolic blood pressure.

^aDefined as HbA_{1c} 7.5%-11.5% and use of ≥3 glucose-lowering medications; or use of insulin plus ≥1 other glucose-lowering medication(s); or ≥2 glucose-lowering medications with ≥1 microvascular or macrovascular complication(s); and/or use of ≥2 glucose-lowering medications and ≥2 BP-lowering medications.¹⁴

^bDefined as SBP ≥130 mm Hg despite concurrent use of ≥3 antihypertensive medications from different classes at maximally tolerated doses, including 1 diuretic, or BP at any level requiring concurrent use of ≥4 antihypertensive medications from different classes.¹⁶

Look beyond common conditions to potentially identify underlying hypercortisolism¹⁷

When CS goes unrecognized, patients may face complications that worsen quality of life and survival outcomes¹²

Comorbidities and complications of CS^{6,11,12,17}



Anxiety or depression



Difficult-to-treat type 2 diabetes



Resistant hypertension



Hyperlipidemia



Insulin resistance



Obesity



Peripheral edema



Infections



Menstrual irregularities



Hypercoagulability



Insomnia or fatigue



Osteoporosis

As prolonged cortisol excess persists, patients may experience greater comorbidity burden and risk of systemic complications.⁵

If you suspect CS in your patient, the next step is to begin testing for hypercortisolism.⁵

CS, Cushing's syndrome.

Different CS etiologies can drive distinct clinical presentations¹⁸

Recognizing these differences can support more accurate diagnosis and tailored management^{13,18}

Cushing's disease

Patients may present with distinct CS features, but may also have symptoms associated with common conditions, such as hypertension and diabetes¹⁹

Ectopic CS

Patients may present with severe and rapidly developing metabolic signs¹⁸

Adrenal carcinomas

Patients may have rapid onset of symptoms and show signs of virilization due to secretion of androgens in addition to cortisol^{18,20}

Adrenal adenomas

Patients may have mild to severe symptoms based on the level of cortisol or aldosterone secretion²¹

Adrenal hyperplasia

Patients may experience a range of symptoms, from mild in macronodular disease to severe in micronodular disease²²

CS, Cushing's syndrome.

Endogenous CS can result from several underlying etiologies^{13,17}

Endogenous CS etiologies can be characterized as ACTH-dependent or ACTH-independent¹²

ACTH-DEPENDENT



Cushing's disease (CD)
A benign pituitary adenoma that secretes ACTH¹³



Ectopic ACTH syndrome (EAS)
Most commonly a lung, mediastinal, pancreas, and medullary thyroid neuroendocrine tumor that secretes ACTH¹³

ACTH-INDEPENDENT



Adrenal adenoma
Unilateral, cortisol-producing, benign adenomas located on the adrenal cortex¹³



Adrenal carcinoma
Unilateral malignant neoplasms on the adrenal cortex¹³



Adrenal hyperplasia
Refers to bilateral adrenal hyperplasia, which is characterized by macronodules or micronodules affecting both adrenal glands, leading to an increase in cortisol secretion¹³



Diagnosis can often be delayed for years⁷

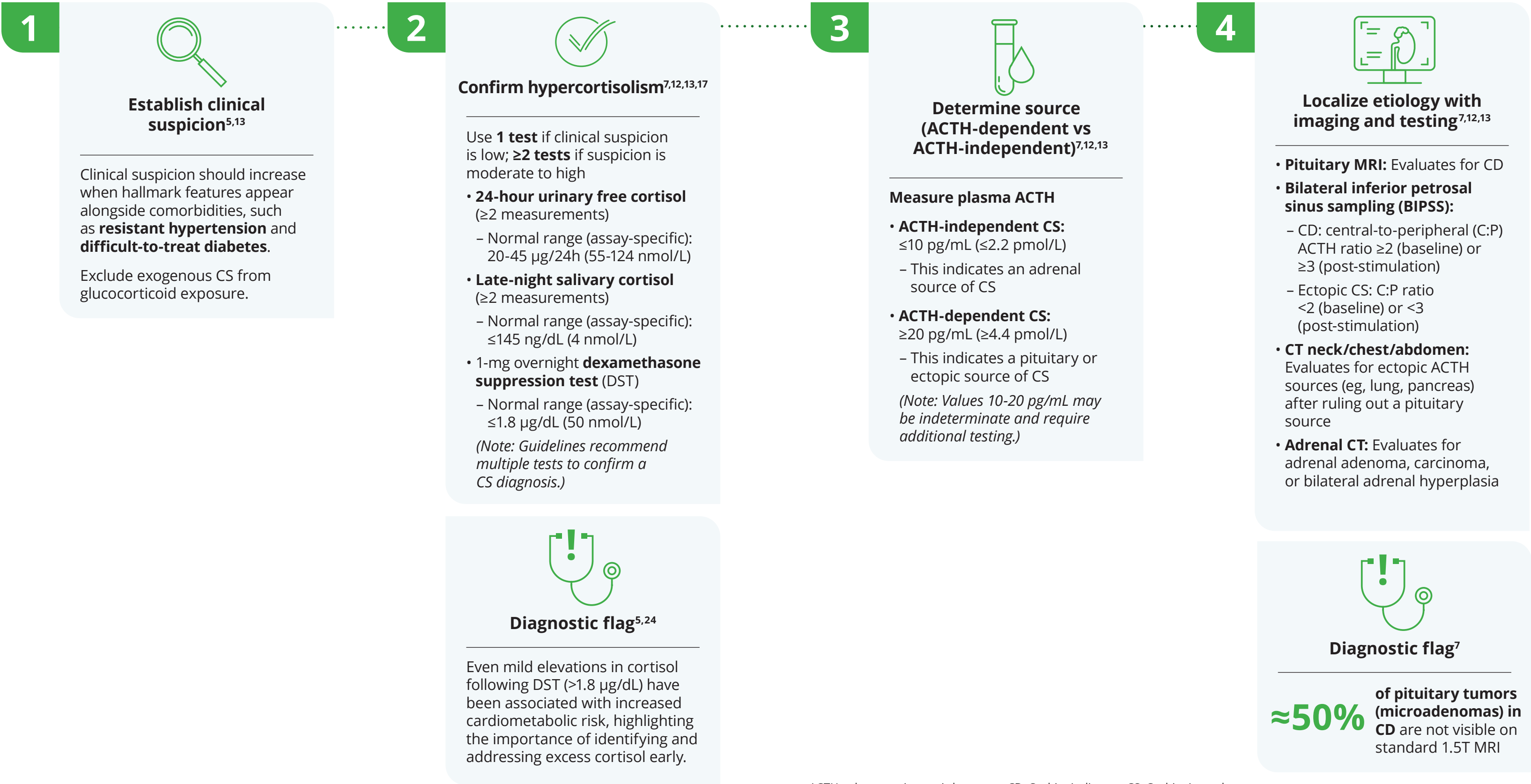
The mean time to diagnosis for CS is reported as 34 months, but can vary by subtype²³

- Ectopic CS: 14 months
- ACTH-independent CS: 30 months
- CD: 38 months

ACTH, adrenocorticotrophic hormone; CS, Cushing's syndrome.

Navigate the path from clinical suspicion to diagnosis with a structured 4-step approach

Early recognition and timely diagnosis of CS are crucial to reducing the long-term burden of hypercortisolism⁵



CS, Cushing's syndrome.

ACTH, adrenocorticotrophic hormone; CD, Cushing's disease; CS, Cushing's syndrome; CT, computed tomography; MRI, magnetic resonance imaging.

