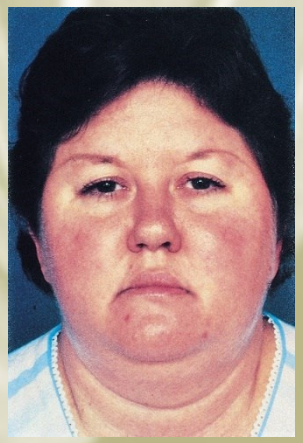
Resistant Cushing's Syndrome

האם אותה גברת בשינוי אדרת ?

Ilan Shimon, MD

Beilinson-Rabin Medical Center Israel

מרכז רפואי רבין
בית חולים בילינסון



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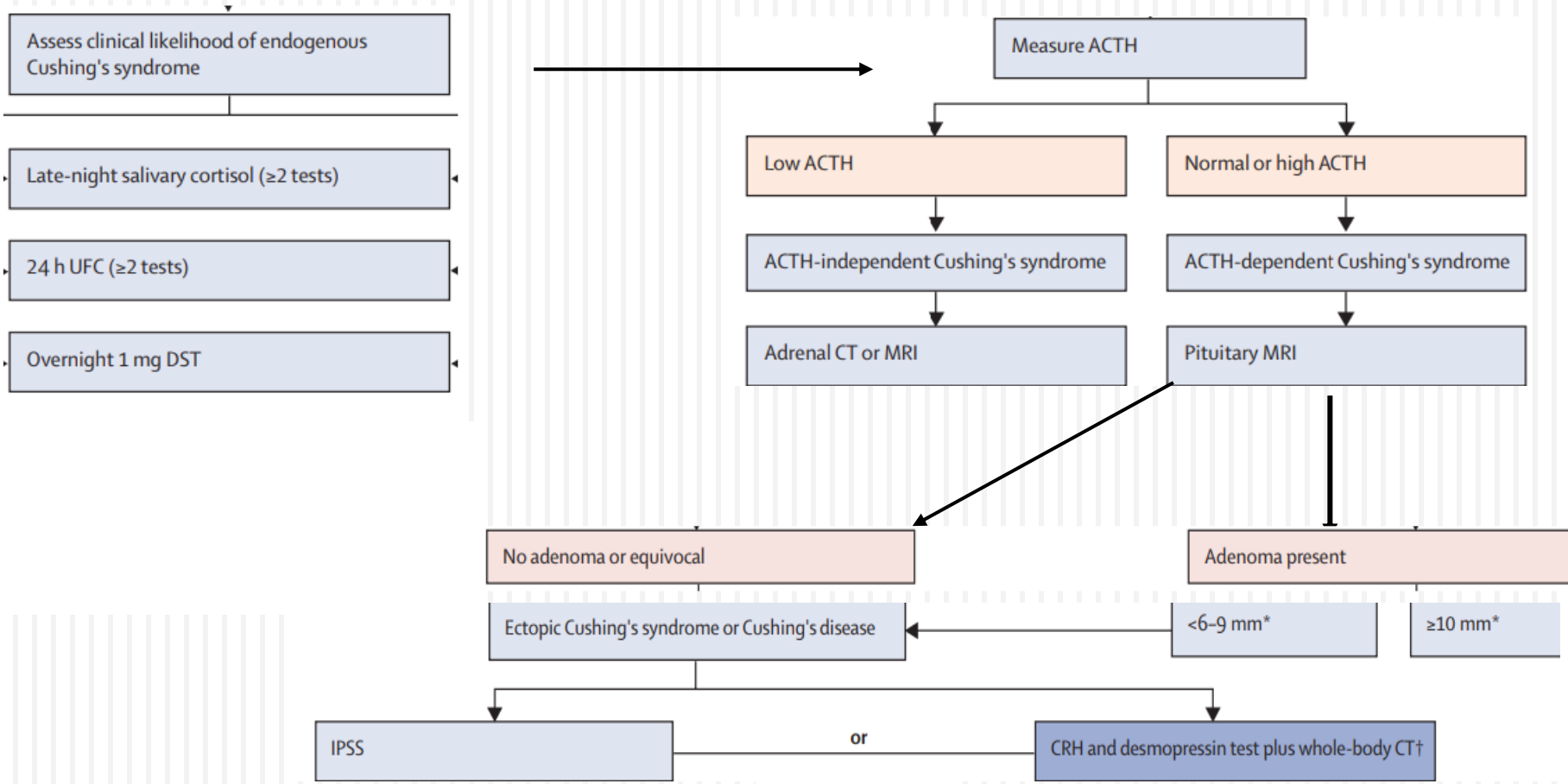
Disclosure

- This presentation is supported by NEOPHARM Israel
- Prof. Shimon served as principal investigator for the SONICS and LOGICS clinical trials

Consensus on diagnosis and management of Cushing's disease: a guideline update

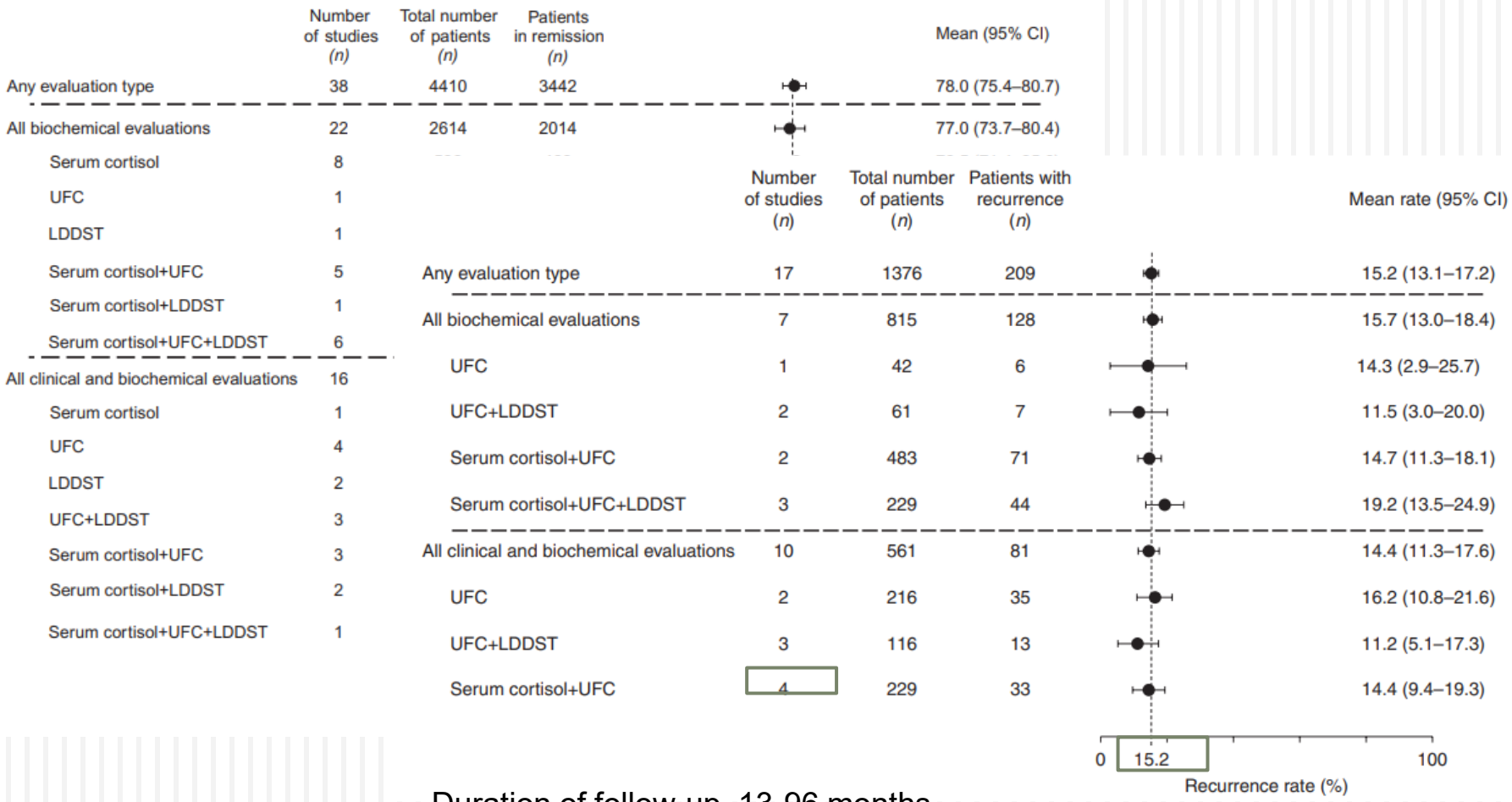
Maria Fleseriu, Richard Auchus, Irina Bancos, Anat Ben-Shlomo, Jerome Bertherat, Nienke R Biermasz, Cesar L Boguszewski, Marcello D Bronstein, Michael Buchfelder, John D Carmichael, Felipe F Casanueva, Frederic Castinetti, Philippe Chanson, James Findling, Mônica Gadelha, Eliza B Geer, Andrea Giustina, Ashley Grossman, Mark Gurnell, Ken Ho, Adriana G Ioachimescu, Ursula B Kaiser, Niki Karavitaki, Laurence Katznelson, Daniel F Kelly, André Lacroix, Ann McCormack, Shlomo Melmed, Mark Molitch, Pietro Mortini, John Newell-Price, Lynnette Nieman, Alberto M Pereira, Stephan Petersenn, Rosario Pivonello, Hershel Raff, Martin Reincke, Roberto Salvatori, Carla Scaroni, Ilan Shimon, Constantine A Stratakis, Brooke Swearingen, Antoine Tabarin, Yutaka Takahashi, Marily Theodoropoulou, Stylianos Tsagarakis, Elena Valassi, Elena V Varlamov, Greisa Vila, John Wass, Susan M Webb, Maria C Zatelli, Beverly M K Biller



