The Cortisol Reports

Episode 1 - Breaking Ground:

2025 Milestones in Cushing Syndrome and Looking Forward to 2026

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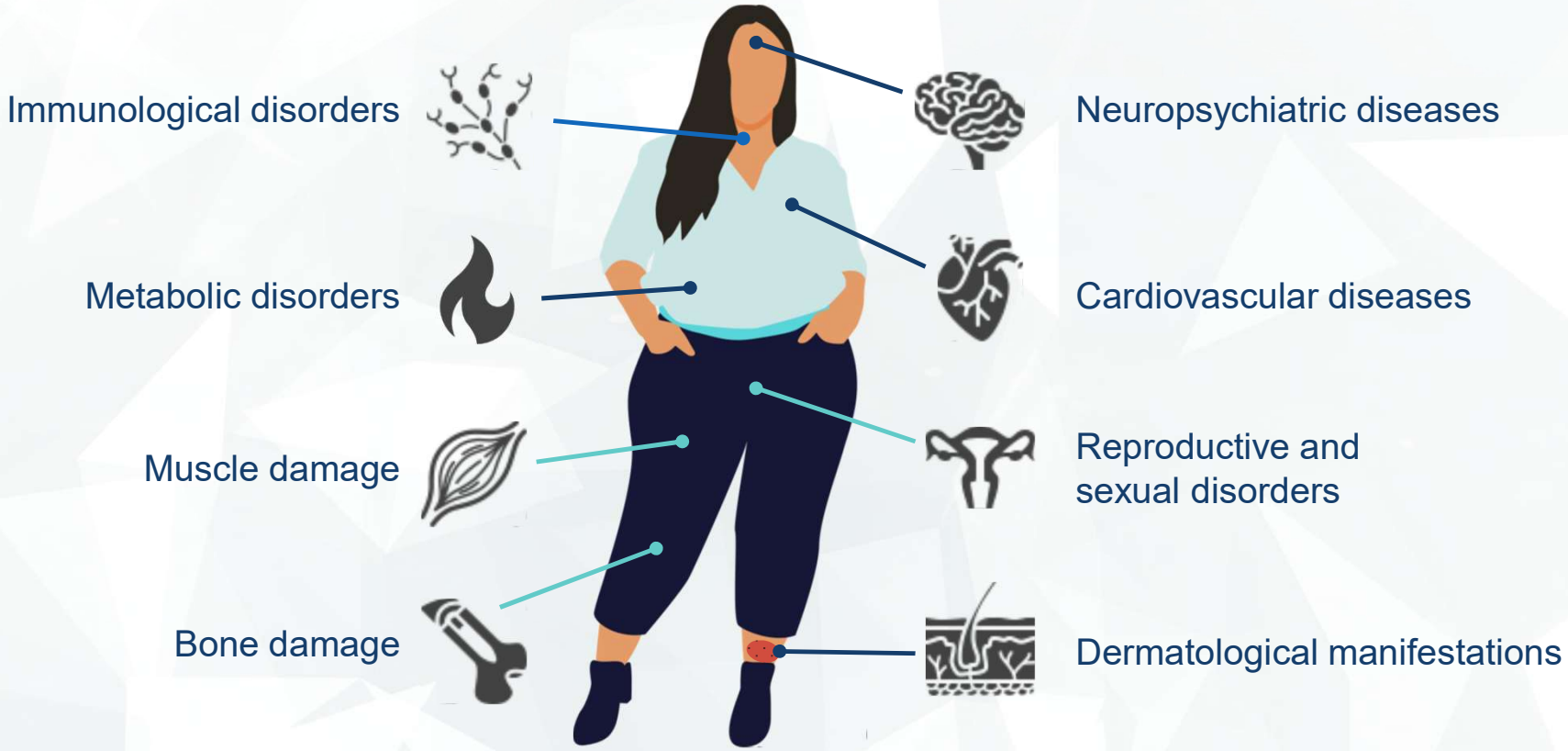
Hypercortisolism and Comorbidities



