



Leading-Edge Strategies
for Diagnosis and
Medical Management of
Cushing Syndrome/
Hypercortisolism

Cushing's at
the Core



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Disclosures



Please see the **Activity CME Information** for all Planner, Faculty, and Reviewer Disclosures:

https://cornerstonemeded.com/wp-content/uploads/2026/02/Cushings-GR-CME-handout-website_2.26.26.pdf



Learning Objectives



- Review the guideline- and evidence-based screening and diagnostic strategies for Cushing Syndrome.
- Evaluate the need for referral to a specialist for Cushing Syndrome treatment.
- Summarize current treatment options for medical management of Cushing Syndrome in patients who are not surgical candidates, are awaiting a surgical consult, or prefer medical therapy over surgery.
- Collaborate as a team to design individualized, evidence-driven screening and medical management plans for patients with Cushing Syndrome, focusing on the role of the interprofessional and interdisciplinary team.
- Apply the principles of shared decision-making to real-world patient cases, focusing on screening, initial treatment and monitoring/follow-up of patients with Cushing Syndrome.

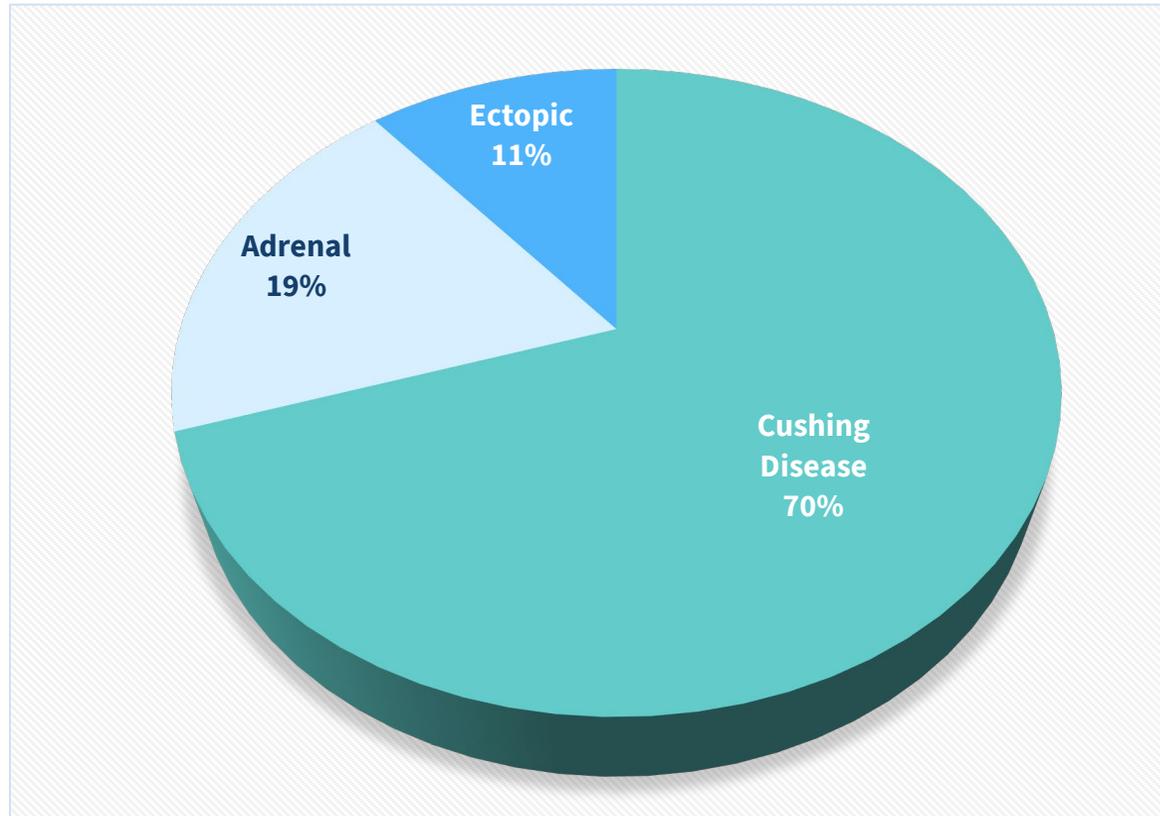


Cortisol Clues: Review of Screening for and Diagnosing Mild Cushing Syndrome



Cortisol Clues: Who to Screen?

The Etiologies of Endogenous Cushing Syndrome



Incidence: 10–15 new cases per million per year
Prevalence: 40–70 cases per million

It is estimated that up to 1 million people in the US may have MACS

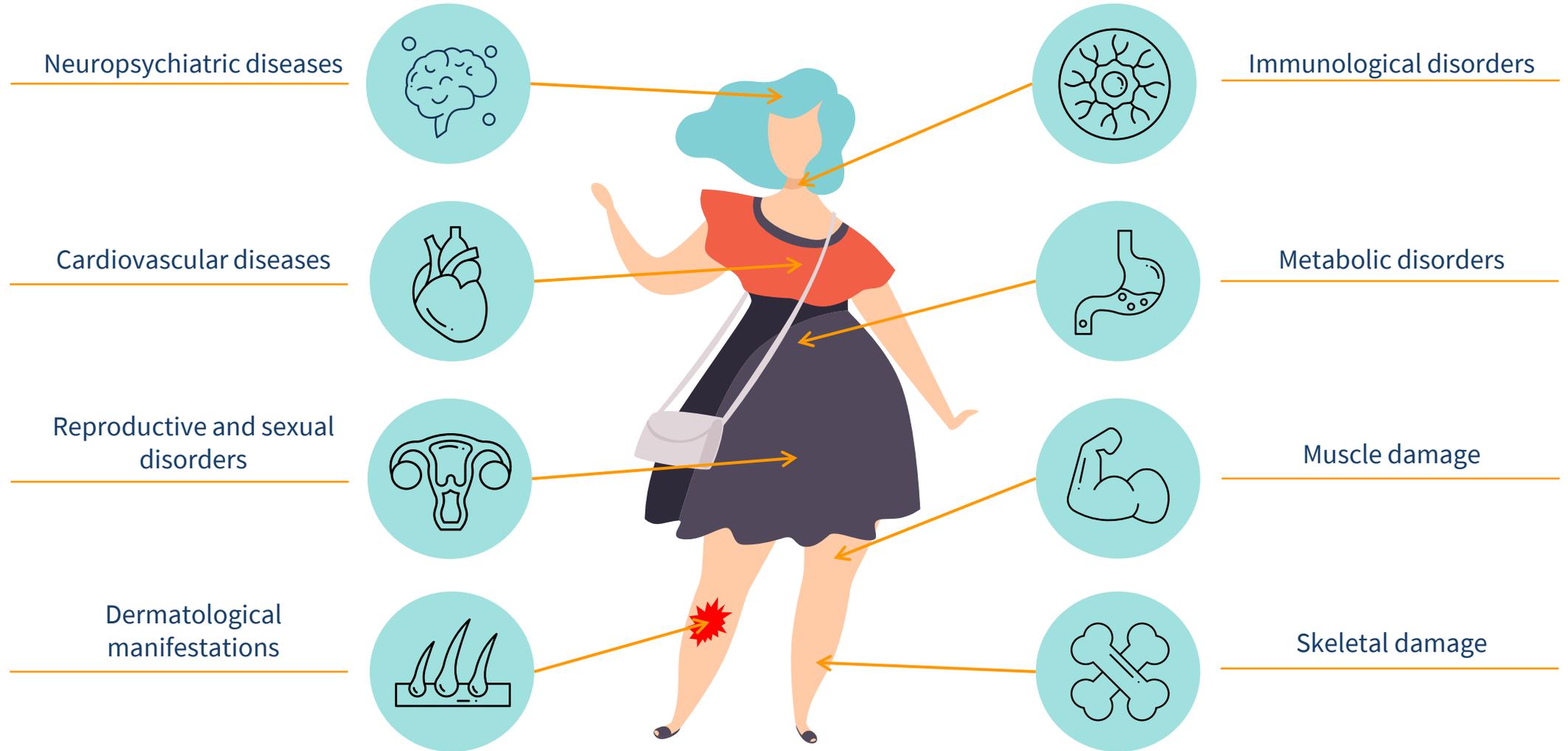
Exogenous Cushing Syndrome



- 33-year-old Arab man was referred to the diabetes clinic
 - Extensive ophthalmologic complaints. He had used glucocorticoid eyedrops such as dexamethasone, prednisolone, and hydrocortisone preparations for 15 years.
 - The patient reported feeling unwell whenever he neglected to use the eyedrops for 1 or 2 days.
 - Cortisol <1 ug/dL, ACTH 9 pg/mL (9-54), T score -3.3 at spine
- Interactions between budesonide, fluticasone and systemic triamcinolone with:
 - Antifungal agents (Azole derivatives)
 - Ritonavir

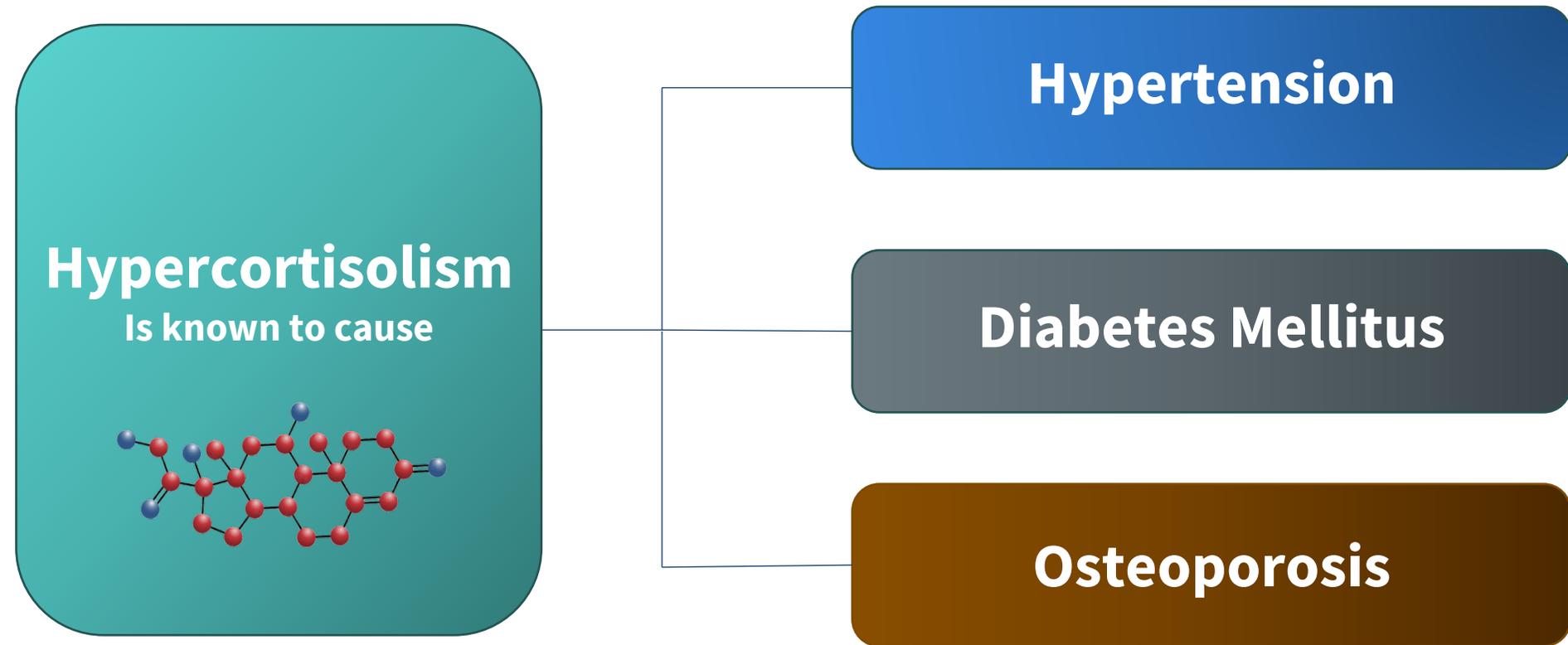


Hypercortisolism and Comorbidities





Excess Cortisol and the Link to T2D and HTN

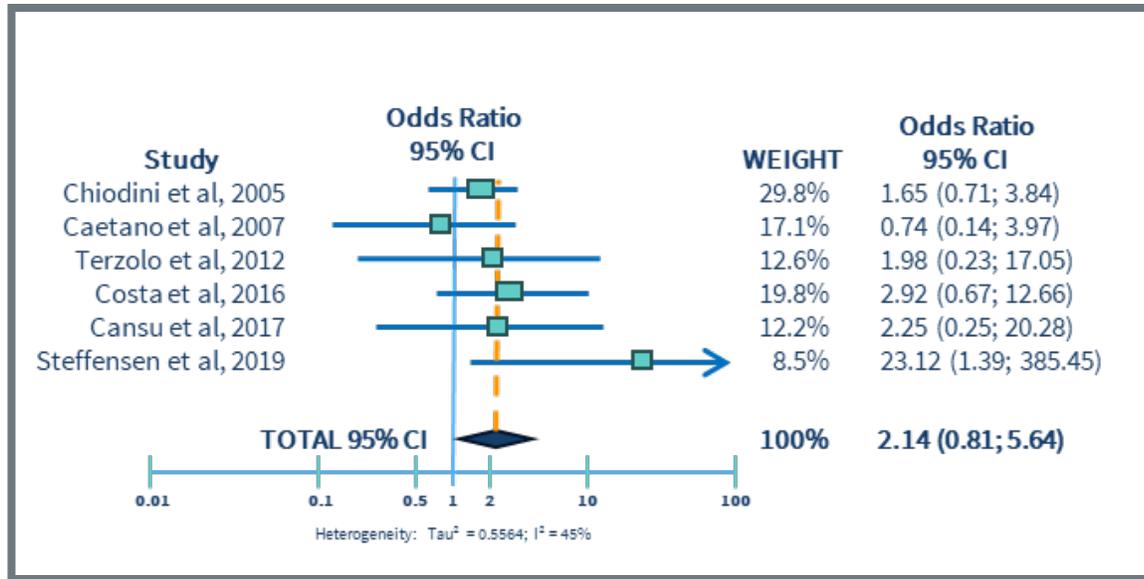


Previously thought prevalence of “hidden” hypercortisolism” was 0.2%-2% (up to 10% of the general population)

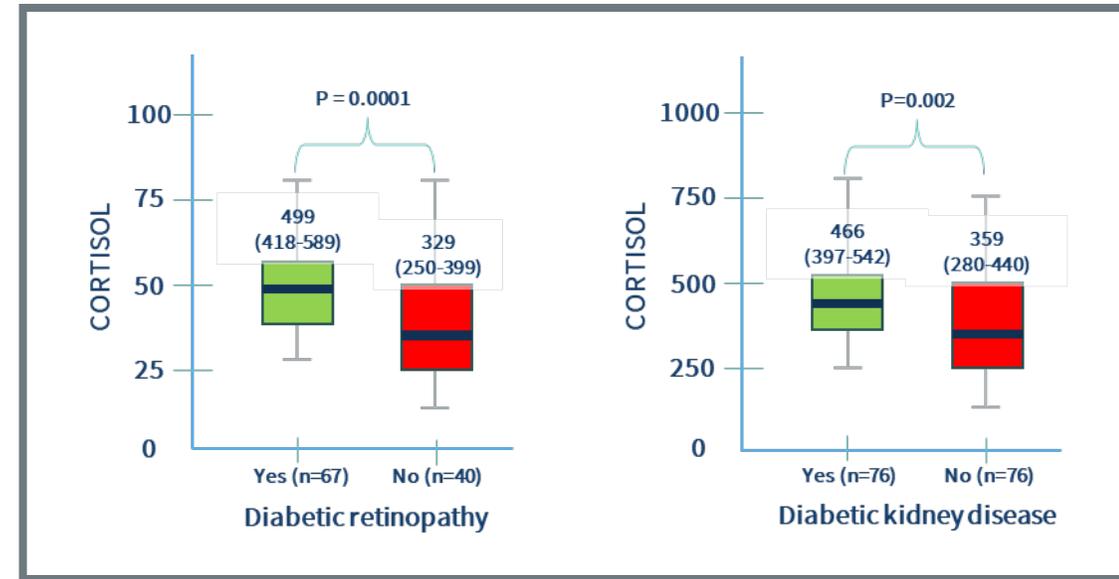
What we Know about Hypercortisolism and Comorbidities



Association of cortisol excess and high blood pressure well-known



Elevated cortisol levels shows to be present especially with additional comorbidities and complications

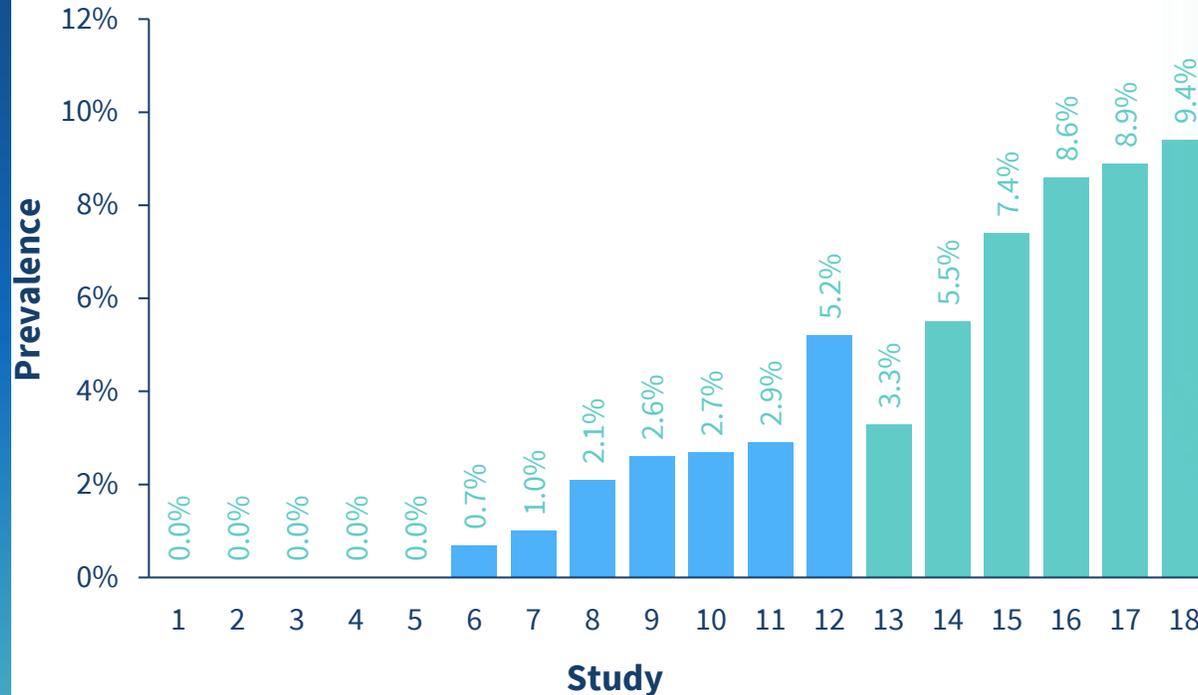


In hypertensive patients with Cushing Syndrome, conventional antihypertensive therapy is not effective until normal cortisol levels are restored, indicating a gap in care and significant need for new therapies

Hypercortisolism in Patients with T2D



Prevalence of hypercortisolism in patients with T2D¹⁻¹⁰



It may be worth screening patients with poorly controlled metabolic disorders for underlying hypercortisolism

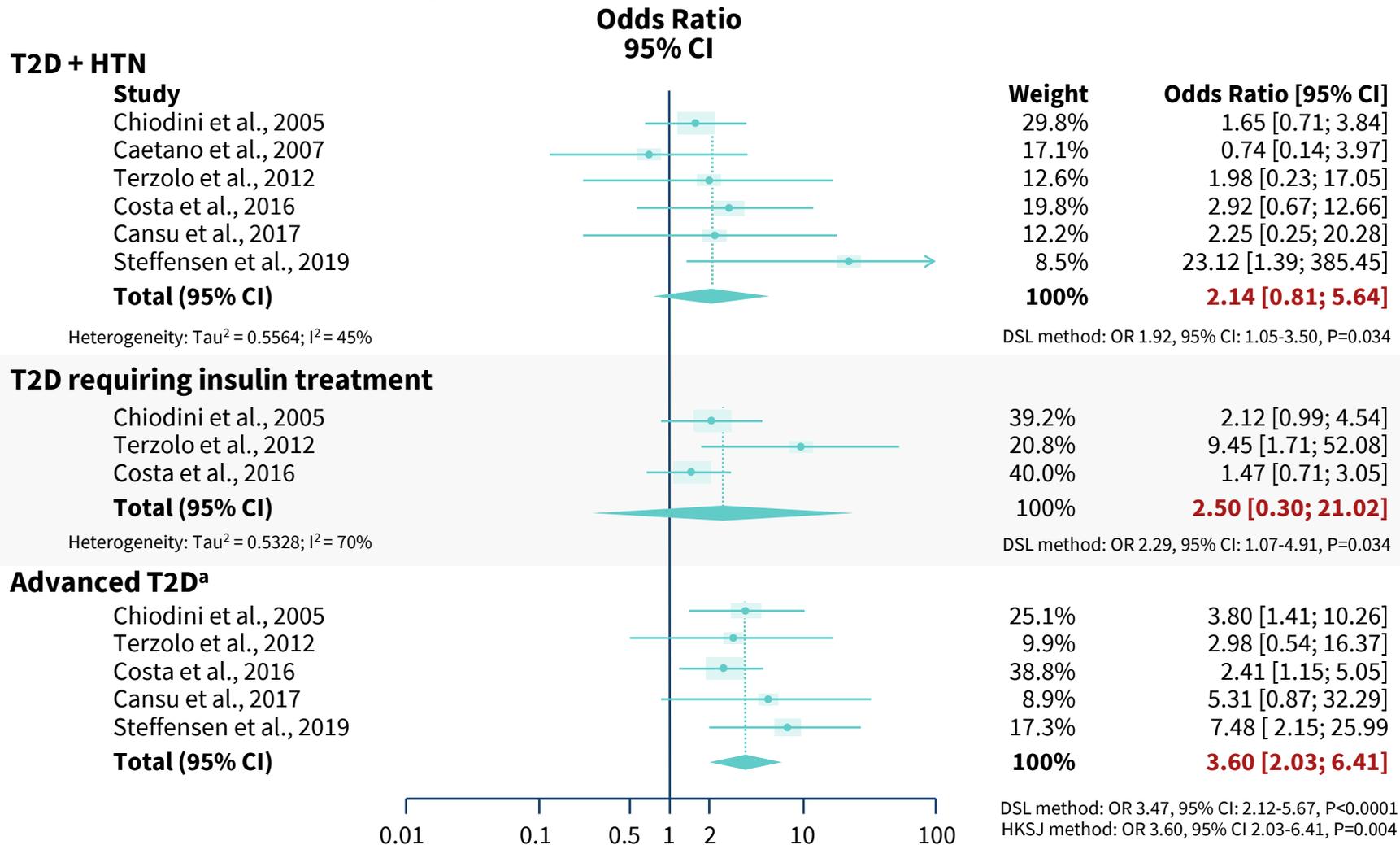
No.	Study	N	Population	Prevalence
1	Liu (2005) ^{1,2}	141	T2D (outpatients)	0%
2	Newsome (2008) ^{1,2}	171	T2D (outpatients)	0%
3	Mullan (2010) ^{1,2}	201	T2D (outpatients)	0%
4	Gagliardi (2010) ^{1,2}	100	T2D (outpatients)	0%
5	Budyal (2015) ^{1,2}	993	T2D (outpatients)	0%
6	Terzolo (2012) ^{1,2}	813	T2D (outpatients)	0.7%
7	Reimondo (2007) ^{1,2}	100	T2D (newly diagnosed)	1%
8	Contreras (2000) ^{1,3}	48	T2D (outpatients)	2.1%
9	Taniguchi (2008) ⁴	77	T2D (inpatients)	2.6%
10	Mert (2012) ¹	148	Obese T2D	2.7%
11	Caetano (2007) ^{1,2}	103	T2D (outpatients)	2.9%
12	Steffensen (2019) ^{1,5}	384	T2D (newly diagnosed)	5.2%

No.	Study	N	Population	Prevalence
13	Leibowitz (1996) ⁶	90	Obese with uncontrolled T2D (inpatients)	3.3%
14	Catargi (2003) ⁷	200	Overweight or obese T2D (poor metabolic control ^a ; inpatients)	5.5%
15	León-Justel (2016) ⁸	353	Obese or uncontrolled T2D/HTN (outpatients)	7.4%
16	Costa (2016) ⁹	393	T2D + high CV risk ^b (outpatients)	8.6%
17	Murakami (2010) ^{1,2}	90	T2D (inpatients)	8.9%
18	Chiodini (2005) ^{2,10}	289	T2D (poor metabolic control ; inpatients)	9.4%

^aHbA1C >8%. ^bIncluded any microvascular or macrovascular complication, with ≥2 other modifiable cardiovascular risk factors.