CS management may require multiple approaches

The goal of treatment for CS is to achieve and maintain normalization of cortisol levels²⁵

First-line treatment



Surgery, when appropriate

Complete surgical resection of the underlying tumor may offer the potential for remission in eligible patients²⁵

In CD, pituitary surgery is **not effective in at least 1 in 3 patients** due to persistent or recurrent disease, often requiring an alternative treatment approach.²

Second-line therapy



Repeat surgery

Repeat surgery may be considered in cases of persistent or recurrent disease²⁵



Medical therapy

Medical therapy is increasingly used across all types of endogenous CS, particularly when^{12,25}

- Surgical treatment has failed or is not feasible
- Persistent or recurrent diseases occur following surgery
- Bridge therapy is needed while awaiting the full effects of radiotherapy
- Rapid biochemical control is required in patients with severe hypercortisolism



Radiation

Radiation may be used as an adjunct treatment in patients with endogenous CS who^{12,25}

- Do not achieve remission
- Are not candidates for surgery
- Have aggressive tumor growth

Advances in medical therapies are redefining CS care

While medical management cannot cure CS, available therapies can help manage excess cortisol production and potentially address the systemic burden of hypercortisolism¹²



Steroidogenesis inhibitors^{2,12,26}

Target enzymes involved in adrenal cortisol synthesis persistent or recurrent disease



Lower circulating cortisol levels regardless of endogenous source



May help address the multisystem consequences of hypercortisolism, including cardiometabolic manifestations

Steroidogenesis inhibitors, in blocking cortisol synthesis, can lead to hypocortisolism and may increase circulating levels of cortisol and aldosterone precursors and androgens. See relevant warnings in the Important Safety Information.¹²

Some available therapies act upstream at the pituitary gland and may not be appropriate for adrenal or ectopic etiologies.²⁶
In contrast, receptor-directed therapies block cortisol activity without reducing circulating cortisol levels, which may limit the ability to fully address the underlying biochemical burden of disease.²⁶

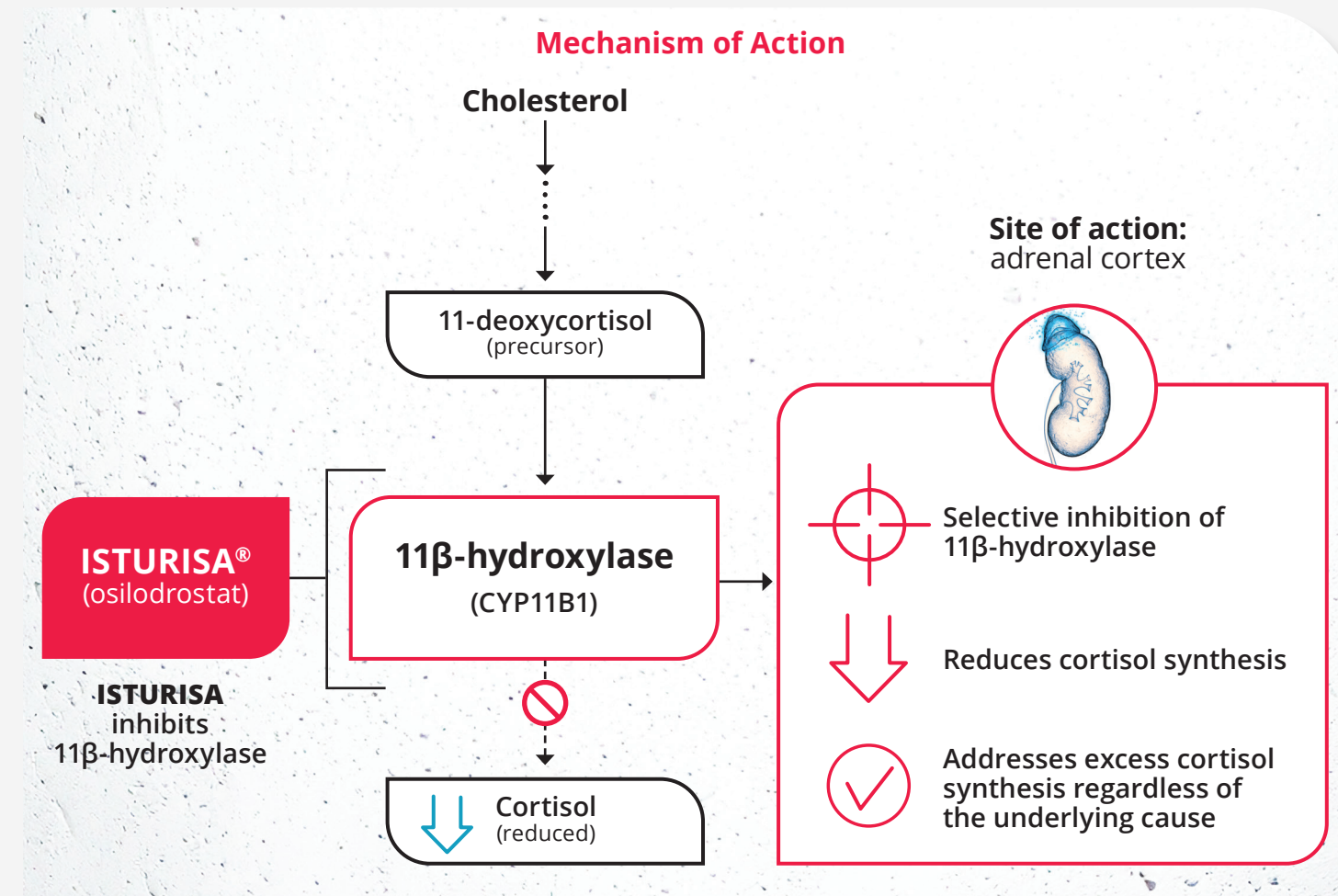
Treatment goals in CS should prioritize **cortisol normalization**, regardless of endogenous source, to help mitigate the systemic effects of hypercortisolism.²⁵

CD, Cushing's disease; CS, Cushing's syndrome.

CS, Cushing's syndrome.

Get to the source: ISTURISA is a targeted cortisol synthesis inhibitor^{1,27}

Target the overproduction of cortisol across a range of patients with mild to severe hypercortisolemia, regardless of the endogenous source, by inhibiting 11 β -hydroxylase, the enzyme central to the process^{1,27,28}



- Changes in the levels of 11-deoxycortisol and ACTH were dose dependent¹
- The effects of ISTURISA may be reversed or decreased upon treatment discontinuation or dose tapering^{1,3}

Explore the science
Watch the MOA video to see how ISTURISA works.



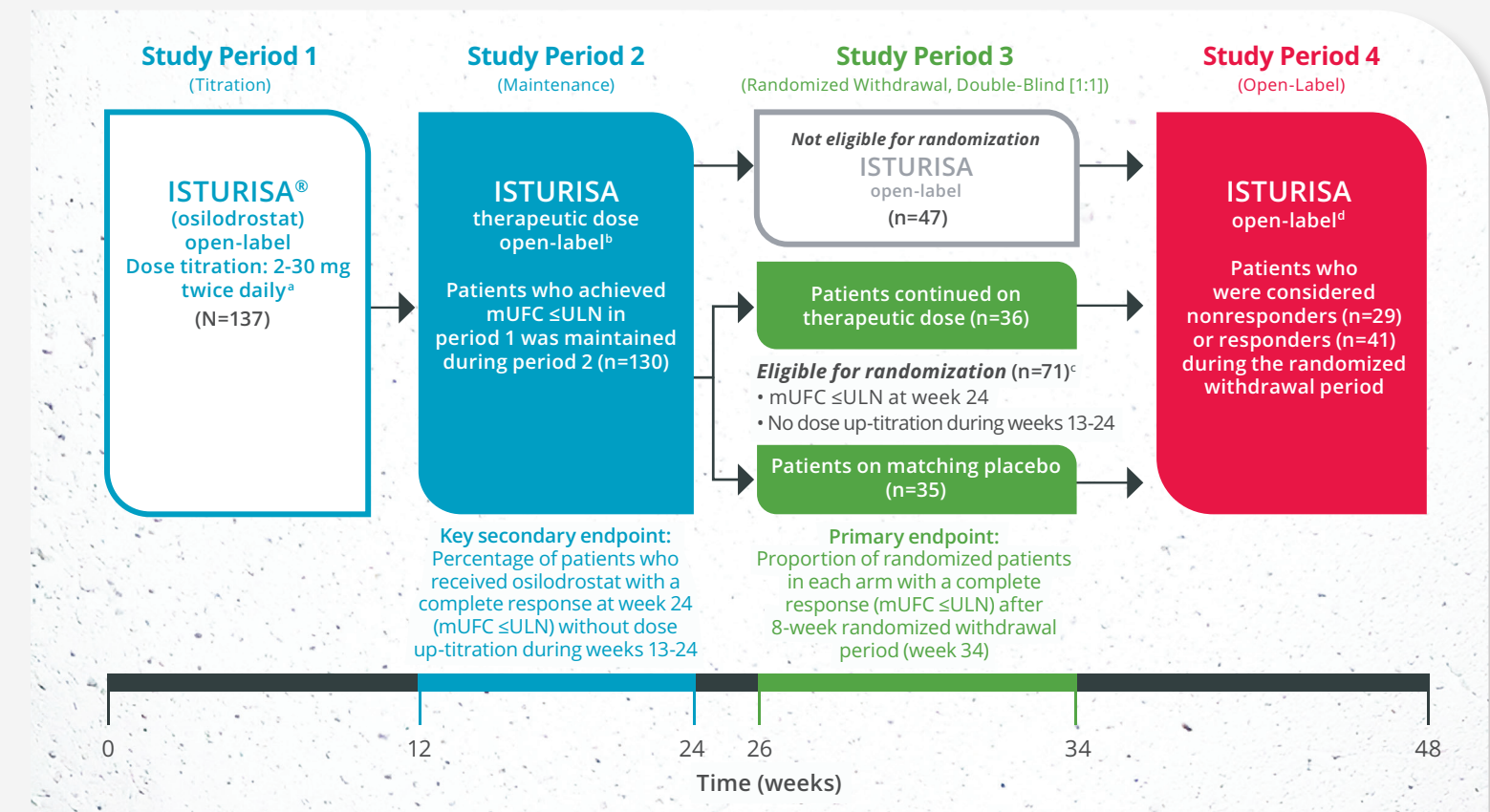
ACTH, adrenocorticotrophic hormone; MOA, mechanism of action.