Lancet Diabetes Endocrinol 2021

Outcomes in patients with Cushing's disease undergoing transsphenoidal surgery: systematic review assessing criteria used to define remission and recurrence

Stephan Petersenn, Albert Beckers[1], Diego Ferone[2], Aart van der Lely[3],



Duration of follow-up, 13-96 months

Eur J Endocrinol 2015

Summary of medical therapies for Cushing's

	Commonly used doses	Efficacy	Adverse effects	Key considerations
Somatostatin receptor ligands				
Pasireotide[179,187,204–206]	0·6–1·8 mg/mL subcutaneously total per day, given twice a day	Phase 3 study showed 15–26% UFC normalisation	Hyperglycaemia, type 2 diabetes, diarrhoea, nausea, abdominal pain, cholelithiasis, fatigue	Widely approved for patients with Cushing's disease in whom pituitary surgery is not an option or has not been curative; may decrease tumour volume; high risk of hyperglycaemia requires careful patient selection; risk of QTc prolongation
Pasireotide long-acting release[181,207–209]	10–30 mg per month, intramuscularly	Phase 3 study showed 40% UFC normalisation; clinical signs and symptoms of hypercortisolism improved	Hyperglycaemia, type 2 diabetes, diarrhoea, nausea, abdominal pain, cholelithiasis, fatigue	Widely approved for patients with Cushing's disease in whom pituitary surgery is not an option or has not been curative; decreases tumour volume; high risk of hyperglycaemia requires careful patient selection; risk of QTc prolongation
Dopamine receptor agonists				
Cabergoline[179,187,210–214]	0·5–7 mg total per week, orally	Retrospective studies showed approximately 40% UFC normalisation initially, but roughly 25–40% escape; clinical signs and symptoms of hypercortisolism improved	Headache, nasal congestion, hypotension, depression, dizziness	Off-label use only for Cushing's disease, decreases tumour volume in up to 50% of the patients evaluated; poor response could be due to under-titration; risk of treatment-induced impulse-control disorder; unclear risk for cardiac valvulopathy
Glucocorticoid receptor blocker				
Mifepristone[179,187,215–218]	300–1200 mg total per day orally, given once a day	Open-label phase 3 study showed significant improvement in glycaemia (approximately 60% of patients) and blood pressure; clinical signs and symptoms of hypercortisolism improved	Gastrointestinal disturbances, headache, hypokalaemia, arthralgia, peripheral oedema, hypertension, vaginal bleeding, adrenal insufficiency	FDA-approved for hyperglycaemia associated with Cushing's syndrome; no cortisol markers of efficacy; challenging to use outside specialised clinical practice; risk of hypokalaemia and adrenal insufficiency, needs close monitoring; careful review of other medications for potential drug–drug interactions is essential

Consensus on diagnosis and management of Cushing's disease: a guideline update

Lancet Diabetes Endocrinol 2021

Summary of medical therapies for Cushing's

	Commonly used doses	Efficacy	Adverse effects	Key considerations
Ketoconazole[179,181–187]	400–1600 mg total per day, orally, given twice or three times a day	Retrospective studies: approximately 65% of patients had UFC normalisation initially, but 15–25% escape	Gastrointestinal disturbances, increased liver enzymes, gynecomastia, skin rash, adrenal insufficiency	EMA-approved for treatment of endogenous Cushing's syndrome, off-label use in USA; increasing doses may be needed to counter escape; needs gastric acid for absorption (avoid proton-pump inhibitors); decrease in testosterone would be preferred in women, men need follow-up for hypogonadism; risk of serious hepatotoxicity, mostly transient but regular liver function test monitoring required; risk of QTc prolongation; careful review of other medications for potential drug–drug interactions is essential
blocks multiple adrenal enzymes				
Metyrapone[179,181,187,193–197]	500 mg to 6 g total per day, orally, given three or four times a day	UFC normalisation in retrospective studies approximately 70%; in a prospective study, 47% at week 12	Increased androgenic and mineralocorticoid precursors (hirsutism, hypertension, hypokalaemia), gastrointestinal disturbances, adrenal insufficiency	EMA-approved for treatment of endogenous Cushing's syndrome, off-label use in USA; rapid decrease in UFC, typically in first month; 11-deoxycortisol can cross-react in cortisol immunoassays; hyperandrogenism needs to be monitored with long-term use in women
11β-hydroxylase inhibitor				
Osilodrostat[181–183,188–192]	4–14 mg total per day, orally, given twice a day as maintenance dose; some patients require lower starting doses at 2 mg per day; 30 mg, twice a day maximum	Phase 3 randomised withdrawal study showed 86% UFC normalisation	Increased androgenic and mineralocorticoid precursors (hirsutism, hypertension, hypokalaemia), gastrointestinal disturbances, asthenia, adrenal insufficiency	FDA-approved for patients with Cushing's disease in whom pituitary surgery is not an option or has not been curative; EMA and Japan have approved for treatment of endogenous Cushing's syndrome; not yet widely available; rapid decrease in UFC; risk of hypocortisolism, hypokalaemia, and QTc prolongation; 11-deoxycortisol can cross-react in cortisol immunoassays; careful monitoring for hyperandrogenism in women
11β-hydroxylase and aldosterone synthase inhibitor				

