CUSHING'S SYNDROME TREATMENT RESEARCH HIGHLIGHTS: ENDO 2024

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Accredited Continuing Education

Disclosures

Dr. Fleseriu discloses the following relevant financial relationships:

- Funding to the University as PI from Crinetics and Sparrow Pharmaceuticals
- Scientific consultant for Crinetics Pharmaceuticals, Recordati Rare Diseases, Sparrow Pharmaceuticals, and Xeris Pharmaceuticals.

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This activity has been supported by medical educational grants from Recordati Rare Diseases Inc. and Xeris Pharmaceuticals.

Learning Objective

At the conclusion of this activity, participants will be able to:

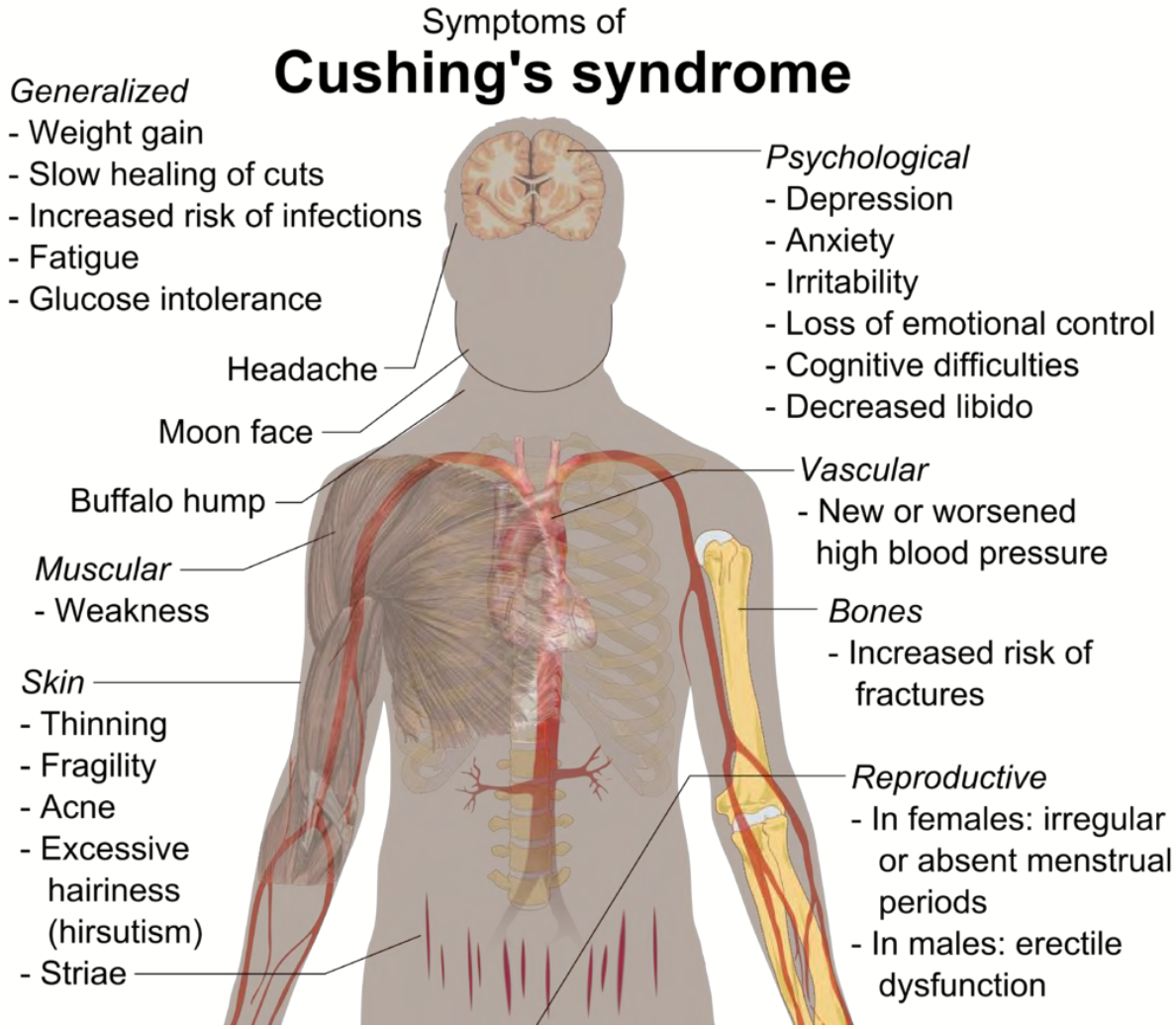
- Describe the latest research being presented to better manage individuals with Cushing's syndrome and its clinical relevance.
- Share new information with their clinical team.

Cushing’s Syndrome (CS) and Cushing’s Disease (CD)

A rare endocrine disorder characterized by chronic hypercortisolism. Incidence of CS is 2–8 per million.

Usually due to a pituitary adenoma producing excessive ACTH leading to hypercortisolism.

Symptoms range from mild to very severe.



Reincke M, Fleseriu M., Cushing syndrome: a review. *JAMA.* 2023; 330:170-181.
Gadelha M, Gatto F, Wildemberg LE, Fleseriu M. Cushing’s syndrome. *Lancet.* 2023;402:2237-2252.