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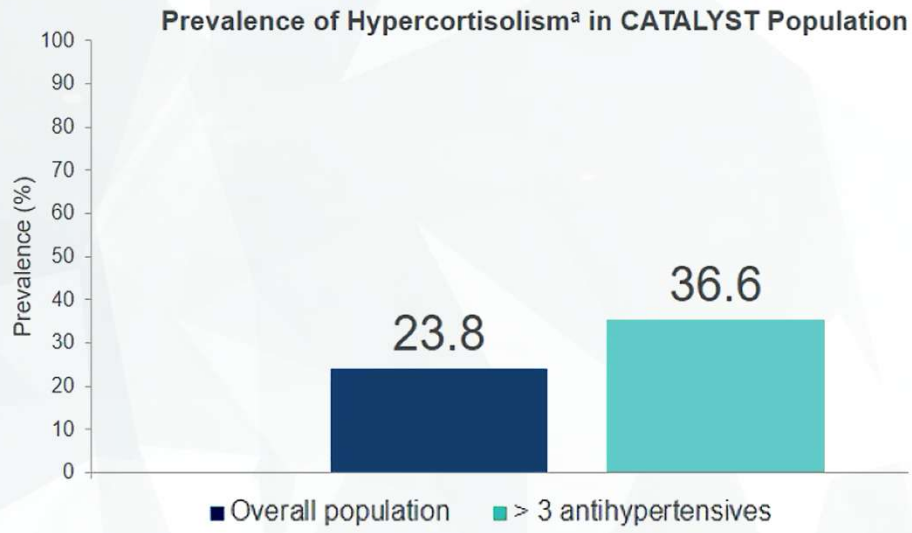
Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2016.

2024: Updated Prevalence of Hypercortisolism in T2D

CATALYST Trial: 1,057 patients with HbA1c > 7.5% despite optimal T2D therapy

Results:

- Prevalence of hypercortisolism (Post-DST cortisol levels >1.8 µg/dL) in people with difficult-to-treat T2D was 23.8%
- Prevalence rose to 36.6% when looking at people with resistant hypertension (on 3 or more antihypertensive agents)
  - The odds of hypercortisolism was nearly 2x as high in this patient population



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Buse JB, et al. *Diabetes Care*. 2025.

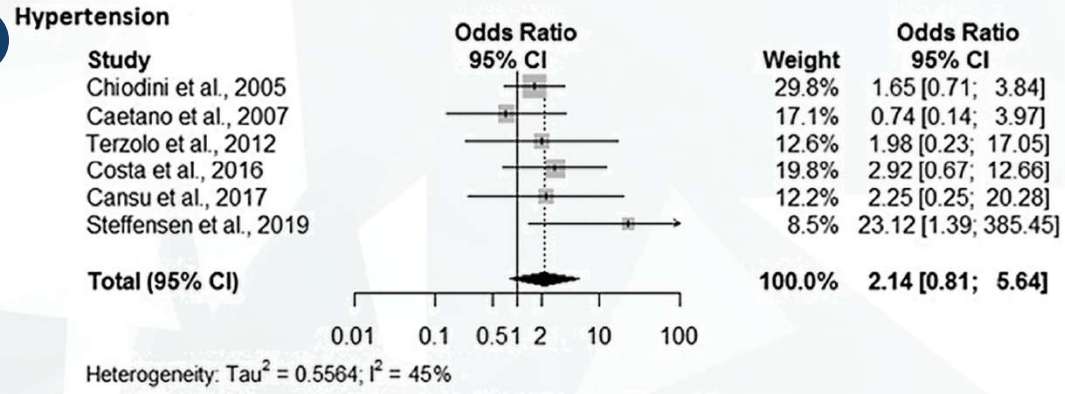
What we Know about Hypercortisolism and Resistant HTN

Association of cortisol excess and high blood pressure well-known **(1)**

Elevated cortisol levels shows to be present especially with additional comorbidities and complications **(2)**

In hypertensive patients with Cushing Syndrome, conventional antihypertensive therapy may not be effective until normal cortisol levels are restored, indicating a gap in care and significant need for new therapies. **(3)**

1



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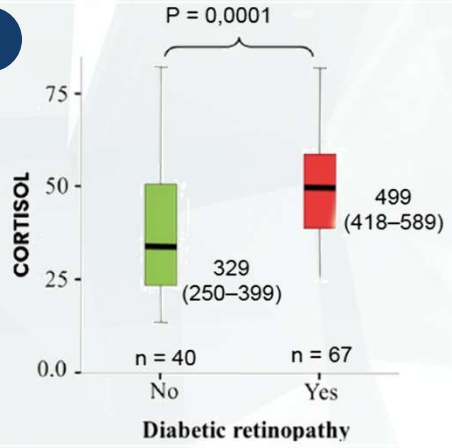