Giovanelli L, et al. *J Endocrinol Invest.* 2021; Scaroni C, et al. *Endocr Rev.* 2017; Contreras LN, et al. *Medicina (B Aires).* 2000; Taniguchi T, et al. *Endocr J.* 2008; Steffensen C, et al. *Horm Metab Res.* 2019; Leibowitz G, et al. *Clin Endocrinol (Oxf).* 1996; Catargi B, et al. *J Clin Endocrinol Metab.* 2003; León-Justel A, et al. *J Clin Endocrinol Metab.* 2016; Costa DS, et al. *J Diabetes Complications.* 2016; Chiodini I, et al. *Eur J Endocrinol.* 2005.

Patients with Advanced T2D have a High Prevalence of Hypercortisolism

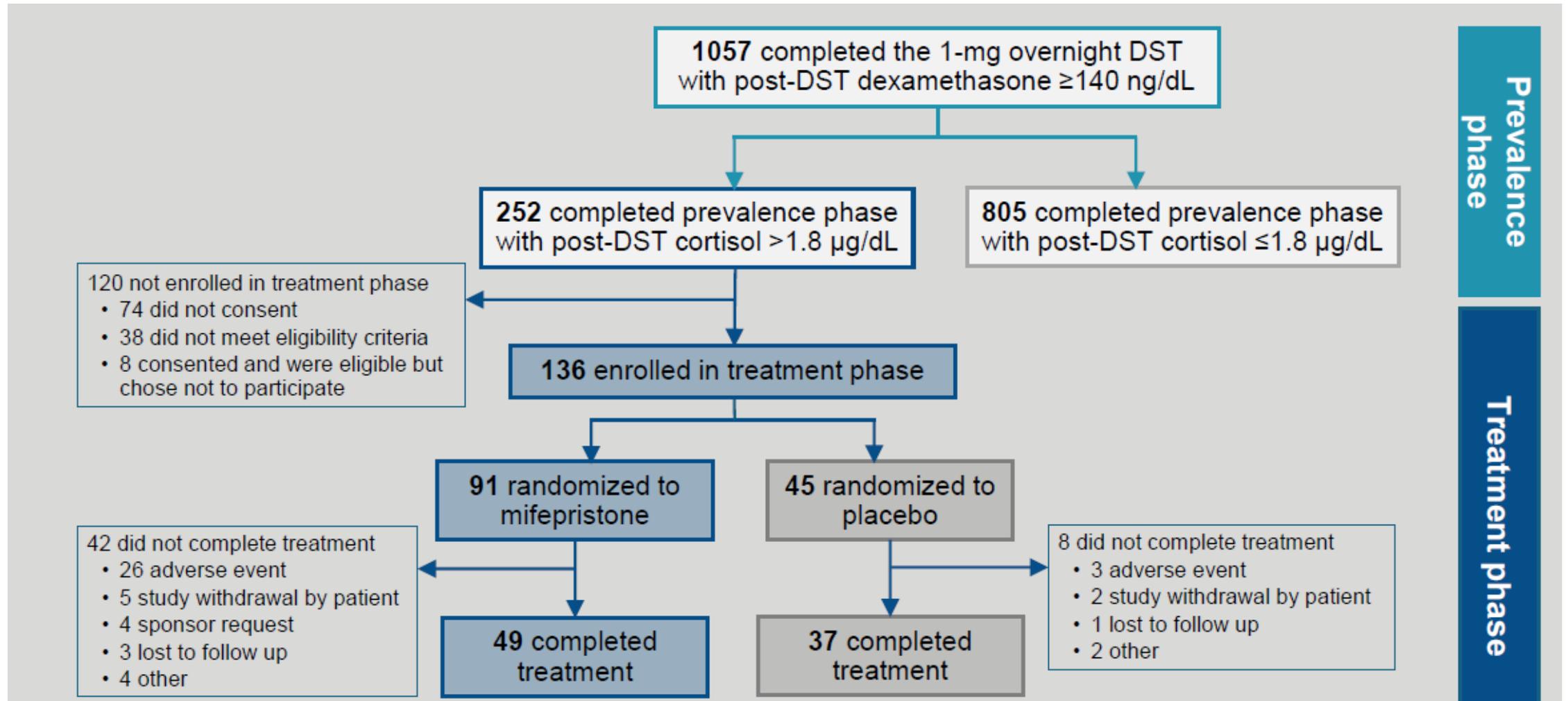


DSL=DerSimonian and Laird method; HKSJ=Hartung-Knapp-Sidik-Jonkman method.

^aPresence of microvascular and/or macrovascular complications or presence of insulin treatment plus HTN or presence of HTN treated with 2 or more drugs.

Aresta C, et al. *Endocr Pract.* 2021.

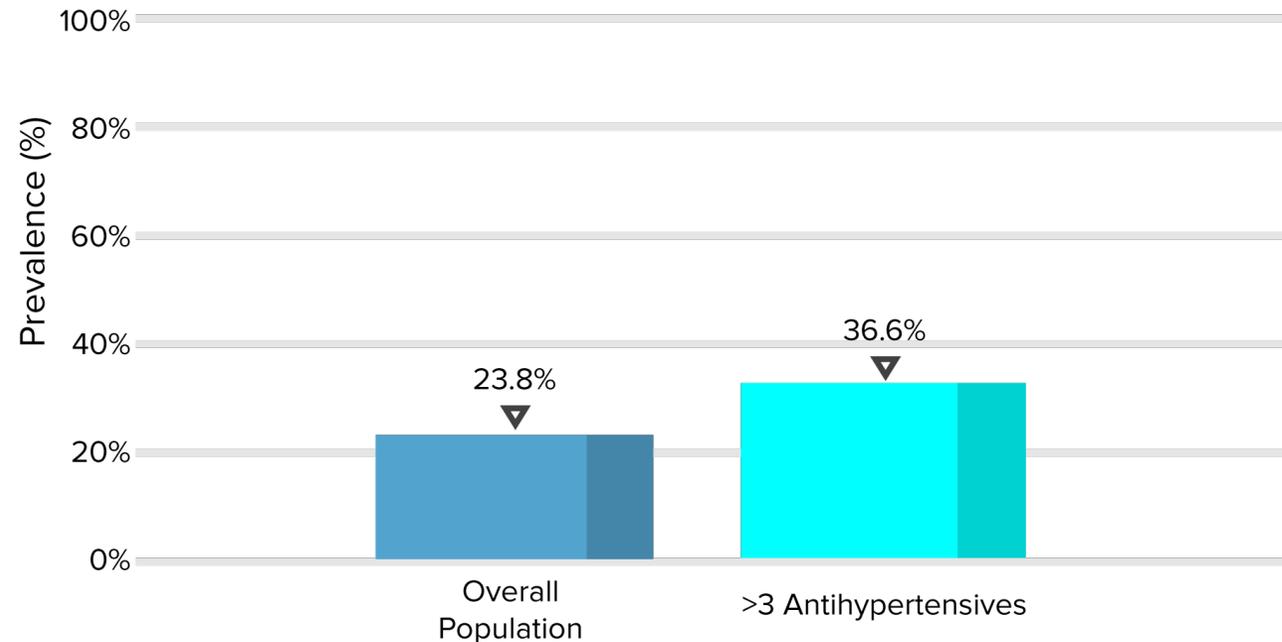
CATALYST: Participant Flow



Updated Prevalence of Hypercortisolism in T2D



CATALYST Trial: 1057 patients with HbA1c > 7.5% despite optimal T2D therapy



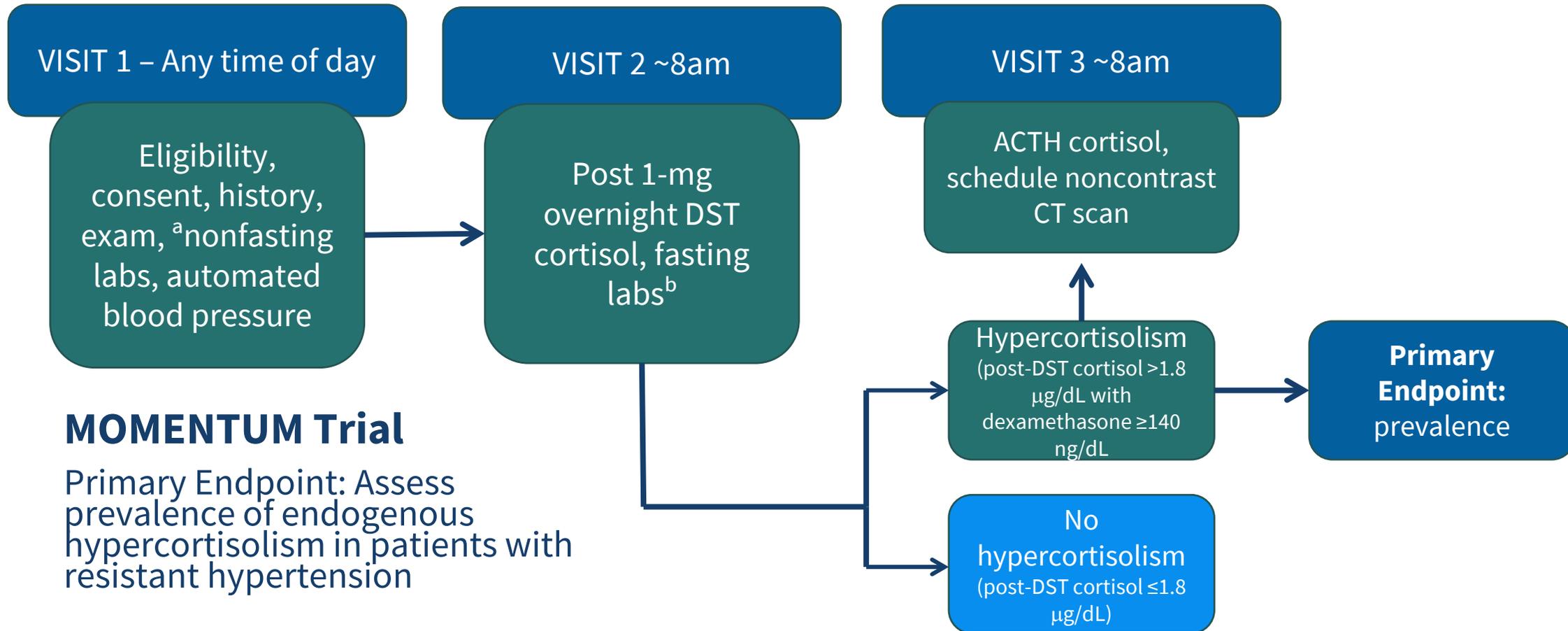
Results:

- Prevalence of hypercortisolism (Post-DST cortisol levels >1.8 $\mu\text{g/dL}$) 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

Updated Prevalence of Hypercortisolism in Resistant HTN is Coming



Adults with resistant hypertension (~1000)



MOMENTUM Trial

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

<https://clinicaltrials.gov/study/NCT06829537?term=MOMENTUM&rank=4>

^aPlasma renin activity, aldosterone, dehydroepiandrosterone sulfate, N-terminal-pro-brain-natriuretic peptide, HbA1C, Fibrosis-4, aspartate aminotransferase-to-platelet-ratio index, uric acid, high-sensitivity C-reactive protein, complete blood count, comprehensive metabolic panel, eGFR and urine-albumin-to-creatinine ratio.

^bACTH, fasting glucose, and fasting lipids

Updated Prevalence of Hypercortisolism in Resistant HTN is Coming



MOMENTUM Trial

- More data coming ACC 2026
 - March 28, 2026 1:30-2:30 PM Session: Featured Clinical Research II

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, Corcept Therapeutics Incorporated, Redwood City, CA, USA 🕒 1:45 PM - 1:55 PM 🕒 10m

 [View abstract](#)  [View biography](#)

Review: Clinical Presentation of Cushing Syndrome



Clinical features that best discriminate hypercortisolism (not correlated to disease severity):

- Easy bruising
- Facial plethora
- Proximal myopathy/muscle weakness
- Reddish-purple striae

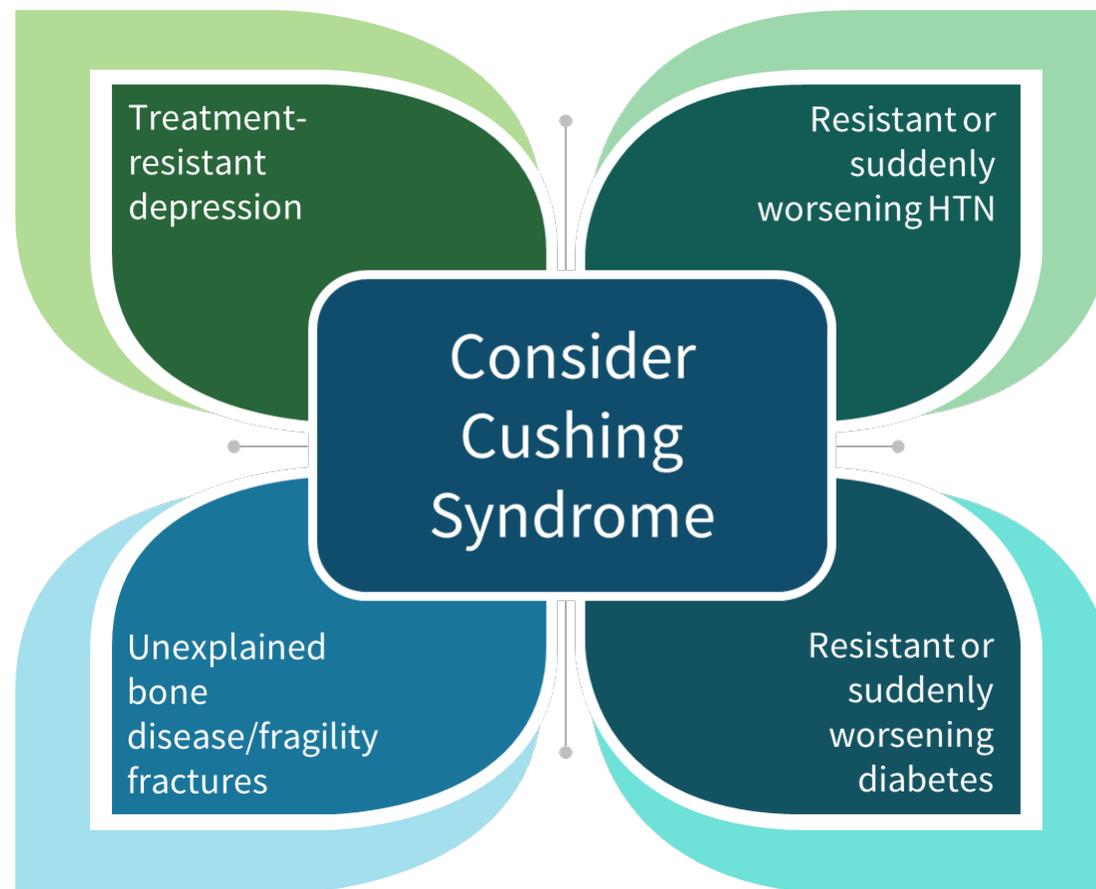
Typical severity of hypercortisolism by etiology (with exceptions):

- Pituitary CS: usually mild to moderate
- Adrenal CS: moderate to severe
- Ectopic CS: usually severe

The Toughest to Recognize: Non-Specific Cushing Syndrome Presentations



When to consider Hypercortisolism: Clustering of Problems from Multiple Organ Systems



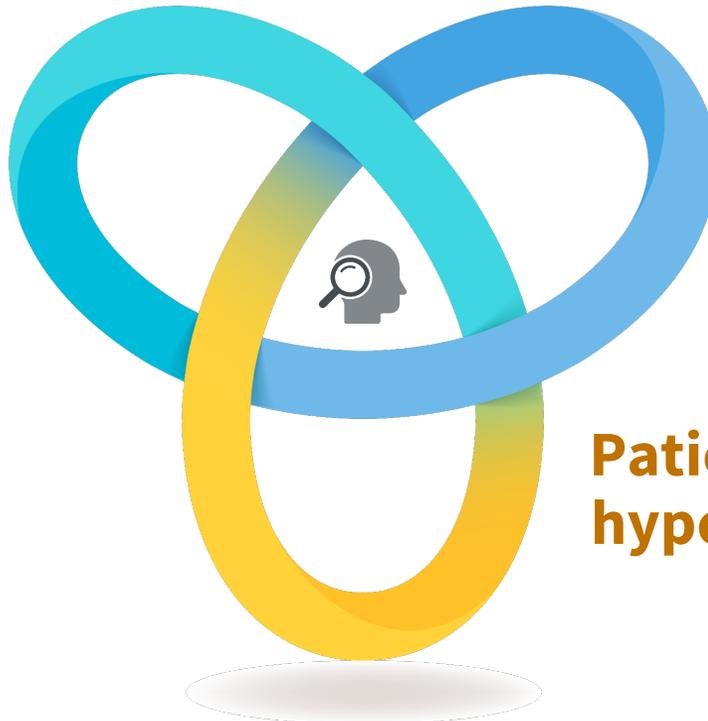
Recognizing the Need for Increased Screening



Consistent with the Endocrine Society Guidelines to screen for hypercortisolism as a secondary cause in patients with uncontrolled **T2D- CATALYST** was the first randomized, placebo-controlled study to demonstrate both prevalence and response to cortisol-directed treatment.

Patients with acute worsening of hypertension and diabetes

Patients with non-neoplastic hypercortisolism respond to treatment with mifepristone



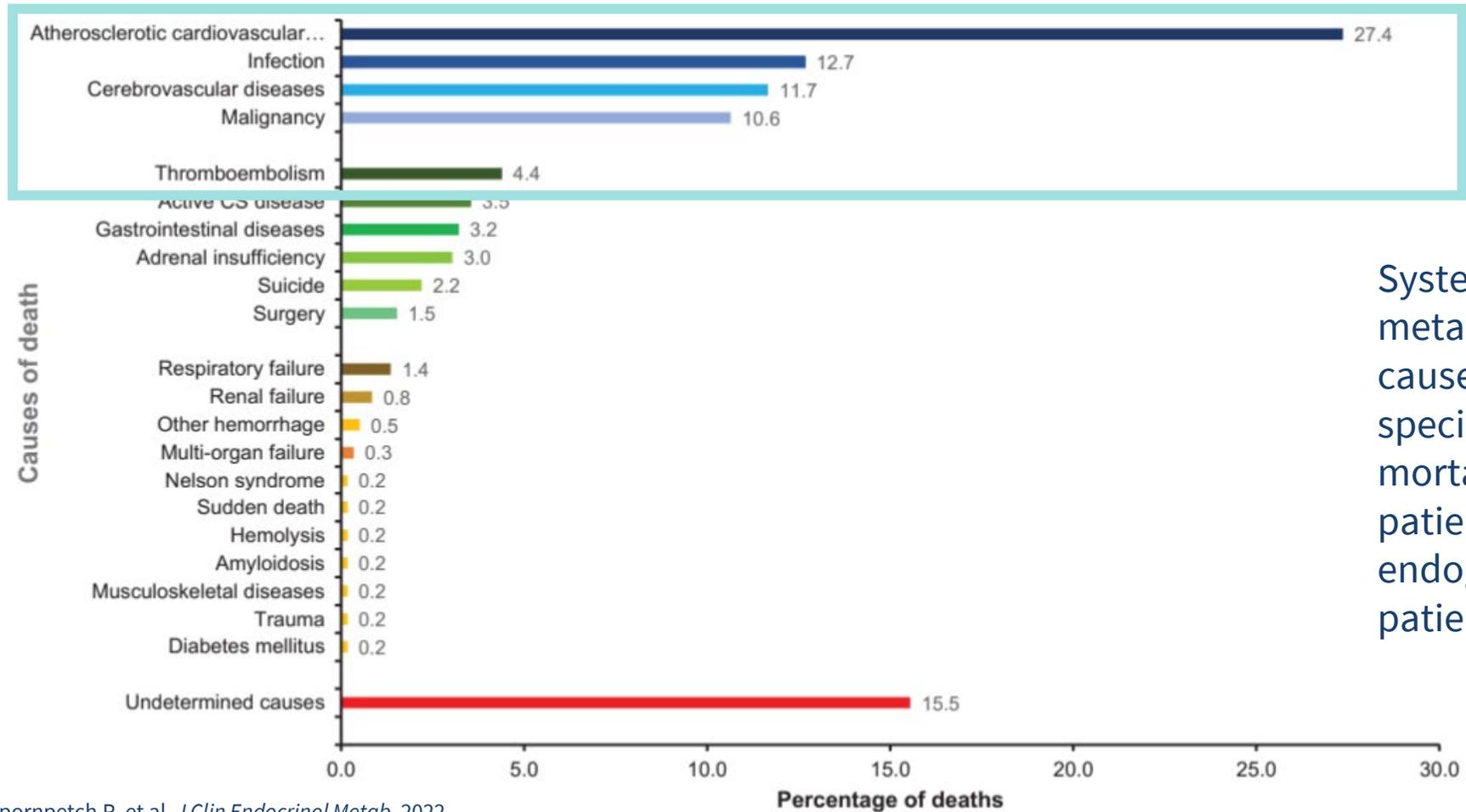
Patients with uncontrolled hypertension and diabetes

Roughly one third will have hypercortisolism

Patients with uncontrolled hypertension and diabetes

~25% will have hypercortisolism

Mortality Ratio of Patients with Benign Endogenous CS

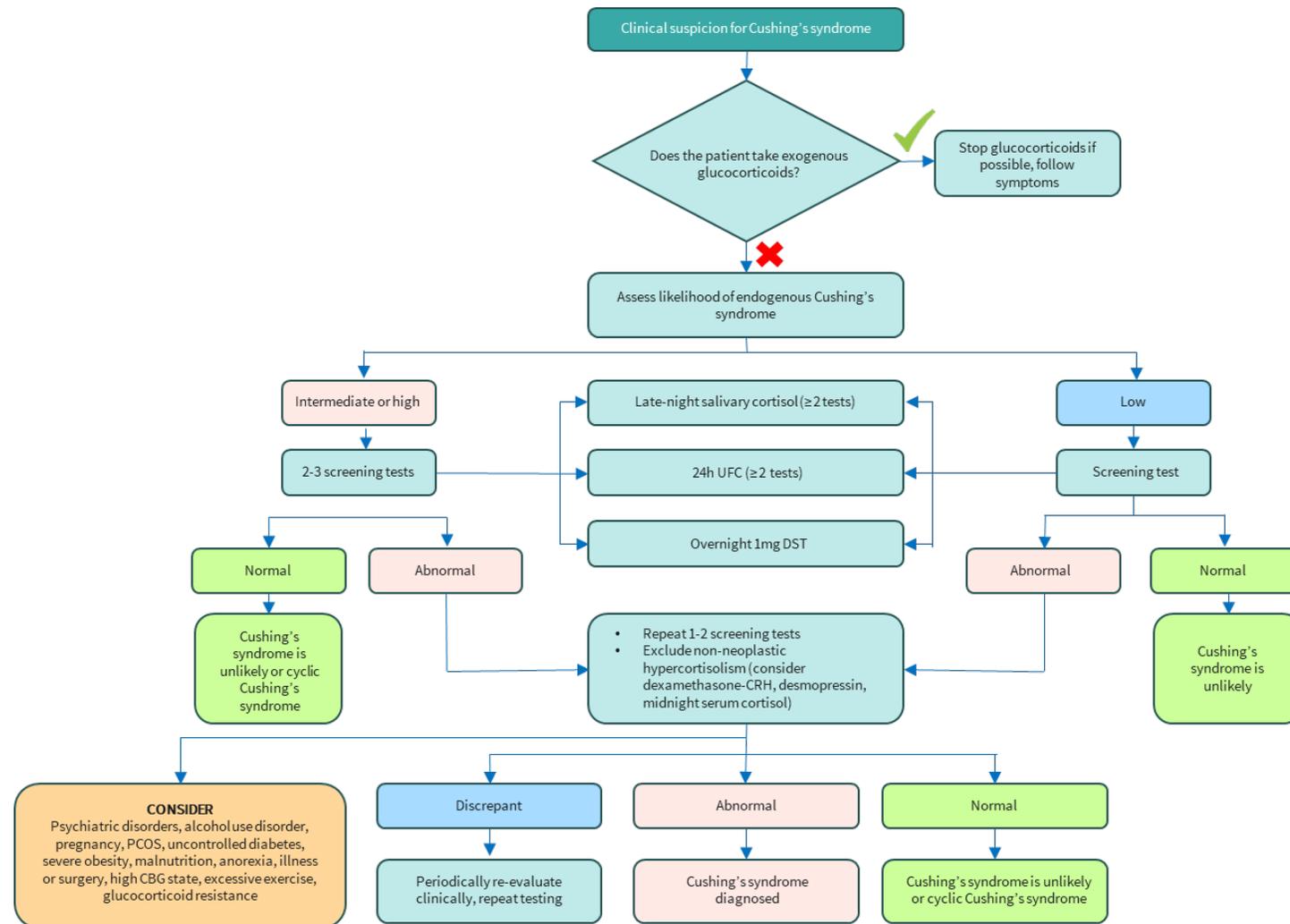


Systematic review and meta-analysis of all-cause and cause-specific standardized mortality ratio of patients with benign endogenous CS (3691 patients)



Cortisol Clues: How to Screen?