Consensus on diagnosis and management of Cushing's disease: a guideline update

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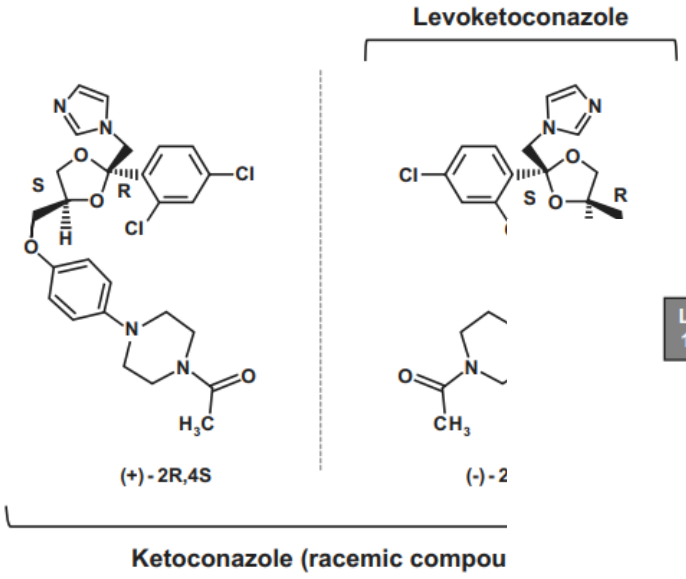
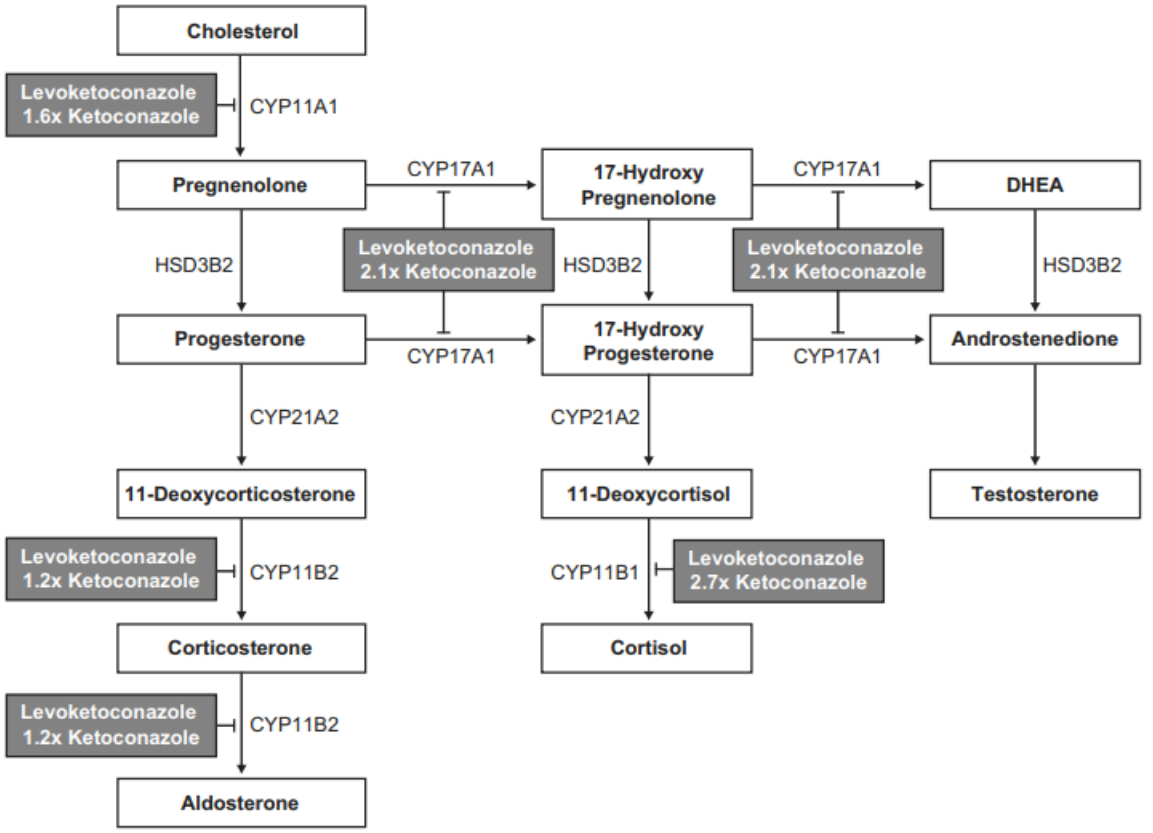
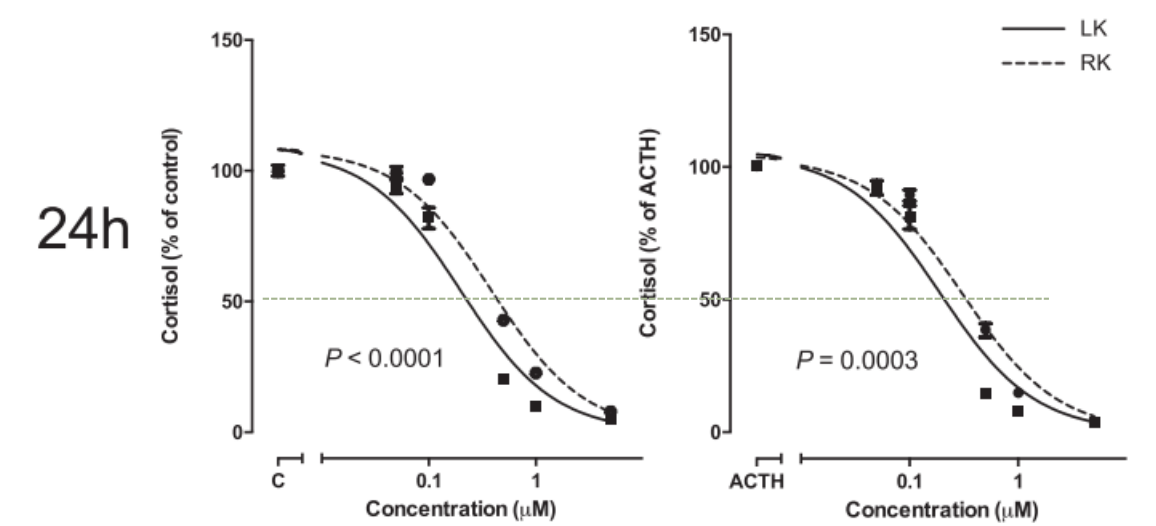
Chemical structure of levoketoconazole (Recorlev)





Dose-dependent effects of levoketoconazole and ketoconazole on cortisol production by HAC15 (Human adrenocortical carcinoma) cells before and after ACTH stimulation

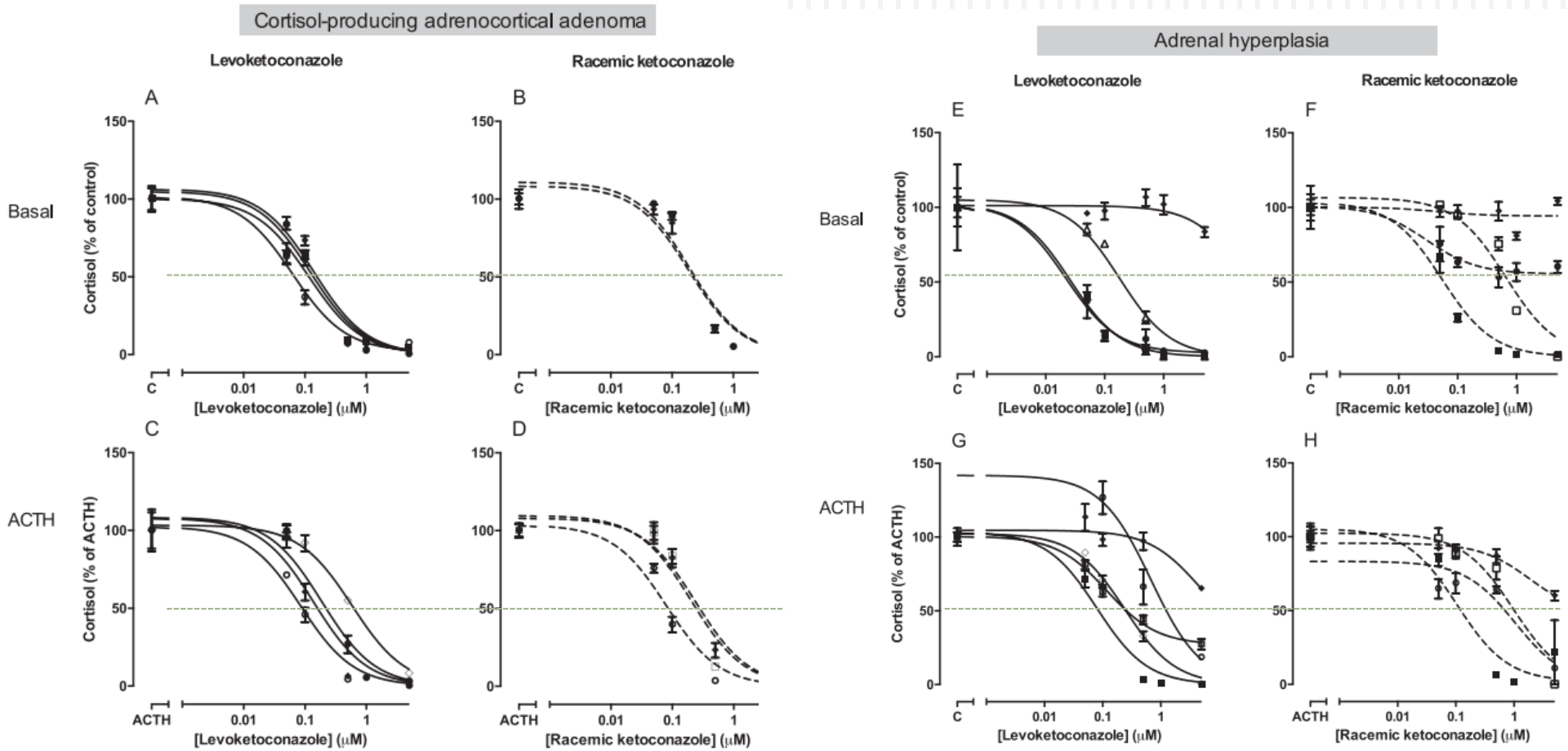
Levoketoconazole, the 2S,4R Enantiomer of Ketoconazole a New Steroidogenesis Inhibitor for Cushing's Syndrome