Treatment Algorithm

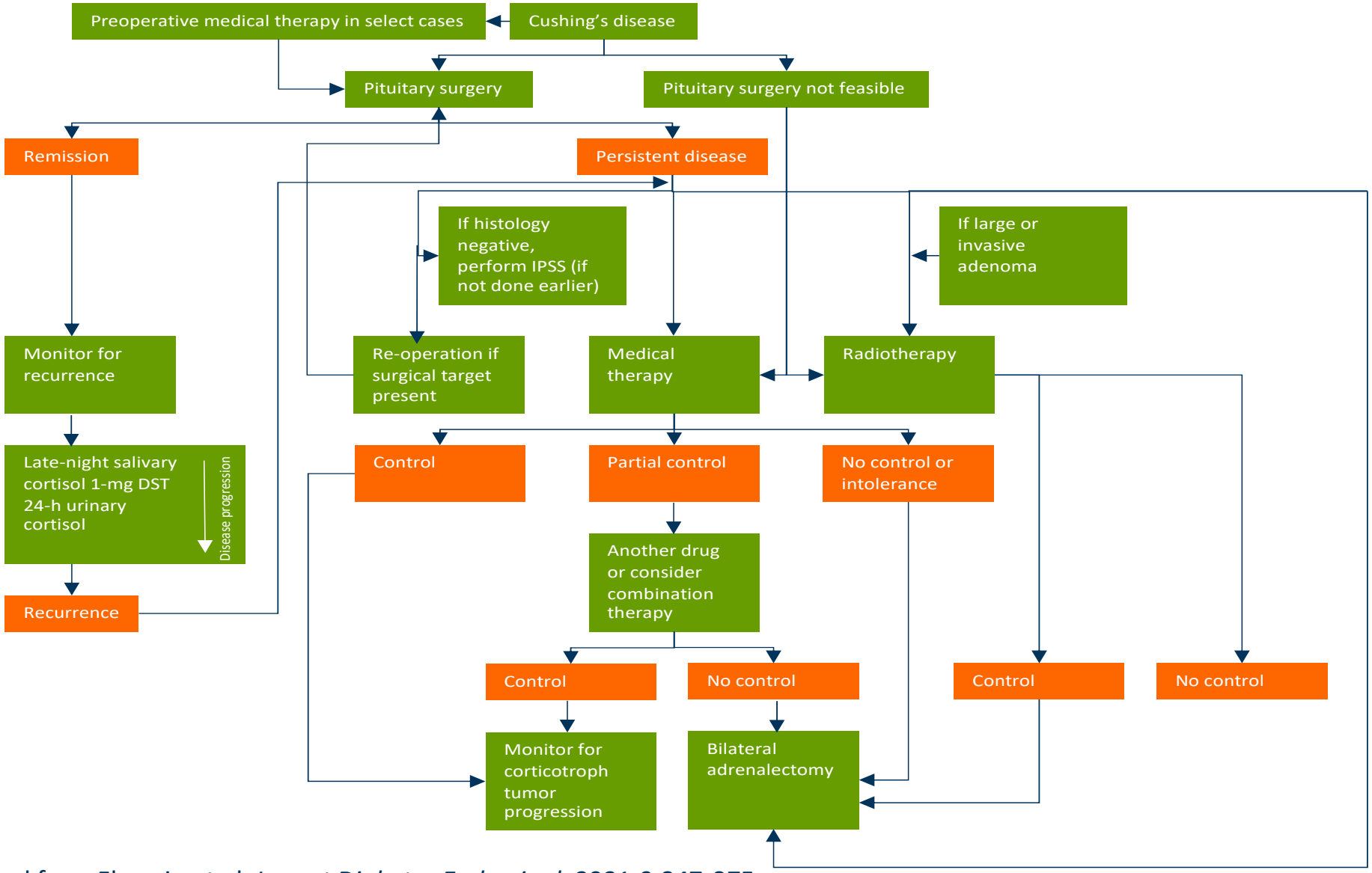


Figure recreated from Fleseriu et al. *Lancet Diabetes Endocrinol*. 2021;9:847-875.

Medical Therapy

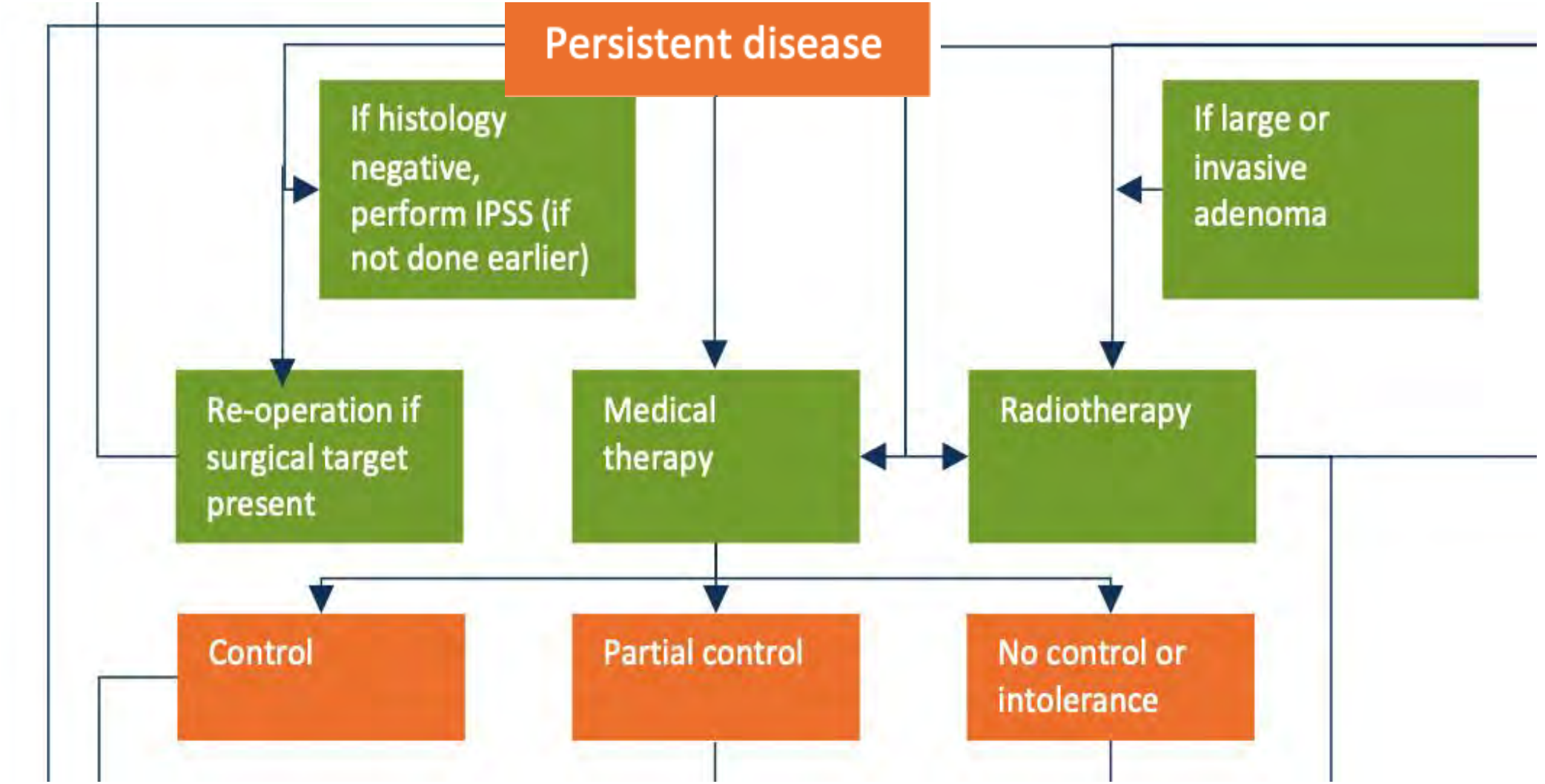


Figure recreated from Fleseriu et al. *Lancet Diabetes Endocrinol*. 2021;9:847-875.

Medical Therapy

Neuromodulators of ACTH release

Pasireotide

Cabergoline

Adrenal steroidogenesis inhibitors

Etomidate

Ketoconazole

Levoketoconazole

Mitotane

Metyrapone

Osilodrostat

Glucocorticoid receptor blockers

Mifepristone

Reincke M, Fleseriu M., Cushing syndrome: a review. *JAMA.* 2023; 330:170-181.
Gadelha M, Gatto F, Wildemberg LE, Fleseriu M. Cushing's syndrome. *Lancet.* 2023;402:2237-2252.

ENDO 2024

- **Endocrine Society Annual Meeting.**
- **Held June 1-4 in Boston, MA.**
- **Clinical trial updates, real world studies, quality of life, comorbidities, and more.**

Real World Impact of CS – A Shared Global Story

- While outcomes have improved, patients with CS continue to report *diagnosis delays*, *confusion about treatments* and *feeling ignored once cortisol is normalized.*
- An international patient committee created a survey
  - 150 questions
  - Received 438 responses from 38 countries
- Respondents answered questions about their daily lives including physical, emotional, mental and social well-being.

Edwin L, Jordan G. Real world impact of Cushing's syndrome: a shared global story. Presented at: ENDO 2024; June 1-4, 2024. Boston, MA.

Real World Impact of CS – A Shared Global Story

Survey Highlights	Respondents (N=438)
Still trying to determine “new normal”	~75% (~329 pts)
Memory problems that didn’t exist before CS	~80% (~350 pts)
Taking longer than six weeks to return to work in any capacity	~90% (~394 pts)
Marriage or long-term relationship ended due to CS (male pts)	~33%
Marriage or long-term relationship ended due to CS (female pts)	~20%
Feeling that their medical team was unable to support them beyond cortisol issues	~50% (~219 pts)
Experiencing suicidal thoughts due to CS	~50% (~219 pts)

- **Results demonstrate the ongoing burden of hypercortisolism, often starting 7+ years before an official diagnosis is made and continuing indefinitely.**

Edwin L, Jordan G. Real world impact of Cushing’s syndrome: a shared global story. Presented at: ENDO 2024; June 1-4, 2024. Boston, MA.

Prospective, Retrospective and Non-interventional Studies with FDA- Approved Therapies

Pasireotide

- Multiligand somatostatin receptor ligand.

- Subcutaneous (BID) and intramuscular (monthly) formulations approved to treat CD in adults for whom surgery has not worked well enough or who cannot have surgery.

Colao A, et al. A 12-month phase 3 study of pasireotide in Cushing's disease. *N Engl J Med*. 2012; 366: 914-924.
Lacroix A et al. Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. *Lancet Diabetes Endocrinol.* 2018; 6: 17-26.