Screening for Cushing Syndrome



Sensitivity, Specificity, and Caveats of Screening Tests for Cushing's Syndrome



Test	Sensitivity	Specificity	Caveat
1 mg DST (<1.8 µg/dL)	91-97%	80-94%	CBG effect, Dex clearance
24-hr UFC	85-92%	45-98%	Improper collection, high fluid intake (>5 liters), CKD
LNSC	88-100%	82-100%	Improper collection, shift workers
2-day LDDST (<1.4 µg/dL)	90-100%	97-100%	CBG effect, Dex clearance
2-day Dex/CRH Test (<1.4 µg/dL)	98-100%	60-100%	CBG effect, Dex clearance

Screening for Suspected Adrenal Cushing Syndrome



Recommended clinically in patients with difficult-to-control T2D



Dexamethasone suppression test (DST)

High sensitivity

No longer recommended routinely



Late-night salivary cortisol (LNSC)

Low sensitivity and specificity in adrenal hypercortisolism

No longer recommended routinely

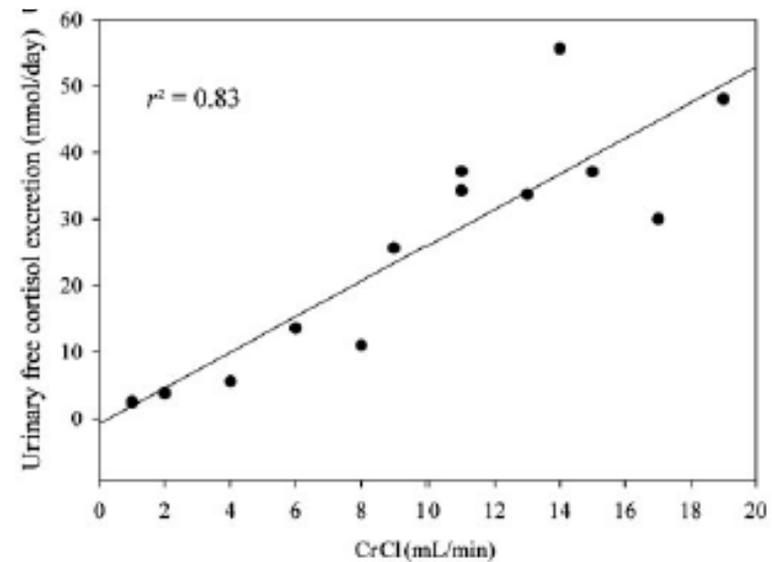
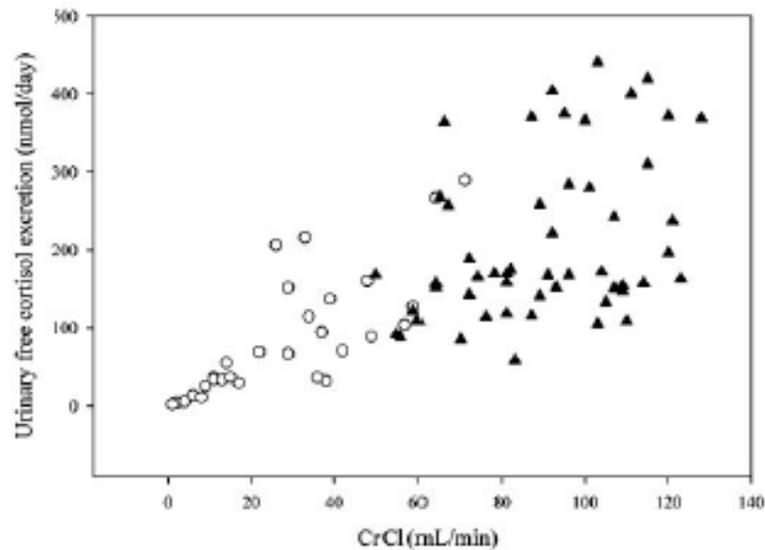


Urinary free cortisol (UFC)



UFC Pitfall

UFC decreases in severe renal failure and is not reliable when Cr Clearance is <20 mL/min



Potential Issues with Other Tests



DST

False positive results possible with increased gut transit time, chronic diarrhea, or celiac disease; concomitant treatment with CYP3A4 inducers; and increased corticosteroid binding globulin (CBG) levels from oral estrogens, pregnancy, or chronic active hepatitis (measuring dexamethasone concomitantly can reduce this risk)



24h urine

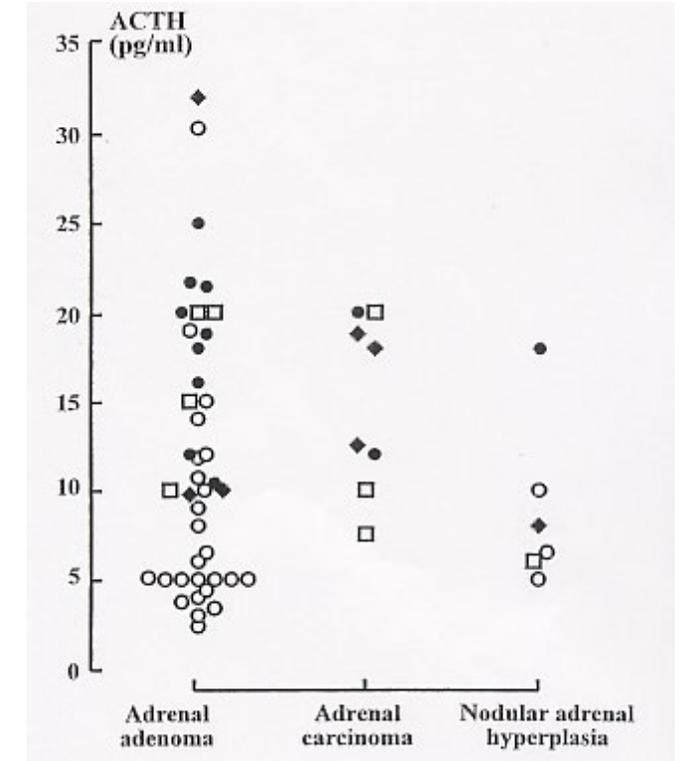
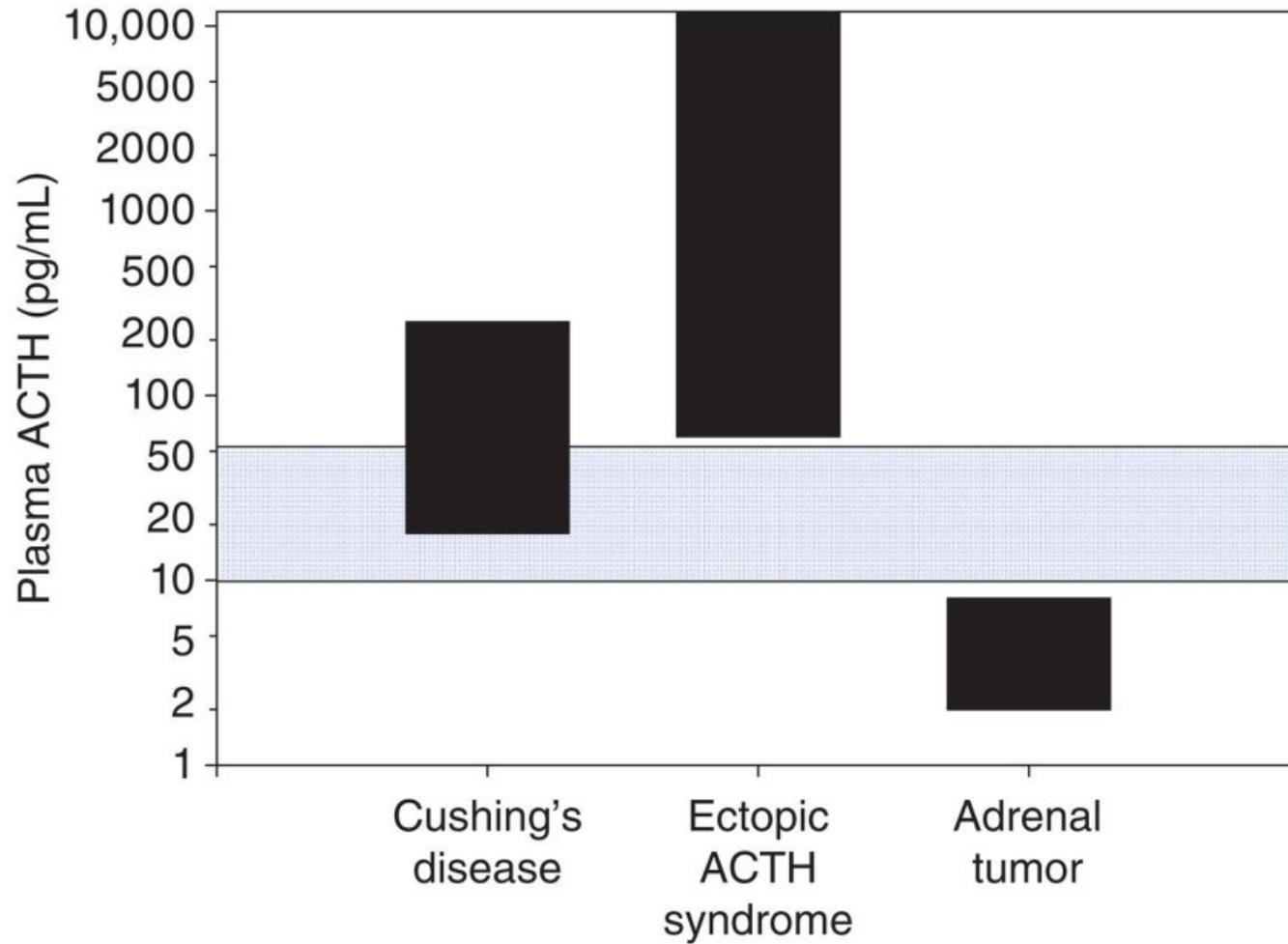
Incomplete collection, high urine volume, cyclicity of hypercortisolism, multiple confounders that increase or decrease urinary cortisol, interference from carbamazepine, cross reactivity with cortisol metabolites and synthetic glucocorticoids



LNSC

Stress/excitement prior to sample collection; contamination from blood- or steroid-containing products; smoking, chewing tobacco or using licorice; susceptibility of immunoassays to cross-reactivity with cortisone, other steroids, and synthetic steroids (facial lotion); susceptibility of MS-MS to interference from exogenous steroids (eg, prednisolone) and certain endogenous metabolites

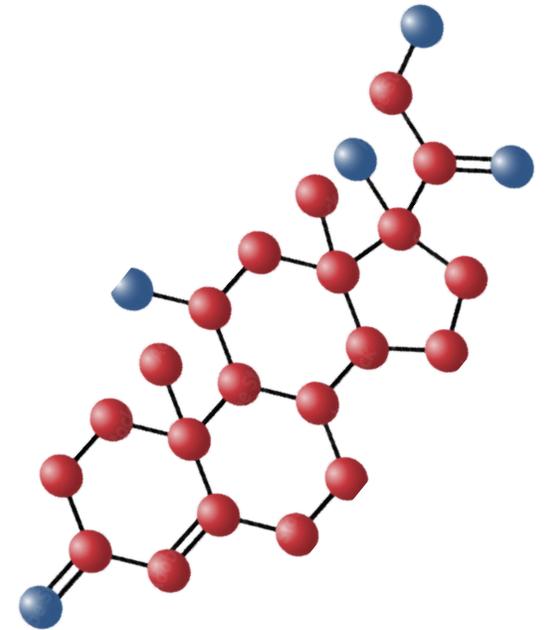
Screening Continued- ACTH



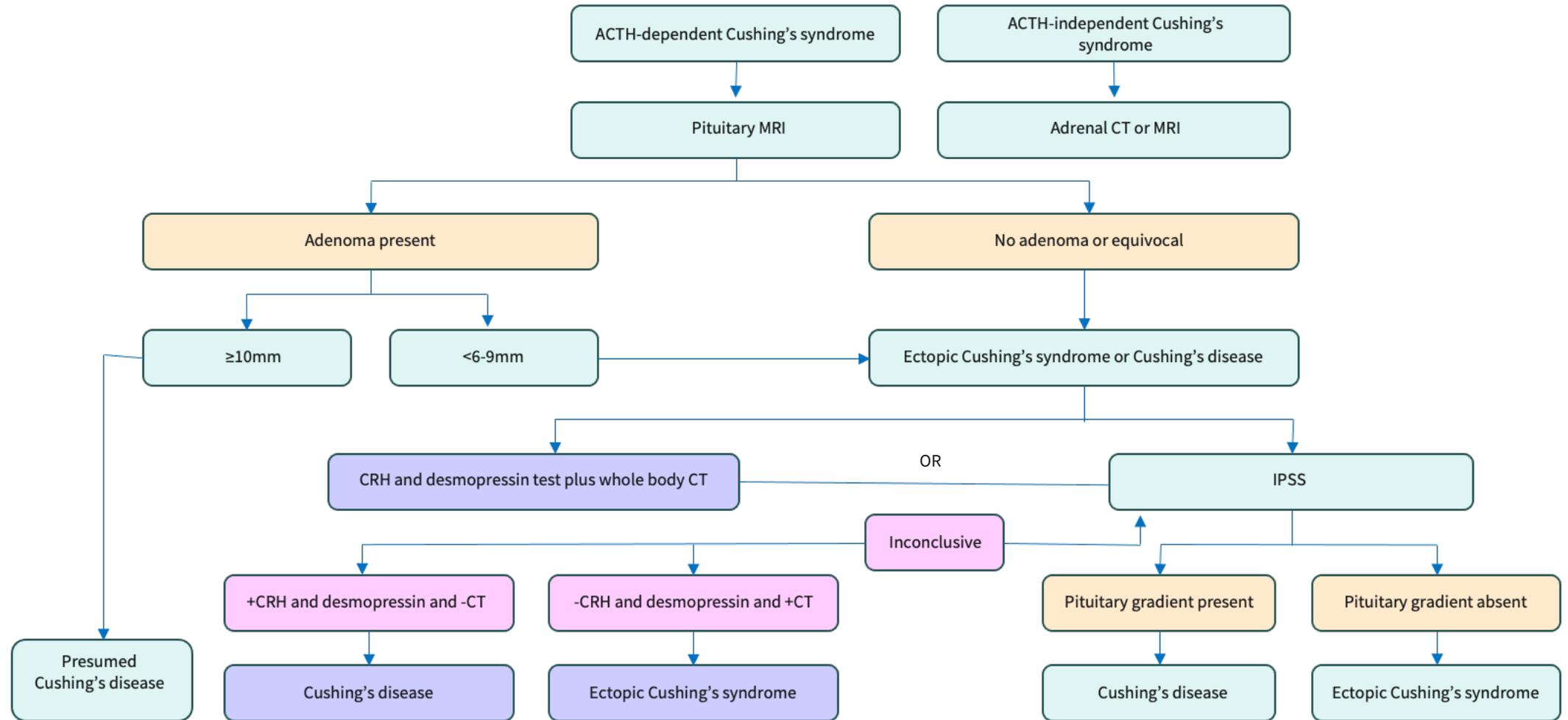
ACTH Independent Hypercortisolism



- ACTH is usually undetectable in adrenal CS
- ACTH is usually (but not always) <15 mg/mL in MACS; DHEAS is usually low in both adrenal CS and MACS
- DHEAS is usually low
- CT abdomen is the localization study of choice
 - If unilateral adrenal mass \rightarrow unilateral adrenal hypercortisolism confirmed
 - If bilateral adrenal mass \rightarrow usually bilateral adrenal hypercortisolism (though unilateral hypercortisolism is possible \rightarrow adrenal vein sampling)
 - If no adrenal tumors \rightarrow (very rare) \rightarrow diagnosis is likely micronodular adrenal hyperplasia (always bilateral)



ACTH Dependent Hypercortisolism



Interprofessional Team Overview: What is the Role(s) of the Care Team?



Physicians: Endocrinologists work with primary care, internists, neurosurgeons, endocrine surgeons, radiologists, pathologists

- Screen, diagnose, determine and oversee treatment plans

Advanced Practice Providers: Nurse Practitioners, Physician Assistants

- Perform patient assessments, manage symptoms, provide follow-up care, and support treatment delivery in collaboration with physicians

Clinical Pharmacy Specialists:

- Optimize pharmacologic treatment plans, educate patients on medication use and side effects, and answer drug information questions

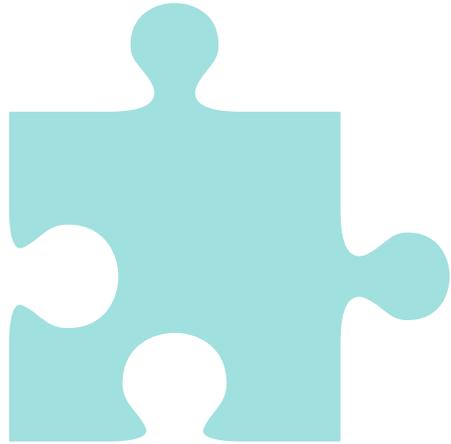
Nurses:

- Provide day-to-day care coordination, triage symptoms, administer treatments, and serve as key points of patient contact
- Educate patients and families about care plans and procedures

Social Workers:

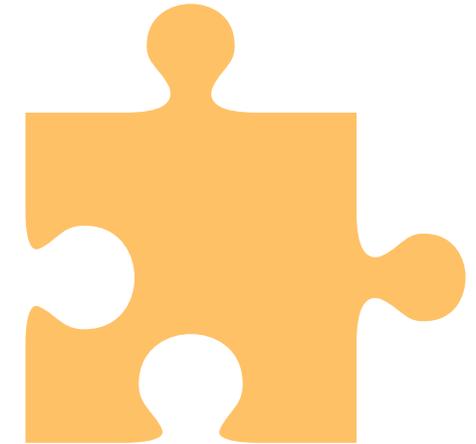
- Address psychosocial needs, coordinate resources (transportation, financial support, counseling), and facilitate communication between patients, families, and the care team

Practicing Motivational Interviewing



Ask open ended questions

- Facilitates discussion
- Ask permission



Practice active listening

- Focus on strengths
- Celebrate small successes
- Repeat or paraphrase
- Summarize



Beyond Surgery: Advances in Medical Management of Cushing Syndrome

Treatment Options for Cushing Syndrome/ Disease



Medical Management

- Pituitary-directed agents
- Adrenal-directed agents
- GR antagonists
- Some are off-label usages or under investigation



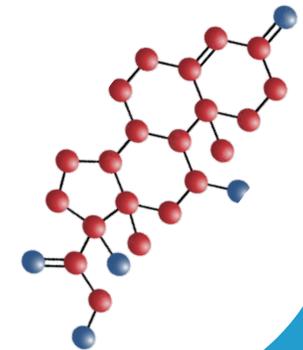
Surgery

- First-line treatment
- Not always curative
- Not always suitable

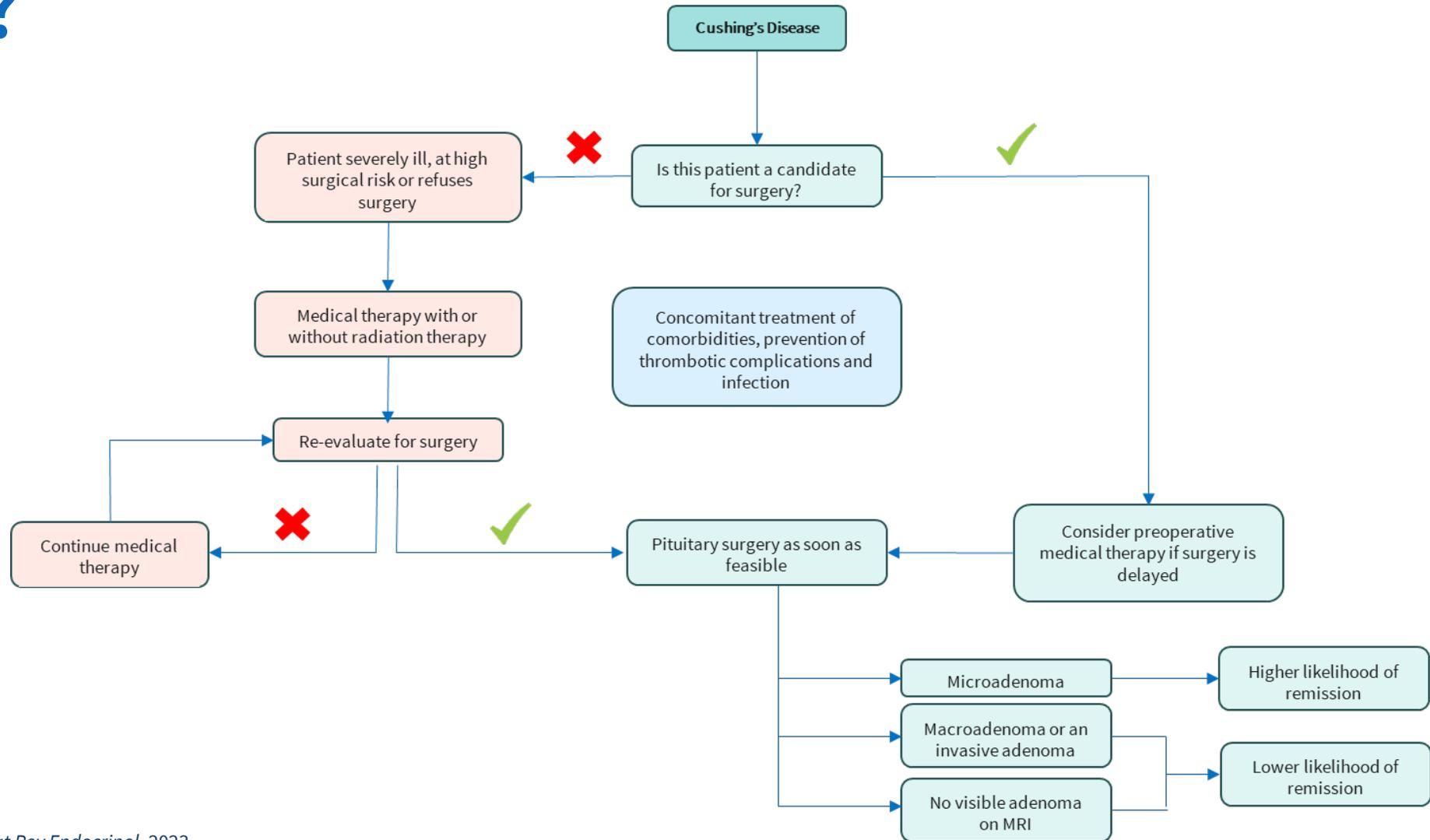


Patient-tailored Treatment

- Consider the patient's comorbidities, MOA of drug, availability and clinical scenario



Cushing Syndrome/Disease: Surgery or Not?