IMPORTANT SAFETY INFORMATION (continued)

Hypocortisolism (continued): Decrease or temporarily discontinue ISTURISA if urine free cortisol levels fall below the target range, there is a rapid decrease in cortisol levels, and/or patients report symptoms of hypocortisolism. Stop ISTURISA and administer exogenous glucocorticoid replacement therapy if serum or plasma cortisol levels are below target range and patients have symptoms of adrenal insufficiency. After ISTURISA interruption or discontinuation, cortisol suppression may persist beyond the 4-hour half-life of ISTURISA.

In the LINC 3 pivotal trial and the extension study, ISTURISA efficacy and safety were assessed in a 48-week pivotal study in patients with CD^{3,29}

LINC 3 was a phase 3 trial that included an open-label, randomized, double-blind, placebo-controlled withdrawal period^{1,3}



Key inclusion criteria

- Patients aged 18 to 75 years with a confirmed diagnosis of persistent, recurrent, or de novo (if not surgical candidates or refused surgery) CD^{1,3}
- Confirmed CD as determined by mean of 3 UFC concentrations of $>1.5 \times \text{ULN}$ at screening¹
- Patients with a history of pituitary surgery had to be at least 30 days post surgery³
- Evidence of a pituitary source of excess ACTH³

Baseline characteristics

- Mean age at enrollment was 41 years^{1,3}
- 77% (106/137) of patients were female^{1,3}
- 88% (120/137) of enrolled patients had previous surgery^{1,3}
- Mean of three 24-hour mUFC at baseline was 365 $\mu\text{g}/24 \text{ h}$ ($\approx 7 \times \text{ULN}$)¹
- Median mUFC was 173 $\mu\text{g}/24 \text{ h}$ ($\approx 3.5 \times \text{ULN}$)¹

ACTH, adrenocorticotrophic hormone; CD, Cushing's disease; LLN, lower limit of normal; mUFC, mean urinary free cortisol; UFC, urinary free cortisol; ULN, upper limit of normal; WNL, within normal limits.

^aDose was up- or down-titrated every 2 weeks if mUFC was greater than ULN (defined as 138 nmol/24 h or 50 $\mu\text{g}/24 \text{ h}$) or if mUFC was lower than LLN (defined as 11 nmol/24 h or 4 $\mu\text{g}/24 \text{ h}$), respectively.³

^bDose adjustments were permitted during study period 2.³
^cPatients who did not require further dose increase, tolerated the drug, and had mUFC levels $\leq \text{ULN}$ at week 24 were considered responders and eligible to enter the randomized withdrawal period. Patients whose mUFC became elevated during the maintenance period could have their dose increased further, if tolerated, up to 30 mg twice daily. These patients were considered nonresponders and did not enter the randomized withdrawal period, but continued open-label treatment together with the patients who did not achieve normal mUFC levels at week 12.¹

^dPatients remained on assigned dose throughout the randomized withdrawal period if their mUFC levels were WNL. Blinded dose reduction or temporary discontinuation for safety or tolerability issues were permitted; however, dose increases were not permitted. Patients with mUFC levels $>1.5 \times \text{ULN}$ or who required a dose increase were considered nonresponders and discontinued from the randomized withdrawal period, but allowed to receive open-label treatment during the open-label period.¹

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Isturisa®
(osilodrostat)

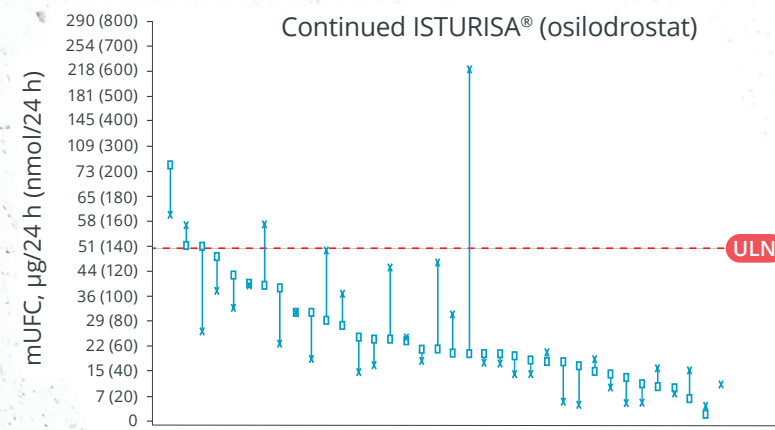
ISTURISA maintained normalization of mUFC in a majority (86%) of patients in the randomized withdrawal period¹

Demonstrated superiority over placebo at maintaining mUFC $\leq$ ULN at the end of the randomized withdrawal period (N=71, Difference 57% [95% CI, 38-76]; $P<.001$)¹

PRIMARY ENDPOINT^{1,3}

Complete responder rate after 8-week randomized withdrawal period (week 34)^a

mUFC, Randomized withdrawal period (week 26-34)

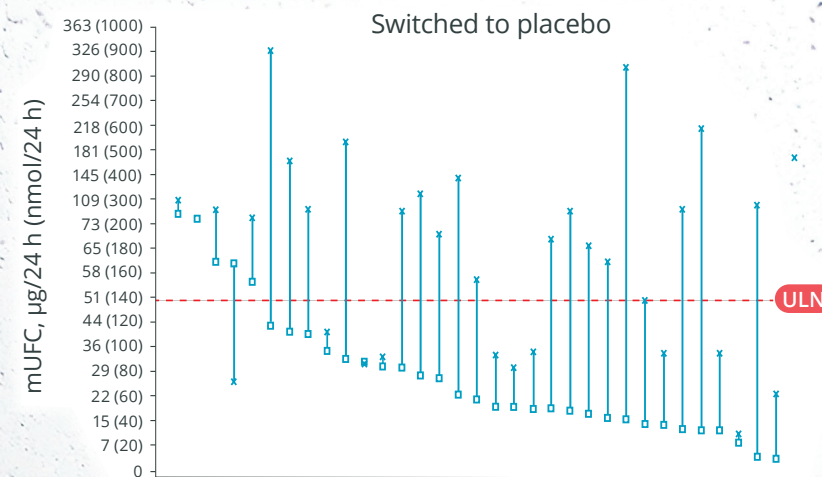


86%

(31/36) of patients who received ISTURISA maintained mUFC levels $\leq$ ULN

Complete response rate

- Value at randomized withdrawal baseline
- Last value on randomly assigned treatment



29%

(10/34) of patients who received placebo maintained mUFC levels $\leq$ ULN

Complete response rate

- Value at randomized withdrawal baseline
- Last value on randomly assigned treatment

Adapted from Pivonello R et al. 2020.

CI, confidence interval; mUFC, mean urinary free cortisol; ULN, upper limit of normal.

^aComplete responder rate was the percentage of patients who had mUFC levels $\leq$ ULN (defined as 138 nmol/24 h or 50 μ g/24 h) at the end of the randomized withdrawal period (week 34) and who neither discontinued randomized treatment or the study nor had any dose increase above their week 26 dose.^{1,3}

IMPORTANT SAFETY INFORMATION (continued)

Hypocortisolism (continued): Educate patients on the symptoms associated with hypocortisolism and advise them to contact a healthcare provider if they occur.

QTc Prolongation: ISTURISA is associated with a dose-dependent QT interval prolongation which may cause cardiac arrhythmias. Perform an ECG to obtain a baseline QTc interval measurement prior to initiating therapy with ISTURISA and monitor for an effect on the QTc interval thereafter.

Correct hypokalemia and/or hypomagnesemia prior to ISTURISA initiation and monitor periodically during treatment with ISTURISA. Use with caution in patients with risk factors for QT prolongation and consider more frequent ECG monitoring.