Pasireotide: Retrospective (3 year) Study

- Adults with CD treated with pasireotide sc monitored for 3 years.
- 'New pasireotide users' (NU; N=45) and in 'prior pasireotide users' (PU; N=107).
- 81% (123/152) discontinued study treatment (NU: n=91% [41/45], PU: 77% [82/107]).

Efficacy	Baseline	Month 12	Month 24	Month 36
mUFC ≤ ULN	NU: 17% (4/23) PU: 67% (30/45)	NU: 30% (3/10) PU: 76% (31/41)	NU: 72% (4/23) PU: 67% (24/36)	NU: 33% (1/3) PU: 60% (9/15)
Median SBP (mmHg)	NU: 130 (range 97-180) PU: 130 (range 90-234)	-	-	NU: 110 (range 106-150) PU: 128 (range 108-150)
Median body weight (Kg)	NU: 84 (range 49-141) PU: 79 (range 41-152)	-	-	NU: 84 (range 55-77) PU: 71 (range 40-131)
Cushing QoL Score	NU: 52 (range 8-65; n=16) PU: 42 (range 8-75; n=25)	-	-	NU: 67 (n=1) PU: 50 (range 35-92; n=5)

Bertherat J, et al. Long-Term Effect of Subcutaneous Pasireotide on Clinical and Quality of Life Endpoints in Patients with Cushing's Disease: Results from a Non-interventional Study. Presented at: ENDO 2024; June 1-4, 2024. Boston, MA

Levoketoconazole

- A cortisol synthesis inhibitor.
- Indicated for the treatment of endogenous hypercortisolemia in adult patients with CS for whom surgery is not an option or has not been curative.
- Oral medication administered twice a day.
- Approval based on SONICS, a phase 3, open-label, single-arm study and LOGICS, a double-blind, placebo-controlled, randomized withdrawal study.

Fleseriu M, et al. Efficacy and safety of levoketocononazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm study. *Lancet Diabetes Endocrinol.* 2019; 7: 855-865.

SONICS Post-hoc Analysis: mUFC

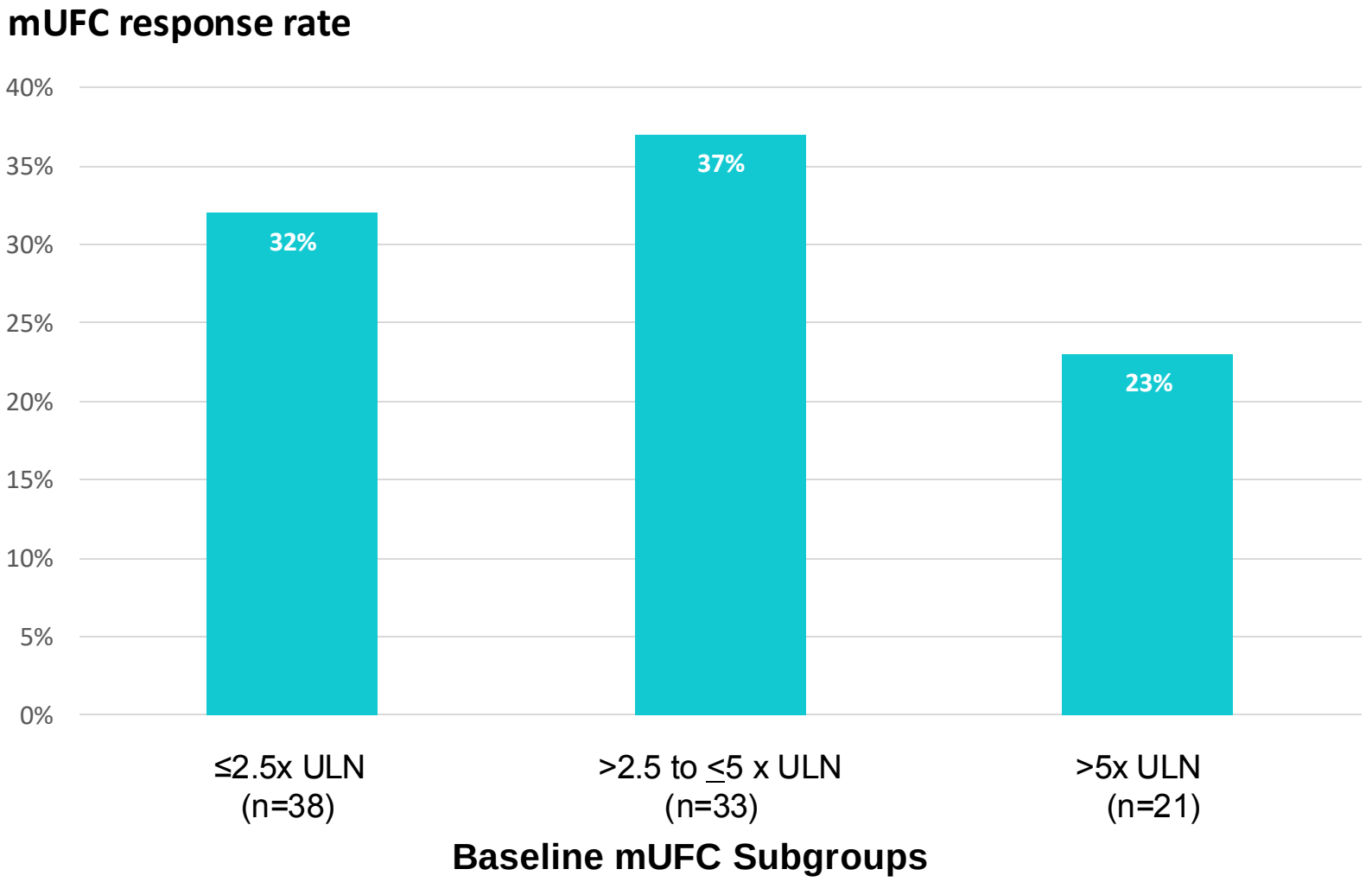
- 94 adults with confirmed CS; levoketoconazole starting dose of 150 mg BID, titrated PRN at 150 mg intervals until a maximum dose of 600 mg BID or adequate response in the investigator's judgment.
- Patients divided into three subgroups based on baseline mUFC.

Subgroup (baseline mUFC)	mUFC response rate	Mean dose after 6 month maintenance phase	Liver-related AEs	AEs leading to discontinuation
1.5x to ≤2.5x ULN	32% (12/38)	566 mg	3%	16%
>2.5x to ≤5x ULN	36% (12/33)	611 mg	7.9%	12%
>5x ULN	24% (5/21)	741 mg	14%	24%

- **mUFC at baseline predicted the likelihood of achieving mUFC normalization and rate of AEs.**

Huang R, et al. Effects of Levoketoconazole on 24-hour Mean UFC (mUFC) in the SONICS Study: Relation to Baseline mUFC in Adults with Cushing's Syndrome: a Post-hoc Analysis. ENDO 2024; June 1-4, 2024. Boston, MA.