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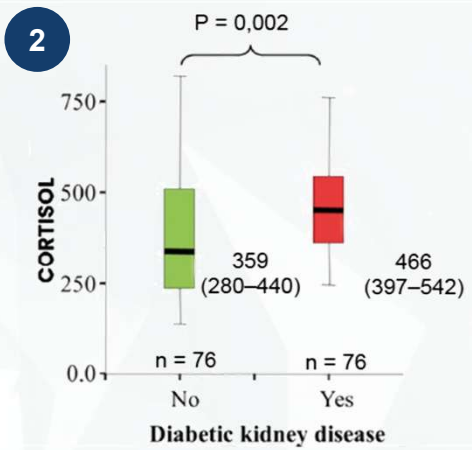

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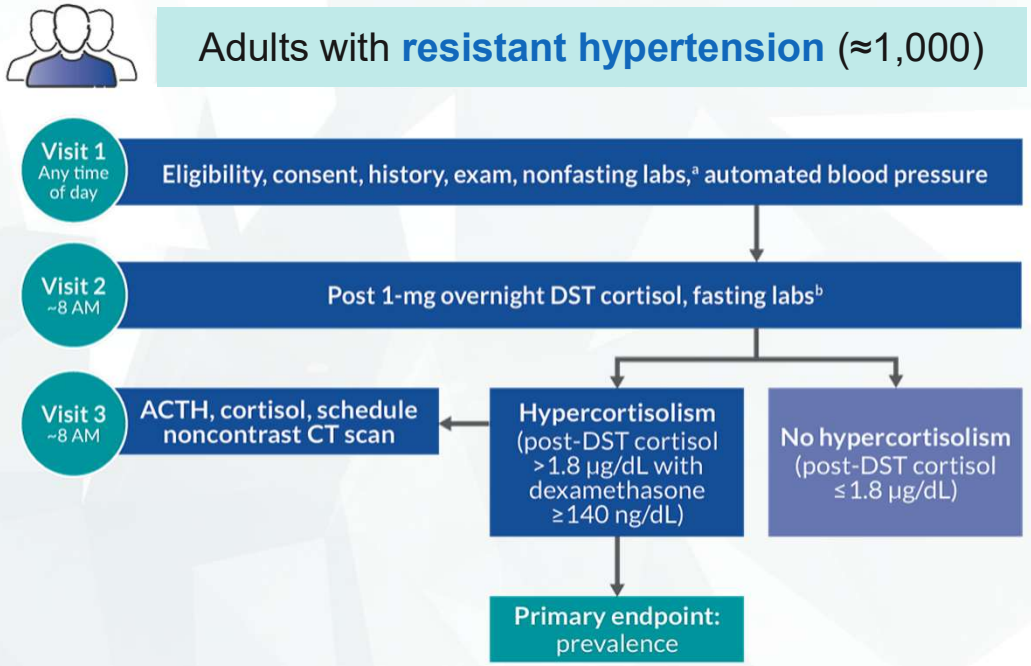
(1) Aresta C, et al. *Endocr Pract*. 2021;
(2) Jusufovic S, et al. *Clin Diabetol*. 2024;
(3) Fallo F, et al. *J Intern Med*. 1993.

Updated Prevalence of Hypercortisolism in Resistant HTN is Coming

MOMENTUM Trial

Primary Endpoint: Assess prevalence of endogenous hypercortisolism in patients with resistant hypertension

Data coming soon



216-09. Prevalence And Clinical Impact Of Hypercortisolism In Individuals With Resistant Hypertension: Primary Results From The Momentum Study

Deepak L. Bhatt, Pam Taub, Luke Laffin, Nishant Shah, Florian Rader, Jan Basile, Matthew J. Budoff, Omar Al Dhaybi, Michael J. Bloch, Raymond Townsend, Guillermo Umpierrez, Jorge Plutzky, John B. Buse Mark Kipnes, Lance Sloan, robert busch, Iulia Cristina Tudor, Daniel Einhorn, MOMENTUM Investigators

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2025 Year in Review for Cushing Syndrome

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Osilodrostat

- LINC 6 Trial: Ongoing prospective, observational phase IV study evaluating the long-term safety and effectiveness of osilodrostat in patients with Cushing Syndrome over 3 years (US & Europe)
  - Ongoing recruitment and follow-up with the last patient visit projected in about 2028 (US and Europe).
  - Planned enrollment: ~ 200 patients
  - Interim analysis: prespecified at 12 and 24 months
  - 1 year interim data was presented at ECE (European Congress of Endocrinology) and Endocrine Society

Bancos I, et al. *J Endocr Soc*. 2024.