J Clin Endocrinol Metab, 2021

Dose-dependent effects of levoketoconazole and ketoconazole on cortisol production in primary human adrenocortical cultures

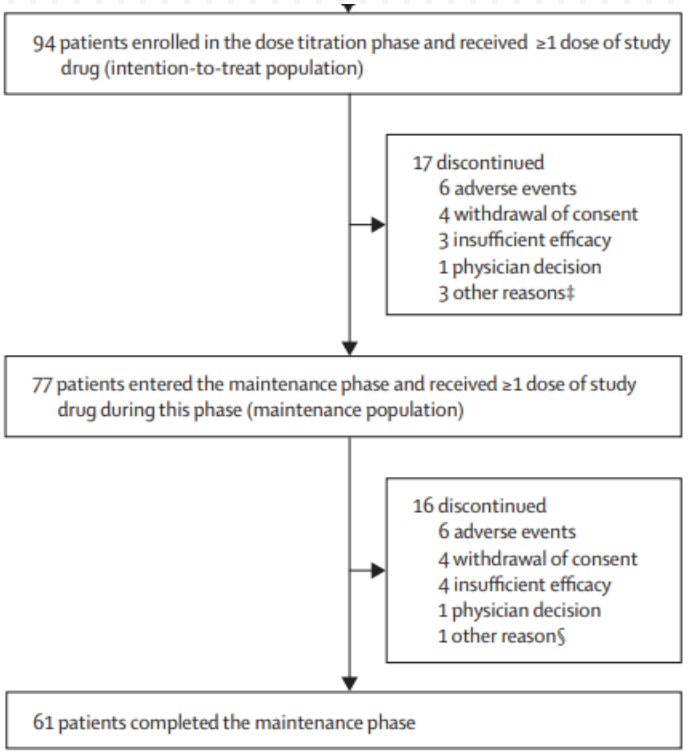
Levoketoconazole, the 2S,4R Enantiomer of Ketoconazole



J Clin Endocrinol Metab, 2021

Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm trial

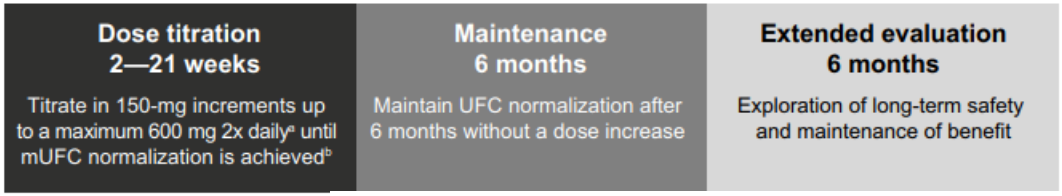
Maria Fleseriu, Rosario Pivonello, Atanaska Elenkova, Roberto Salvatori, Richard J Auchus, Richard A Feelders, Eliza B Geer, Yona Greenman, Przemyslaw Witek, Fredric Cohen, Beverly M K Biller



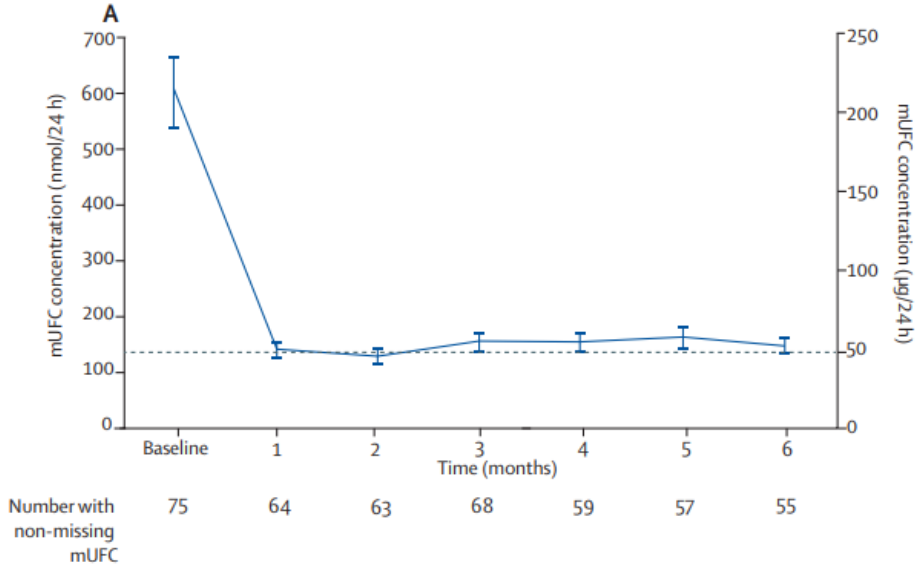
	Patients (n=94)
Age (years)	
Mean	43·7 (13·4)
Median	44·0 (18–75)
Sex	
Women	77 (82%)
Men	17 (18%)
Ethnicity	
White	90 (96%)
Black	1 (1%)
Other	1 (1%)
Unknown	2 (2%)
Mean bodyweight (kg)	84·0 (23·4)
Mean BMI (kg/m²)*	30·8 (8·2)
Time since Cushing's syndrome diagnosis (months)	
Mean	68·0 (80·4)
Median	33·7 (0·7–434·0)
Biological cause	
Cushing's disease	80 (85%)
Ectopic ACTH secretion	1 (1%)
Adrenal dependent	8 (9%)
Unknown	5 (5%)
Diabetes	36 (38%)
Hypertension	67 (71%)
Hypercholesterolaemia	34 (36%)
Baseline mUFC†	
Molar concentration (nmol/24 h)	
Mean	671·4 (743·1)
Median	407·9 (162·0–4168·(
Mass concentration (µg/24 h)	
Mean	243·3 (269·3)
Median	147·8 (58·7–1510·1)
Baseline mUFC × ULN‡	
Mean	4·9 (5·4)
Median	3·0 (1·2–30·2)§
Previous treatment¶	
Surgery	65 (69%)
Medication	11 (12%)
Radiotherapy	9 (10%)
None	26 (28%)

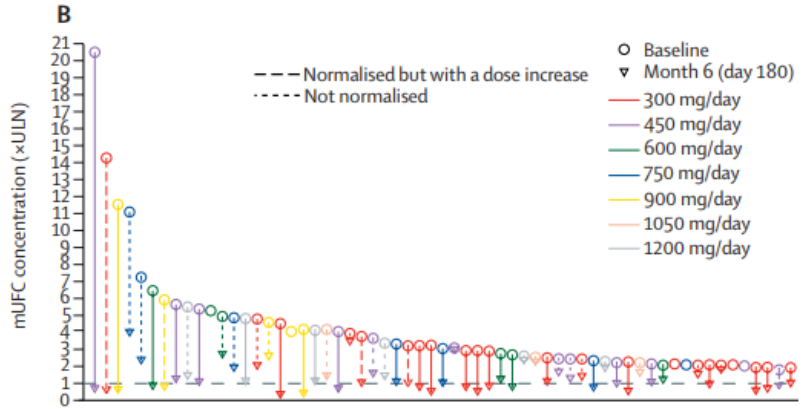
Lancet Diabetes Endocrinol 2019

SONICS


Dose titration
2—21 weeks
Titrate in 150-mg increments up to a maximum 600 mg 2x daily[a] until mUFC normalization is achieved[b]
Maintenance
6 months
Maintain UFC normalization after 6 months without a dose increase
Extended evaluation
6 months
Exploration of long-term safety and maintenance of benefit

Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm trial



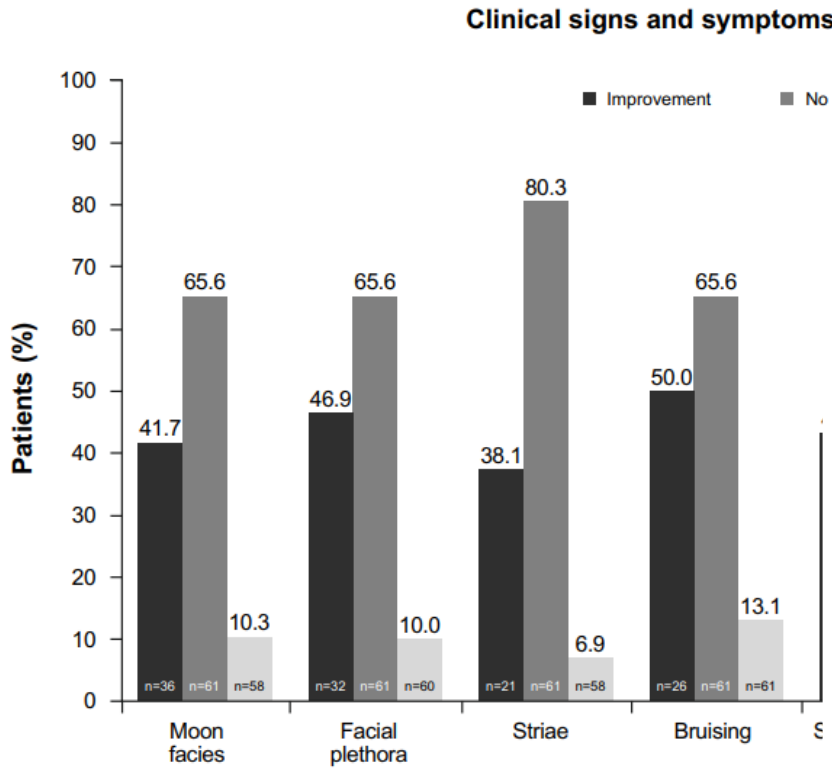


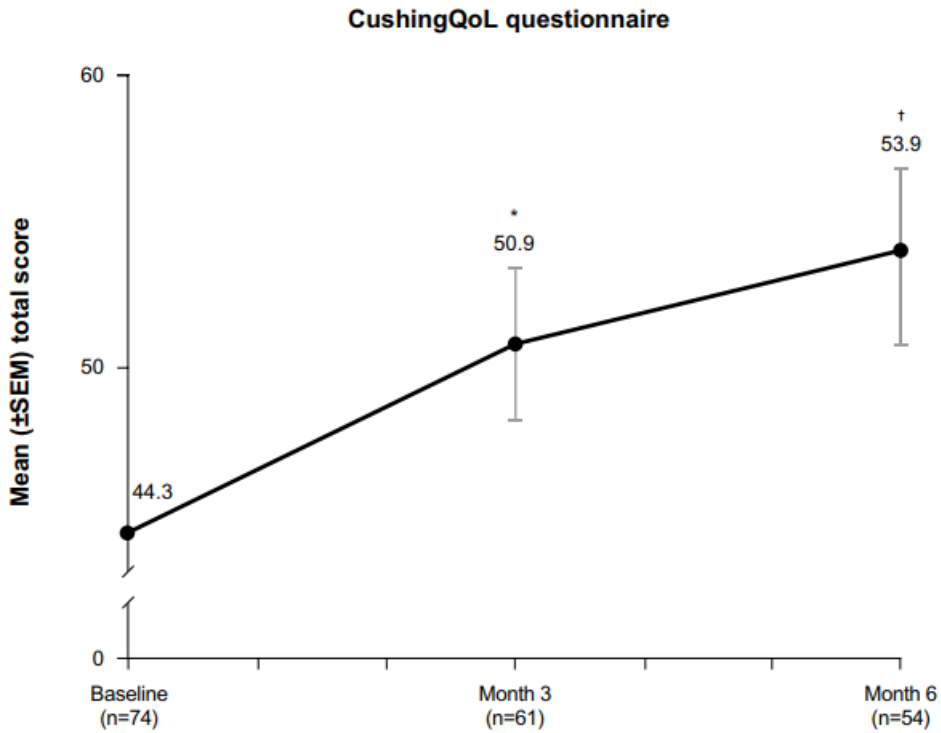
	Response rate	Response rate LS mean
mUFC normalisation without a dose increase*†		
Month 1	41/85	0·48 (0·37–0·59)
Month 2	44/88	0·50 (0·39–0·61)
Month 3	41/92	0·44 (0·34–0·55)
Month 4	31/90	0·35 (0·25–0·46)
Month 5	32/90	0·36 (0·26–0·47)
Month 6 (primary endpoint)	29/94	0·30 (0·21–0·40)
mUFC normalisation at month 6 (irrespective of dose increase)*‡	34/94	0·36 (0·26–0·46)
mUFC normalisation at month 6 (irrespective of dose increase, with imputation)*‡§	36/94	0·38 (0·28–0·49)
Analysis of observed rate at month 6 with imputation for missing mUFC after month 3‡¶	40/94	0·43 (0·32–0·53)
≥50% mUFC decrease or normalisation at month 6 (irrespective of dose increase)*‡	43/94	0·46 (0·35–0·56)
≥50% mUFC decrease or normalisation at month 6 (irrespective of dose increase, with imputation)*‡§	45/94	0·48 (0·37–0·58)
Participants who completed the maintenance phase with mUFC data and mUFC normalisation at month 6 (irrespective of dose increase)‡‖	34/55 (62%)	..
Participants who completed the maintenance phase with mUFC data and ≥50% mUFC decrease or normalisation at month 6 (irrespective of dose increase)‡‖	43/55 (78%)	..

Lancet Diabetes Endocrinol 2019

Levoketoconazole improves clinical signs and symptoms and patient-reported outcomes in patients with Cushing's syndrome

Eliza B. Geer[1] · Roberto Salvatori[2] · Atanaska Elenkova[3] · Maria Fleseriu[4] · Rosario Pivonello[5] · Przemyslaw Witek[6] · Richard A. Feelders[7] · Marie Bex[8] · Stina W. Borresen[9] · Soraya Puglisi[10] · Beverly M. K. Biller[11] · Fredric Cohen[12] · Francesca Pecori Giraldi[13,14]





Pituitary, 2021

Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm trial

Adverse events

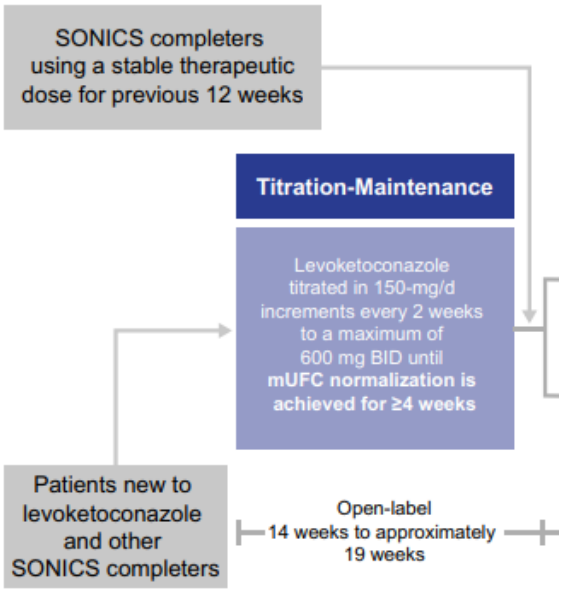
	Patients (n=94)
Any adverse event	92 (98%)
Serious adverse event	14 (15%)
Drug-related adverse event*	40 (43%)
Adverse event leading to discontinuation	12 (13%)
Intensity of adverse events	
Mild	21 (22%)
Moderate	54 (57%)
Severe	15 (16%)
Life-threatening	1 (1%)
Death	1 (1%)
Most common adverse events†	
Nausea	30 (32%)
Headache	26 (28%)
Peripheral oedema	18 (19%)
Hypertension	16 (17%)
Fatigue	15 (16%)
Diarrhoea	14 (15%)
ALT increased‡	14 (15%)
GGT increased‡	12 (13%)
AST increased‡	11 (12%)
Nasopharyngitis	11 (12%)
Urinary-tract infection	11 (12%)
Arthralgia	10 (11%)
Dizziness	10 (11%)
Dry skin	10 (11%)
Hypokalaemia	10 (11%)
Myalgia	10 (11%)
Vomiting	10 (11%)