SONICS Post-hoc Analysis: mUFC



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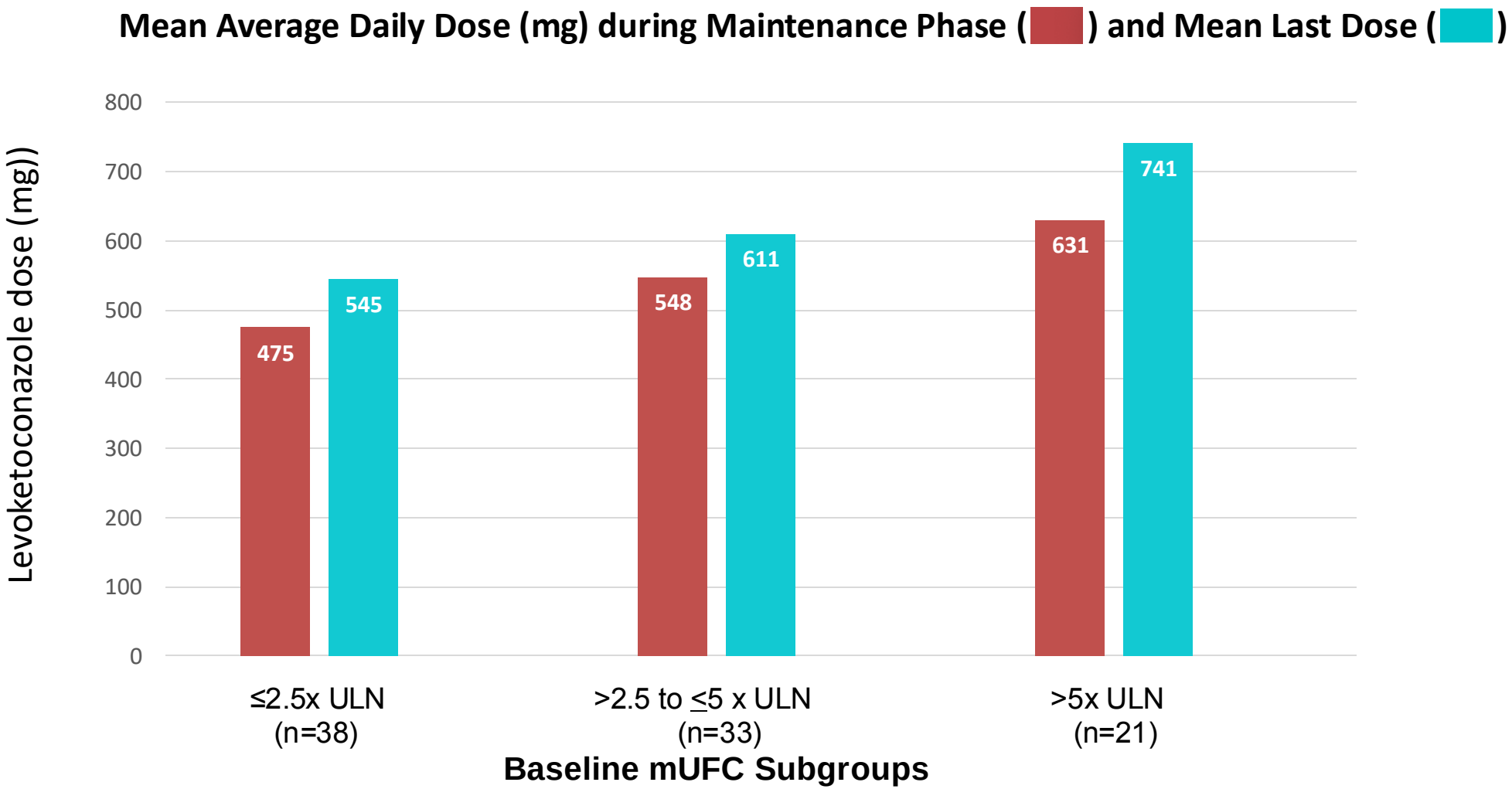
SONICS Post-hoc Analysis: Dose Exposure



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Recurrent CS: Case Studies

- **Case 1**: 44-yr-old male with CS who previously took ketoconazole and stopped after transsphenoidal surgery.
- Several years later, CD recurred (UFC 26x ULN) and patient refused surgery. Underwent radiation therapy and started levoketoconazole – first at 150 mg BID, then 300 mg BID.
- Normal UFC but mild nausea. Reduced dose to 150 mg and UFC remained in normal range.

Chamorro-Pareja N et al. Treatment with Cushing's with levoketoconazole: a case series. Presented at: ENDO 2024; June 1-4, 2024. Boston, MA

Recurrent CS: Case Studies

- **Case 2**: 56-yr-old male with CD underwent two transsphenoidal surgeries and radiation.
- Third recurrence of CD was initially treated with pasireotide but discontinued due to abnormal liver tests. Switched to ketoconazole (400 mg /day) but LNSC remained elevated.
- Switched to levoketoconazole (150 mg BID). LNSC normalized and CD symptoms (brain fog, mood disturbances) improved.

Chamorro-Pareja N et al. Treatment with Cushing's with levoketoconazole: a case series. Presented at: ENDO 2024; June 1-4, 2024. Boston, MA

Recurrent CS: Case Studies

- **Case 3**: 54-yr-old female with presumed cyclic CD (insomnia, fatigue, and mood disturbances).
- Transsphenoidal surgery was performed with negative pathology. The patient was intolerant to and/or uncontrolled with 4 medications.
- Started levoketoconazole (150 mg BID) and achieved normal LSNCS and UFC after one month. Drug later discontinued due to the development of a rash (also observed with ketoconazole).

Chamorro-Pareja N et al. Treatment with Cushing's with levoketoconazole: a case series. Presented at: ENDO 2024; June 1-4, 2024. Boston, MA

Osilodrostat

- A cortisol synthesis inhibitor, mostly 11 beta-hydroxylase inhibitor.
- Approved for the treatment of adults with CD who cannot have pituitary surgery, or who have had pituitary surgery, but the surgery did not cure their hypercortisolism.
- Oral medication administered twice a day.
- Approval based on two phase 3 studies - LINC 3, LINC 4.
- Other LINC studies in progress and presented at ENDO.

Fleseriu M et al, . Long-term outcomes of osilodrostat in Cushing's disease: LINC 3 study extension. *Eur J Endocrinol.* 2022;187:531-541
Gadelha M et al. Randomized trial of olisodrostat for the treatment of Cushing disease. *J Clin Endocrinol Metab*. 2022; 107:e2882-e2895.

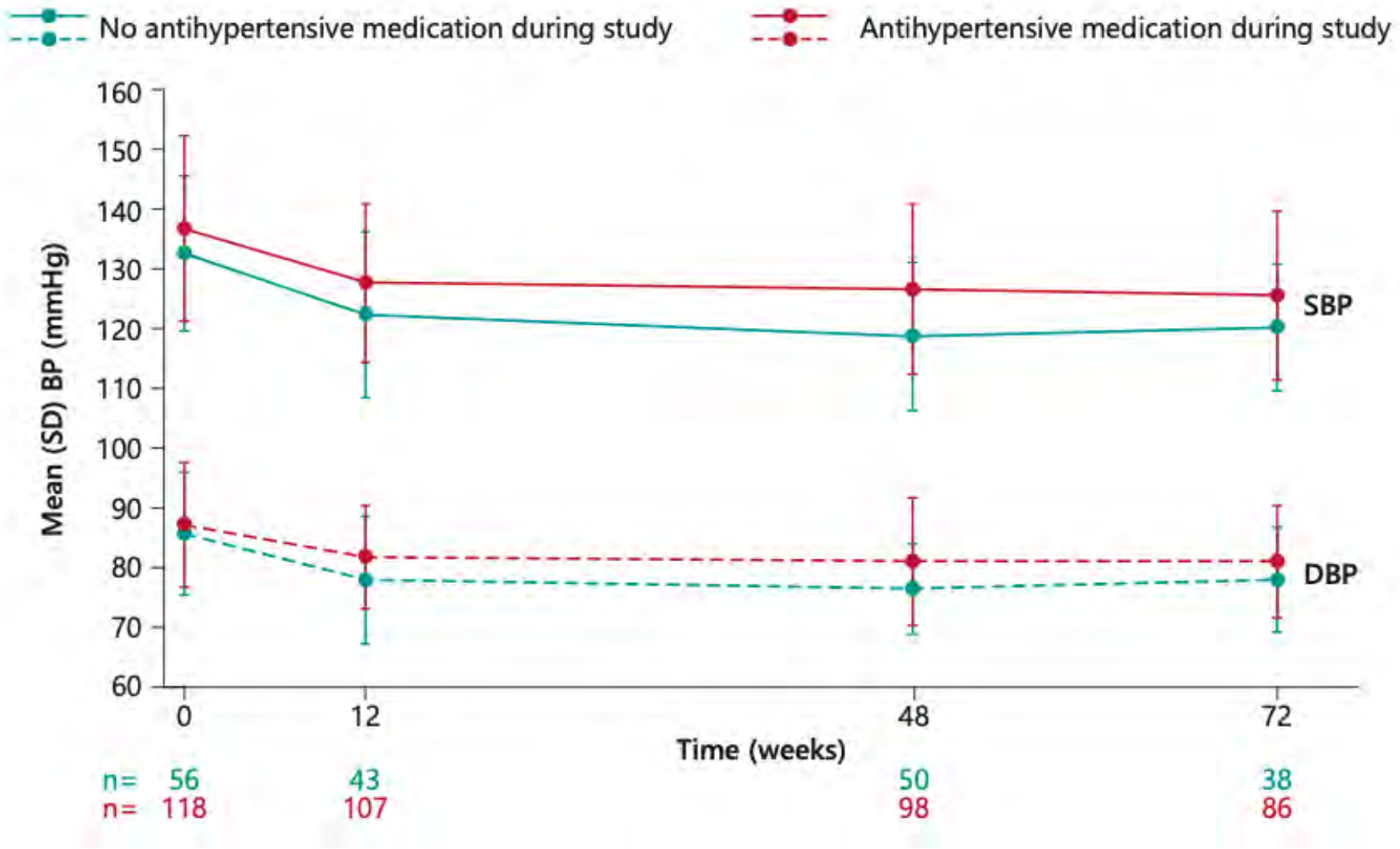
LINC 3 and 4: Hypertension and Diabetes Control