2-Year Interim Data from LINC 6

- Presented at ENDO 2025: Long-Term, Real-World, Safety and Effectiveness of Osilodrostat In Patients With Pituitary and Non-Pituitary Cushing's Syndrome
- Primary objective: long-term safety and tolerability of osilodrostat with a focus on hypocortisolism, adrenal hormone precursor accumulation, arrhythmia/QT prolongation, and pituitary tumor enlargement-related adverse events.
- Effectiveness endpoints: change in mean urinary free cortisol (mUFC) and late-night salivary cortisol (LNSC).
- 205 patients, 75.6% female, age 53.0 ± 14.4 years.
  - 161 pts had CD, and 44 had non-PCS.
  - Osilodrostat exposure: 8.3 months (0.0-20.8) and 5.0 mg/day (0.5-80.0).

Bancos I, et al. *J Endocr Soc*. 2025.

Safety- LINC 6 study

- About 20% of patients reported treatment-related AEs
  - Most were mild or moderate. The most common AEs were adrenal insufficiency, diarrhea, dizziness, fatigue, hirsutism, joint stiffness, nausea, hypokalemia, and nervous system disorders.
  - 17 (10.6%) CD and 10 (22.7%) non-PCS pts reported 29 and 16 SAEs (7 and 4 were considered treatment related), respectively.
  - 5 (3.1%) CD and 2 (4.5%) non-PCS pts discontinued because of treatment-related AEs.
  - There were 22 adrenal hormone precursor accumulation-related AEs, and 3 arrhythmogenic potential/QT interval prolongation.
- There were 3 pituitary tumor enlargements in patients with CD.

Bancos I, et al. *J Endocr Soc*. 2025.

Efficacy- LINC 6 study

- Month 3: mUFC and LNSC were normal in 73.9% (n=34/46) and 56.3% (n=18/32) of pts.
- Month 6: mUFC and LNSC were normal in 63.0% (n=29/46) and 30.4% (n=7/23) of pts.
- Authors' Conclusion:
  - The LINC 6, 2-year interim data show that osilodrostat is effective for the management of different etiologies of CS.
  - AEs were mostly mild or moderate, with few leading to treatment discontinuation.

Bancos I, et al. *J Endocr Soc*. 2025.

Osilodrostat Expanded Indication to Cushing Syndrome

- Interim data already supported FDA label expansion from CD to all endogenous CS.
  - In April 2025, the FDA approved an expanded indication for osilodrostat for the treatment of endogenous hypercortisolemia in adults with Cushing syndrome.

Relacorilant

- Relacorilant is an investigational selective glucocorticoid receptor (GR) modulator designed to modulate excess cortisol activity at the GR to treat the manifestations of endogenous hypercortisolism.
  - Highly selective for the GR, with no activity at the progesterone, mineralocorticoid, or androgen receptors; structurally different from the nonselective GR antagonist mifepristone.
  - Avoids unwanted off-target progesterone receptor effects (e.g., endometrial hypertrophy, vaginal bleeding).
  - Because of a lack of increase in ACTH and no clinically significant increase in cortisol, it does not induce hypokalemia and appears not to be associated with adrenal insufficiency or QT interval prolongation.

Jabbour S, et al. *Poster Presented at Heart in Diabetes June 6-8, 2025*. Abstract 0097; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

Why Does QT Interval Matter in Cushing Syndrome Management?