Surgical Management Overview for Cushing Syndrome/Disease



- Surgery is first-line treatment.
- Surgery achieves adequate control of Cushing Disease in 65%-90% of patients.
- Many patients have post-surgical recurrence
 - Up to 35% within 5 years
 - Up to 69% within 10 years

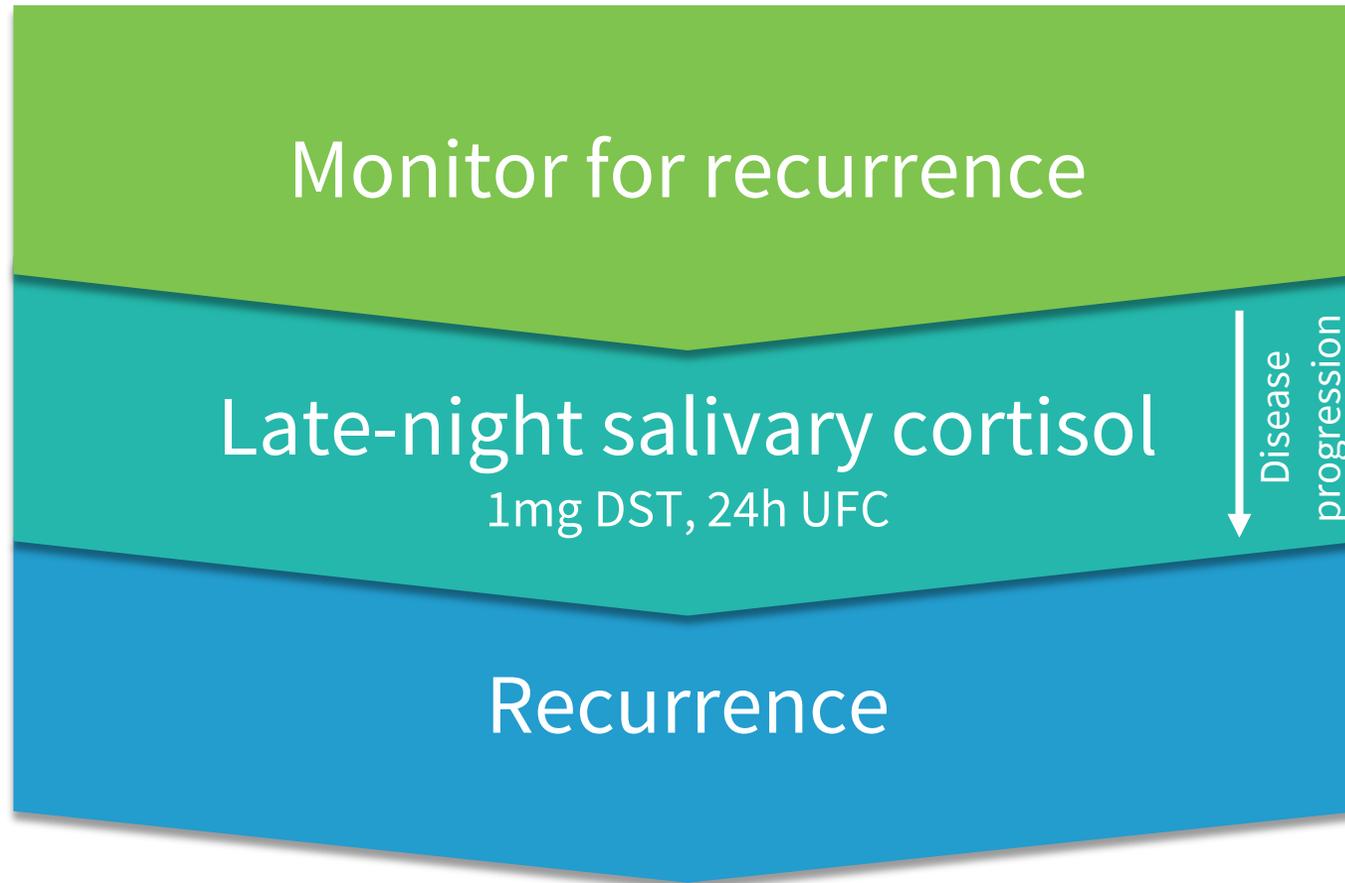
Recent Data on Surgery Treatment Success



	All CS, n = 296	ACS, n = 84	ECS, n = 27	CD, n = 185
First-line surgical therapy, n (%)	284 (96)	83 (99) ADX, unilateral adenoma: 53/54 BADX, MiBAH: 7/7 BADX, PBMAH: 4/23 ADX, PBMAH: 18/23 BADX, PBMAH: 1/23	21 (78) Tumor resection: 16 (59) BADX: 3(11) Unnecessary TSS:2 (7)	180 (97) TSS: 175 (95) BADX: 5 (3)
First-line medical therapy	11 (4)	Osilodrostat: 1	Metyrapone: 6 (22) Additional ketoconazole: 4 (15)	Pasireotide: 2 seconds.c.(1) Cabergolin:3 (2)
Persistence	54 (18)	5 (6)	4 (15)	45 (24)
Recurrence	40 (14)	3 (4)	4 (15)	33 (18)
Second-line therapy		ADX li: 1 Metyrapone: 2 Osilodrostat: 1 No therapy: 4 (mild CS, patients' preference)	Tumor resection: 2 BASX: 4 Metyrapone: 1 Other medications: 1	TSS: 31 BADX: 10 Radiation: 8 Pasireotide: 14 (8 seconds.c., 6 LAR) Cabergoline: 3 Metyrapone: 6 Osilodrostat: 4 Ketoconazole: 8 Other medications: 5
No remission	52	6	2	44
Further lines of therapy		Metyrapone: 2 Osilodrostat: 1 No therapy: 3 (mild CS, patients' preference)	Tumor resection: 1 BASX: 2	TSS: 10 BADX: 18 Radiation: 8 Pasireotide: 5 (2 seconds.c., 2 LAR, 1 both) Cabergoline: 4 Metyrapone: 10 Osilodrostat: 4 Ketoconazole: 6
No remission	20	5	0	15

Ritzel K, et al. *J Clin Endocrinol Metab.* 2025.

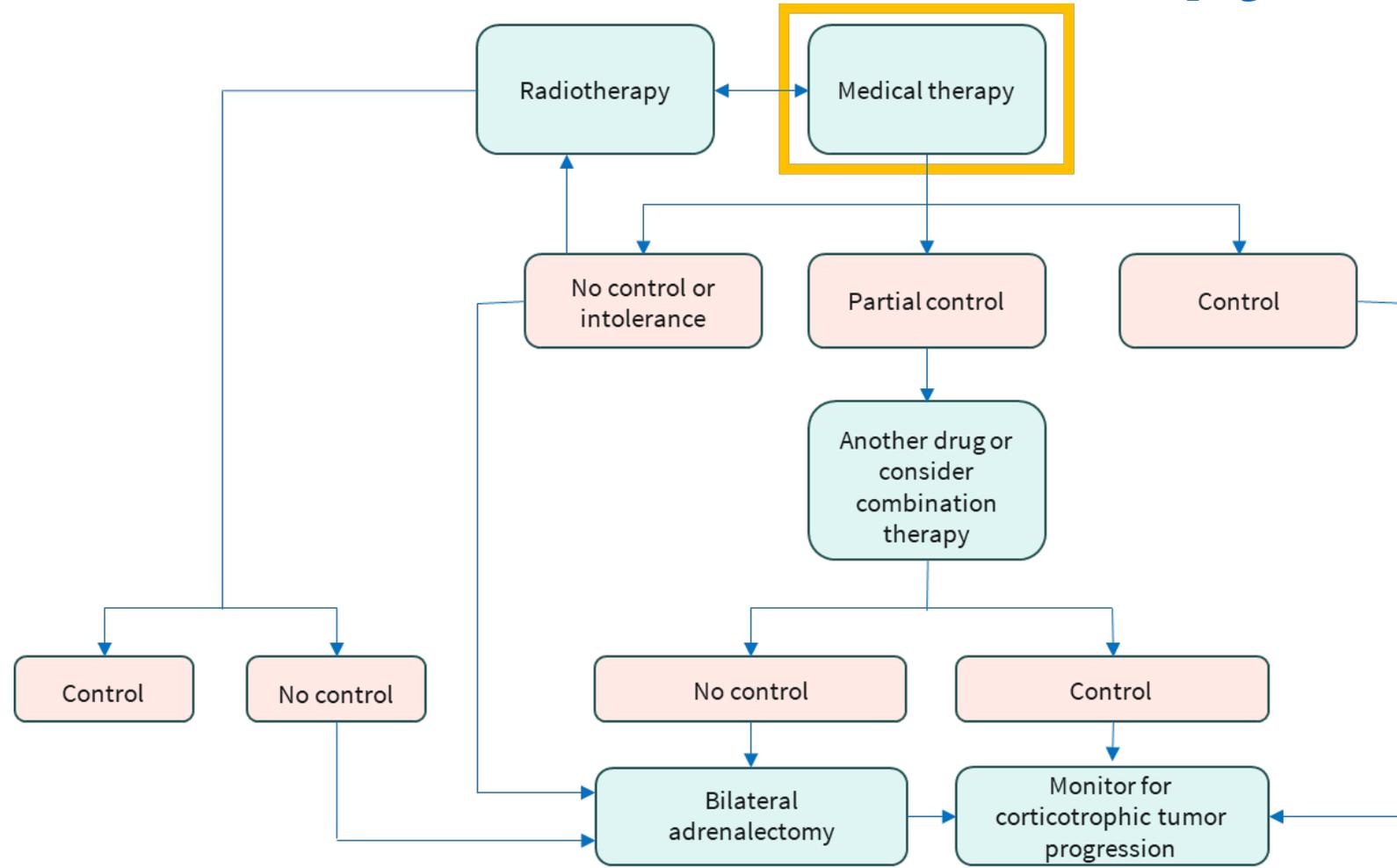
Monitoring for Recurrence Post-Surgery



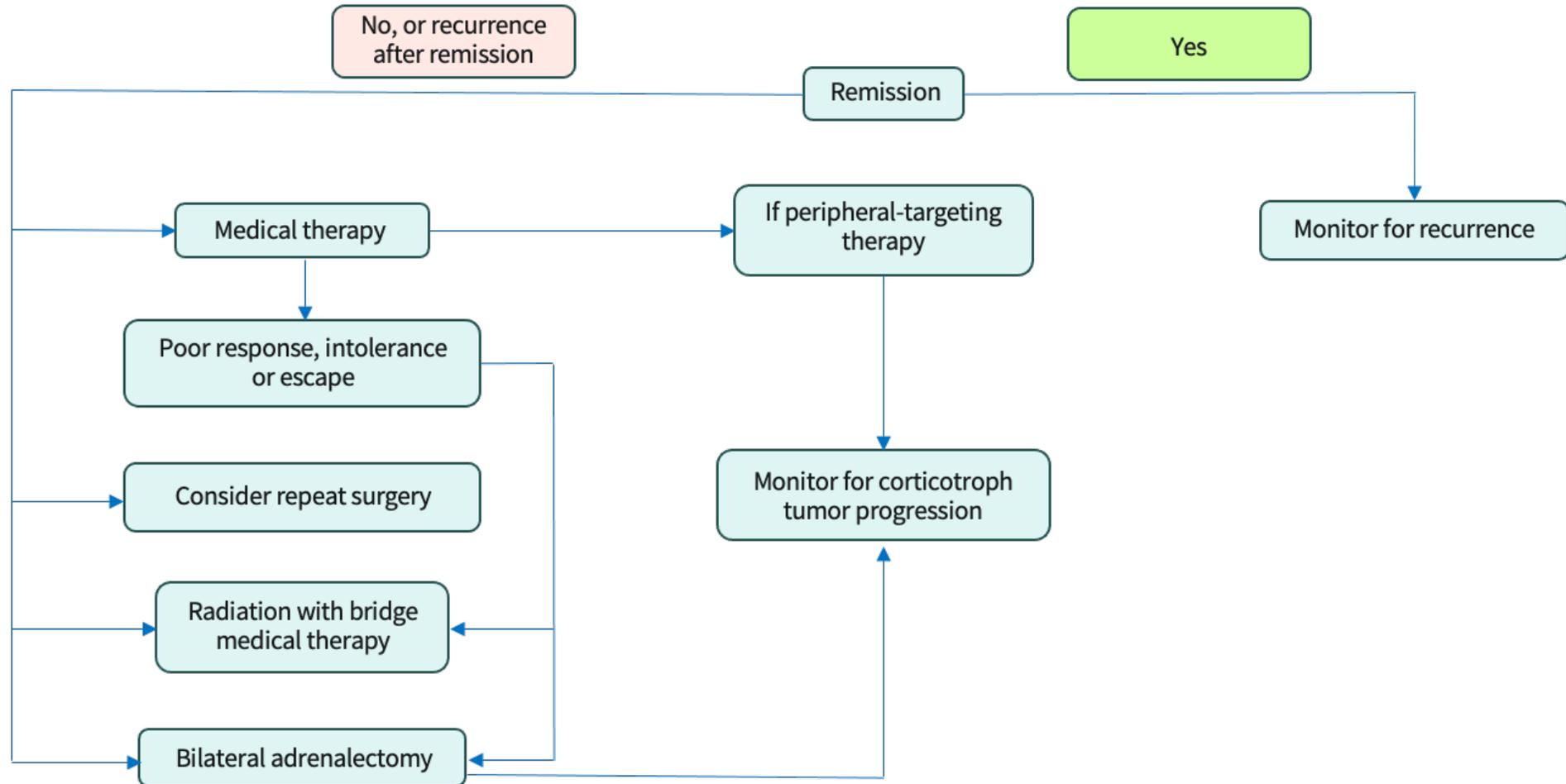
Fleseriu M, et al. *Lancet Diabetes Endocrinol.* 2021.

DST: dexamethasone suppression test
UFC: urinary free cortisol

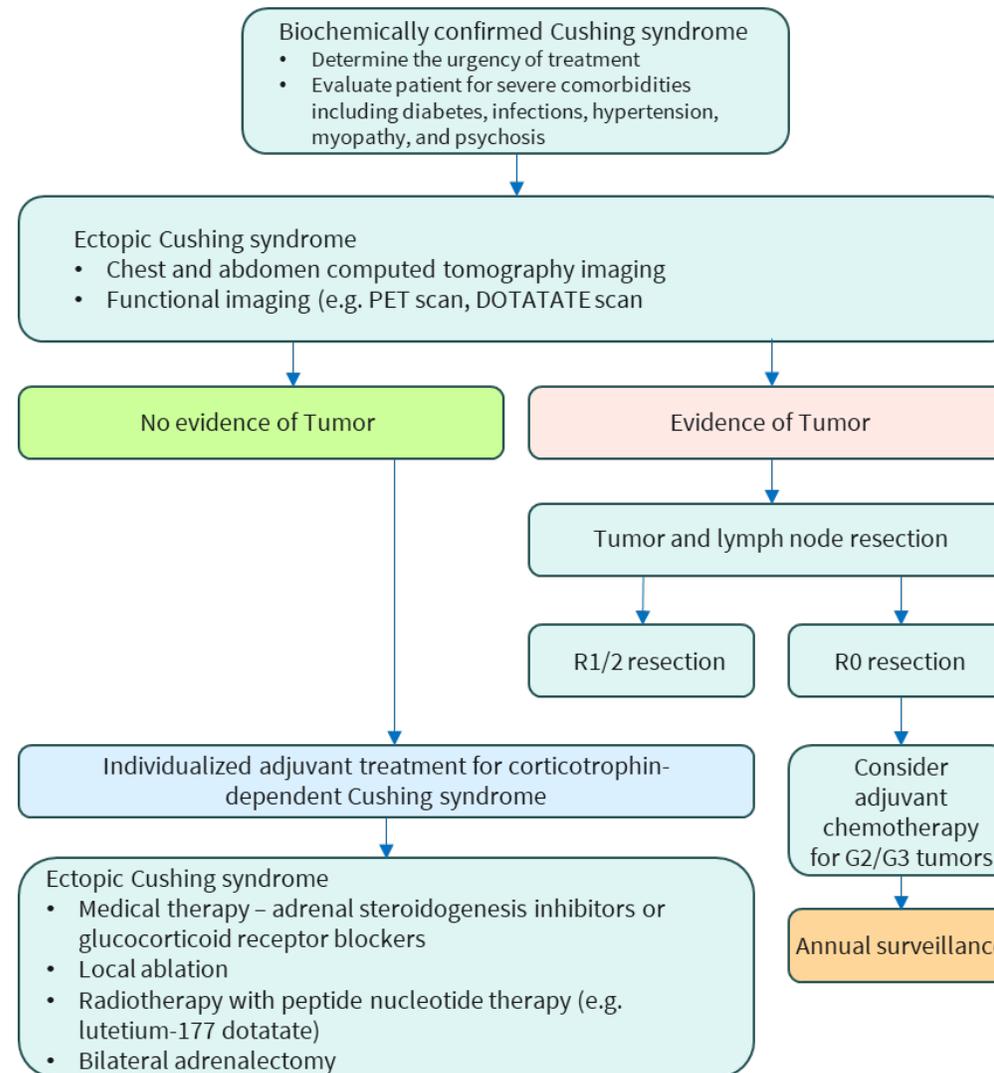
2021 Pituitary Society Guidelines: What is the Role of Medical Therapy?



Cushing Syndrome/Disease: Role of Medical Management Post-Surgery



Ectopic Cushing's Syndrome Management



When Medical Management is Indicated



- When surgery is not an option or is refused
- When disease persists after surgery
- When disease recurs after successful surgery
- When severe symptoms present and emergency treatment is needed
- While awaiting surgery or radiation therapy

Medical Therapies for Cushing's Syndrome



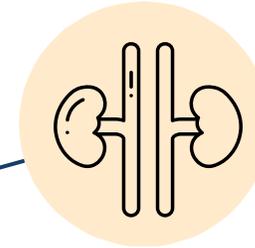
Pituitary-Directed Agents

- Pasireotide (subQ and LAR)
- Cabergoline



Adrenal-Directed Agents: Steroidogenesis Inhibitors

- Osilodrostat
- Levoketoconazole
- Ketoconazole
- Metyrapone
- Mitotane
- Etomidate



Glucocorticoid Receptor Blocker/Modulator

- Mifepristone
- Relacorilant



Licensed in US for Cushing's indications

Used off-label/Not approved in US

LAR-long-acting release; sq, subcutaneous.

Gadelha M, et al. *Lancet*. 2023; Reincke M, et al. *JAMA*. 2023; Fleseriu M, et al. *Nat Rev Endocrinol*. 2023.

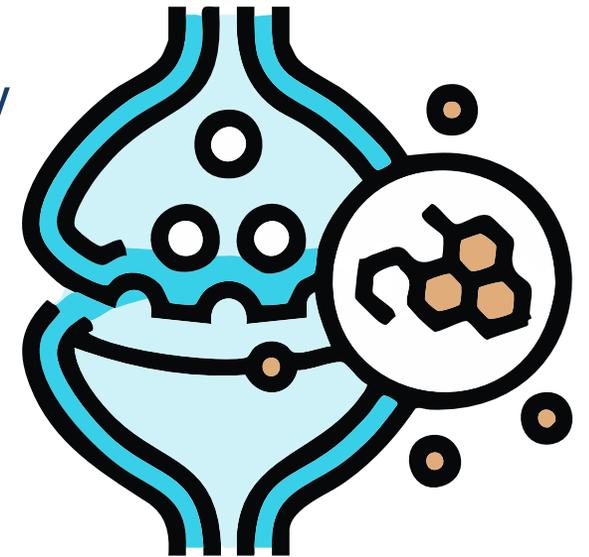


Glucocorticoid Receptor- Directed Agents (Glucocorticoid Receptor Modulator)

Mechanism of Action



- Glucocorticoid Receptor (GR)-Directed Agents work by blocking binding of cortisol to the GR receptor
- Mifepristone is a GR antagonist, but also a progesterone receptor antagonist
 - May causes vaginal bleeding and endometrial hypertrophy
- Relacorilant is a selective glucocorticoid receptor modulator antagonizes only the GRs and NOT progesterone receptors
 - Mild side effect profile
 - Increased selectivity may overcome side effects related to mechanism of action of mifepristone

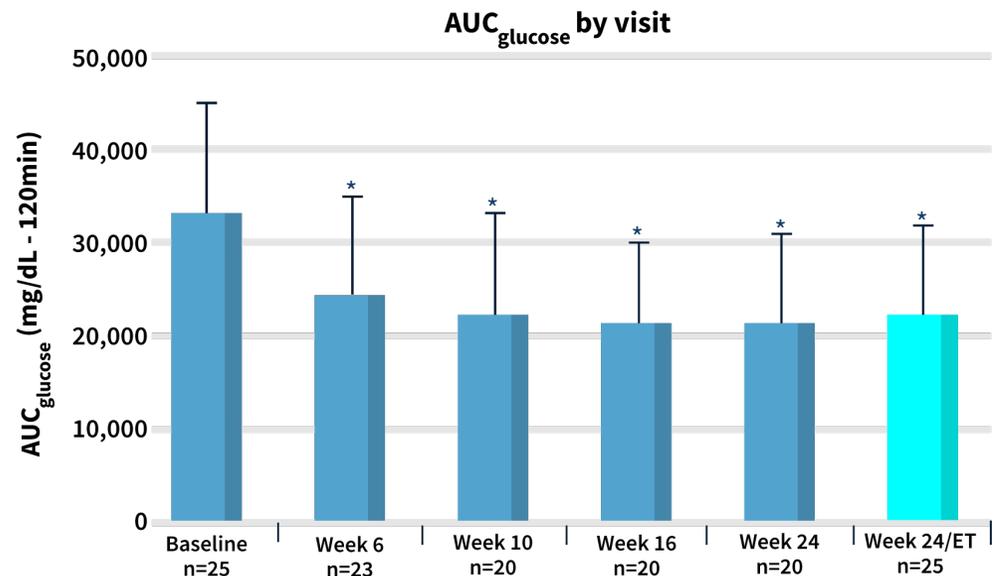


Mifepristone

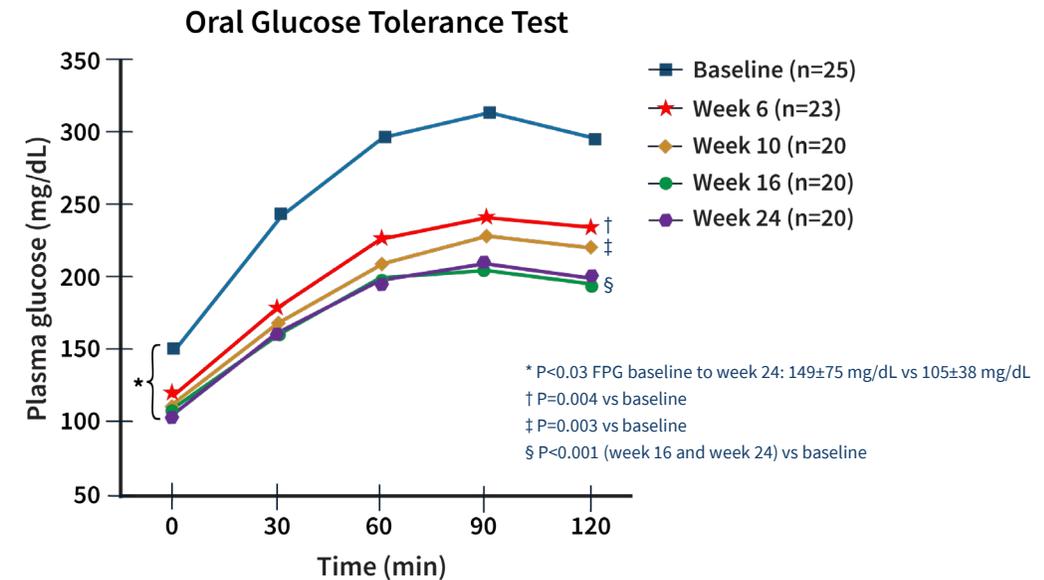


- SEISMIC Study: Efficacy and Safety in Endogenous CS
- 24-wk multicenter, open-label trial after failed multimodality therapy
- Participants: 50 adults with endogenous CS associated with T2DM/impaired glucose tolerance (C-DM) or a diagnosis of hypertension alone (C-HT)
- Primary Endpoints:
 - C-DM: change in area under the curve for glucose from baseline to wk 24
 - C-HT: change in DBP from baseline to wk 24

Changes in glycemic parameters



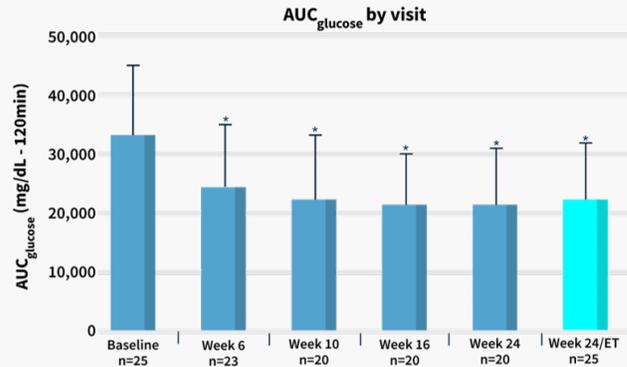
Error bars in graph are SD * P<0.001 vs baseline