- LINC 3: a 48-week core phase, including an 8-week randomized withdrawal phase for eligible patients.
- LINC 4 : a 12-week, double-blind, randomized, placebo-controlled period followed by a 36-week open-label osilodrostat period.
- Data from LINC 3 and LINC 4 pooled in a secondary exploratory analysis (all descriptive) (N=210).

- **Blood Pressure Control**
  - Patients taking antihypertension agents at start of either study: 54.3%; at week 72: 47.3%.
- **Diabetes Control**
  - Patients taking antidiabetic agents at start of either study: 21.9%; at week 72: 17.1%.

Fleseriu M, et al. Continued Improvements in Hypertension and Diabetes During Long-Term Osilodrostat Therapy in Patients with Cushing's Disease: A Pooled Analysis from the Phase III LINC 3 and LINC 4 Studies. Presented at: ENDO 2024; June 1-4, 2024. Boston, MA

LINC 3 and 4: Hypertension Control



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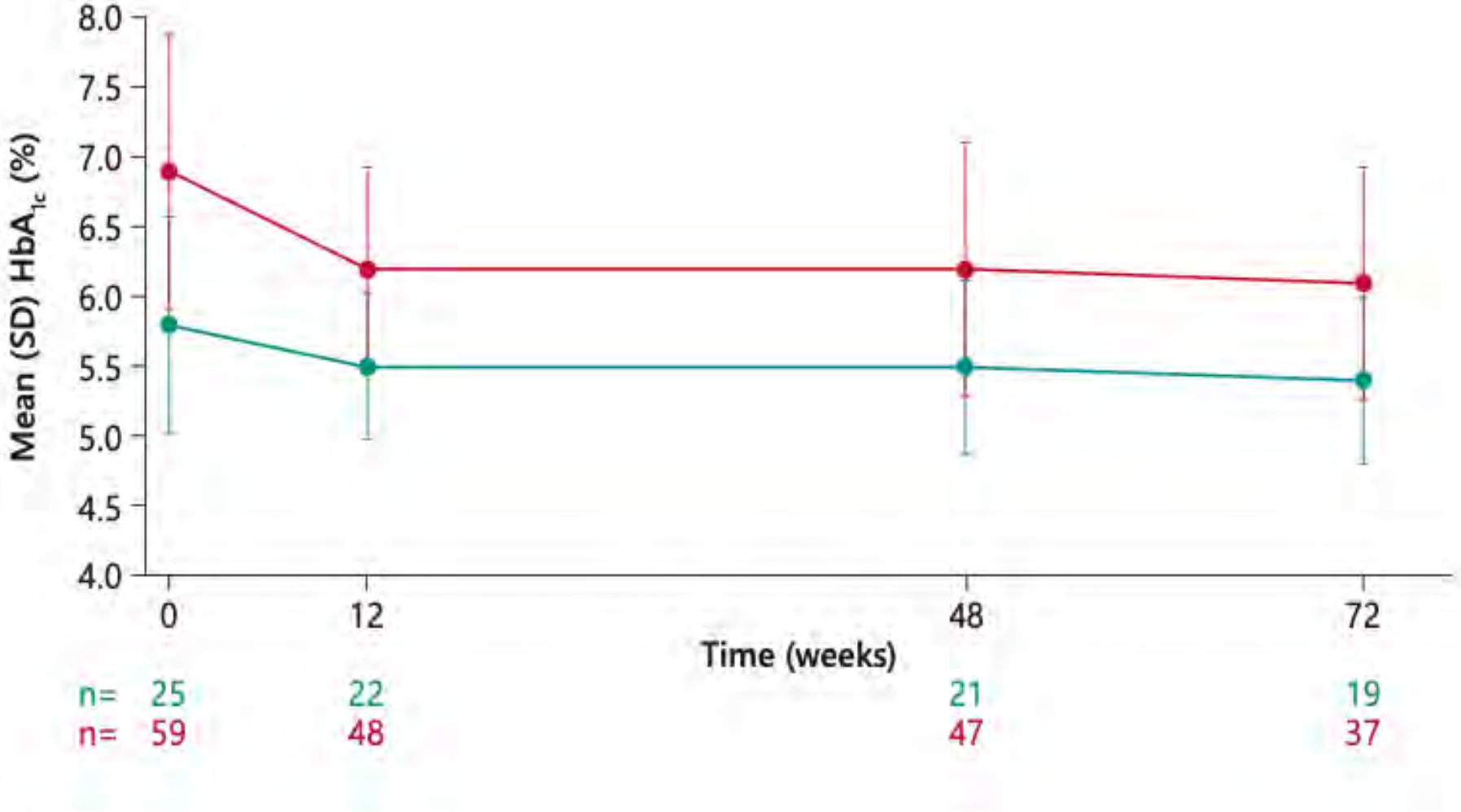
LINC 3 and 4: Diabetes Control