ISTURISA may rapidly normalize mUFC levels^{3,a}

More than half of patients maintained normalized mUFC with ISTURISA® (osilodrostat) at the therapeutic dose established during the titration period^{3,a}

^aThe ULN for UFC was defined as 138 nmol/24 h or 50 μ g/24 h.³

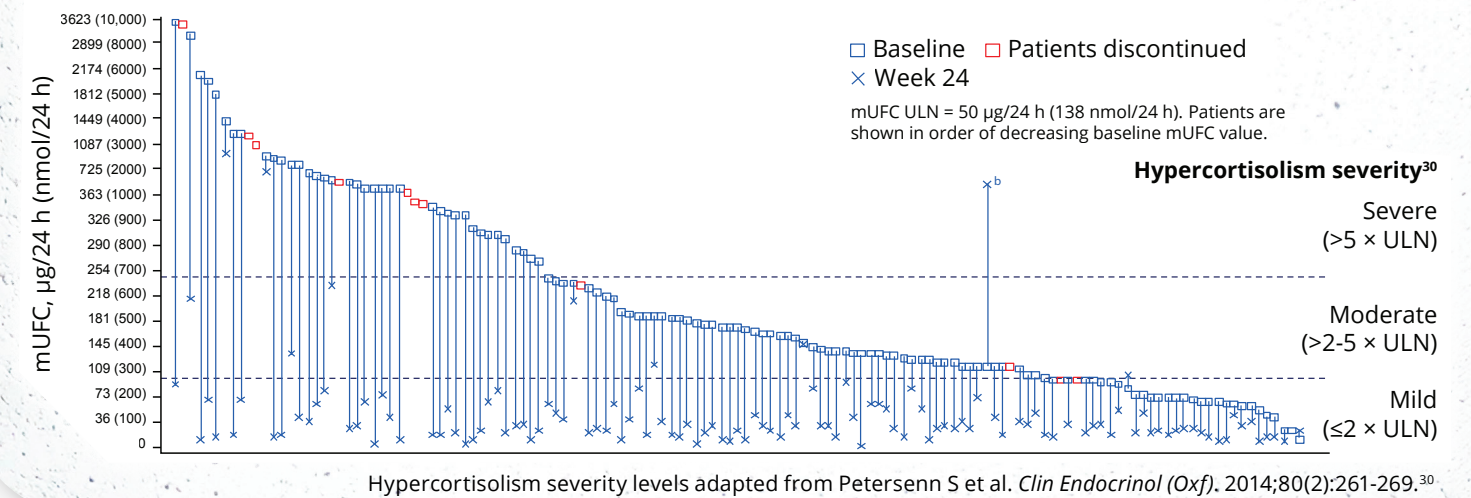
KEY SECONDARY ENDPOINT^{1,3}

Complete responder rate at week 24 (end of maintenance period) without up-titration after week 12^b

53% (72/137; 95% CI, 43.9-61.1) of patients who received ISTURISA maintained mUFC $\leq$ ULN at week 24 without dose up-titration after week 12.^{1,3}

- The lower bound of the 95% CI exceeded 30%, the prespecified threshold for statistical significance and minimum threshold for clinical benefit¹

Changes in mUFC for individual patients from baseline to week 24^{3,30,c}



SECONDARY ENDPOINT^{3,c}

Irrespective of dose increase,

68%

(93/137) of patients achieved mUFC $\leq$ ULN at week 24 (prespecified endpoint)

^bComplete responder rate was the percentage of patients who had mUFC levels $\leq$ ULN (defined as 138 nmol/24 h or 50 μ g/24 h).^{1,3}

^cThe study was not powered to assess statistical significance in non-key secondary endpoints and no definitive conclusions can be drawn.

Post hoc analysis: additional analyses indicate other signs of improvement with ISTURISA³

96%

(132/137) of patients achieved cortisol normalization at least once during the study

The median time to first complete response (mUFC $\leq$ ULN) was

41 days

These data were not included in primary or secondary endpoint analyses and were assessed post hoc; therefore, no definitive conclusions should be drawn.^{1,3}

CI, confidence interval; mUFC, mean urinary free cortisol; UFC, urinary free cortisol; ULN, upper limit of normal.

 **Isturisa**
(osilodrostat)

Please see IMPORTANT SAFETY INFORMATION throughout and accompanying full PRESCRIBING INFORMATION.

Safety profile demonstrated through 48 weeks¹

Adverse reactions among 137 patients with CD who received at least 1 dose of ISTURISA® (osilodrostat) in the study¹

Adverse reactions in >15% of patients (N=137)

Adrenal insufficiency^a	43.1%	Headache^c	30.7%	Vomiting	19.0%
Fatigue^b	38.7%	Edema^d	21.2%	Arthralgia	17.5%
Nausea	37.2%	Nasopharyngitis	19.7%	Back pain	15.3%
				Rash^e	15.3%

Among the **43%** of patients who were deemed to have experienced adrenal insufficiency, 1/3 had low cortisol levels indicative of adrenal insufficiency.^{1,a}

Hypocortisolism was reported at a rate of 31% during weeks 1 to 12 and 18% during weeks 12 to 26¹

- In most cases, hypocortisolism is addressed by reducing the dose of ISTURISA and/or adding low-dose, short-term glucocorticoid therapy¹
- 36% (25/70) of patients with 1 or more hypocortisolism-related events received glucocorticoid supplementation during the duration of the study³

Hirsutism was observed in 12% (13/106) of female patients.^{1,3} This adverse event was considered mild to moderate,^f and no patient discontinued as a result.³

CD, Cushing's disease.

^aAdrenal insufficiency includes glucocorticoid deficiency, adrenocortical insufficiency acute, steroid withdrawal syndrome, cortisol free urine decreased, cortisol decreased. One-third of the patients with this event had low cortisol levels indicative of adrenal insufficiency. The majority of patients had normal cortisol levels suggesting a cortisol withdrawal syndrome.¹

^bFatigue includes lethargy, asthenia.¹

^cHeadache includes head discomfort.¹

^dEdema includes edema peripheral, generalized edema, localized edema.¹

^eRash includes rash erythematous, rash generalized, rash maculopapular, rash papular.¹

^fMild to moderate = severity rated by investigator as 1 or 2 in the LINC 3 clinical trial.³¹

IMPORTANT SAFETY INFORMATION (continued)

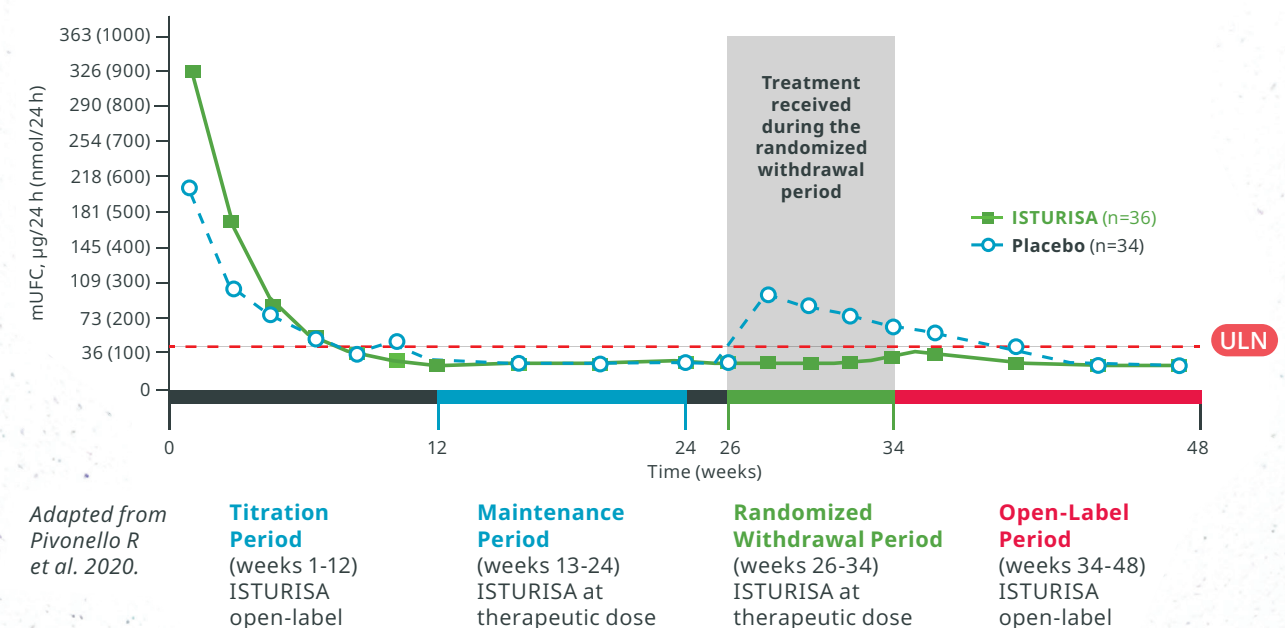
Elevations in Adrenal Hormone Precursors and Androgens: ISTURISA blocks cortisol synthesis and may increase circulating levels of cortisol and aldosterone precursors and androgens. This may activate mineralocorticoid receptors and cause hypokalemia, edema and hypertension. Hypokalemia should be corrected prior to initiating ISTURISA. Monitor patients treated with ISTURISA for hypokalemia, worsening of hypertension and edema. Inform patients of the symptoms associated with hyperandrogenism and advise them to contact a healthcare provider if they occur.