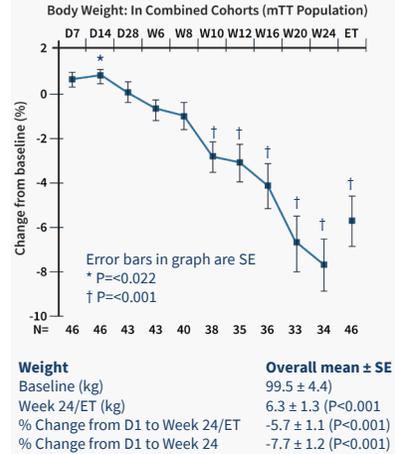
Mifepristone



- SEISMIC Study: Efficacy and Safety in Endogenous CS

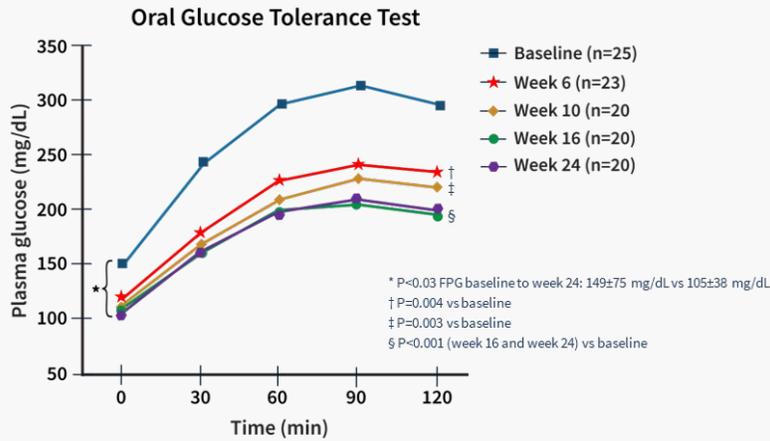
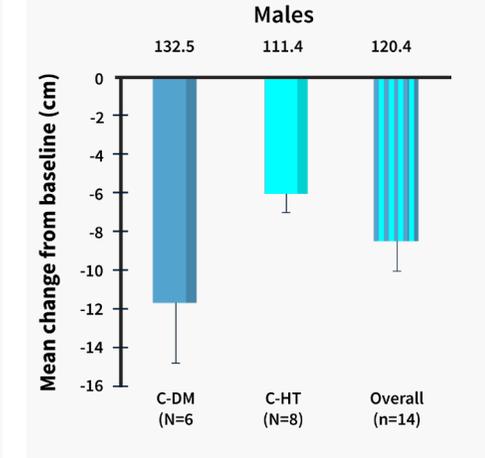
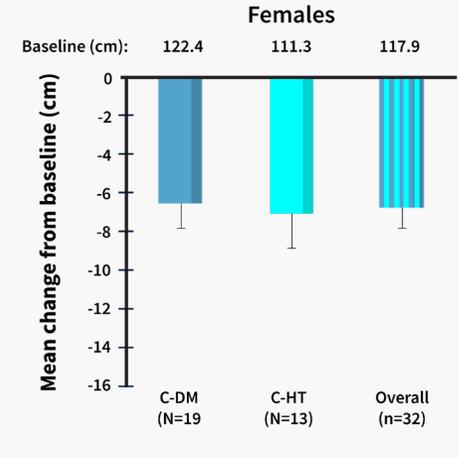


Error bars in graph are SD * P<0.001 vs baseline

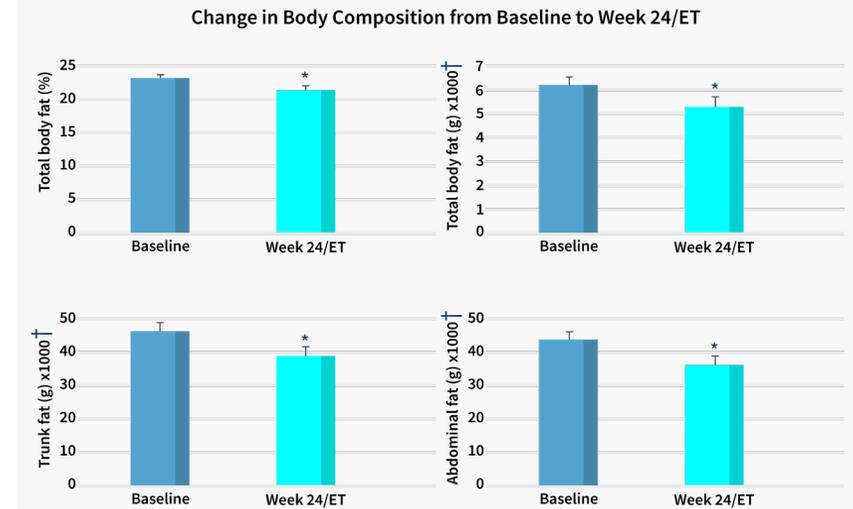


Weight
 Baseline (kg) 99.5 ± 4.4
 Week 24/ET (kg) 6.3 ± 1.3 (P<0.001)
 % Change from D1 to Week 24/ET -5.7 ± 1.1 (P<0.001)
 % Change from D1 to Week 24 -7.7 ± 1.2 (P<0.001)

Overall mean ± SE
 99.5 ± 4.4
 6.3 ± 1.3 (P<0.001)
 -5.7 ± 1.1 (P<0.001)
 -7.7 ± 1.2 (P<0.001)



* P<0.03 FPG baseline to week 24: 149±75 mg/dL vs 105±38 mg/dL
 † P=0.004 vs baseline
 ‡ P=0.003 vs baseline
 § P<0.001 (week 16 and week 24) vs baseline



Error bars in graph are SE
 * P<0.001 vs baseline
 † Absolute fat measured

Mifepristone



- SEISMIC Study: Efficacy and Safety in Endogenous CS
- Common AEs were:

- Nausea (48%)
- Fatigue (48%)
- Headache (44%)
- Decreased blood K⁺ (34%)
- Arthralgia (30%)
- Vomiting (26%)
- Peripheral edema (26%)
- HTN (24%)
- Dizziness (22%)
- Decreased appetite (20%)
- Endometrial thickening (20%)

Table 3. Summary of responders analyses (mITT population)

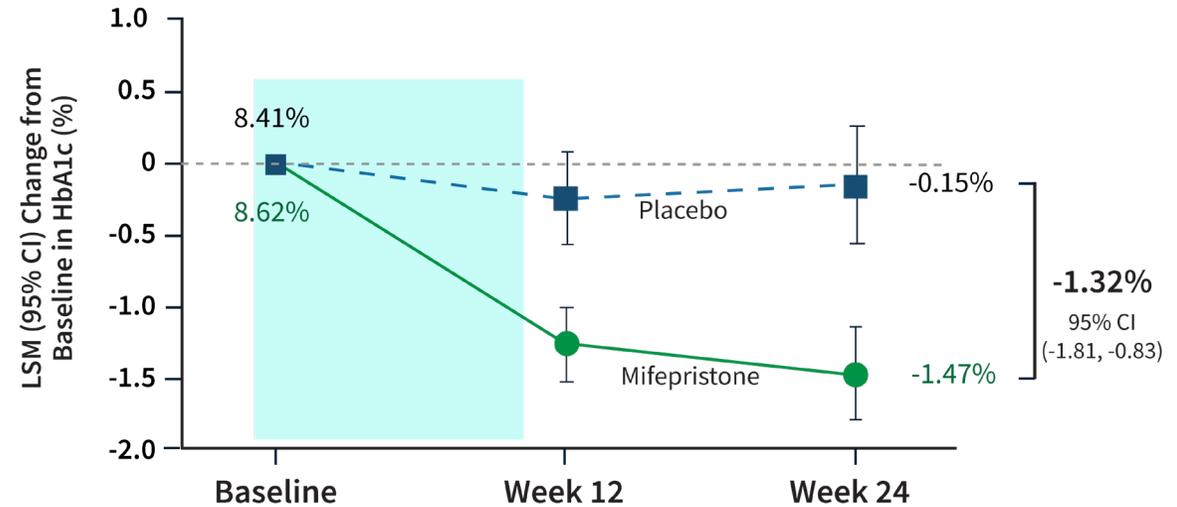
Statistics (mITT population)	Responder [n (%)]	Nonresponder [n (%)]	Lower bound one-sided 95% exact binomial CI (95%)	P value
C-DM (n=25)				
• Participants with or without a 25% reduction from baseline in AUC _{glucose} at wk 24/ET	15 (60)	10 (40)	41.7	<0.0001
C-HT (n=21)				
• Participants who had ≥5 Hg reduction from baseline in DBP at wk 24/ET	8 (38.1)	13 (61.9)	20.6	<0.05
C-HT and C-DM with HTN at screening (n=40)				
• Participants who had ≥5 Hg reduction from baseline in DBP at wk 24/ET	17 (42.5)	23 (57.5)		
• Participants who had a reduction in antihypertensive meds at wk24/ET	11 (27.5)	29 (72.5)		
• Participants who either had ≥5 Hg reduction from baseline in DBP or had a reduction in antihypertensive meds at wk24/ET	21 (52.5) ^a	19 (47.5)		
Median clinical improvement score of +1 at any reviewed visit ^b				
• Combined cohorts (n=46)	40 (87.0)	6 (13.0)	75.9	<0.0001
• C-DM (n=25)	23 (92.0)	2 (8.0)	76.9	
• C-HT (n=21)	17 (81.0)	4 (19.0)	61.6	

Mifepristone



CATALYST Part 2: Treatment Phase

- A Randomized, Placebo-Controlled Study
- Adults with inadequately controlled T2D and hypercortisolism (based on DST)- N=136
- Primary endpoint: change in HbA1c from baseline to week 25



Number of participants

Mifepristone	86	74	62
Placebo	44	40	38
P-value		<0.001	<0.001

Mifepristone



CATALYST Part 2: Other Findings

- Improvements in glycemic control were accompanied by reductions in:
 - Glucose-lowering medications
 - Body weight (-4.4 kg)
 - BMI and waist circumference (-1.5 kg/m² and -5.2 cm)

No. (%)	Placebo	Mifepristone
Long-acting insulin	3 (13.0)	32 (49.2)
Fast-acting insulin	2 (10.5)	10 (30.3)
Sulfonylureas	2 (10.5)	4 (22.2)
GLP-1 RAs	0	4 (12.1)
Tirzepitide	0	2 (10.5)
Metformin	0	1 (1.5)
SGLT2 Inhibitors	1 (3.7)	0
Total, No.	8	53

Relacorilant

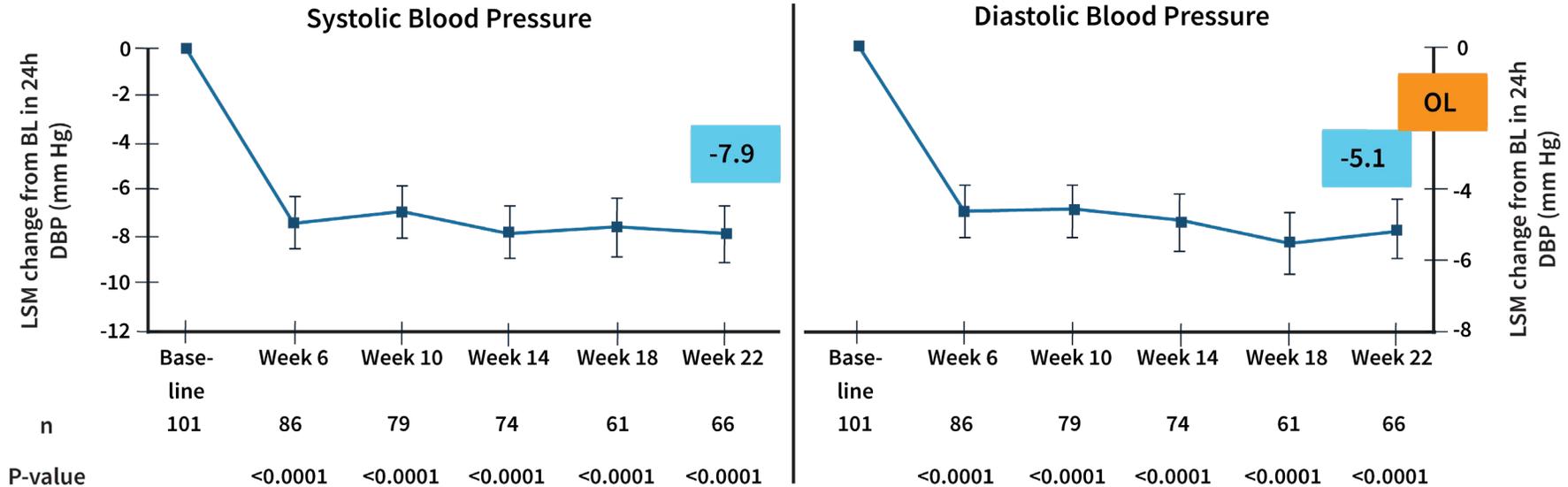


- Relacorilant is an investigational selective glucocorticoid receptor (GR) modulator designed to modulate excess cortisol activity at the GR to treat the manifestations of endogenous hypercortisolism.
 - Highly selective for the GR, with no activity at the progesterone, mineralocorticoid, or androgen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

Relacorilant



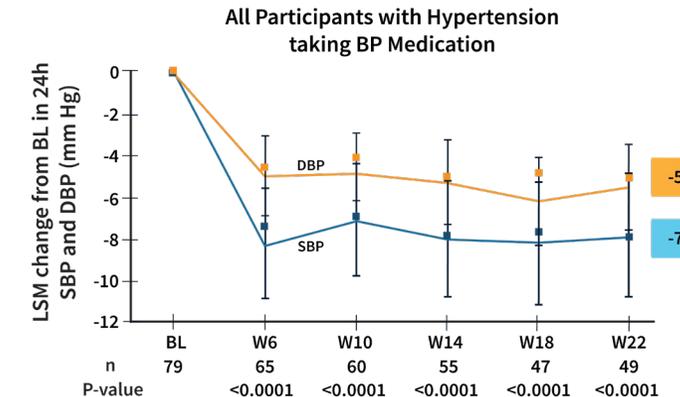
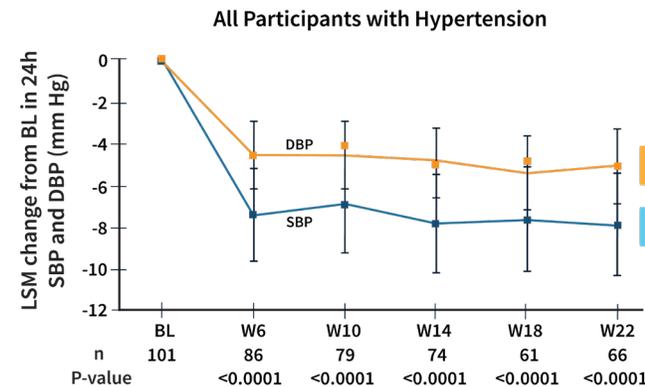
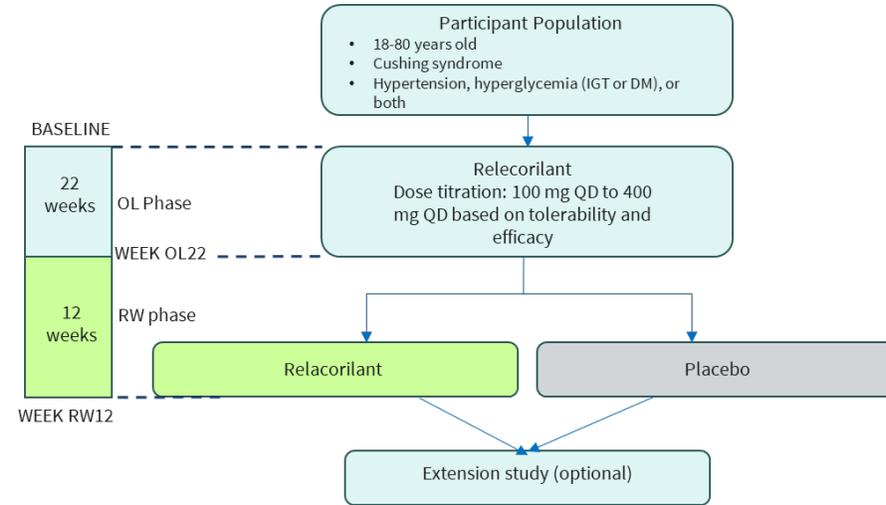
- GRACE Study: Efficacy and Safety in Cushing Syndrome (CS)
 - Phase 3 open-label (OL) trial followed by 12 week double-blind, placebo-controlled random withdrawal (RW) phase
 - Participants: 152 adults with CS and uncontrolled HTN and/or hyperglycemia (DM/IGT)
 - N=31 with HTN, n=50 with DM/IGT, n=71 with both
 - OL Phase Results (relacorilant 100mg daily, up to 400 mg daily, as tolerated): rapid and sustained improvements in blood pressure (ambulatory blood pressure monitoring)



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/m ² , 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]

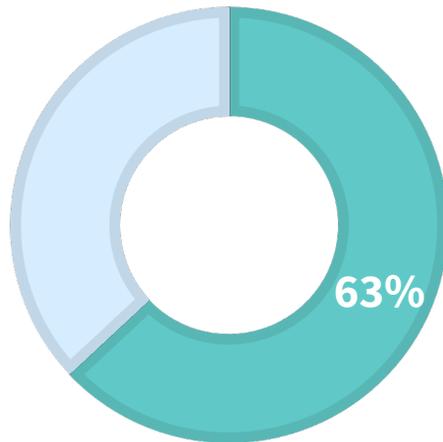


Additional GRACE Trial Results: OL Phase



Patients with DM/IGT with or without HTN(n=121) mean change (SD)

- AUC (glucose): -3.3 (6.7) h*mmol/L; P<.0001
- HbA1c: -0.3% (1.0%); P<.001)



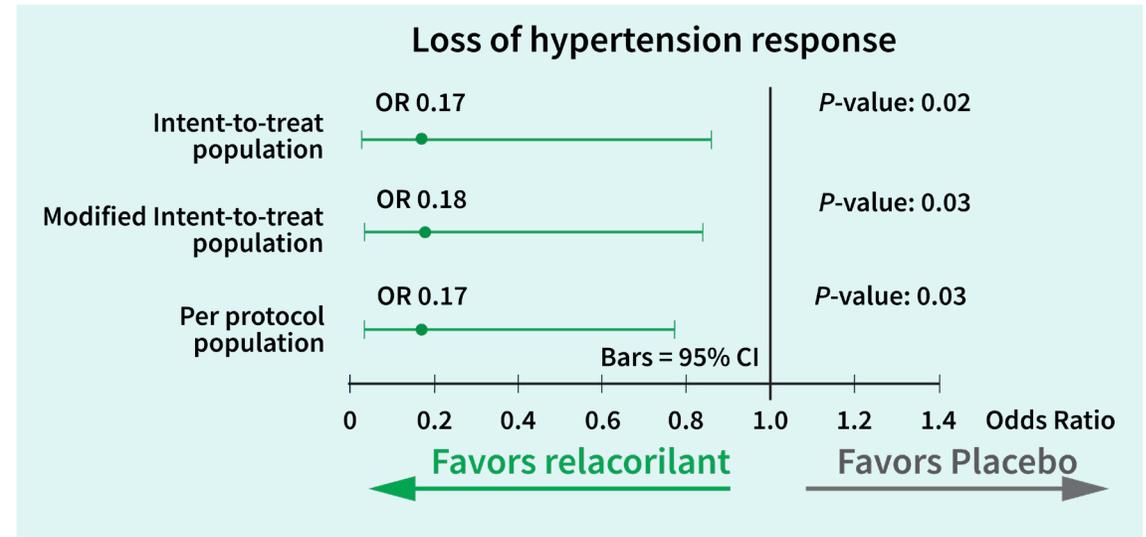
Patients who achieved HTN and/or hyperglycemia control

Relacorilant

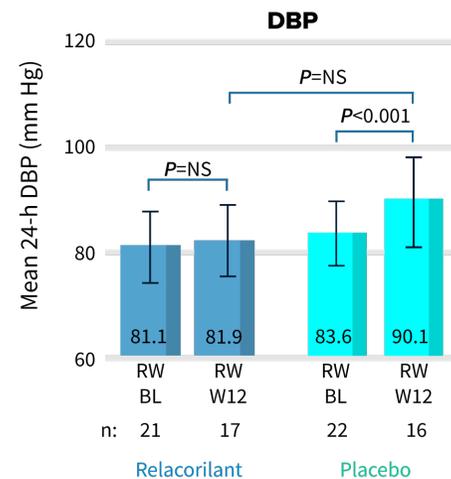
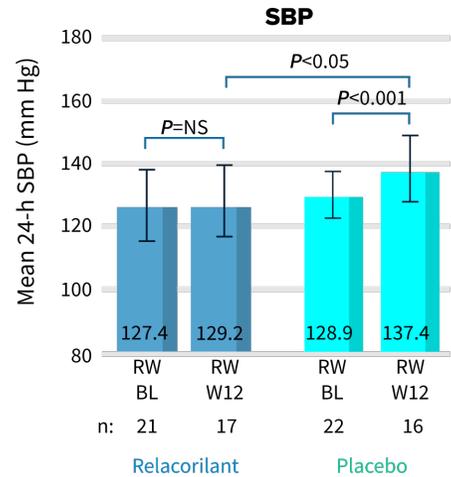


GRACE Study Continued: Efficacy during RW phase

- 65% of patients who completed the OL phase continued to the RW phase
- N=32 receiving placebo; n=30 continued with relacorilant
- RW Phase Results
 - Blood Pressure: patients taking placebo more likely to lose control of HTN and patients receiving relacorilant were 6x more likely to maintain HTN response
 - Systolic Blood Pressure: -12.6 (6.5) mm Hg; P<.0001
 - Diastolic Blood Pressure : -8.3 (4.9) mm Hg; P<.001)
 - Glycemic Control:
 - AUC (glucose): -6.2 (6.5) h*mmol/L; P<.0001
 - HbA1c: -0.7% (1.1%); P<.001)
 - Other Metabolic Parameters:
 - Weight Loss: -3.3 (5.9) kg, P<.0001
 - Waist Circumference: -2.8 (6.2) cm, P<.0001
 - Improvements in Quality of Life (QoL):
 - +7.4 (14.6) points on Cushing QoL normalized total score, P<.0001



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)	20.0 (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)

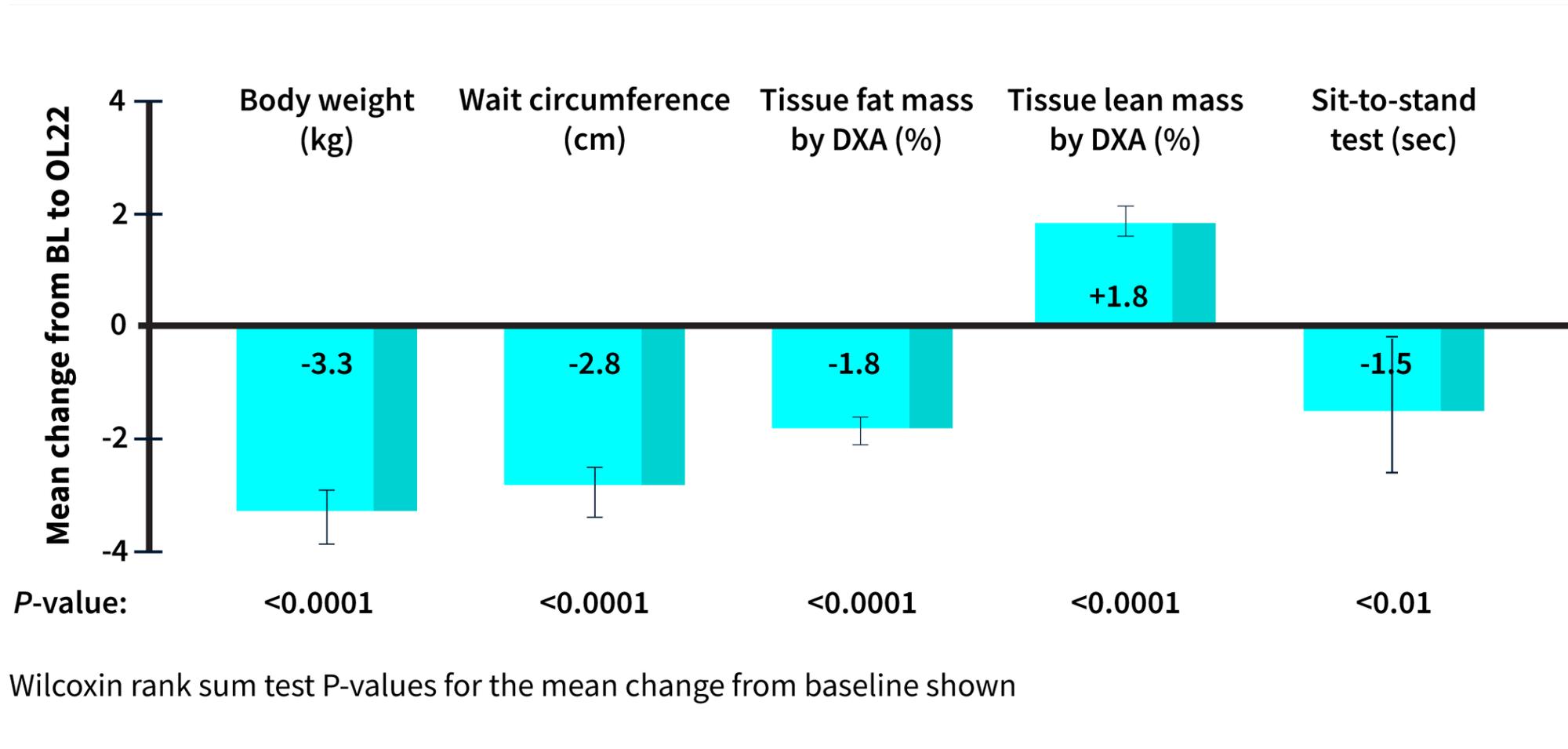
GRACE Trial Results: Withdrawal Phase, Impact on Glycemic Measures