QT interval may be influenced by medical therapies, therefore monitoring before and during treatment is crucial, especially in those patients who:

- Use other drugs influencing QT or inducing hypokalemia
- Use a combination of different medications for CS both inducing longer QT intervals

Medication	Study	QT Prolongation, (%)
Pasireotide SC	SOM230B2305	2.0
Pasireotide LAR	SOM230G2304	3.0
Osilodrostat	LINC 3	4.0
Levoketoconazole	SONICS; LOGICS	5.3; 10.7

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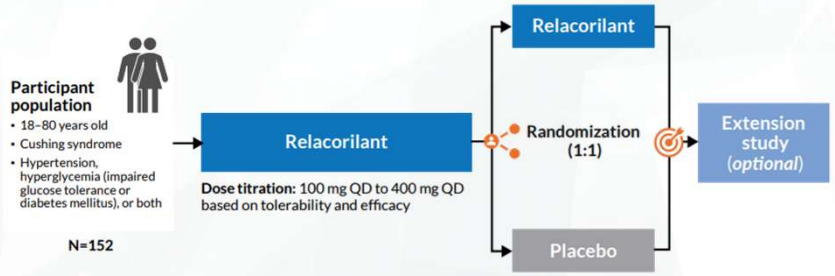
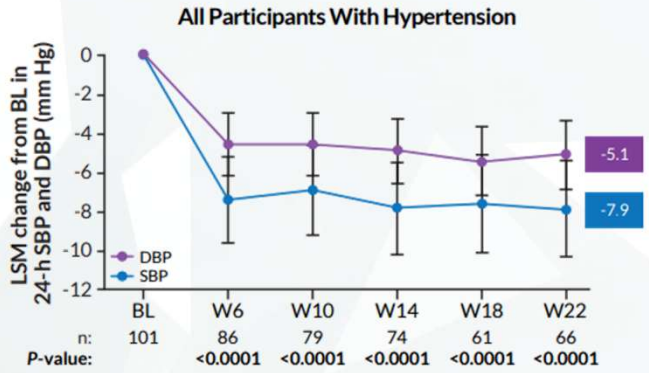
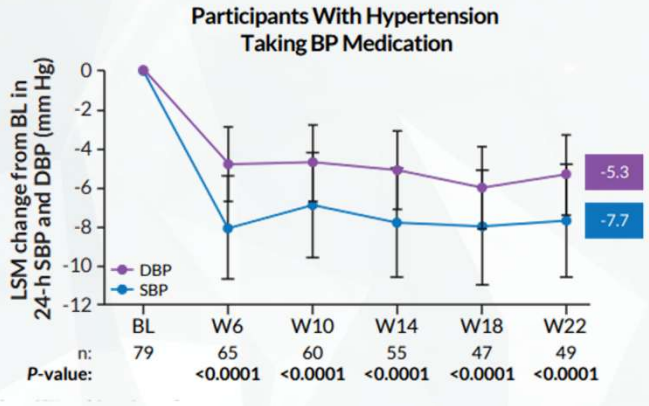
Colao A, et al. *N Engl J Med*. 2012; Lacroix A, et al. *Lancet Diabetes Endocrinol*. 2018; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2020; Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2019; Pivonello R, et al. *Pituitary*. 2022.

GRACE Trial Results: OL Phase



	Participants (n=102)
Age, years, mean (SD)	48.6 (12.7)
Female, n (%)	85 (83.3)
Weight, kg, mean (SD)	95.1 (26.1)
BMI, kg/m², mean (SD)	34.7 (9.0)
Waist circumference, cm, mean (SD)	115.1 (19.5)
HbA1c, mean (%)	6.7 (1.6)
24-h SBP, mm Hg, mean (SD) [n]	140.6 (10.6) [101]
24-h DBP, mm Hg, mean (SD) [n]	88.9 (7.2) [101]





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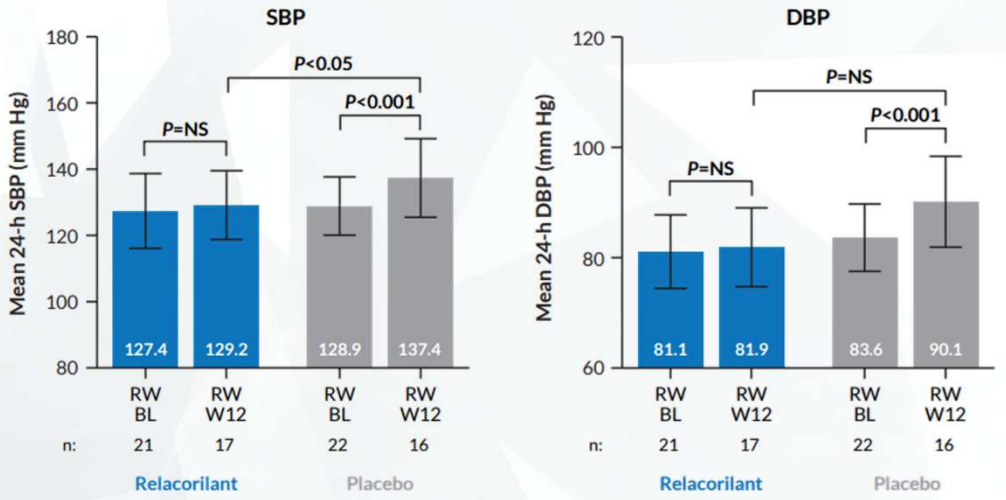
Jabbour S, et al. *Poster Presented at Heart in Diabetes June 6-8, 2025*. Abstract 0097; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

