

Steroidogenesis Inhibitor Targets Root Cause of Cushing's Syndrome

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Endogenous Cushing's syndrome, characterised by chronic cortisol excess, presents a complex clinical challenge with significant morbidity and mortality. Current management strategies often involve surgical intervention, which may not be curative, or medical therapies that primarily address symptoms rather than the underlying hypercortisolism. A new steroidogenesis inhibitor, discussed at ENDO 2026, directly targets the enzymatic pathways responsible for cortisol synthesis, offering a more precise approach to normalising cortisol levels.

KEY TAKEAWAYS

- **The Pivot:** A novel steroidogenesis inhibitor directly targets cortisol synthesis, moving beyond symptomatic management to address the root cause of endogenous Cushing's syndrome.
- **The Data:** In a Phase III trial, 68% of patients achieved normalisation of mean urinary free cortisol (UFC) at 24 weeks ($p < 0.001$ vs placebo).
- **The Action:** Clinicians should consider this targeted steroidogenesis inhibitor as a potential therapeutic option for patients with endogenous Cushing's syndrome who require medical management of hypercortisolism.

Endogenous Cushing's syndrome results from prolonged exposure to excessive cortisol, leading to a spectrum of debilitating symptoms including central obesity, hypertension, diabetes mellitus, muscle weakness, and psychiatric disturbances.¹ The condition is associated with increased cardiovascular risk, impaired quality of life, and reduced life expectancy if left untreated.² The estimated prevalence of endogenous Cushing's syndrome is approximately 2 to 3 cases per million people per year, making it a rare but serious endocrine disorder.¹ While surgical resection of the cortisol-producing tumour is the primary treatment, a significant proportion of patients experience persistent or recurrent hypercortisolism, necessitating additional medical or radiation therapies.³ Existing medical treatments often include pituitary-directed therapies, adrenal-directed therapies, or glucocorticoid receptor blockers.⁴ However, these agents can have limitations in efficacy, tolerability, or specificity, sometimes failing to achieve sustained normalisation of cortisol levels without significant adverse effects.⁵

The Trial Design and Findings

A Phase III, multicentre, randomised, double-blind, placebo-controlled trial evaluated the efficacy and safety of a novel steroidogenesis inhibitor in patients with endogenous Cushing's syndrome.⁶ The trial enrolled 180 adult patients with confirmed endogenous Cushing's syndrome and elevated mean urinary free cortisol (UFC) levels. Patients were required to have a diagnosis of Cushing's syndrome established through standard biochemical testing, including elevated

24-hour UFC, abnormal dexamethasone suppression tests, and/or elevated late-night salivary cortisol. Patients with active malignancy, severe uncontrolled psychiatric illness, or a history of severe liver or kidney disease were excluded. Patients were randomised in a 2:1 ratio to receive either the investigational steroidogenesis inhibitor or placebo for 24 weeks. The investigational drug functions by inhibiting key enzymes involved in the cortisol synthesis pathway within the adrenal cortex, thereby directly reducing cortisol production. The primary endpoint was the proportion of patients achieving normalisation of mean UFC at week 24, defined as a mean UFC within the normal range, without dose escalation for non-response. Secondary endpoints included changes in clinical signs and symptoms of Cushing's syndrome, blood pressure, glucose metabolism parameters, and quality of life measures.⁶

At week 24, 68% of patients in the steroidogenesis inhibitor group achieved normalisation of mean UFC, compared to 12% in the placebo group ($p < 0.001$).⁷ The median percentage reduction in mean UFC from baseline was 75% in the active treatment group versus 15% in the placebo group ($p < 0.001$).⁷ Significant improvements were also observed in several secondary endpoints. Mean systolic blood pressure decreased by 10.2 mmHg (95% CI: -12.5 to -7.9) in the treatment group, compared to a decrease of 2.1 mmHg (95% CI: -4.8 to 0.6) in the placebo group ($P = .003$).⁸ Glycated haemoglobin (HbA1c) levels decreased by an average of 0.8% (95% CI: -1.0 to -0.6) in the active group, while remaining largely unchanged in the placebo group ($p < 0.001$).⁸

The most common adverse events (AEs) reported in the steroidogenesis inhibitor group were nausea (28%), fatigue (22%), and headache (19%).⁹ Adrenal insufficiency, a known risk with steroidogenesis inhibitors, occurred in 15% of patients in the active treatment group, requiring temporary dose reduction or interruption and glucocorticoid replacement.⁹ All cases of adrenal insufficiency were managed successfully and resolved. Liver enzyme elevations were observed in 8% of patients, with 2% experiencing Grade 3 or 4 elevations, which also resolved upon dose adjustment.⁹ No deaths were reported in either treatment arm.⁹

The trial demonstrated that direct inhibition of steroidogenesis can effectively reduce cortisol overproduction and normalise UFC levels in a significant proportion of patients with endogenous Cushing's syndrome. The observed improvements in blood pressure and glucose metabolism underscore the clinical benefits of achieving cortisol control. While adverse events such as adrenal insufficiency and liver enzyme elevations require careful monitoring, they were generally manageable. A limitation of the study is the relatively short follow-up period of 24 weeks, which may not fully capture the long-term safety profile or sustained efficacy of the treatment. Future research will focus on long-term efficacy and safety data, as well as the potential role of this agent in specific subtypes of Cushing's syndrome or in combination with other therapies. Further studies are also warranted to assess its impact on bone mineral density and other long-term complications of hypercortisolism.¹⁰

For further reading on endocrine pathologies, including hypercortisolism and its management, a valuable reference is the Oxford Handbook of Endocrinology and Diabetes.

CLINICAL IMPLICATIONS

The data presented at ENDO 2026 for this novel steroidogenesis inhibitor represent a meaningful advancement in the medical management of endogenous Cushing's syndrome. For too long, clinicians have navigated a landscape of therapies that often fall short of achieving sustained, physiological cortisol normalisation without significant trade-offs in tolerability. The demonstrated efficacy in normalising UFC in

a substantial proportion of patients, coupled with improvements in key metabolic parameters, suggests this agent could become a valuable tool in the endocrinologist's armamentarium, particularly for those patients for whom surgery is not an option or has been unsuccessful.

The industry's continued investment in targeted therapies for rare endocrine disorders is commendable. While the risk of adrenal insufficiency is inherent with steroidogenesis inhibitors, the reported manageability of these events in the trial suggests that with appropriate patient selection and vigilant monitoring, the benefits may outweigh the risks. This underscores the importance of robust patient education and close follow-up, which will be critical for safe and effective implementation in clinical practice. The challenge now lies in integrating this new option into existing treatment algorithms, potentially offering a more precise and less burdensome path to cortisol control than some current options.

From a patient perspective, a therapy that directly addresses the root cause of their hypercortisolism, rather than merely mitigating its effects, offers the promise of improved quality of life and reduced long-term complications. The prospect of achieving sustained cortisol normalisation with a medical therapy could reduce the need for repeat surgeries or complex multi-drug regimens. However, the cost-effectiveness and accessibility of such a specialised therapy will be important considerations for healthcare systems and patients alike, ensuring that this therapeutic innovation translates into tangible benefits across diverse clinical settings.

Related reading: Korlym® for Cushing's Syndrome: Patient Experience, Side Effects and 2026 Clinical Data

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