	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 <ul style="list-style-type: none"> • N • Mean (SD) • Wilcoxon signed rank sum P-value^a 	15 +1.1 (4.7) ns	19 +4.9 (6.1) 0.0003
Change from RW baseline to week RW12 in HbA1c (in patients with hyperglycemia at study entry), % <ul style="list-style-type: none"> • N • Mean (SD) • Wilcoxon signed rank sum P-value^a 	16 +0.1 (0.8) ns	19 +0.3 (0.6) 0.03
Change from RW baseline to week RW12 in HbA1c (in patients with diabetes at study entry), % <ul style="list-style-type: none"> • N • Mean (SD) • Wilcoxon signed rank sum P-value^a 	13 +0.1 (0.8) ns	13 +0.4 (0.6) 0.04

^aWilcoxin signed-rank test P-values within each treatment arm

GRACE Trial Results: Impact of Relacorilant on Body Composition



Relacorilant



GRACE Study Continued: Safety Profile

- Overall: efficacy observed without serious side effects



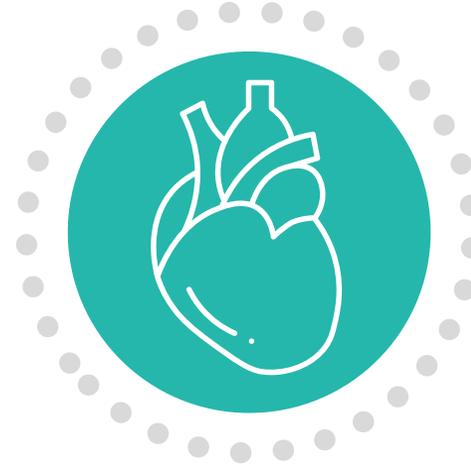
Metabolic Side Effects:

- No increase in cortisol concentrations
- No hypokalemia associated with excess cortisol



Gynecologic Side Effects:

- No excess vaginal bleeding
- No endometrial hyperplasia



Cardiac Side Effects:

- No confirmed QT interval prolongation



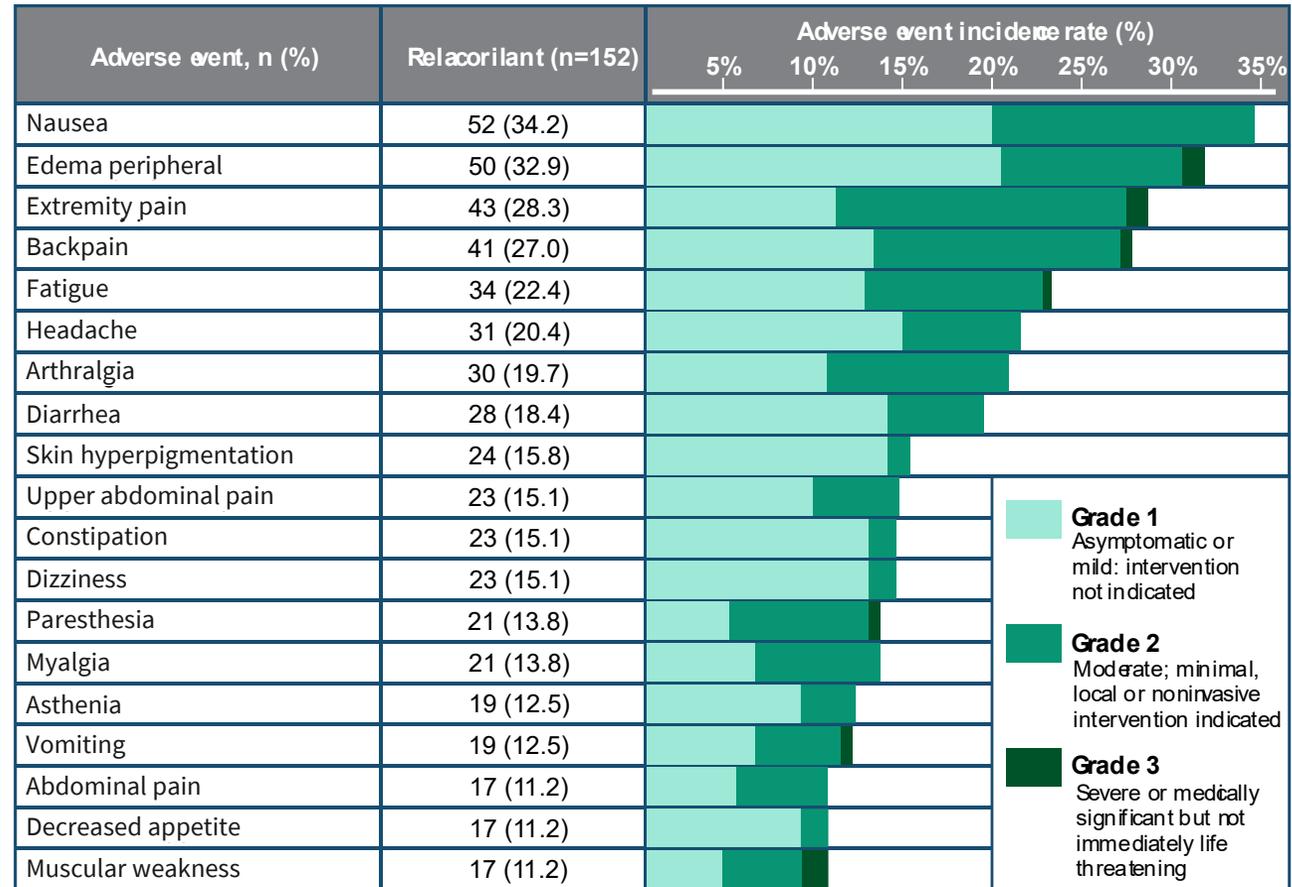
Common adverse events:

- Nausea, peripheral edema, pain in extremity, back pain, and fatigue ($\geq 20\%$)

GRACE Trial Results: Safety



Adverse events occurring in $\geq 10\%$ of patients



Data updated based on database lock: analysis date 5 July 2024, TEAE's and CTCAE grade shown.

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 as soon as possible to determine the path forward.

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:

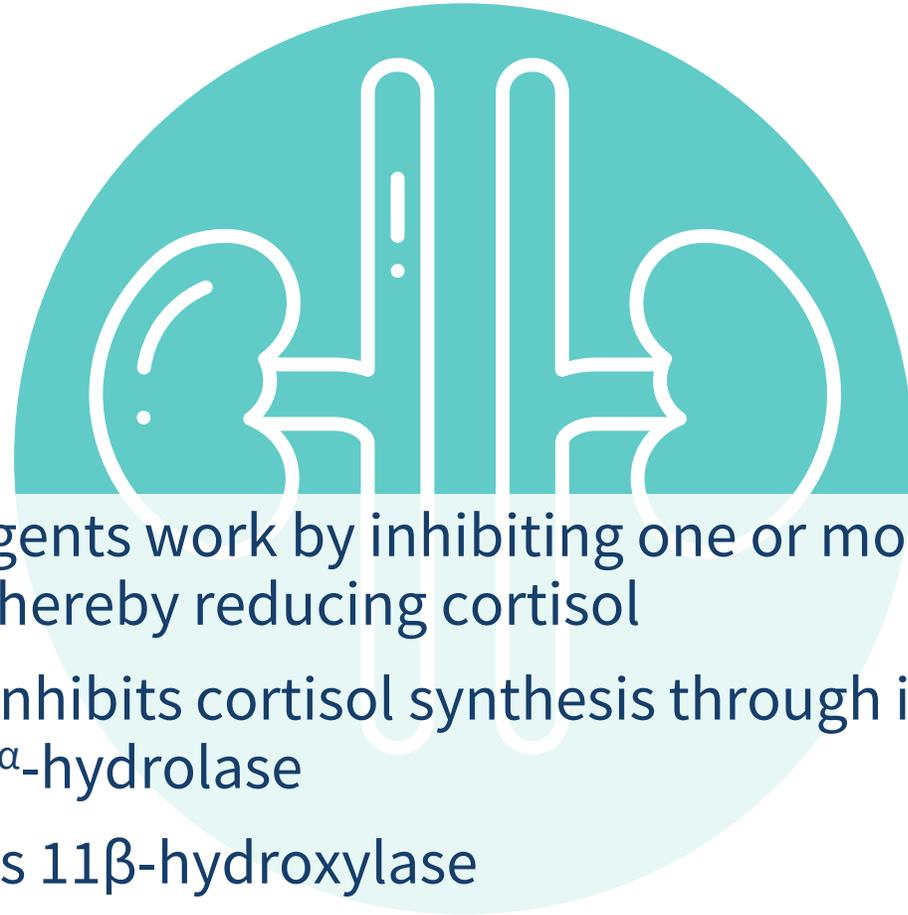
- Use other drugs influencing QT or inducing hypokalemia
- Use a combination of different medications for CS both inducing longer QT intervals

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



Adrenal- Directed Agents: Steroidogenesis Inhibitors

Mechanism of Action



- Adrenal-Directed Agents work by inhibiting one or more enzymes necessary for cortisol synthesis, thereby reducing cortisol
- Levoketoconazole inhibits cortisol synthesis through inhibition of 11 β -hydroxylase and 17 α -hydroxylase
- Osilodrostat inhibits 11 β -hydroxylase
- Other agents used off-label: ketoconazole, etomidate, metyrapone, mitotane

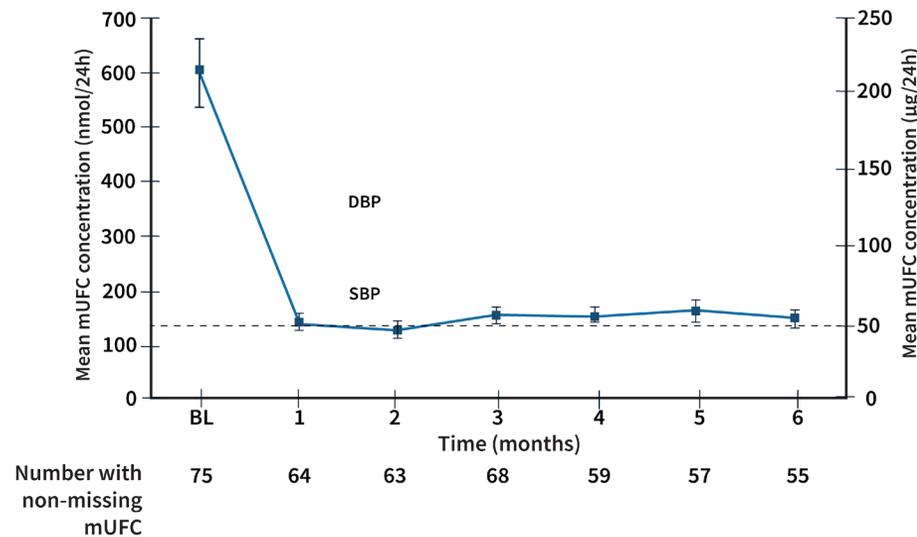
Levoketoconazole



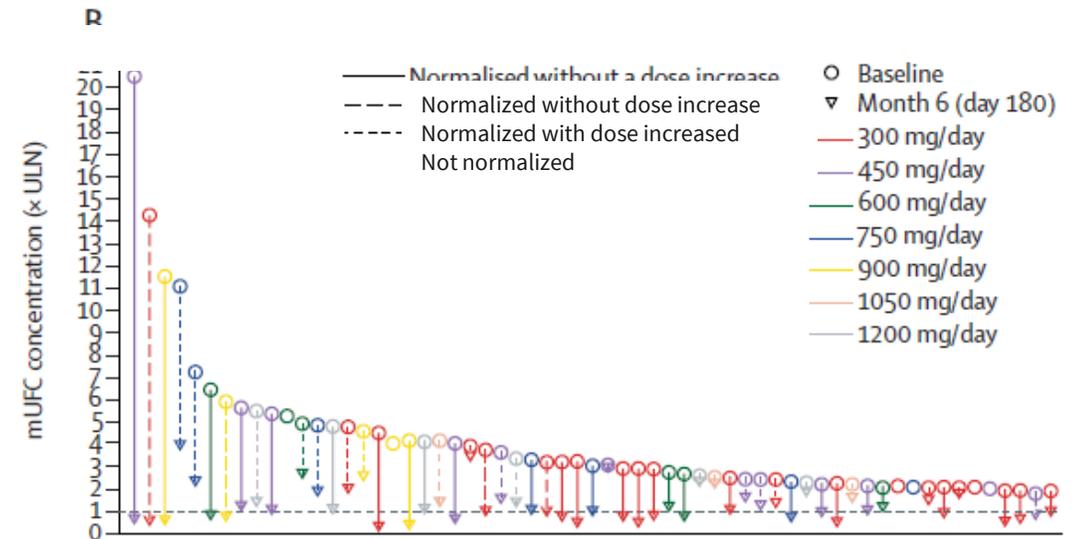
SONICS Study: Efficacy

- Primary outcome: proportion of patients with mUFC normalization at end of maintenance, without dose increase during the maintenance

mUFC Concentration From Baseline of the Dose Titration Phase Through the End of the Maintenance Phase (Month 6)



Change in Individual mUFC Concentrations From Baseline of the Dose Titration Phase to the End of Maintenance Phase (Month 6)



Levoketoconazole



SONICS Study: Safety

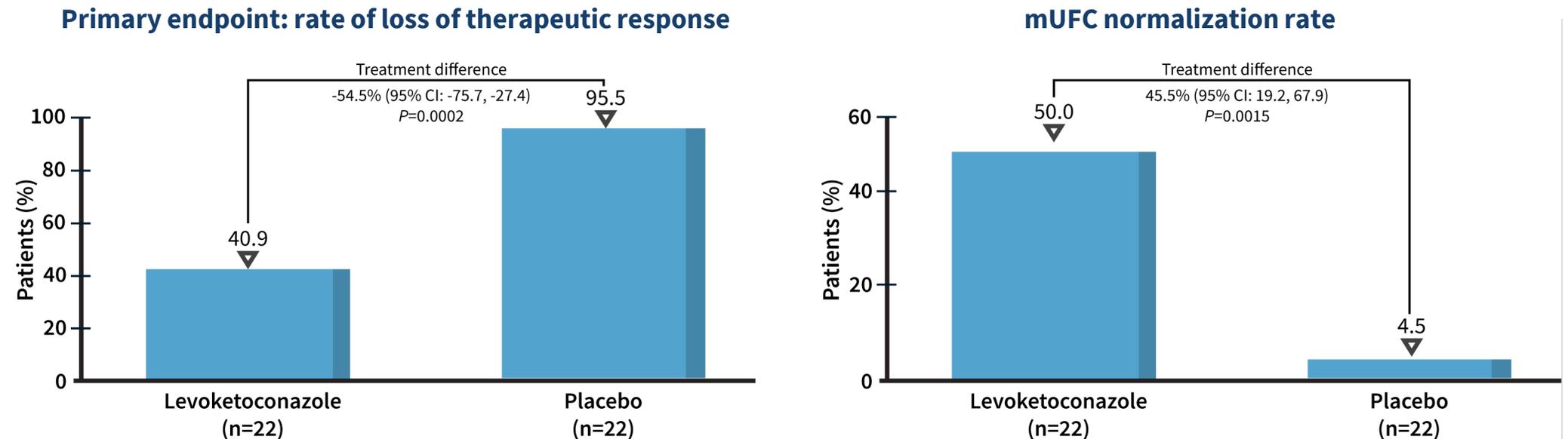
	Patients (n=94)
Any adverse event	92 (98%)
• Serious adverse event	14 (15%)
• Drug-related adverse event	40 (43%)
• Adverse event leading to discontinuation	12 (13%)
Intensity of adverse events	
• Mild	21 (22%)
• Moderate	54 (57%)
• Severe	15 (16%)
• Life threatening	1 (1%)
• Death	1 (1%)
Most common adverse events	
• Nausea	30 (32%)
• Headache	26 (28%)
• Peripheral edema	18 (19%)
• Hypertension	16 (17%)
• Fatigue	15 (16%)
• Diarrhea	14 (15%)
• ALT increase	14 (15%)
• GGT increase	12 (13%)
• AST increase	11 (12%)

Levoketoconazole



LOGICS Study

- Phase 3, placebo-controlled, randomized-withdrawal study with open-label titration-maintenance (14–19 weeks) followed by double-blind, randomized-withdrawal (~ 8 weeks), and restoration (~ 8 weeks) phases

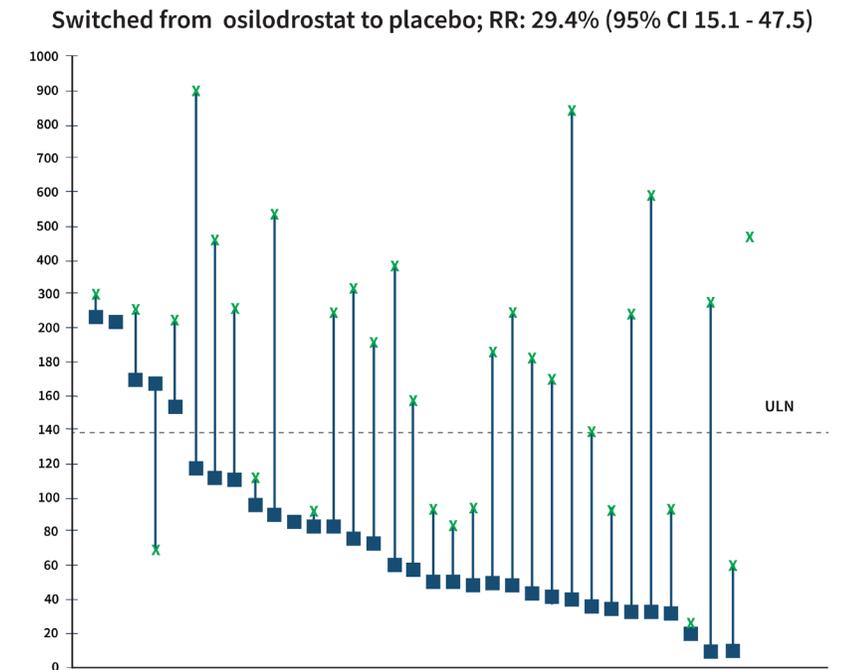
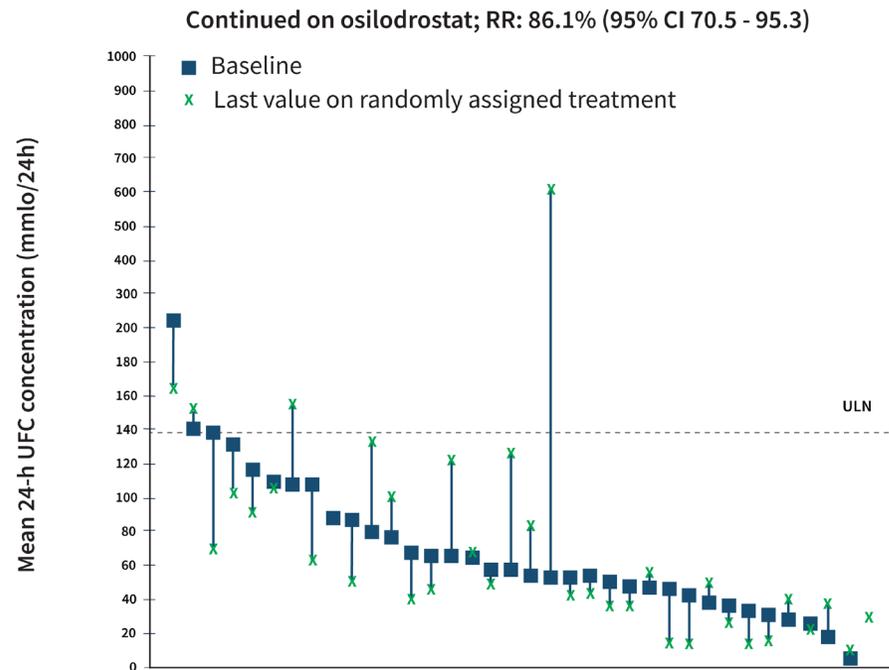


Osilodrostat



LINC-3 Study: Phase 3 Safety and Efficacy in Cushing Disease

- Primary endpoint: Proportion of participants with a complete response (ie, mean 24-h UFC concentration of \leq ULN) at the end of the randomized withdrawal period (week 34), without up-titration during this period (N=137)
- Hypocortisolism occurred in 51% patients and AEs related to adrenal hormone precursors occurred in 42% patients
- Most common adverse events (ie, occurred in >25% of participants) were:
 - nausea (42%)
 - headache (34%)
 - fatigue (28%)
 - adrenal insufficiency (28%)

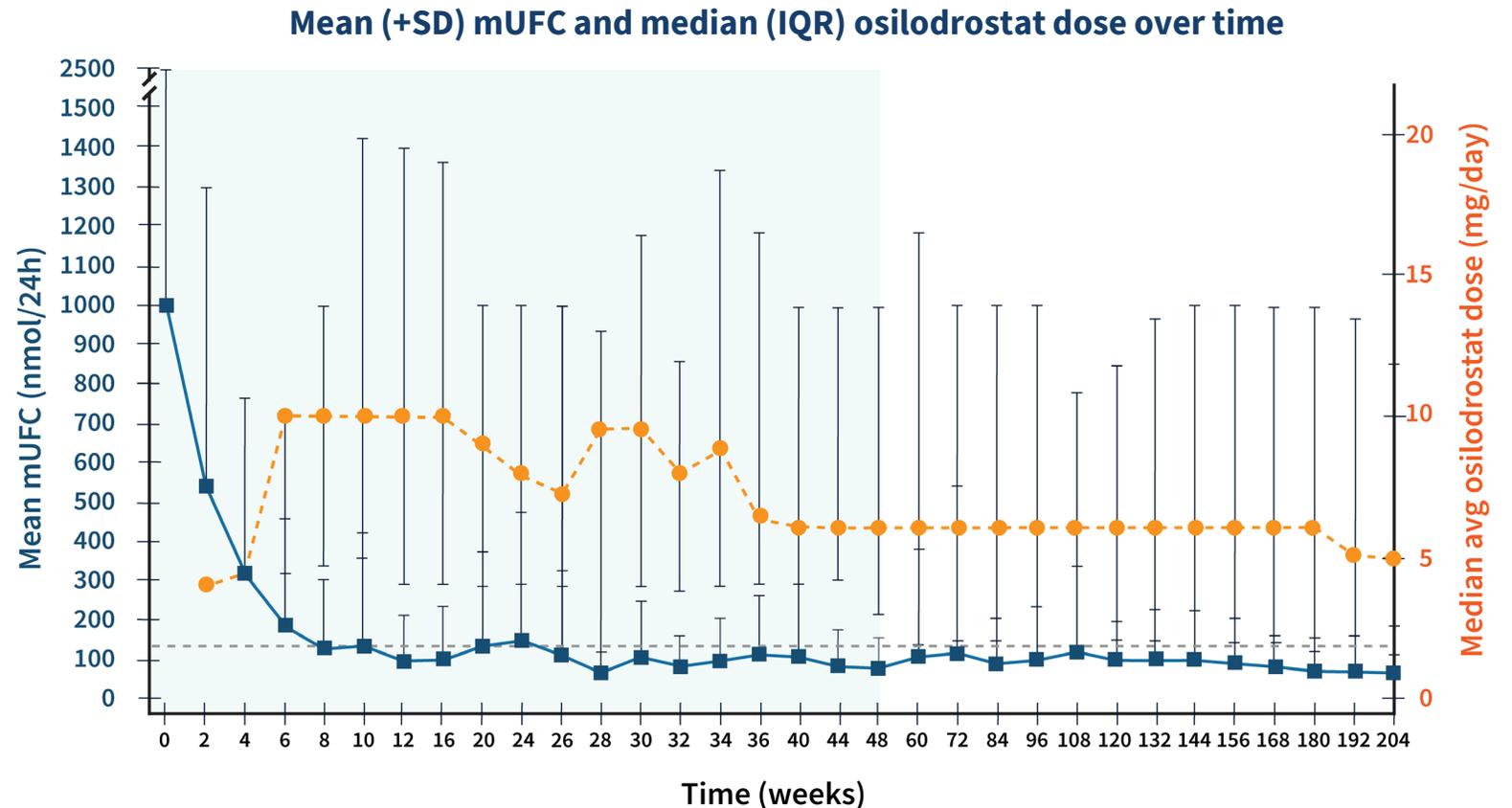


Osilodrostat



LINC-3 Extension Study: Long-Term Outcomes in Cushing Disease

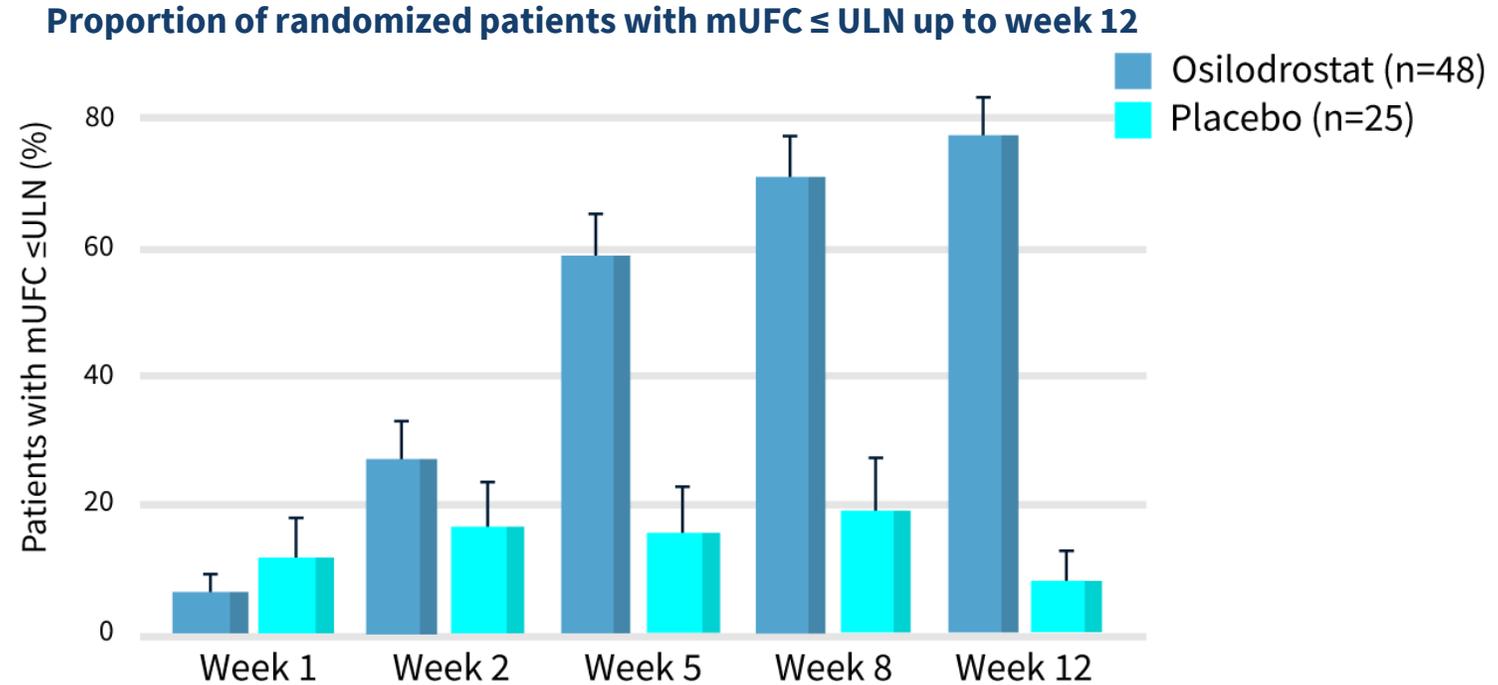
- Rates of mUFC normalization: 66.4% at week 48; 81.1% at week 60; 81.1% at week 72
- Improvements in cardiovascular/metabolic-related parameters, physical manifestations of hypercortisolism, and quality of life were maintained or improved further during the extension
- No new safety signals were reported: 10.9% (core) and 11.3% (extension) patients discontinued for adverse events



Osilodrostat



LINC-4: Osilodrostat in the Treatment of Cushing Disease



The most common AEs during the placebo-controlled period included decreased appetite (37%), arthralgia (35%), and nausea (31%).