ISTURISA sustained normal mUFC up to 48 weeks in a majority of patients with CD¹

48-WEEK STUDY SECONDARY ENDPOINT^{1,3} (ITT analysis, end of open-label period)

66% of patients who received ISTURISA® (osilodrostat) maintained mUFC levels ≤ULN at week 48 (91/137; 95% CI, 57.9-74.3)^{1,31}

- In patients who received ISTURISA, mean mUFC decreased rapidly during the titration period, then remained below baseline through week 48^{31,a}



- Average daily ISTURISA dose for all patients through 48 weeks was 10 mg/d^{32,b}
- The study was not powered to assess statistical significance in non-key secondary endpoints and no definitive conclusions can be drawn

CD, Cushing's disease; CI, confidence interval; ITT, intent-to-treat; mUFC, mean urinary free cortisol; ULN, upper limit of normal.

^aPatients who received ISTURISA had an open-label titration period (weeks 1-12), then a maintenance period (weeks 13-24), and a randomized withdrawal period (weeks 26-34). Patients could participate in an open-label period (weeks 34-48) if they had mUFC ≤ULN at week 24 without a dose increase after week 12.³

^bAmong patients who were ineligible for the randomized withdrawal period, the average daily ISTURISA dose was 11 mg/d.³²

IMPORTANT SAFETY INFORMATION (continued)

The most common adverse reactions (incidence >20%) are adrenal insufficiency, fatigue, nausea, headache, edema, decreased appetite, arthralgia, myalgia, and diarrhea.

Please see IMPORTANT SAFETY INFORMATION throughout and accompanying full PRESCRIBING INFORMATION.

 **Isturisa**
(osilodrostat)

Look beyond cortisol control: ISTURISA was associated with improvements in cardiometabolic, HRQOL, and psychosocial outcomes^{1,3,a}

In patients taking ISTURISA® (osilodrostat), mean improvements were observed from baseline in the following parameters^{31,32}

	Baseline	Week 24	Week 48
 Systolic blood pressure (mm Hg) ^b	132.2	124.9 (-4.1%)	121.7 (-6.8%)
 Diastolic blood pressure (mm Hg) ^b	85.3	81.0 (-3.8%)	78.9 (-6.6%)
 Body weight (kg)	80.8	77.3 (-3.0%)	75.5 (-4.6%)
 Waist circumference (cm)	103.5	99.1 (-2.6%)	97.4 (-4.7%)
 HbA _{1c} (%) ^b	6.0	5.6 (-4.6%)	5.6 (-5.4%)
 Total cholesterol (mg/dL)	205.0	181.8 (-9.0%)	185.6 (-8.8%)
 CushingQoL (total score) ^c	42.2	52.1 (42.4%)	58.3 (52.4%)
 BDI-II (total score) ^d	16.8	12.9 (-19.2%)	10.7 (-31.8%)

Complete responder rate at the end of the randomized withdrawal period was the percentage of patients who had mUFC levels ≤ULN (defined as 138 nmol/24 h or 50 µg/24 h) at the end of the randomized withdrawal period (week 34) and who neither discontinued randomized treatment or the study nor had any dose increase above their week 26 dose.^{1,3}

Study limitations

^aThe study was not powered to assess statistical significance in non-key secondary endpoints and no definitive conclusions can be drawn.

^bBecause the study allowed initiation of antihypertensive and antidiabetic medications and dose increases in patients already receiving such medications, and given the absence of a control group, the individual contribution of ISTURISA or of antihypertensive and antidiabetic medication adjustments cannot be clearly established.¹

Study methodology

^cCushingQoL is proven to be a reliable and valid instrument for measuring HRQOL in patients with CS. Scores correlate with relevant clinical parameters.³³

^dThe BDI-II is a proven valid and reliable 21-item self-report multiple-choice inventory tool used to evaluate depressive states that occur at high prevalence among the medically ill.³⁴

BDI-II, Beck Depression Inventory-II; CS, Cushing’s syndrome; CushingQoL, Cushing’s Quality of Life questionnaire; HbA_{1c}, hemoglobin A_{1c}; HRQOL, health-related quality of life; mUFC, mean urinary free cortisol; ULN, upper limit of normal.

Improvements in mUFC were maintained during the 72-week open-label extension²⁹

ISTURISA sustained normal mUFC for over a year in the majority of patients who entered the open-label extension (N=106)^{29,a,b}

^aPatients who had mUFC ≤ULN (defined as 138 nmol/24 h or 50 µg/24 h) were classified as complete responders, while patients who had mUFC >ULN but a ≥50% reduction from baseline were classified as partial responders.²⁹

LINC 3 EXTENSION RESULTS

Complete responder rate at week 72^{29,a,b}

81% of patients who entered the extension maintained mUFC ≤ULN at week 72 (86/106; 95% CI, 72.4-88.1)^{29,a,b}

The majority of patients who started ISTURISA remained on therapy for 72 weeks²⁹

- Of the 137 patients enrolled in the study, 106 (77.4%) entered the extension phase and 98 (71.5%) completed 72 weeks of treatment
- Median duration of ISTURISA treatment from baseline to study end for all enrolled patients was 130 weeks, with a median dose of 7.4 mg/d

PRESPECIFIED SECONDARY ENDPOINT

Improvements in cardiometabolic-related parameters were maintained^{2,29,b}

	72 Weeks Mean change from core baseline
 Systolic blood pressure (mm Hg) ^c	-10.1
 Diastolic blood pressure (mm Hg) ^c	-5.8
 HbA _{1c} (%) ^c	-0.4%
 BMI (kg/m ²)	-1.8

AE, adverse event; BMI, body mass index; CI, confidence interval; HbA_{1c}, hemoglobin A_{1c}; mUFC, mean urinary free cortisol; ULN, upper limit of normal.

No new safety signals reported during long-term treatment²⁹

- Most hypocortisolism-related AEs emerged during the first 26 weeks of treatment, and AEs related to adrenal hormone precursor accumulation were less frequent in the extension²⁹
- Mean testosterone levels in women increased upon initiation of ISTURISA but tended to return to baseline levels and within the normal range at 72 weeks (0.8 × ULN)³⁵

Study limitations

^bThe study was not powered to assess statistical significance in non-key secondary endpoints and no definitive conclusions can be drawn.

^cBecause the study allowed initiation of antihypertensive and antidiabetic medications and dose increases in patients already receiving such medications, and given the absence of a control group, the individual contribution of ISTURISA or of antihypertensive and antidiabetic medication adjustments cannot be clearly established.¹

IMPORTANT SAFETY INFORMATION (continued)