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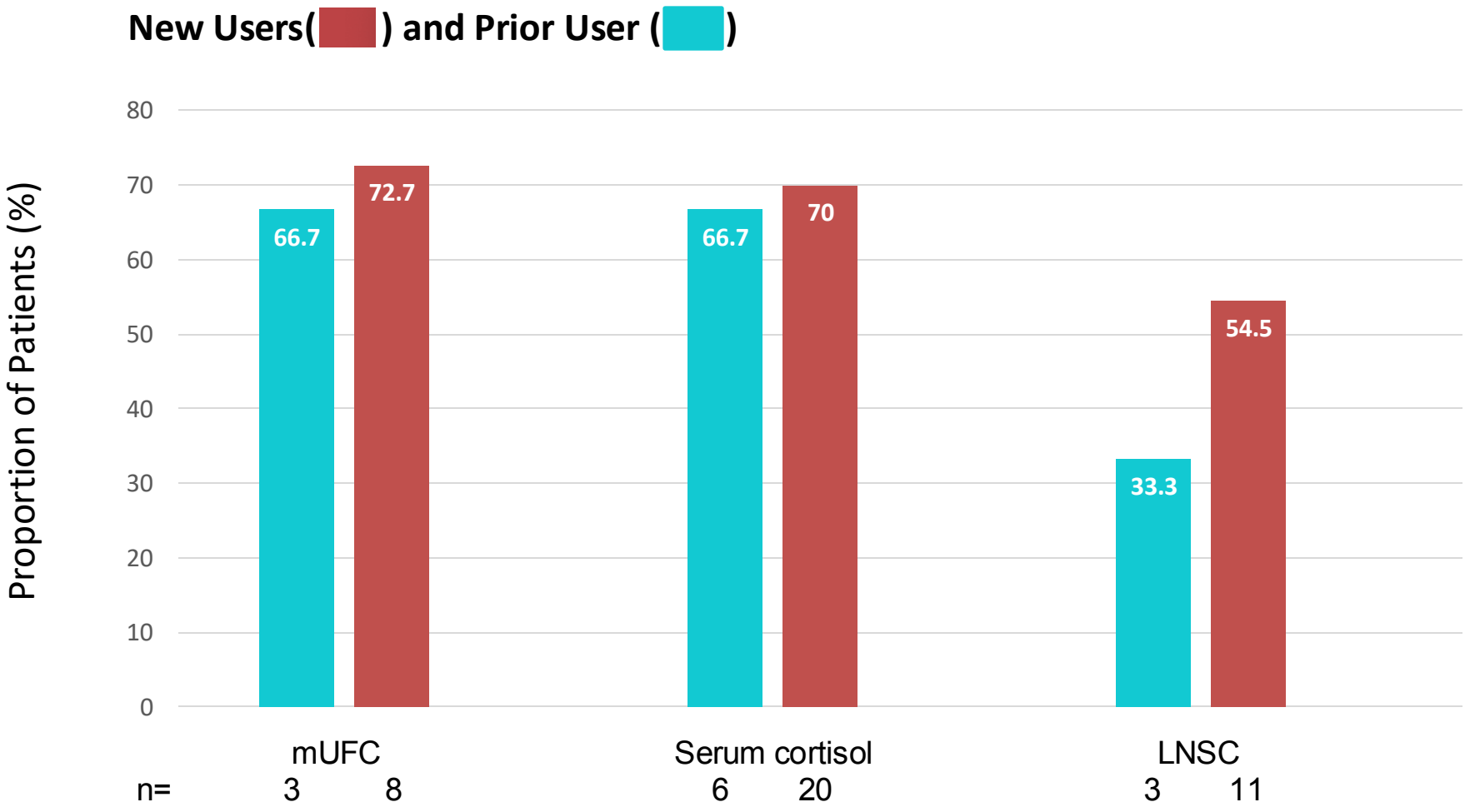
LINC 6: 1-year Interim Report

- Adults with CD (n=78) and CS (n=16) included in 1-year interim analysis.
- Mean age 53.2 years (12.7); 70.2% female.
- Median osilodrostat exposure was **5.5 months** (minimum 0.1 months, maximum 13.9 months).
- **Median osilodrostat dose 5.0 mg/day (minimum 1.0 mg/day, maximum 60 mg/day).**
- 29 patients reported 109 adverse events (AEs). Most common were asthenia and vomiting (5.5%).
- 12 patients reported 44 AEs thought to be treatment-related. Most common were vomiting and dizziness (9.1%).
- 4 patients discontinued treatment due to AEs.

Interim 3-month efficacy data	
Normalized mean urinary free cortisol (mUFC)	**71.4% (n=10/14)**
Normalized serum cortisol	69.2% (n=18/25)
Late-night salivary cortisol (LNSC)	50.0% (n=7/14)

Bancos I, et al. A Non-interventional, Multinational, Phase IV Study to Evaluate the Long-Term Safety and Efficacy of Osilodrostat in Patients with Endogenous Cushing's Syndrome (LINC 6): 1-Year Real-World Interim Analysis. Presented at: ENDO 2024; June 1-4, 2024. Boston, MA.

LINC 6: Efficacy



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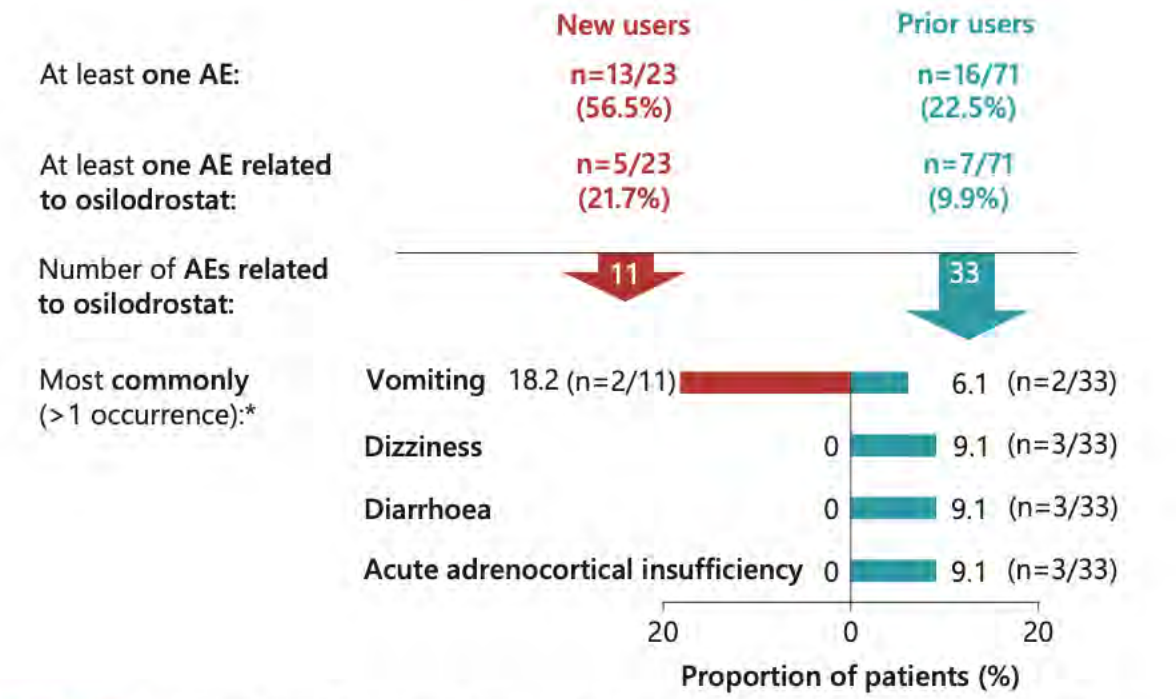
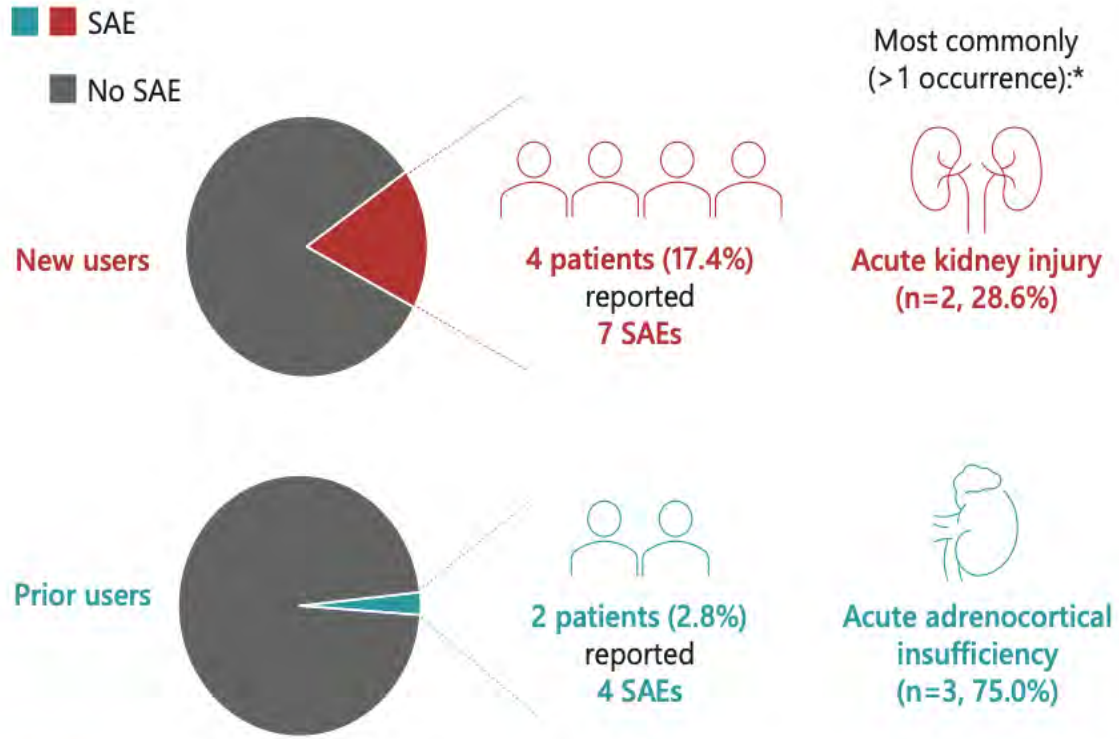
LINC 6: Most AEs Were Mild and in New Users