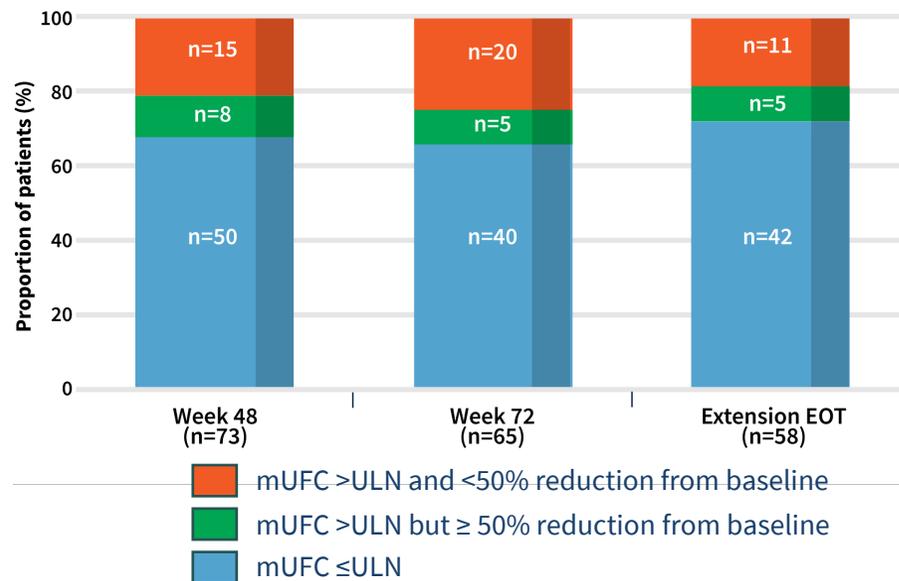
Osilodrostat



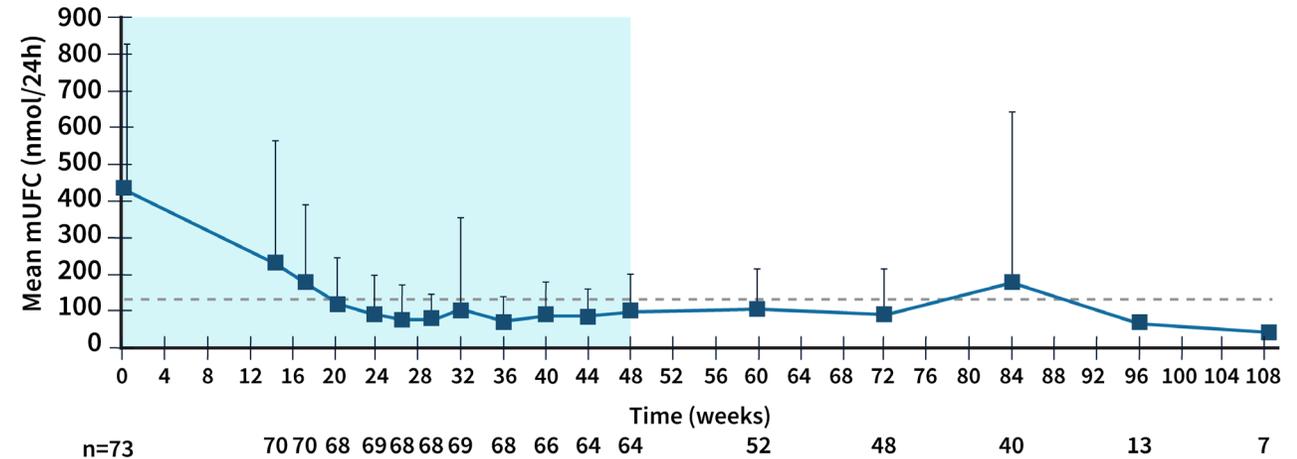
LINC-4 Extension Study:

Long-Term Efficacy and Safety of Osilodrostat in the Treatment of Cushing Disease

Proportion of patients with mUFC response over time



Mean mUFC over time



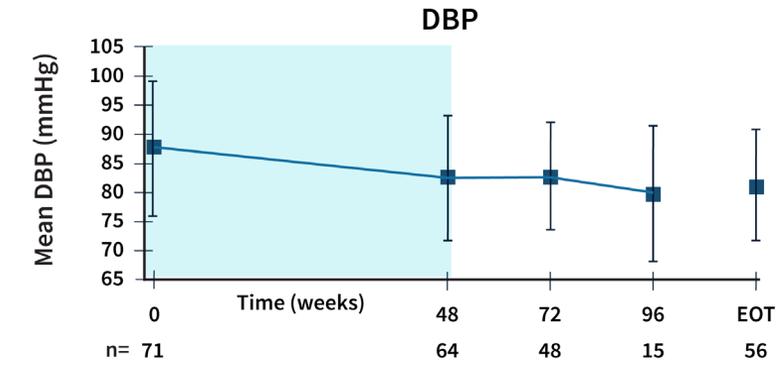
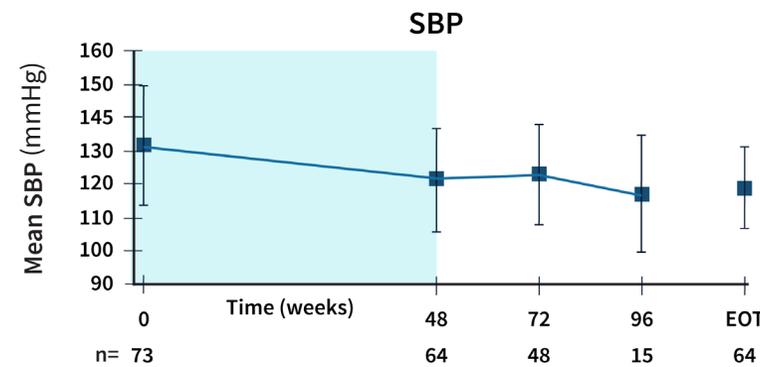
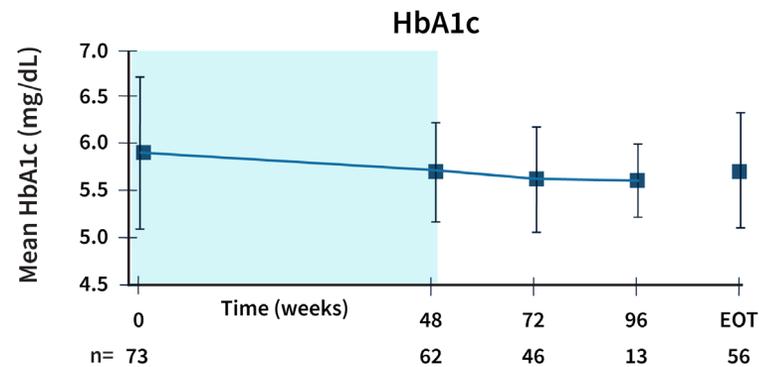
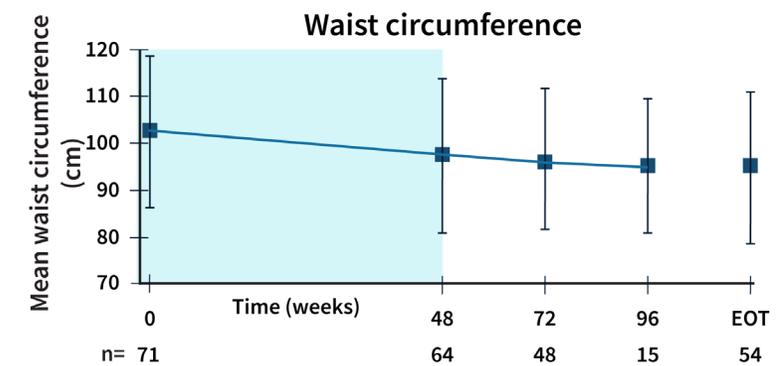
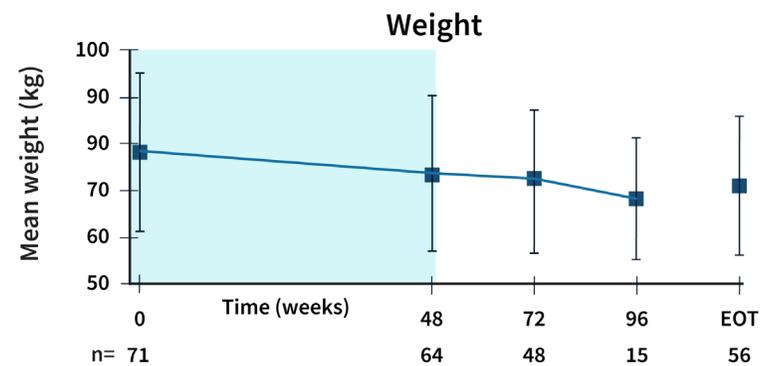
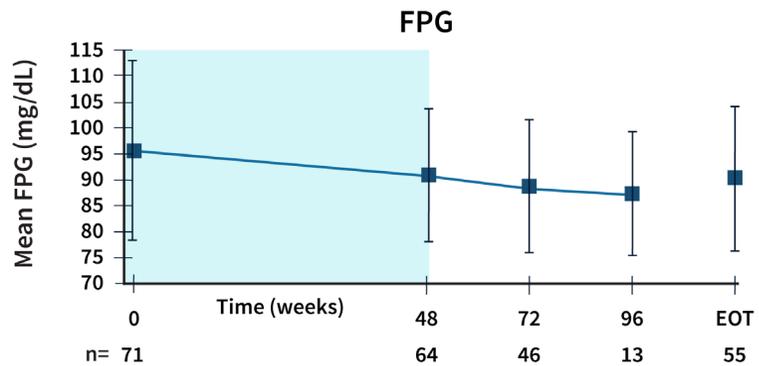
Osilodrostat



LINC-4 Extension Study:

Long-Term Efficacy and Safety of Osilodrostat in the Treatment of Cushing Disease

Changes in cardiovascular-related metabolic



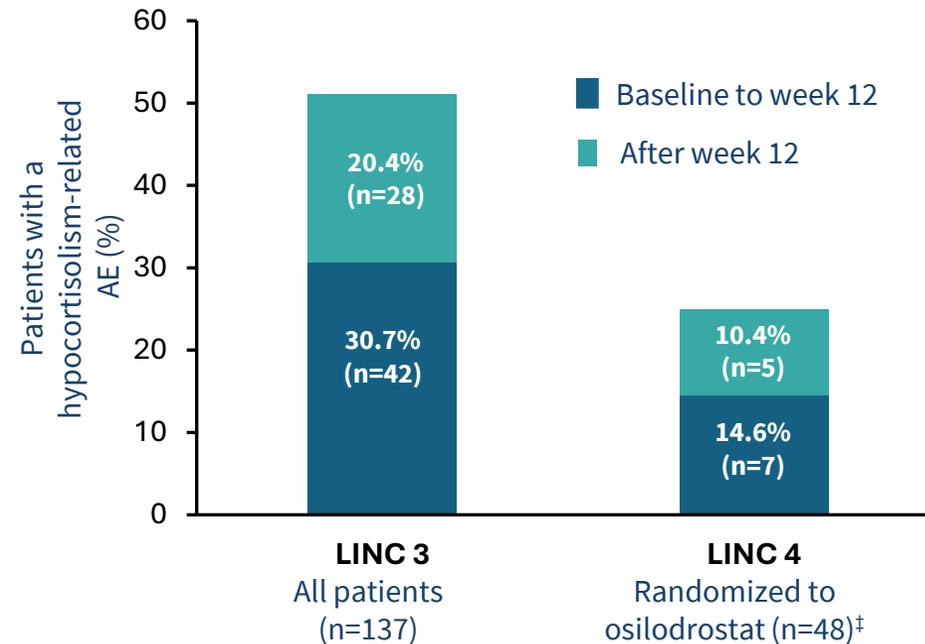
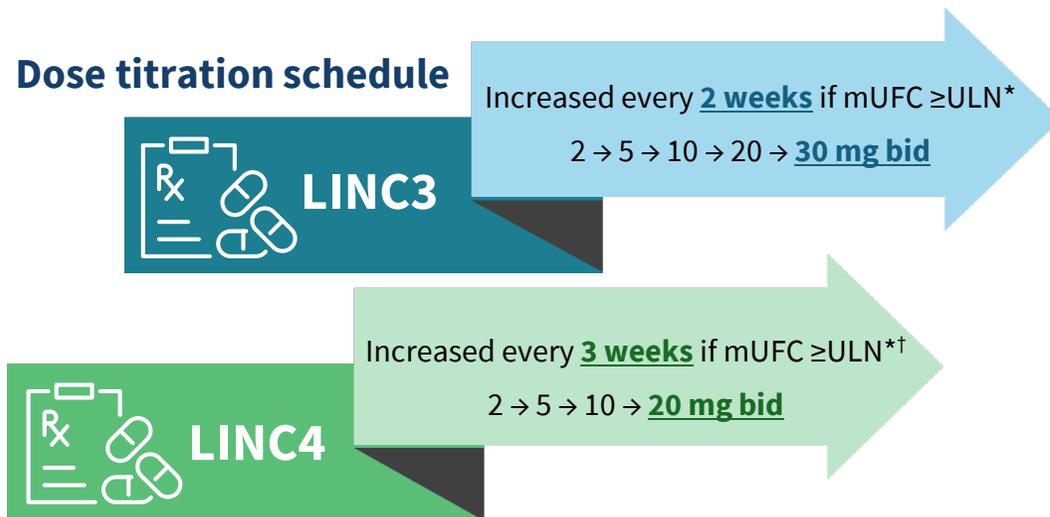
Osilodrostat



Dose Increases and Hypocortisolism-Related Adverse Events

Osilodrostat: initiated at a low dose, with incremental dose increases based on individual response/tolerability

- Monitor for:
 - Adrenal insufficiency
 - Hypo/Hyperkalemia
 - Pituitary tumor changes in CD



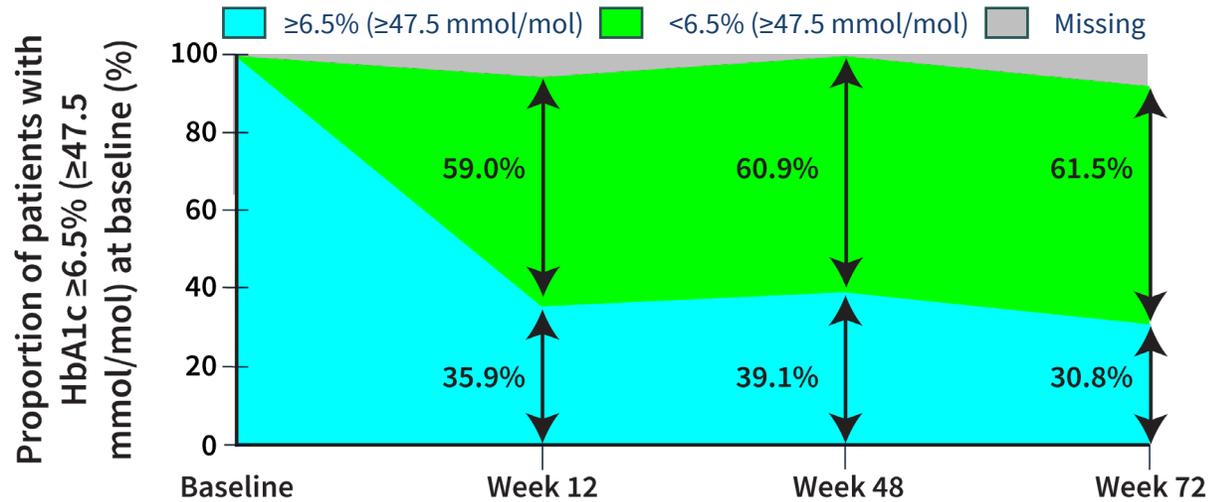
*Provided no tolerability issues; †In LINC 4, dose titration decisions were made by independent non-blinded endocrinologists until week 12; ‡Patients randomized to osilodrostat during the initial 12-week randomized, double-blind, placebo-controlled period; 8 patients who were initially randomized to placebo also experienced a hypocortisolism-related AE after switching to open-label osilodrostat

Osilodrostat

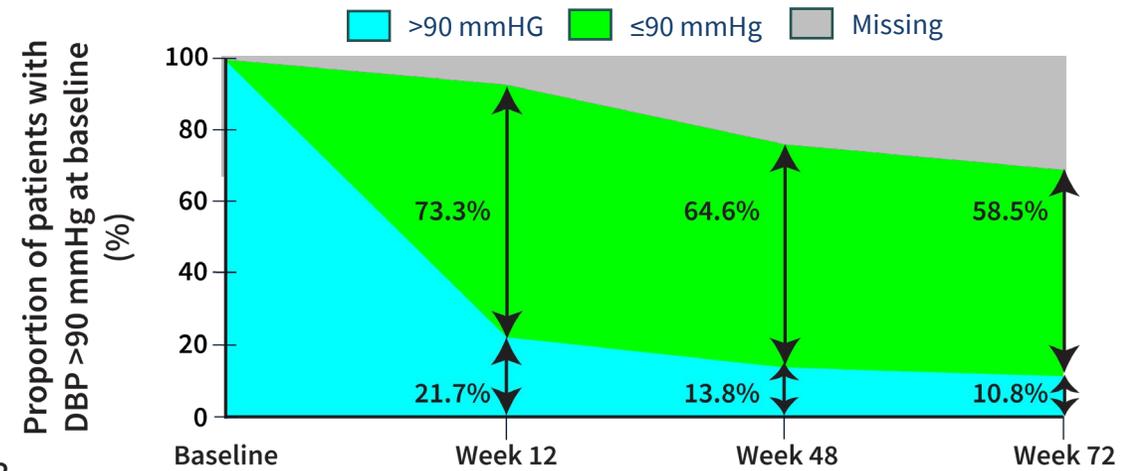


Linc Studies (N=210)- Effect on metabolic parameters

Effect on Glucose



Effect on Blood Pressure



Osilodrostat: LINC 6



- Long-Term, Real-World, Safety and Effectiveness of Osilodrostat In Patients With Pituitary and Non-Pituitary Cushing's Syndrome: 2-Year Interim Data From LINC 6
- 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).

Osilodrostat 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.

Osilodrostat 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.

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 ISTURISA[®] (osilodrostat) for the treatment of endogenous hypercortisolemia in adults with Cushing syndrome.