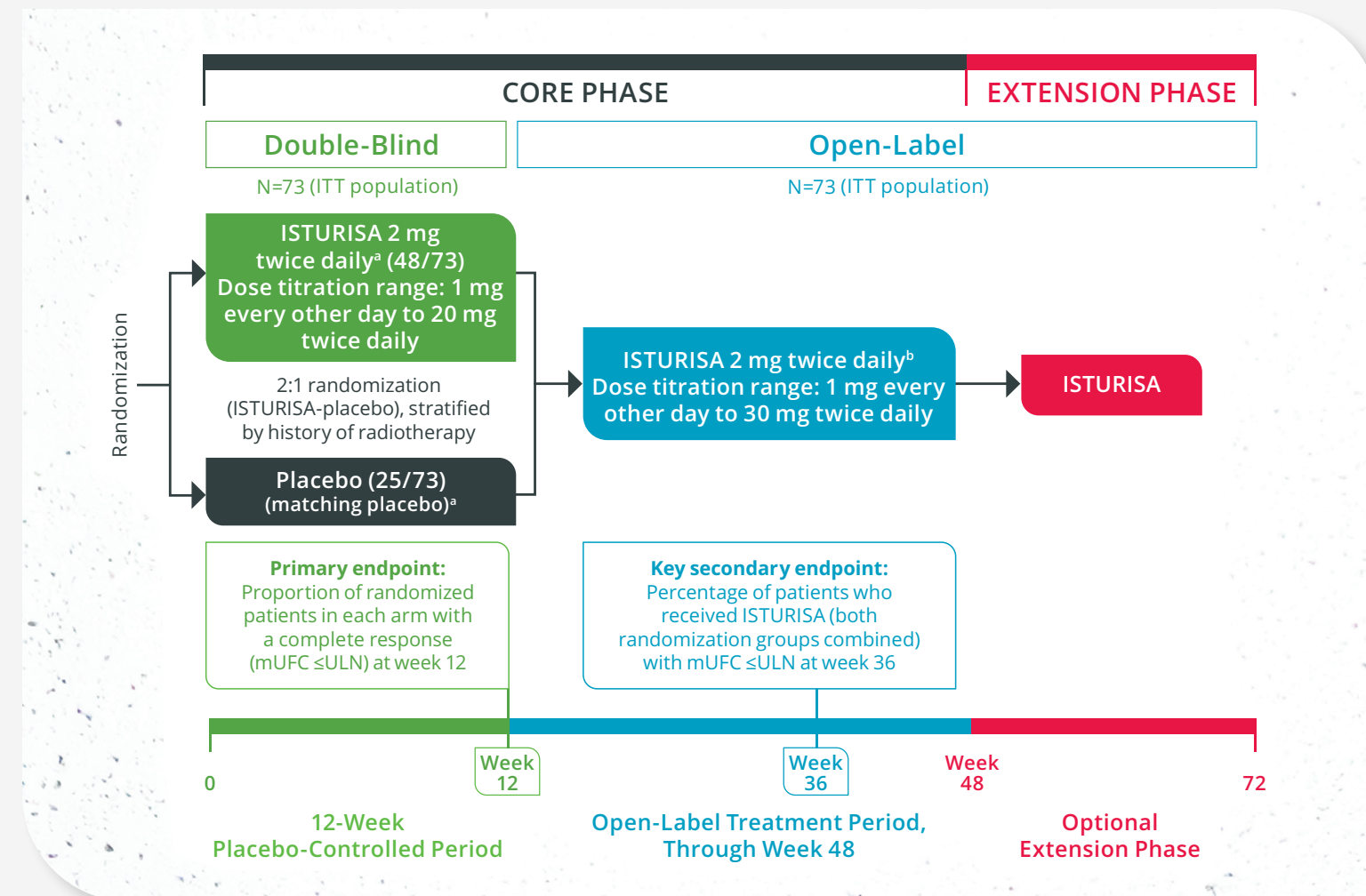
To report SUSPECTED ADVERSE REACTIONS, contact Recordati Rare Diseases Inc. at 1-888-575-8344, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see IMPORTANT SAFETY INFORMATION throughout and accompanying full PRESCRIBING INFORMATION.



The safety and efficacy of ISTURISA were also assessed in a placebo-controlled multicenter study⁴

LINC 4 was a randomized, double-blind, parallel, placebo-controlled clinical trial with optional extension to evaluate the safety and efficacy of ISTURISA® (osilodrostat) among 73 patients with CD (mUFC >1.3 × ULN)⁴



ACTH, adrenocorticotrophic hormone; CD, Cushing's disease; ITT, intent-to-treat; LLN, lower limit of normal; mUFC, mean urinary free cortisol; UFC, urinary free cortisol; ULN, upper limit of normal.

^aPatients started on ISTURISA 2 mg twice daily (baseline median mUFC was 2.5 × ULN [0.7-12.5]) or matching placebo (baseline median mUFC was 2.2 × ULN [0.2-18.9]). Dose adjustments to normalize mUFC or to address safety issues were permitted at week 2, week 5, and week 8 (range 1-20 mg twice a day) based on considerations of all data for each patient, including mUFC level, rate of decrease of mUFC, and tolerability of ISTURISA. ULN was defined as 138 nmol/24 h or 50 µg/24 h, and LLN was defined as 11 nmol/24 h or 4 µg/24 h.^{4,36}

^bStarting at week 12, all patients restarted open-label ISTURISA (2 mg twice a day unless they were receiving a lower dose), with dose adjustments permitted (range 1 mg every other day to 30 mg twice a day).⁴

Inclusion criteria⁴

- Patients aged 18 to 75 years with a confirmed diagnosis of persistent, recurrent, or de novo (if not surgical candidates) CD
- Confirmed CD as determined by mean of 3 UFC concentrations of >1.3 × ULN
- Evidence of a pituitary source of excess ACTH

Baseline characteristics⁴

- Median age at enrollment was 39 years
- 84% (61/73) of patients were female
- 88% (64/73) of enrolled patients had previous surgery
- Mean mUFC at baseline was 157 µg/24 h (≈3.1 × ULN)
- Median mUFC at baseline was 123 µg/24 h (≈2.5 × ULN)

ISTURISA rapidly normalized cortisol levels in a majority of patients^{4,a}

Demonstrated superiority over placebo at normalizing cortisol (mUFC ≤ ULN) at week 12 (N=73, 95% CI, 7.1-343.2; $P<.0001$)^{4,a}

^aPatients taking ISTURISA achieved mUFC ≤ ULN rapidly, as early as 12 weeks. Among patients who received ISTURISA, 77% (37/48) achieved normal mUFC compared to 8% (2/25) of patients who received placebo (OR 43.4; 95% CI, 7.1-343.2; $P<.0001$).⁴

PRIMARY ENDPOINT⁴

Proportion of randomized patients with mUFC ≤ ULN at week 12
Significantly more patients had mUFC ≤ ULN with ISTURISA at week 12 ($P<.0001$)⁴

12-week, randomized, double-blind, placebo-controlled period (N=73)⁴

Among patients who received

ISTURISA

77%

(37/48) achieved
normal mUFC^{4,b}

$P<.0001$
(OR 43.4; 95%
CI, 7.1-343.2)

Among patients who
received **placebo**

8%

(2/25) achieved
normal mUFC^{4,b}

Dose adjustments were made at weeks 2, 5, and 8, followed by adjustments approximately every 3 weeks, based on considerations of all data for each patient, including mUFC level, rate of decrease of mUFC, and tolerability of ISTURISA.^{4,b}

CI, confidence interval; LLN, lower limit of normal; mUFC, mean urinary free cortisol; OR, odds ratio; ULN, upper limit of normal.

^bPatients started on ISTURISA 2 mg twice daily (baseline median mUFC was 2.5 × ULN [0.7-12.5]) or matching placebo (baseline median mUFC was 2.2 × ULN [0.2-18.9]). Dose adjustments to normalize mUFC or to address safety issues were permitted at week 2, week 5, and week 8 (range 1-20 mg twice a day) based on considerations of all data for each patient, including mUFC level, rate of decrease of mUFC, and tolerability of ISTURISA. ULN was defined as 138 nmol/24 h or 50 µg/24 h, and LLN was defined as 11 nmol/24 h or 4 µg/24 h.^{4,36}

IMPORTANT SAFETY INFORMATION (continued)

Drug Interactions:

- **CYP3A4 Inhibitor:** Reduce the dose of ISTURISA by half with concomitant use of a strong CYP3A4 inhibitor.
- **CYP3A4 and CYP2B6 Inducers:** An increase of ISTURISA dosage may be needed if ISTURISA is used concomitantly with strong CYP3A4 and CYP2B6 inducers. A reduction in ISTURISA dosage may be needed if strong CYP3A4 and CYP2B6 inducers are discontinued while using ISTURISA.

Please see IMPORTANT SAFETY INFORMATION throughout and accompanying full PRESCRIBING INFORMATION.

 **Isturisa**
(osilodrostat)

ISTURISA effectively sustained cortisol normalization in a majority of patients⁴

Maintained mUFC ≤ULN for 4 out of 5 patients at week 36 in the open-label period (N=73)⁴

KEY SECONDARY ENDPOINT⁴
Proportion of patients with mUFC ≤ULN at week 36

81% of patients who received ISTURISA® (osilodrostat) maintained normalized mUFC (mUFC ≤ULN) at week 36 (59/73)⁴

SECONDARY ENDPOINT

The median duration of ISTURISA exposure until first controlled response (mUFC ≤ULN) was 35 days for patients randomized to ISTURISA^{4,a}

MEDIAN DOSE

Median osilodrostat dose over the treatment period (48 weeks) was 5 mg/d²⁹

mUFC, mean urinary free cortisol; ULN, upper limit of normal.

^aThis study was not powered to assess statistical significance in secondary endpoints and no definitive conclusions can be drawn.

IMPORTANT SAFETY INFORMATION *(continued)*

Use in Specific Populations:

- **Lactation:** Breastfeeding is not recommended during treatment with ISTURISA and for at least one week after treatment.

Dosage Interruptions and Modifications: If treatment is interrupted, re-initiate ISTURISA at a lower dose when cortisol levels are within target ranges and patient symptoms have been resolved. ISTURISA® (osilodrostat) tablets, for oral use, is available as 1 mg and 5 mg tablets.