GRACE Trial Results: Withdrawal Phase

	Relacorilant (n=21)	Placebo (n=22)
Age, years, mean (SD)	46.1 (11.4)	49.0 (13.3)
Female, n (%)	15 (71.4)	20 (90.9)
Weight, kg, mean (SD)	93.7 (32.0)	85.0 (21.4)
BMI, kg/m^2, mean (SD)	32.5 (8.4)	31.6 (6.8)
Waist circumference, cm, mean (SD)	113.1 (20.5)	105.9 (16.7)
24-h SBP, mm Hg, mean (SD)	137.9 (11.0)	140.8 (10.6)
24-h DBP, mm Hg, mean (SD)	89.2 (7.0)	90.6 (5.5)



In the placebo-controlled RW phase, participants with hypertension who continued to receive relacorilant were 5.9x more likely to maintain hypertension response

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Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

GRACE Trial Results: Withdrawal Phase, Impact on Glycemic Measures

	Relacorilant (n=30)	Placebo (n=32)
Change from RW baseline to week RW12 in:		
$AUC_{glucose}$ (in patients with hyperglycemia at study entry), h*mmol/L		
n	15	19
Mean (SD)	+1.1 (4.7)	+4.9 (6.1)
Wilcoxon signed rank sum *P*-value[a]	ns	**0.0003**
HbA1c (in patients with hyperglycemia at study entry), %		
n	16	19
Mean (SD)	+0.1 (0.8)	+0.3 (0.6)
Wilcoxon signed rank sum *P*-value[a]	ns	**0.03**
HbA1c (in patients with diabetes at study entry), %		
n	13	13
Mean (SD)	+0.1 (0.8)	+0.4 (0.6)
Wilcoxon signed rank sum *P*-value[a]	ns	**0.04**

$AUC_{glucose}$, glucose area under the curve; HbA1c, hemoglobin A1c; ns, not significant ($P \geq 0.05$); RW, randomized withdrawal. Wilcoxon rank sum test *P*-values for the observed mean within each treatment arm shown. [a]Wilcoxon signed-rank test P-values within each treatment arm.

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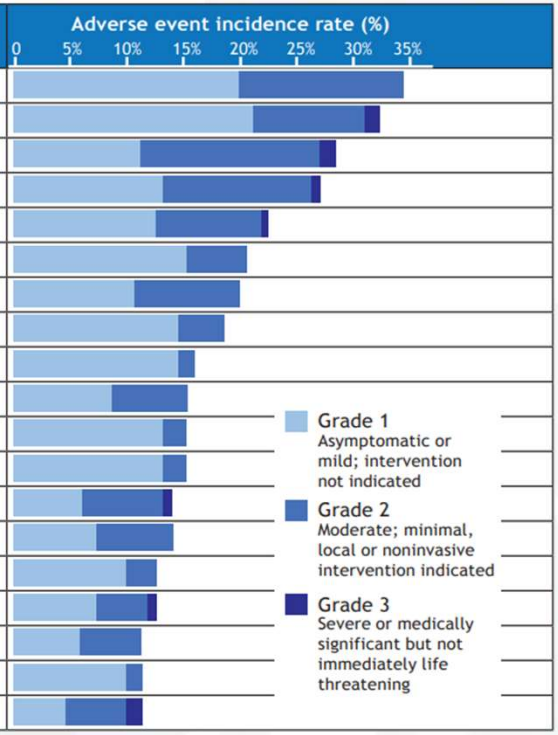
Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