Lancet Diabetes Endocrinol 2019

Levoketoconazole in the treatment of patients with endogenous Cushing's syndrome: a double-blind, placebo-controlled, randomized withdrawal study (LOGICS)

Rosario Pivonello[1] · Sabina Zacharieva[2] · Atanaska Elenkova[2] · Miklós Tóth[3] · Ilan Shimon[4] · Antonio Stigliano[5] Corin Badiu[6] · Thierry Brue[7] · Carmen Emanuela Georgescu[8,9] · Stylianos Tsagarakis[10] · Fredric Cohen[11] · Maria Fleseriu[12]

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



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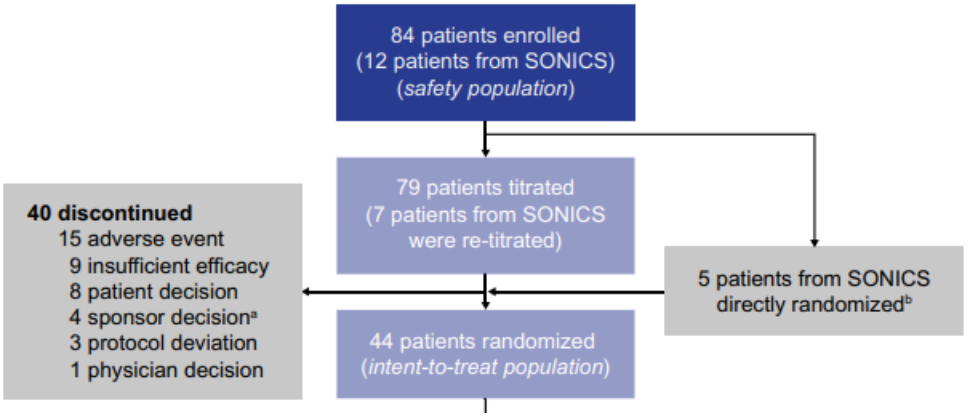

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Levoketoconazole in the treatment of patients with endogenous Cushing's syndrome: a double-blind, placebo-controlled, randomized withdrawal study (LOGICS)

Table 1 LOGICS study: demographics and baseline characteristics

Characteristics	Safety population (n = 84)	Intent-to-treat population	
		Levoketoconazole (n = 22)	Placebo (n = 22)
Age, years, mean (SD)	44.7 (12.7)	45.0 (12.0)	43.6 (11.0)
Female, n (%)	64 (76.2)	15 (68.2)	19 (86.4)
Race, n (%)			
White	78 (92.9)	18 (81.8)	22 (100)
Black	4 (4.8)	3 (13.6)	0 (0)
Asian	1 (1.2)	0 (0)	0 (0)
Unknown	1 (1.2)	1 (4.5)	0 (0)
BMI, kg/m^2, mean (SD)	31.0 (6.8)	31.6 (8.5)	30.8 (4.8)
Time since CS diagnosis, months			
Mean (SD)	63.4 (71.8)	66.8 (72.5)	92.2 (78.8)
Median (range)	30.1 (0–254.1)	35.8 (0.5–241.0)	82.1 (0.2–254.1)
Etiology, n (%)			
Cushing's disease	70 (83.3)	18 (81.8)	20 (90.9)
Adrenal-dependent	8 (9.5)	3 (13.6)	1 (4.5)
Ectopic ACTH secretion	2 (2.4)	0 (0)	0 (0)
Unknown	4 (4.8)	1 (4.5)	1 (4.5)
Diabetes, n (%)	35 (41.7)	8 (36.4)	7 (31.8)
Hypertension, n (%)	68 (81.0)	21 (95.5)	16 (72.7)
Baseline mUFC, nmol/24 h[a]			
Mean (SD)	746.7 (916.3)	738.7 (1067.0)	411.6 (436.2)
Median (range)	441.6 (53.1–5752.9)	382.9 (101.9–5004.9)	266.8 (53.1–2171.3)
Baseline mUFC, × ULN[a,b]			
Mean (SD)	5.4 (6.6)	5.4 (7.7)	3.0 (3.2)
Median (range)	3.2 (0.4–41.7)[c]	2.8 (0.7–36.3)[c]	1.9 (0.4–15.7)[c]

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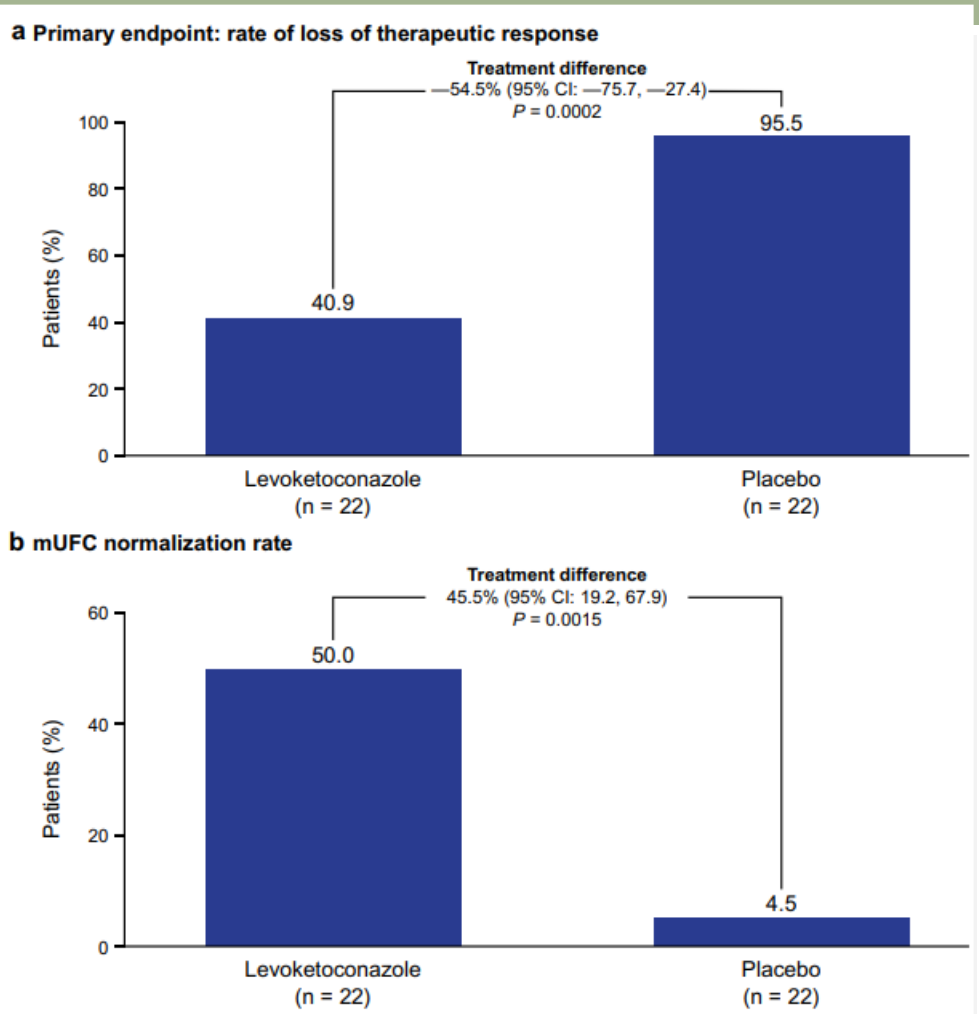
Levoketoconazole in the treatment of patients with endogenous Cushing's syndrome: a double-blind, placebo-controlled, randomized withdrawal study (LOGICS)