Established safety profile for ISTURISA^{1,4}

Adverse reactions were evaluated among 48 patients with CD who received ISTURISA during the 12-week placebo-controlled period^{1,4}

Adverse reactions in ≥15% of patients (n=48)

Decreased appetite	38%	Myalgia^b	23%	Tachycardia^c	15%
Arthralgia	35%	Diarrhea	21%	Nasopharyngitis^d	15%
Nausea	31%	Dizziness	19%	Hypotension^e	15%
Fatigue^a	29%	Adrenal insufficiency	15%		

Note: Adverse events related to hypocortisolism occurred in 15% of patients who received ISTURISA vs 0% of patients who received placebo during titration.⁴

^aFatigue includes asthenia, fatigue, and malaise.¹
^bMyalgia includes myalgia and fibromyalgia.¹
^cTachycardia includes tachycardia and sinus tachycardia.¹
^dNasopharyngitis includes upper respiratory tract infection, nasopharyngitis, and pharyngitis.¹
^eHypotension includes hypotension and orthostatic hypotension.¹

KEY LEARNINGS FROM LINC 4 STUDY⁴

ISTURISA provides rapid and sustained normalization of cortisol levels

ISTURISA has a demonstrated safety profile

Response and tolerability may be managed with close monitoring and dose adjustments

CD, Cushing’s disease.

IMPORTANT SAFETY INFORMATION *(continued)*

Hypocortisolism: ISTURISA lowers cortisol levels and can lead to hypocortisolism and sometimes life-threatening adrenal insufficiency. Lowering of cortisol can cause nausea, vomiting, fatigue, abdominal pain, loss of appetite, and dizziness. Significant lowering of serum cortisol may result in hypotension, abnormal electrolyte levels, and hypoglycemia.

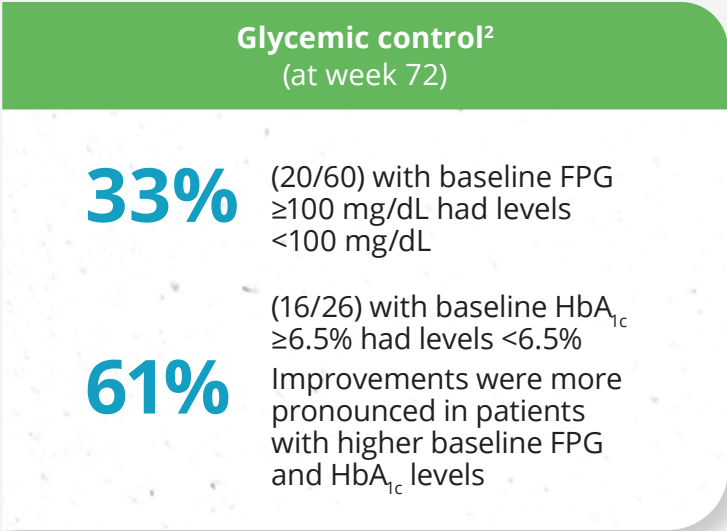
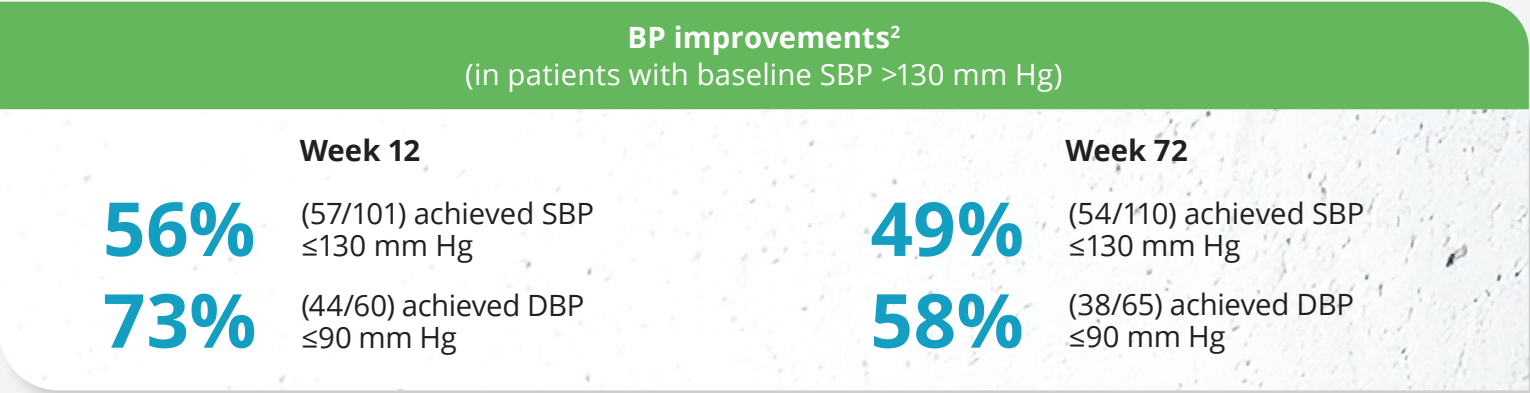
Please see IMPORTANT SAFETY INFORMATION throughout and accompanying full PRESCRIBING INFORMATION.



In a pooled post hoc analysis of LINC 3 and LINC 4,

Changes in BP and glycemic parameters were observed while taking ISTURISA²

ISTURISA: BP and glycemic measures observed by week 12—up to week 72^{2,a,b}



- Patients with higher baseline BP experienced greater reductions with ISTURISA²
- Patients with higher baseline blood glucose levels experienced greater reductions in FPG and HbA_{1c} with ISTURISA²

^aResults should be interpreted with caution as post hoc analyses are not prespecified and cannot be regarded as confirmatory.²

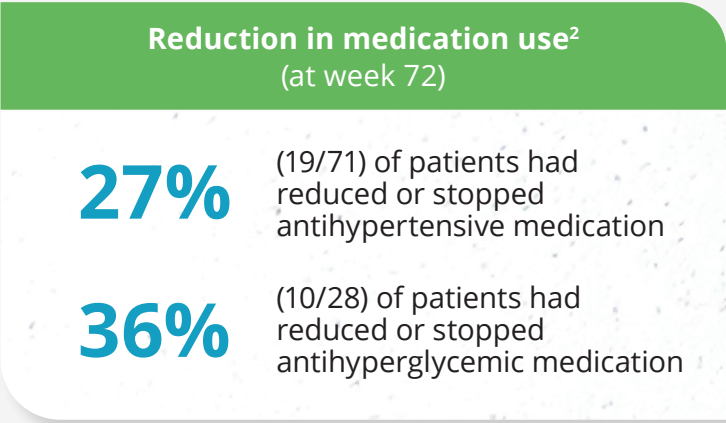
BP, blood pressure; CD, Cushing’s disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; SBP, systolic blood pressure.

^bIn patients with CD who met baseline criteria for hypertension or diabetes.²

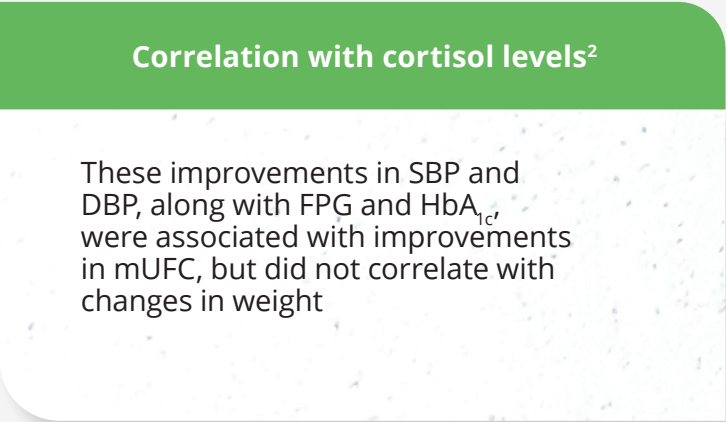
IMPORTANT SAFETY INFORMATION (continued)

Hypocortisolism (continued): Hypocortisolism can occur at any time during ISTURISA treatment. Evaluate patients for precipitating causes of hypocortisolism (infection, physical stress, etc.). Monitor 24-hr urine free cortisol, serum or plasma cortisol, and patient’s signs and symptoms periodically during ISTURISA treatment.

Reductions in concomitant antihypertensive and antihyperglycemic medication use were observed during treatment with ISTURISA²



Changes in cardiometabolic parameters were associated with cortisol control²



DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; mUFC, mean urinary free cortisol; SBP, systolic blood pressure.

IMPORTANT SAFETY INFORMATION (continued)

Hypocortisolism (continued): Decrease or temporarily discontinue ISTURISA if urine free cortisol levels fall below the target range, there is a rapid decrease in cortisol levels, and/or patients report symptoms of hypocortisolism. Stop ISTURISA and administer exogenous glucocorticoid replacement therapy if serum or plasma cortisol levels are below target range and patients have symptoms of adrenal insufficiency. After ISTURISA interruption or discontinuation, cortisol suppression may persist beyond the 4-hour half-life of ISTURISA.