*New users also reported adrenal insufficiency, constipation, dyspepsia, gastrointestinal disorder, nausea, fatigue, decreased appetite, muscular weakness and dizziness (all n=1, 9.1%); prior users reported adrenal insufficiency, nausea, asthenia, irregular heart rate, weight increase, decreased appetite, hyperkalaemia, joint swelling, muscular weakness, musculoskeletal stiffness, myalgia, balance disorder, headache, somnolence, micturition urgency, urinary incontinence, alopecia, skin hyperpigmentation, inadequate blood pressure control and hypertension (all n=1, 3.0%)



*New users also reported adrenal insufficiency, haematoma infection, pneumonia, dehydration, loss of consciousness (all n=1, 14.3%); prior users also reported increase of pituitary tumour size (n=1, 25.0%)

Bancos I, et al. A Non-interventional, Multinational, Phase IV Study to Evaluate the Long-Term Safety and Efficacy of Osilodrostat in Patients with Endogenous Cushing's Syndrome (LINC 6): 1-Year Real-World Interim Analysis. Presented at: ENDO 2024; June 1-4, 2024. Boston, MA

LINC 7: Real-World Setting

- LINC 7 was a retrospective, non-interventional study evaluating the safety and effectiveness of osilodrostat in patients with **non-pituitary CS, in a real-world setting.**
- 103 patients enrolled:
  - Ectopic adrenocorticotropic hormone secretion (51.5%)
  - Macronodular adrenal hyperplasia (13.6%)
  - Adrenocortical carcinoma (ACC; 18.4%)
  - Adrenal adenoma (16.5%)
- Median (min-max) osilodrostat exposure and dose at baseline was 164 days (1-1178) and 5.0 mg/day (1-60).

Tabarin A, et al. Safety And Effectiveness Of Osilodrostat In Patients With Non-Pituitary Cushing's Syndrome: Results From The Retrospective Observational LINC 7 Study Presented at: ENDO 2024; June 1-4, 2024. Boston, MA.

LINC 7: Results

- mUFC ≤ULN:
  - 44% at week 12; 50% at week 24.
- Treatment-emergent AEs:
  - Adrenal insufficiency (28.2%) and hypokalemia (17.5%).
  - Hypocortisolism-related AEs (30.1%).
  - 28% died during the study.
  - 34% discontinued because of investigator-reported AEs, 10% because of neoplasm progression.
  - 14% discontinued because of planned surgery for CS.
- **Conclusion**
  - Osilodrostat provides sustained cortisol control in non-pituitary CS patients with a safety profile consistent with that found in other clinical trials.

Tabarin A, et al. Safety And Effectiveness Of Osilodrostat In Patients With Non-Pituitary Cushing's Syndrome: Results From The Retrospective Observational LINC 7 Study Presented at: ENDO 2024; June 1-4, 2024. Boston, MA.

Retrospective Studies with off - label Therapies

Ketoconazole

- A cortisol synthesis inhibitor.
- Approved in Europe to treat CS.

Ketoconazole: Efficacy

- Ketoconazole use could be limited by hepatotoxicity.
- Retrospective review of 65 records of inpatients receiving ketoconazole 2004-2023 to assess efficacy and hepatotoxicity.
- 35 patients evaluated for efficacy (treatment success: AM serum cortisol ≤12 ug/dL).

	Controlled patients
Achieved goal of AM serum cortisol ≤12 mcg/dL	17/35 pts, median 3 days
Median days between doses	2 (vs. 4 uncontrolled, p=0.025)
On stable KTZ dose for ≥ 3 days after increase	19/35 pts
Mean AM serum cortisol decrease from Day 0	
Day 1	-19%, p=0.01
Day 3	-38%, p=0.0001
Day 4	-25%, p=0.04
Mean AM serum cortisol decrease from Day 1	
Day 2	-13%, p=0.03
Day 3	-14%, p=0.03

Elenius H, et al. Efficacy and hepatotoxicity of ketoconazole in Cushing's syndrome. Presented at: ENDO 2024; June 1-4, 2024. Boston, MA.

Ketoconazole: Safety

- 37 patients were evaluated for safety.
- Data supports raising ketoconazole doses every 72 hrs for rapid control.
- **An LFT rise > 30% seen in most patients. Should not prompt treatment cessation if < 3 ULN.**

	Controlled patients
Base LFT <3ULN	34/37 pts
LFTs rose ≥30%	27/34 pts
≥1 LFT rise to ≥3ULN	10/27 pts
Mean base AST	75% of ULN
Mean cum. KTZ doses	10080 mg
Mean daily KTZ doses	927 mg
Day AST increased by ≥30%	4 days
Day ALP increased by ≥30%	6 days
Continued with same dose	15/27 pts
No change in LFTs	8/15
Rise in LFTs	5/15
Reduction in LFTs	2/15
Remained > ULN	13/37
Remained < ULN	8/37 pts

Elenius H, et al. Efficacy and hepatotoxicity of ketoconazole in Cushing's syndrome. Presented at: ENDO 2024; June 1-4, 2024. Boston, MA

Etomidate

- A cortisol synthesis inhibitor.

- **Case Study:** 28-year-old women with metastatic adrenocortical carcinoma with severe hypercortisolism
  - Poor surgical candidate due to tumor size and position.
  - Required intubation due to respiratory complications, thereby limiting CS treatment options.
- After 8 days, cortisol decreased from 351.3 ug/dl levels to goal of 25.0 ug/dl on low dose etomidate infusions.

Jamil A, et al. Continuous low-dose etomidate infusion for the management of severe hypercortisolism in metastatic adrenocortical carcinoma. . Presented at: ENDO 2024; June 1-4, 2024. Boston, MA

Prospective Studies with Investigational Drugs

Relacorilant

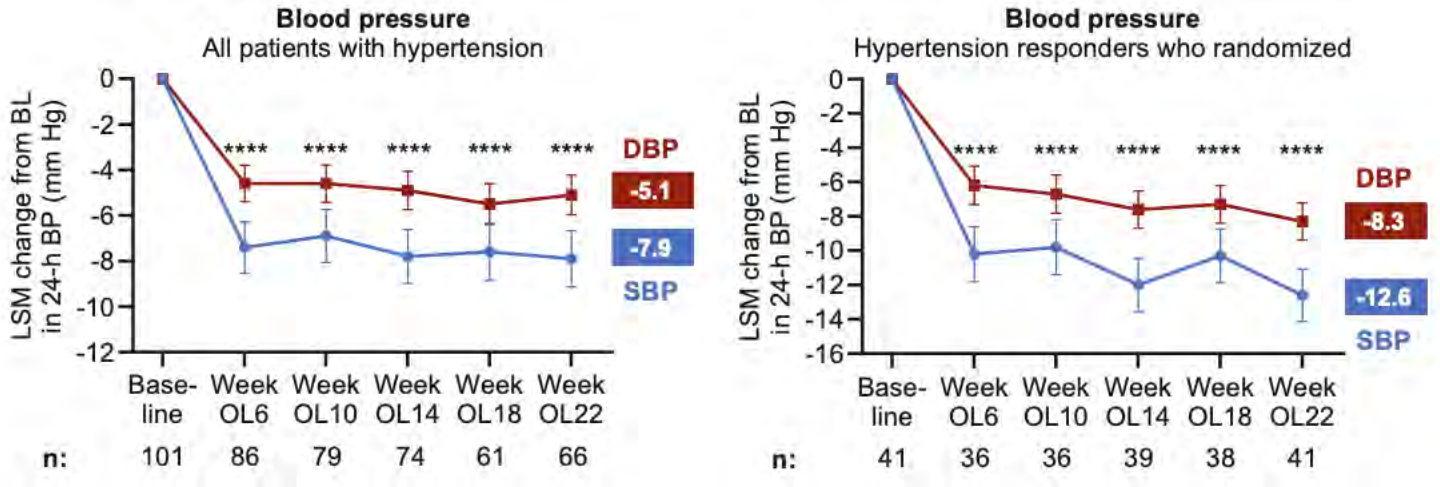
- A selective glucocorticoid receptor modulator.
- Highly selective with no activity at progesterone, mineralocorticoid, or androgen receptors.