GRACE Trial Results: Safety

Adverse events occurring in ≥10% of patients

Adverse event, n (%)	Relacorilant (n=152)
Nausea	52 (34.2)
Edema peripheral	50 (32.9)
Pain in extremity	43 (28.3)
Back pain	41 (27.0)
Fatigue	34 (22.4)
Headache	31 (20.4)
Arthralgia	30 (19.7)
Diarrhea	28 (18.4)
Skin hyperpigmentation	24 (15.8)
Abdominal pain upper	23 (15.1)
Constipation	23 (15.1)
Dizziness	23 (15.1)
Paresthesia	21 (13.8)
Myalgia	21 (13.8)
Asthenia	19 (12.5)
Vomiting	19 (12.5)
Abdominal pain	17 (11.2)
Decreased appetite	17 (11.2)
Muscular weakness	17 (11.2)



Data updated based on database lock; analysis date 5 July 2024. TEAEs and CTCAE grade shown. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; OL, open label; TEAE, treatment-emergent adverse event.

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Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

Relacorilant NDA Submission

- Corcept submitted an NDA for Relacorilant as a treatment for hypertension secondary to hypercortisolism based on the Phase 3 GRACE trial (primary endpoint met) and supporting GRADIENT trial data.
- The FDA issued a complete response letter stating that while GRACE met its primary endpoint and GRADIENT provided confirmatory evidence, additional evidence of effectiveness is required for a favorable benefit-risk assessment.
- Corcept plans to meet with the FDA to determine the path forward.

Atumelnant in ACTH-dependent Cushing syndrome

- It is once-daily oral, nonpeptide, first-in-class, competitive and selective ACTH receptor antagonist. Preliminary results of phase 1b/2a study in ACTH dependent CS was presented during the Endocrine Society 2024 meeting.
  - It showed promising early results in ACTH-dependent Cushing's syndrome, demonstrating rapid reductions in cortisol levels and improvements in symptoms, with good tolerability.
  - Most adverse events coincided with development of AI and mostly improved with HC add-block.
- Crinetics plans to initiate Phase 2/3 atumelnant in ACTH-dependent Cushing syndrome in the first half of 2026.

Elenius H, et al. *J Endocr Soc.* 2024

11β-HSD1 inhibitors

- 11β-HSD1 inhibitors work by blocking the enzyme that reactivates glucocorticoids in peripheral tissues (liver, muscle, adipose tissue), allowing local tissue cortisol levels to be reduced while maintaining systemic cortisol necessary for homeostasis.
  - **Clofutriben** developed by Sparrow Pharmaceuticals, is in Phase 2 development for adrenocortical hyperfunction, RESCUE Trial
  - **S-707106** An 11β-HSD1 inhibitor evaluated in a Phase I/IIa open-label Japanese trial
  - **AZD4017** by AstraZeneca, a selective 11β-HSD1 inhibitor, was evaluated in the TICSI trial.

Clofutriben for Endogenous CS

Phase 2 Randomized Rescue Trial

- **3/8 patients taking Clofutriben and 0/6 patients on placebo normalized urinary free cortisol (UFC)** without suppressing serum cortisol to levels indicating adrenal insufficiency risk.
  - Morning serum cortisol levels remained >10 ug/dL, demonstrating no signs of adrenal insufficiency.
- Metabolic and cardiovascular improvement:
  - **HbA1c decreased by 0.6%** (vs. 0.2% with placebo)
  - **Systolic blood pressure decreased by 8 mmHg** (vs. 3 mmHg with placebo)
  - **LDL cholesterol decreased by 25 mg/dL** (vs. increased by 29 mg/dL with placebo)
  - **Concomitant antidiabetic and antihypertensive medications** were reduced in 4 clofutriben-treated patients
- One serious adverse event of vomiting led to temporary drug interruption. All eligible patients who completed the trial elected to continue in OL extension.

Fleseriu M, et al. *J Endocr Soc.* 2025.

Key Takeaways

- Hypercortisolism screening in people with difficult-to-control cardio-metabolic conditions is being shown to be an important driver and screening for excess cortisol is necessary in order to effectively treat these patients.
- Significant advancements are being made in the medical treatment of Cushing Syndrome, with multiple drug classes displaying efficacy and new investigational agents progressing through clinical trials.
  - Expanded indications for osilodrostat
  - FDA discussion for relacorilant NDA
  - Updates on clinical trials for atumelnant and 11B HSD1 inhibitors