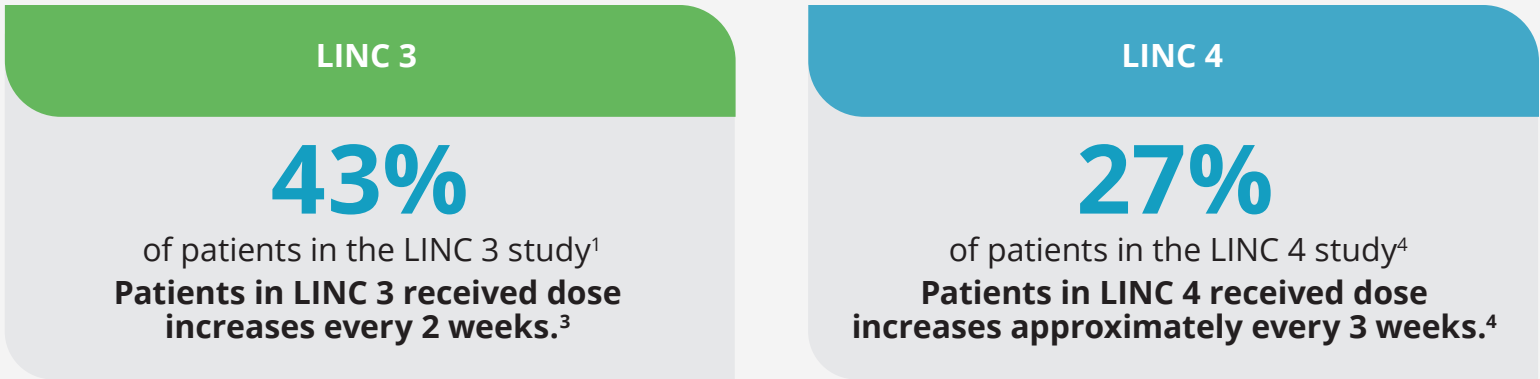
Educate patients on the symptoms associated with hypocortisolism and advise them to contact a healthcare provider if they occur.

Please see **IMPORTANT SAFETY INFORMATION** throughout and accompanying full **PRESCRIBING INFORMATION**.



Some patients may experience signs of adrenal insufficiency,^a which can be managed with patient-specific titration¹

Percentage of hypocortisolism-related events in each study



^aAdrenal insufficiency includes glucocorticoid deficiency, adrenocortical insufficiency acute, steroid withdrawal syndrome, cortisol free urine decreased, and cortisol decreased.¹

Among the **43%** of patients who were deemed to have experienced adrenal insufficiency, 1/3 had low cortisol levels indicative of adrenal insufficiency.^{1,a}

ISTURISA® (osilodrostat) titration was slower in LINC 4 and did not compromise its ability to normalize cortisol in patients with CD. In LINC 4, decisions to increase dose took into consideration all data for each patient, including mUFC level, rate of decrease of mUFC, and tolerability of ISTURISA.^{4,37}

Patients should be monitored regularly and educated on the symptoms of adrenal insufficiency, such as nausea, vomiting, fatigue, abdominal pain, loss of appetite, and dizziness, to allow prompt management. Adrenal insufficiency can be managed through dosage reduction or interruption.¹



Counsel patients to recognize and report the symptoms suggestive of hypocortisolism¹

• Nausea	• Abdominal pain	• Low blood pressure
• Vomiting	• Loss of appetite	• Syncope
• Fatigue	• Dizziness	

CD, Cushing's disease; mUFC, mean urinary free cortisol.

IMPORTANT SAFETY INFORMATION (continued)

QTc Prolongation: ISTURISA is associated with a dose-dependent QT interval prolongation which may cause cardiac arrhythmias. Perform an ECG to obtain a baseline QTc interval measurement prior to initiating therapy with ISTURISA and monitor for an effect on the QTc interval thereafter.

Precise dosing, individualized to the patient¹

Different dosing strategies allow for the adjustment of therapy to suit each patient's unique needs during the titration and maintenance stages¹

BEFORE STARTING ISTURISA¹

- Test potassium and magnesium levels and correct for hypokalemia and hypomagnesemia
- Obtain baseline ECG



01 → START
ISTURISA 2 mg twice daily, *with or without food*^{1,a}

02 → TITRATE
Up in 1- or 2-mg increments twice daily, no more than once every 2 weeks, based on the rate of cortisol changes, individual tolerability, and improvement in signs and symptoms of CS. If your patient tolerates 10 mg twice daily and continues to have elevated 24-hour UFC levels above the ULN, you may up-titrate by 5 mg twice daily every 2 weeks¹



03 → MONITOR
Cortisol levels every 1 to 2 weeks until adequate clinical response is maintained. Consider less frequent monitoring thereafter. Monitor 24-hour UFC, serum or plasma cortisol, and patient's signs and symptoms periodically during treatment¹

Help stay in control by monitoring your patient's changes in cortisol.

ISTURISA® (osilodrostat) allows you to objectively monitor each patient's individual changes in cortisol.¹

CS, Cushing's syndrome; ECG, electrocardiogram; UFC, urinary free cortisol; ULN, upper limit of normal.

^aThe recommended starting dose for patients with moderate hepatic impairment (Child-Pugh B) is 1 mg twice daily; for patients with severe hepatic impairment (Child-Pugh C), the recommended starting dose is 1 mg once daily in the evening.¹

IMPORTANT SAFETY INFORMATION (continued)

QTc Prolongation (continued): Correct hypokalemia and/or hypomagnesemia prior to ISTURISA initiation and monitor periodically during treatment with ISTURISA. Use with caution in patients with risk factors for QT prolongation and consider more frequent ECG monitoring.

Please see IMPORTANT SAFETY INFORMATION throughout and accompanying full PRESCRIBING INFORMATION.



ISTURISA® (osilodrostat) enrollment is administered exclusively through the R.A.R.E.® Patient Support Program

Designed to ensure your patients taking ISTURISA receive dedicated, multipoint services and support every step of the way.



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Fax: **1-855-813-2039**

A clinical pharmacist is always available.

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Indicated for endogenous hypercortisolemia in Cushing's syndrome¹

LINC 3

Demonstrated superiority over placebo at maintaining mUFC $\leq$ ULN after randomized withdrawal

86% complete responder rate with ISTURISA (31/36) vs 29% with placebo (10/34) (N=71, $P<.001$)^{1,3}



LINC 4

Significantly more patients had mUFC $\leq$ ULN with ISTURISA at week 12

77% complete responder rate with ISTURISA (37/48) vs 8% with placebo (2/25) (N=73, $P<.0001$)⁴



- Two tablet dose strengths and administration, with or without food, provide the flexibility to individualize therapy¹
- The most common adverse reactions were
 - Adrenal insufficiency,^a fatigue,^b nausea, headache,^c and edema^d in LINC 3 (incidence $>20\%$)¹
 - Decreased appetite, arthralgia, nausea, fatigue,^b myalgia,^e and diarrhea in LINC 4 (incidence $>20\%$)^{1,4}



Explore ISTURISA.com/hcp
Learn how ISTURISA helps treat endogenous hypercortisolemia in CS.¹

CS, Cushing's syndrome; mUFC, mean urinary free cortisol; ULN, upper limit of normal.

^aAdrenal insufficiency includes glucocorticoid deficiency, adrenocortical insufficiency acute, steroid withdrawal syndrome, cortisol free urine decreased, cortisol decreased. One-third of the patients with this event had low cortisol levels indicative of adrenal insufficiency. The majority of patients had normal cortisol levels suggesting a cortisol withdrawal syndrome.¹

^bFatigue includes lethargy, asthenia.¹

^cHeadache includes head discomfort.¹

^dEdema includes edema peripheral, generalized edema, localized edema.¹

^eMyalgia includes myalgia and fibromyalgia.¹

IMPORTANT SAFETY INFORMATION (continued)

Elevations in Adrenal Hormone Precursors and Androgens: ISTURISA blocks cortisol synthesis and may increase circulating levels of cortisol and aldosterone precursors and androgens. This may activate mineralocorticoid receptors and cause hypokalemia, edema and hypertension. Hypokalemia should be corrected prior to initiating ISTURISA. Monitor patients treated with ISTURISA for hypokalemia, worsening of hypertension and edema. Inform patients of the symptoms associated with hyperandrogenism and advise them to contact a healthcare provider if they occur.

Please see IMPORTANT SAFETY INFORMATION throughout and accompanying full PRESCRIBING INFORMATION.



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