- GRACE: a phase 3, double-blind, randomized-withdrawal study.
  - Adults with CS and hypertension, hyperglycemia, or both (N=152).
  - Primary endpoints: loss of hypertension control; safety.
  - Secondary endpoints: hyperglycemia control and other cortisol-related comorbidities.

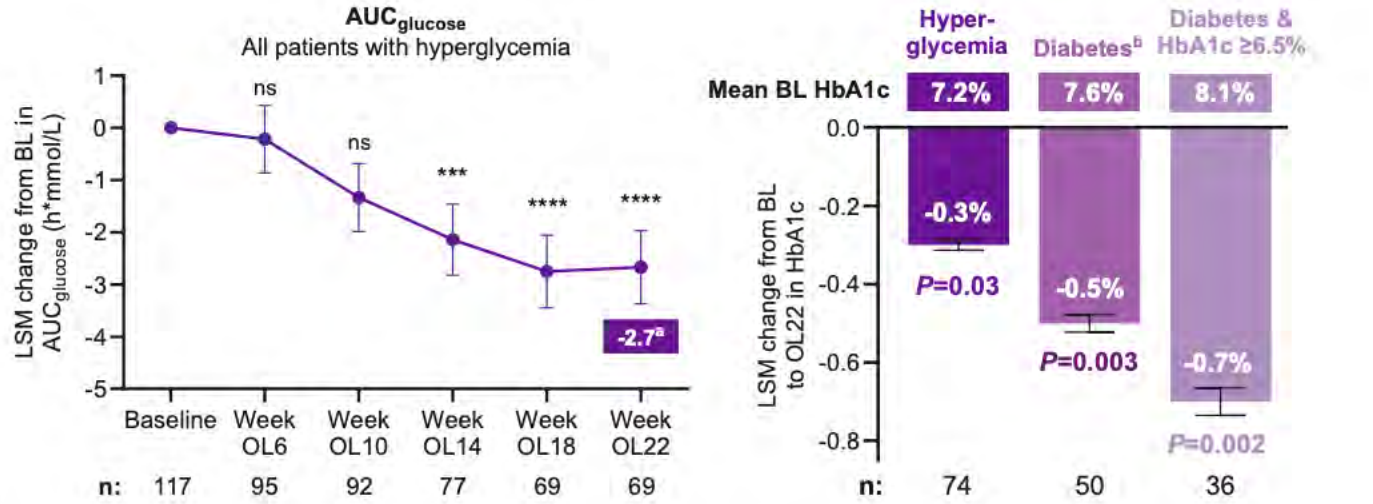
Pivonello R, et al. Results from GRACE, a phase 3 double-blind randomized-withdrawal study of the selective glucocorticoid receptor modulator relacorilant for the treatment of endogenous hypercortisolism (Cushing syndrome). Presented at: ENDO 2024; June 1-4, 2024. Boston, MA

Relacorilant

Hypertension



Hyperglycemia



Pivonello R, et al. Results from GRACE, a phase 3 double-blind randomized-withdrawal study of the selective glucocorticoid receptor modulator relacorilant for the treatment of endogenous hypercortisolism (Cushing syndrome). Presented at: ENDO 2024; June 1-4, 2024. Boston, MA

Relacorilant

- In the randomized-withdrawal phase, significantly more patients who switched to placebo lost hypertension control compared to those who continued to receive relacorilant (*P*=0.02).

- Patients receiving relacorilant were 5.9x more likely to maintain the hypertension response achieved during the open-label phase compared to patients receiving placebo.

- No clinically meaningful differences in adverse events were observed between the relacorilant and placebo arms.

Pivonello R, et al. Results from GRACE, a phase 3 double-blind randomized-withdrawal study of the selective glucocorticoid receptor modulator relacorilant for the treatment of endogenous hypercortisolism (Cushing syndrome). Presented at: ENDO 2024; June 1-4, 2024. Boston, MA

Atumelnant

- Once-daily oral, nonpeptide, first-in-class competitive and selective melanocortin type 2 receptor (MC2R) antagonist that blocks ACTH-mediated G-protein activation and subsequent signaling.

- Phase 1b/2a open-label study presented at ENDO:

  - Five patients with ACTH-dependent CS (4 with CD, 1 with ectopic ACTH) received atumelnant 80 mg every morning, 10 days followed by a 4-day washout.
  - By day 2, all participants experienced signs of adrenal insufficiency (early morning cortisol <5 ug/dL) and started hydrocortisone (later discontinued if early morning cortisol >7 ug/dL).
  - Many features of CS improved : poor concentration, insomnia (n=3 each); brain fog, anxiety, irritability (n=2 each); fatigue, poor memory, low libido, depression, edema, and bloating (n=1 each).
  - Atumelnant was generally well-tolerated.

Elenius H, et al. Atumelnant (crn044894) induces rapid and sustained reductions in serum and urine cortisol. Presented at: ENDO 2024; June 1-4, 2024. Boston, MA.

Clofutriben

- HSD-1 inhibitor, clofutriben, utilizes a novel mechanism of action to target a source of cortisol.
- **Oral, once-a-day administration, complex monitoring might not be necessary.**
- Clofutriben has demonstrated the ability to lower intracellular cortisol levels in vital organs, with a favorable safety and tolerability profile in five clinical trials (outside the CS arena) which also showed improvement in glucose, HbA1c, cholesterol, and triglycerides.
- **Ongoing studies in CD and adrenal CS.**

Katz D, HSD-1 inhibition reducing toxicities of glucocorticoids, Presented at: ENDO 2024; June 1-4, 2024. Boston, MA.

Clinical Pearls

- International QoL survey demonstrate the ongoing burden of hypercortisolism, often starting 7+ years before an official diagnosis is made and continuing indefinitely.
- Pasireotide showed increasing full response rates over time in new users, stable rates in prior users, and improvements in clinical signs of CS at 36 months, suggesting it may be an effective long-term therapy for selected patients.
- Lower mUFC at baseline predicted the likelihood of achieving mUFC normalization following 6 months of levoketoconazole maintenance therapy. Lower mUFC at baseline was also associated with lower maintenance dose requirements and lower rates of potentially clinically important liver-related AEs.

Clinical Pearls

- Osilodrostat is generally well tolerated and provides early and sustained cortisol control in patients with both CD and other causes of CS, with improvements maintained or enhanced during long-term therapy, aligning with previous clinical trial data.
- Cortisol normalization is associated with improvements in hypercortisolism-associated comorbidities in patients with CS.
- Doses in real world setting vary by etiology and severity of the disease; in LINC 6 median osilodrostat dose was 5.0 mg/day (minimum 1.0 mg/day, maximum 60 mg/day).
- Hypocortisolism related events are the main AEs, especially at the start of the treatment.

Clinical Pearls

- A retrospective review suggests raising ketoconazole doses q72 hours for rapid control, with liver toxicity risk correlating with baseline AST levels. While most patients experience an LFT rise of ≥30%, treatment should not be stopped unless LFTs exceed 3ULN.
- Etomidate is effective in controlling cortisol levels in patients requiring intubation due to respiratory complications (case study).
- Relacorilant, a selective glucocorticoid receptor modulator, appears to be safe and effective in phase 3 studies.
- Atumelnant, an oral MC2R antagonist shows promise in early clinical studies.

Very exciting time for the community of patients, caregiver and physicians dedicated to CS

Thank you!