Loss of therapeutic response defned as mUFC>1.5×ULN or mUFC>40% above baseline

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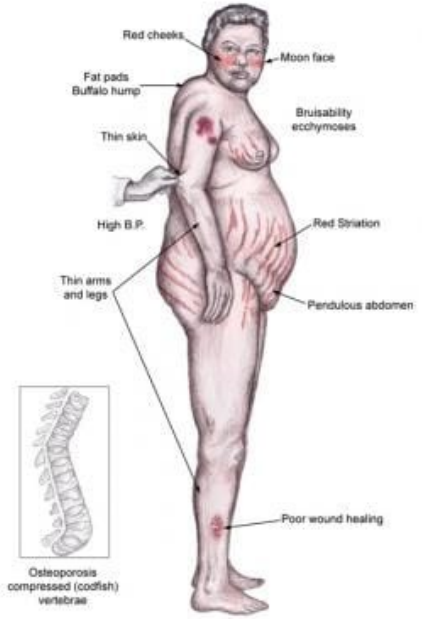
Liver safety profile of Levoketoconazole and Ketoconazole

Table 3. Safety profiles of levoketoconazole and ketoconazole.

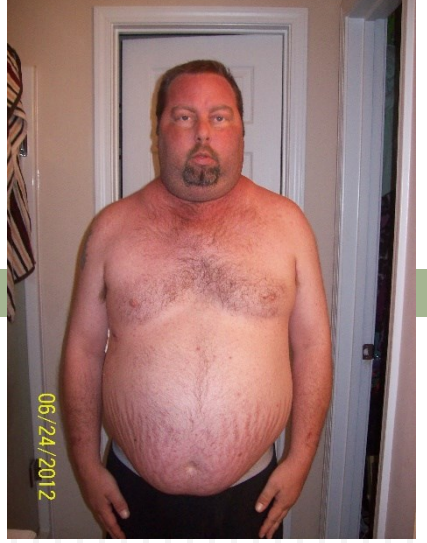
	Levoketoconazole	Ketoconazole
Adverse events of interest Liver function	• SONICS study (N = 94) [57]: • Liver-related AEs: 7.4% • ALT >5X ULN: 3.2% • AST >3X ULN: 4.3% • GGT >5X ULN: 2.1% • ALP >3X ULN: 0% • Total bilirubin >2X ULN: 0%	• Ketoconazole use as an antifungal therapy • Incidence of asymptomatic increases in liver enzymes: ~12% (range of 0–48%) [73,74] • Incidence of symptomatic, potentially serious hepatic injury: 1 in 15,000 pts (rare) [73,74] • EMA withdrew marketing authorization for use as an antifungal agent because of hepatotoxic risk [28]; remain approved for CS • US FDA requires a boxed warning for hepatotoxicity in the label for fungal infection indication [25] • Ketoconazole use for treatment of CS • French compassionate use program (47 ketoconazole treatment-naïve pts treated for 6 months*) [72]: • Liver injury†: 8.5% • ALT ≥5X ULN: 12.9% • AST ≥3X ULN: 3.2% • GGT ≥5X ULN: 16.7% • ALP ≥3X ULN: 3.4% • Total bilirubin ≥3X ULN: 5.0% • Increase in liver enzymes in a large retrospective study (N = 200): 16% of treated pts [51]

Case study



- 40-year-old male
- 2003 – Cushing disease, obesity, hypertension
- MRI – Rt. 3-mm microadenoma; IPSS – pituitary disease
- 8/2003 – TSS with hormonal remission
- 2012 –bariatric surgery (sleeve gastrectomy); weight loss, 74 kg
- 2017 – weight gain – 110 kg, hypertension
- UFC – 309 (-75); ACTH – 100
- 3/2018 – TSS for suspected Lt. microadenoma, negative pathology
- 6/2018 – Rt. Explorative TSS, normal pituitary, UFC – 232

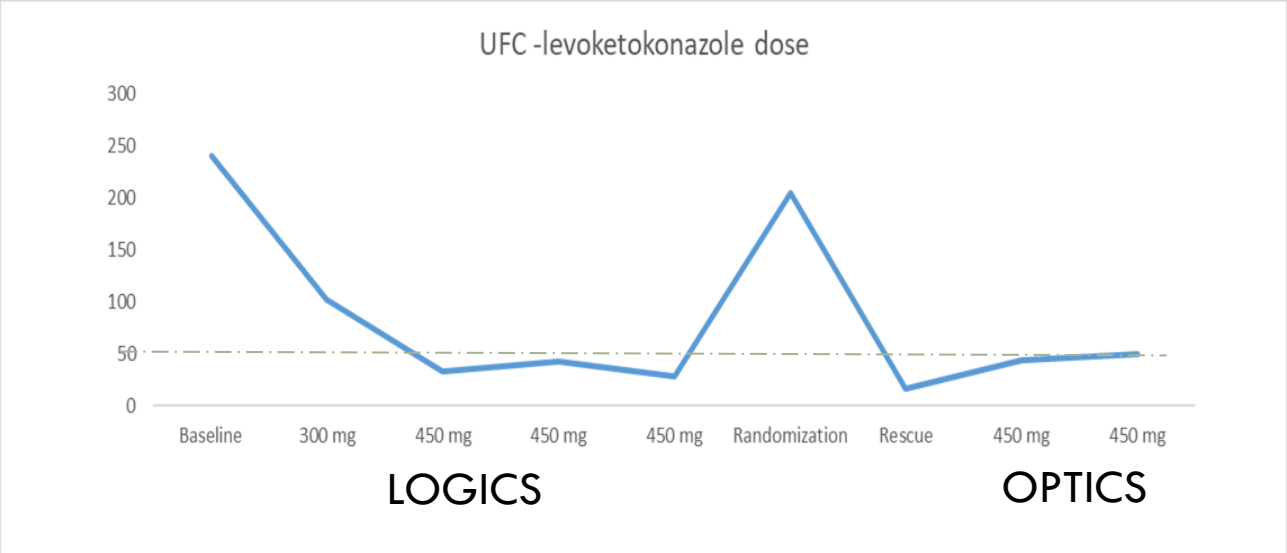
LOGICS study



- 8/2018 – baseline UFC – 245, 244, 215 (normal, 50)
- Central hypothyroidism – Euthyrox initiated
- Following Euthyroidism – UFC -322, 182, 215; Slivary cortisol – 0.27,0.24
- 11/2018 - **Levoketoconazole** 300 mg/day, one week – UFC – 137, 67; Salivary cortisol – 0.17
- 12/2018 - **Levoketoconazole** 450 mg/day – UFC – 42, 24 (-50); Salivary – 0.11, myalgia resolved
- 2/2019 - **Levoketoconazole** 450 mg/day – UFC – 60, 25. Salivary – 0.1
- 2/2019 – before randomization – UFC – 32, 32, 20; Salivary <0.1
- 3/2019 – 2 weeks following randomization – UFC – 58, 112, 442; Salivary – 0.15; clinical deterioration
- 5/2019 – rescue treatment – UFC – 13, 23, 12