Reduce Cortisol in Peripheral Tissues

11 β -HSD1 inhibitors



- 11 β -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 11 β -HSD1 inhibitor evaluated in a Phase I/IIa open-label Japanese trial
 - **AZD4017** by AstraZeneca, a selective 11 β -HSD1 inhibitor, was evaluated in the TICS1 trial

Clofutriben for endogenous Cushing Syndrome - Phase 2 Rescue Trial

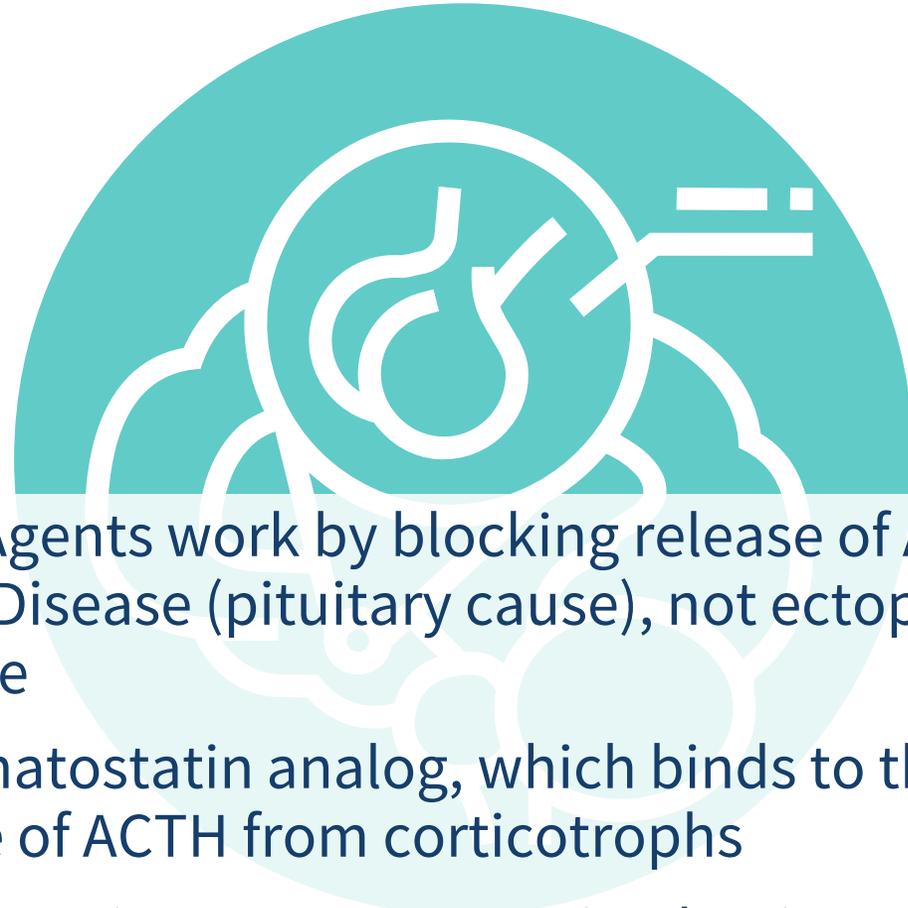


- **>60% of patients normalized urinary free cortisol (UFC)** without suppressing serum cortisol to levels indicating adrenal insufficiency risk
 - Morning serum cortisol levels remained >10 ug/dL, demonstrating no signs of adrenal insufficiency
- Metabolic and cardiovascular improvement:
 - **HbA1c 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



Pituitary- Directed Agents

Mechanism of Action



- Pituitary-Directed Agents work by blocking release of ACTH, therefore ONLY work for Cushing's Disease (pituitary cause), not ectopic Cushing or adrenal Cushing's Syndrome
- Pasireotide is a somatostatin analog, which binds to the somatostatin receptor to block the release of ACTH from corticotrophs
- Cabergoline is a dopamine receptor agonist that is used off-label

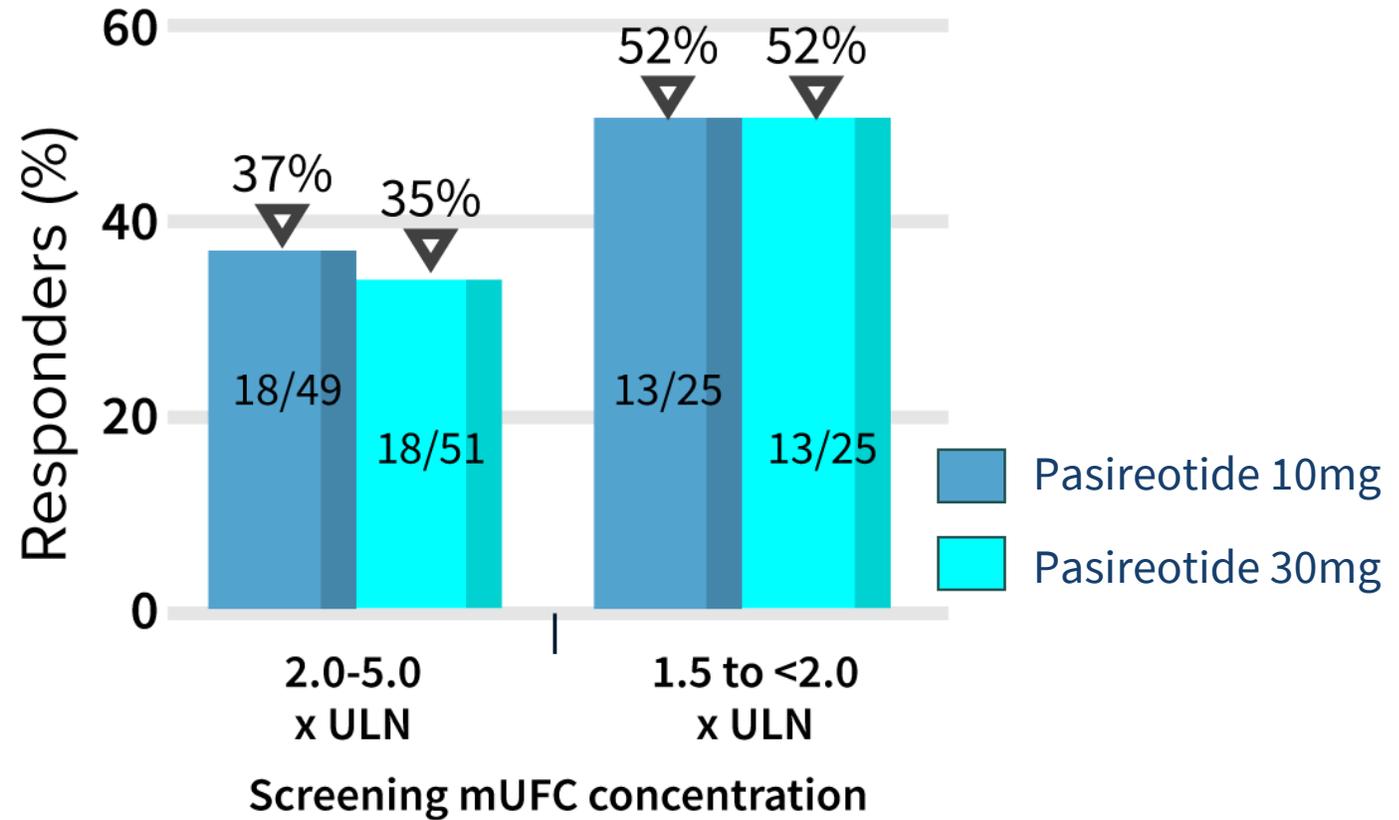
Pasireotide LAR



Phase 3 study in Cushing Disease

Proportion of patients with an mUFC concentration \leq ULN at month 7, according to mUFC stratum

Primary endpoint:
Proportion of patients with an mUFC concentration \leq ULN at month 7 (N=150)



Pasireotide LAR Safety Profile



Phase 3 study in Cushing Disease

- The most common AEs were:
 - Hyperglycaemia (49% in the 10 mg group and 47% in the 30 mg group)
 - Diarrhea (35% and 43%)
 - Cholelithiasis (20% and 45%)
 - Diabetes mellitus (19% and 24%)
 - Nausea (20% and 21%)

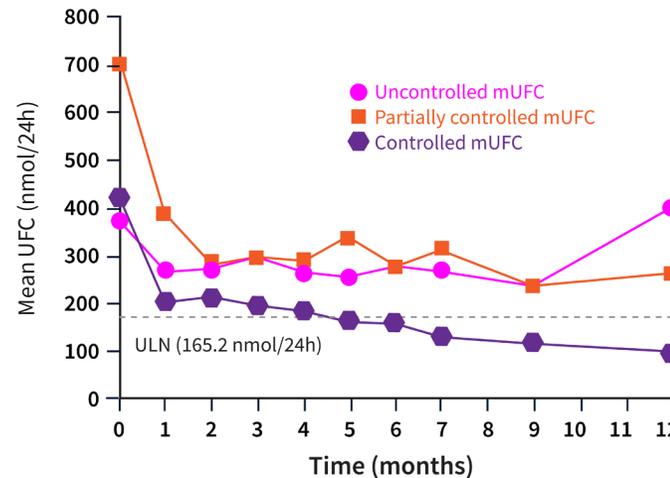
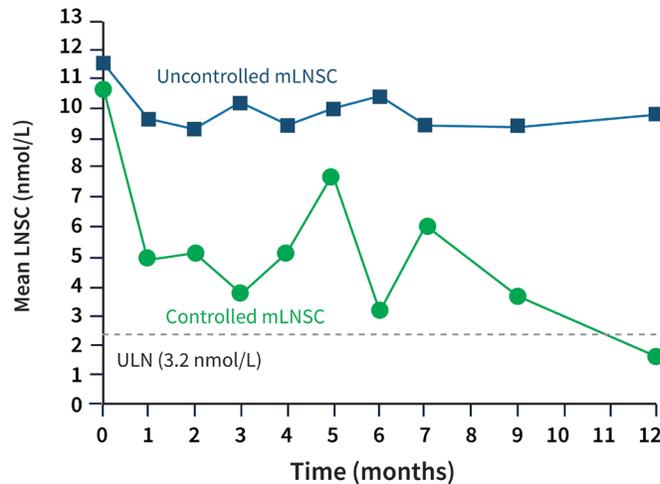
Pasireotide LAR



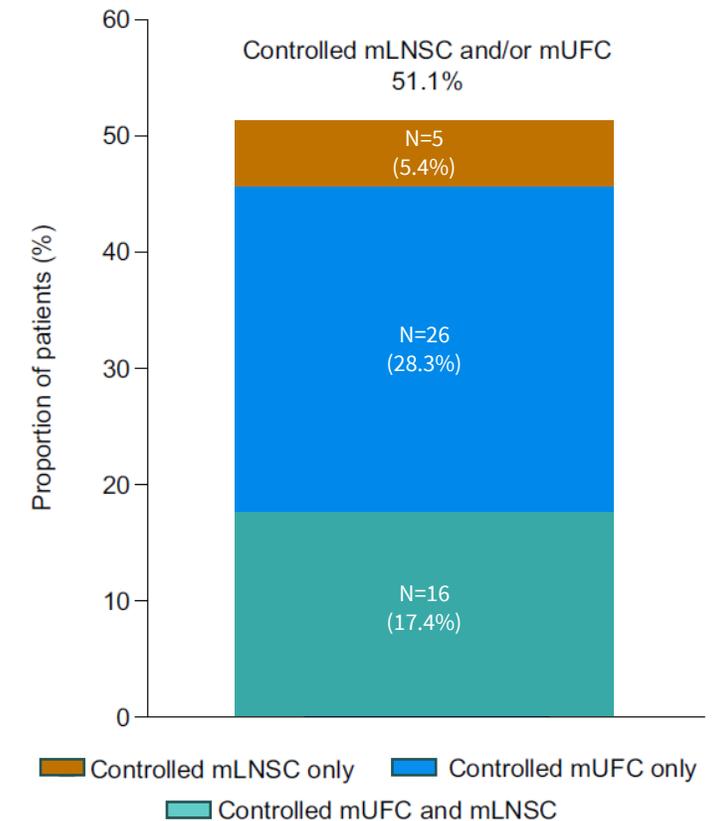
Phase 3 study in Cushing Disease: Clinical Improvement

- Exploratory analysis evaluating LNSC of long-acting pasireotide in Cushing's disease (N=137)

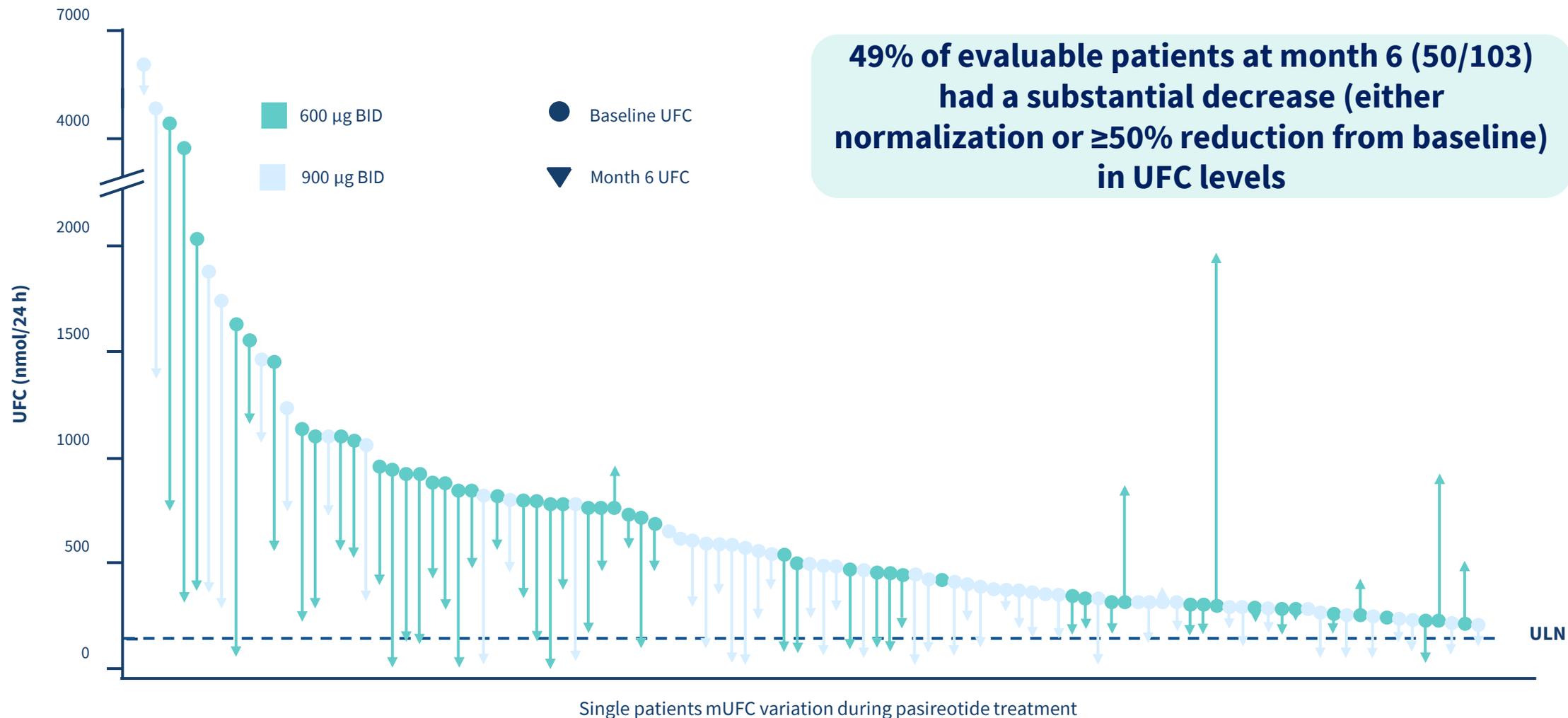
mLNSC and mUFC levels at baseline and during LAR pasireotide treatment according to mLNSC and mUFC response status respectively at month 12



Proportion of patients with controlled mLNSC and/or mUFC at month 12



Pasireotide Efficacy in Reducing UFC Levels



UFC, urinary free cortisol; ULN, upper limit of normal.
Colao A, et al. *N Engl J Med.* 2012.

Safety Profile: Most Common AEs at 12 Months



AE	Overall (N=162)	
	All grades n (%)	Grades 3 or 4 n (%)
Hyperglycaemia related	118 (72.8)	40 (24.7)
Diarrhoea related	95 (58.6)	5 (3.1)
Nausea related	85 (52.5)	4 (2.5)
Gallbladder and biliary related	54 (33.3)	4 (2.5)
Liver chemistry related	26 (16.0)	7 (4.3)
Bradycardia related	23 (14.2)	3 (1.9)
Hypocortisolism related	13 (8.0)	4 (2.5)
QT prolongation related	13 (8.0)	4 (2.5)
Hypothyroidism related	7 (4.3)	0

Grading (1–4) of AEs follows the US HHS Common Terminology Criteria for Adverse Events (CTCAE) 2009. Common AE terms were pooled.

Colao A, et al. *N Engl J Med*. 2012.

6% of patients discontinued due to hyperglycaemia-related AEs

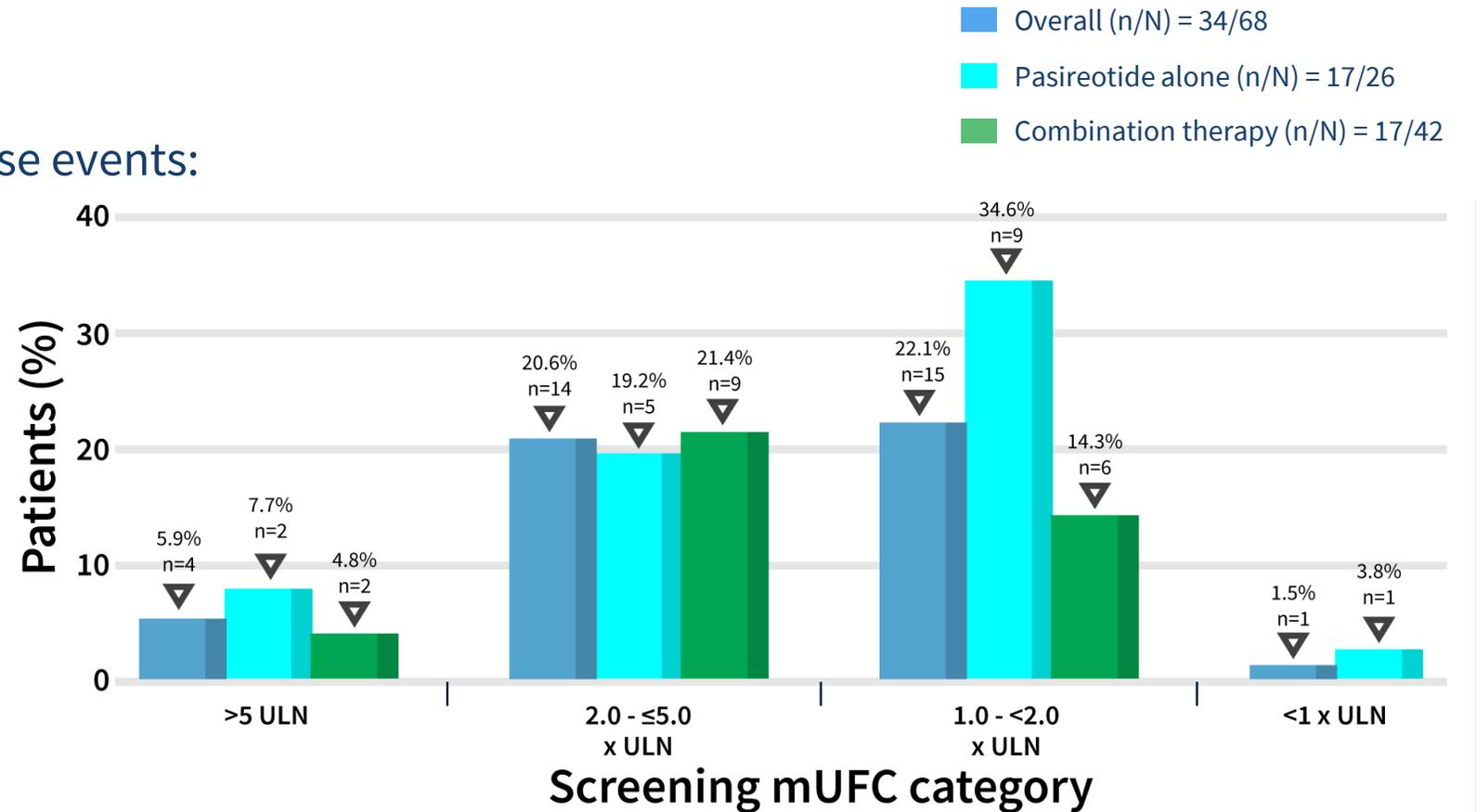
Combination Pasireotide LAR and Cabergoline



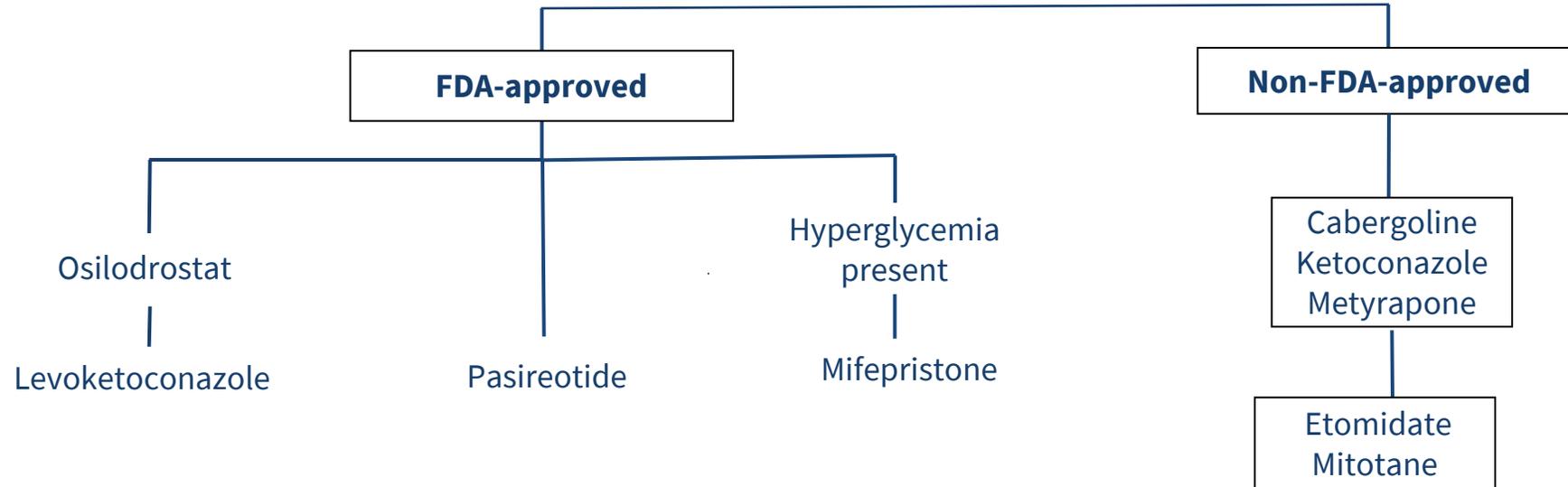
Primary endpoint: Proportion of patients with a mUFC level not exceeding the ULN at week 35 (N=68)

Safety: most common adverse events:

- Hyperglycemia (51.5%)
- Nausea (51.5%)
- Diarrhea (44.1%)
- Cholelithiasis (33.8%)



Medical Management of Cushing Syndrome



Special circumstances

- Etomidate for parenteral usage in severe hypercortisolism
- Metyrapone and cabergoline during pregnancy
- Pasireotide in patients with large tumors
- Combination therapies in patients with severe hypercortisolism
- Cabergoline or ketoconazole may be considered as first-line drug therapy when the cost is an issue
- Temozolomide in patients with aggressive or metastatic disease



Medical Management Monitoring

Monitoring Medical Therapy for Cushing Syndrome: Expert Recommendations



1

Monitor biochemical response

- Not applicable to mifepristone
- Serial urinary free cortisol and late-night salivary cortisol
- Morning serum cortisol as needed to assess adrenal insufficiency

2

Monitor clinical response

- Weight, blood pressure, skin condition, muscle strength, glycaemic control

3

Monitor for adverse effect or intolerance

- Metabolic parameters prior to any new drug therapy
- Liver enzymes with ketoconazole, levoketokonazole, mitotane and pasireotide
- Electrocardiogram (QT interval) prior to ketoconazole, levoketokonazole, osilodrostat, metyrapone, mitotane, mifepristone and pasireotide

4

Close monitoring

- Hypertension and oedema with osilodrostat, metyrapone and mifepristone
- Acne and hirsutism with metyrapone and osilodrostat
- Male hypogonadism with ketoconazole and levoketoconazole
- Hyperglycaemia with pasireotide
- Impulse control disorders with cabergoline

5

Monitor for corticotroph tumour mass progression

- Adrenocorticotrophic hormone levels and MRI every 6-12 months with adrenal steroidogenesis inhibitors and mifepristone
- MRI as needed with pituitary-targeted therapy based on initial tumour mass size

6

Periodic assessments during treatment

- Potassium & magnesium with ketoconazole, levoketokonazole, osilodrostat, metyrapone, mifepristone & pasireotide
- Liver enzymes w/ ketoconazole, levoketokonazole, metyrapone & pasireotide
- Electrocardiogram w/ ketoconazole, levoketokonazole, metyrapone, mifepristone & pasireotide
- Consider adrenal insufficiency or glucocorticoid withdrawal with all meds. If adrenal insufficiency is present: dexamethasone (2-4mg) w/ mifepristone, hydrocortisone for all other therapies

Safety Comparison of Classes



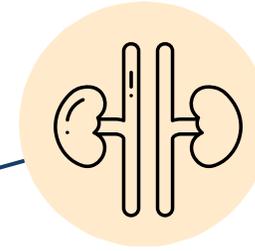
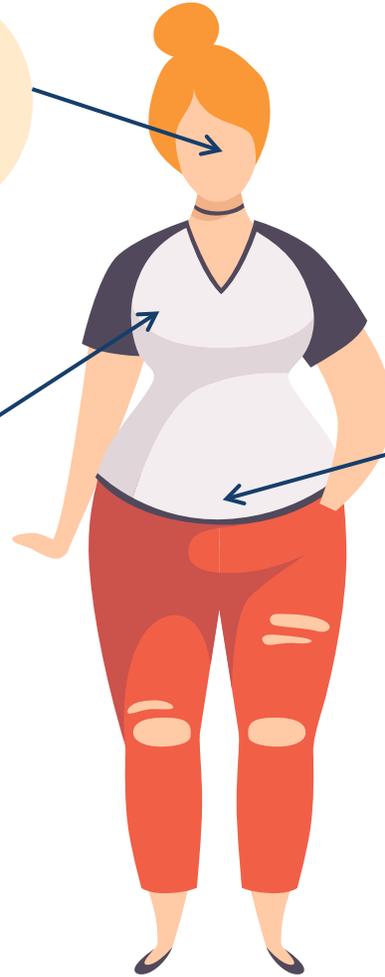
Pituitary-Directed Agents

- Hyperglycemia common in first 3 months
- Works for pituitary causes of Cushing Disease ONLY



Glucocorticoid Receptor Blocker/Modulator

- Need to titrate dose slowly to prevent glucocorticoid withdrawal syndrome
- Can have increases in blood pressure- consider initiating with spironolactone



Adrenal-Directed Agents: Steroidogenesis Inhibitors

- Overtreating causes adrenal insufficiency, hypotension, and hypoglycemia
- Monitor carefully for QT prolongation
- Accumulation of adrenal hormone precursors