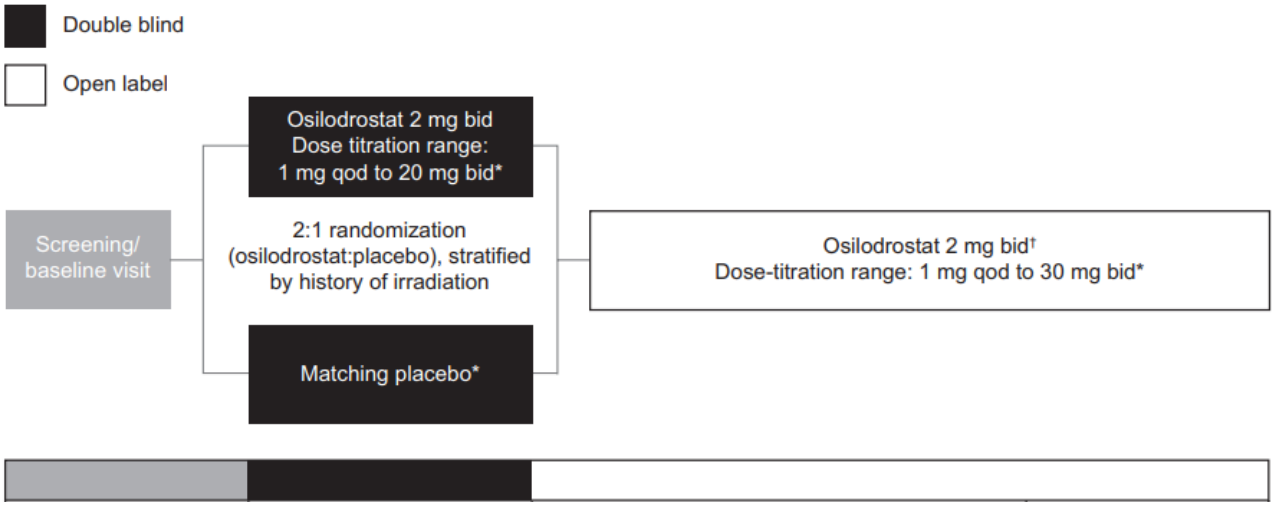
OPTICS study – open label extension

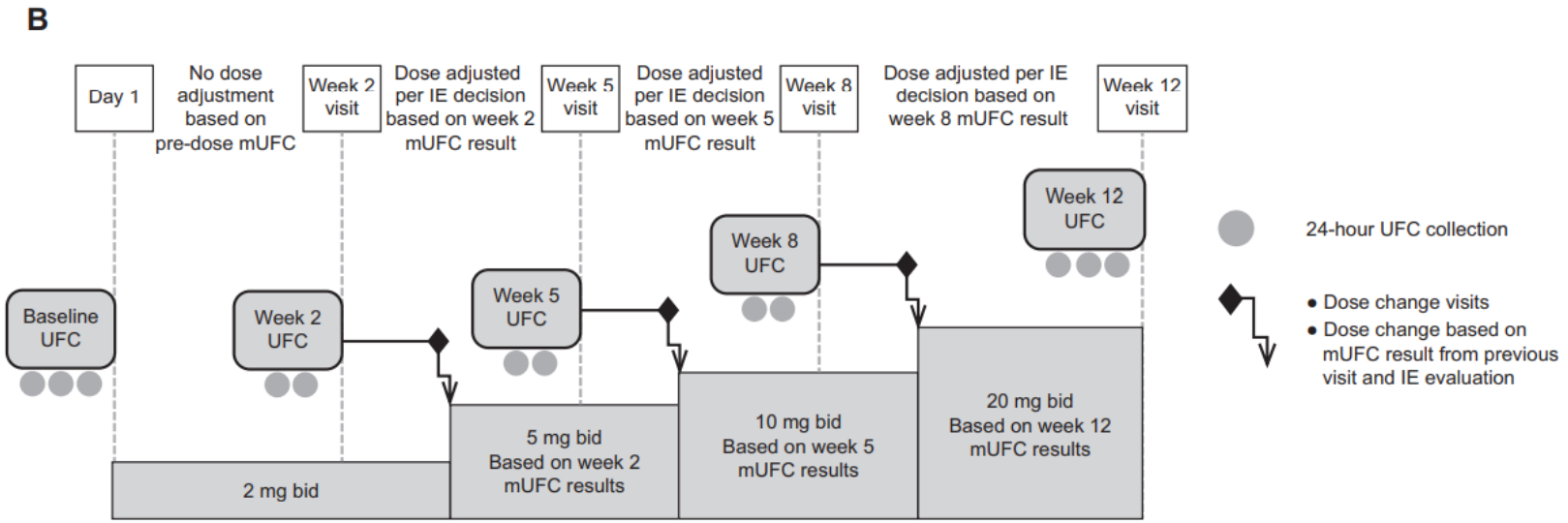
- 11/2019 – **Levoketoconazole** 450 mg/day – UFC – 49, 47, 35
- 5/2020 – UFC – 82, 24, 43; Salivary- 0.11
- 12/2020 – bariatric surgery; before surgery – 115 kg
- 1/2021 - 99.5 kg
- 3/2021- anastomotic ulcer; started PPI (Nexium); Levoketoconazole discontinued
- 5/2021- UFC – 576, 529, 313 (-50); Salivary – 0.87
-



Randomized Trial of Osilodrostat for the Treatment of Cushing Disease LINC 4

Mônica Gadelha,[1] Marie Bex,[2] Richard A. Feelders,[3] Anthony P. Heaney,[4] Richard J. Auchus,[5]





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Osilodrostat LINC 4

Table 1. Demographics and baseline characteristics of all patients and by randomized treatment group

Demographic variable	Osilodrostat (n = 48)	Placebo (n = 25)	All patients (N = 73)
Age, years			
Median	41.0	37.0	39.0
Range	21.0–67.0	19.0–63.0	19.0–67.0
Sex, n (%)			
Female	43 (89.6)	18 (72.0)	61 (83.6)
Male	5 (10.4)	7 (28.0)	12 (16.4)
Race, n (%)			
White	34 (70.8)	15 (60.0)	49 (67.1)
Asian	9 (18.8)	8 (32.0)	17 (23.3)
Black/African American	2 (4.2)	0	2 (2.7)
Other	1 (2.1)	1 (4.0)	2 (2.7)
Unknown	2 (4.2)	1 (4.0)	3 (4.1)
Median time since diagnosis,[a] months (IQR)	69.9 (22.9–92.0)	65.0 (30.4–103.8)	67.4 (26.4–93.8)
Previous pituitary surgery, n (%)	41 (85.4)	23 (92.0)	64 (87.7)
Previous medical therapy for Cushing's disease, n (%)	26 (54.2)	19 (76.0)	45 (61.6)
Previous pituitary irradiation, n (%)	6 (12.5)	3 (12.0)	9 (12.3)
mUFC, nmol/24 hours			
Mean (SD)	421.4 (291.3); 3.1 × ULN	451.5 (535.1); 3.3 × ULN	431.7 (388.6); 3.1 × ULN
Median (IQR)	342.2 (252.6–519.9); 2.5 × ULN	297.6 (211.2–518.8); 2.2 × ULN	340.3 (221.3–518.8); 2.5 × ULN

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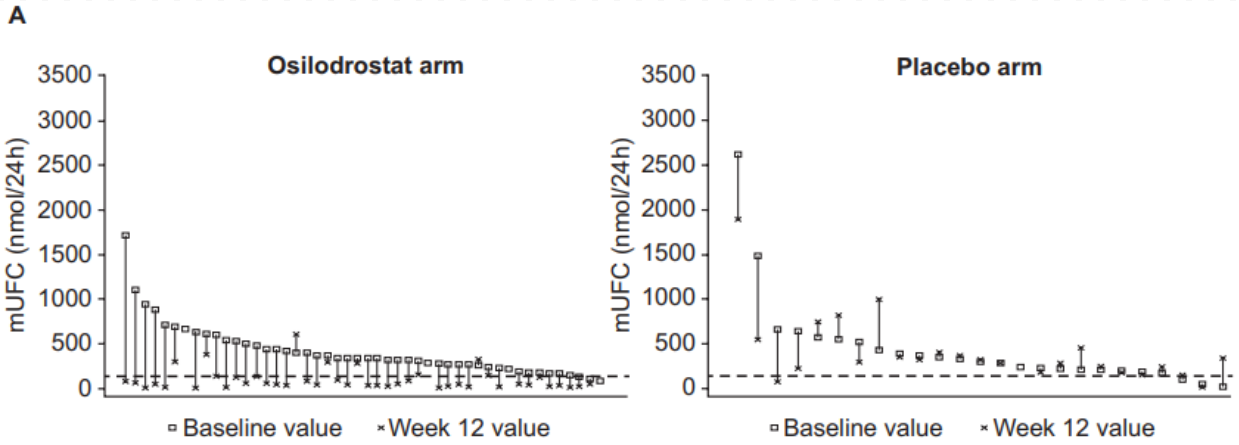

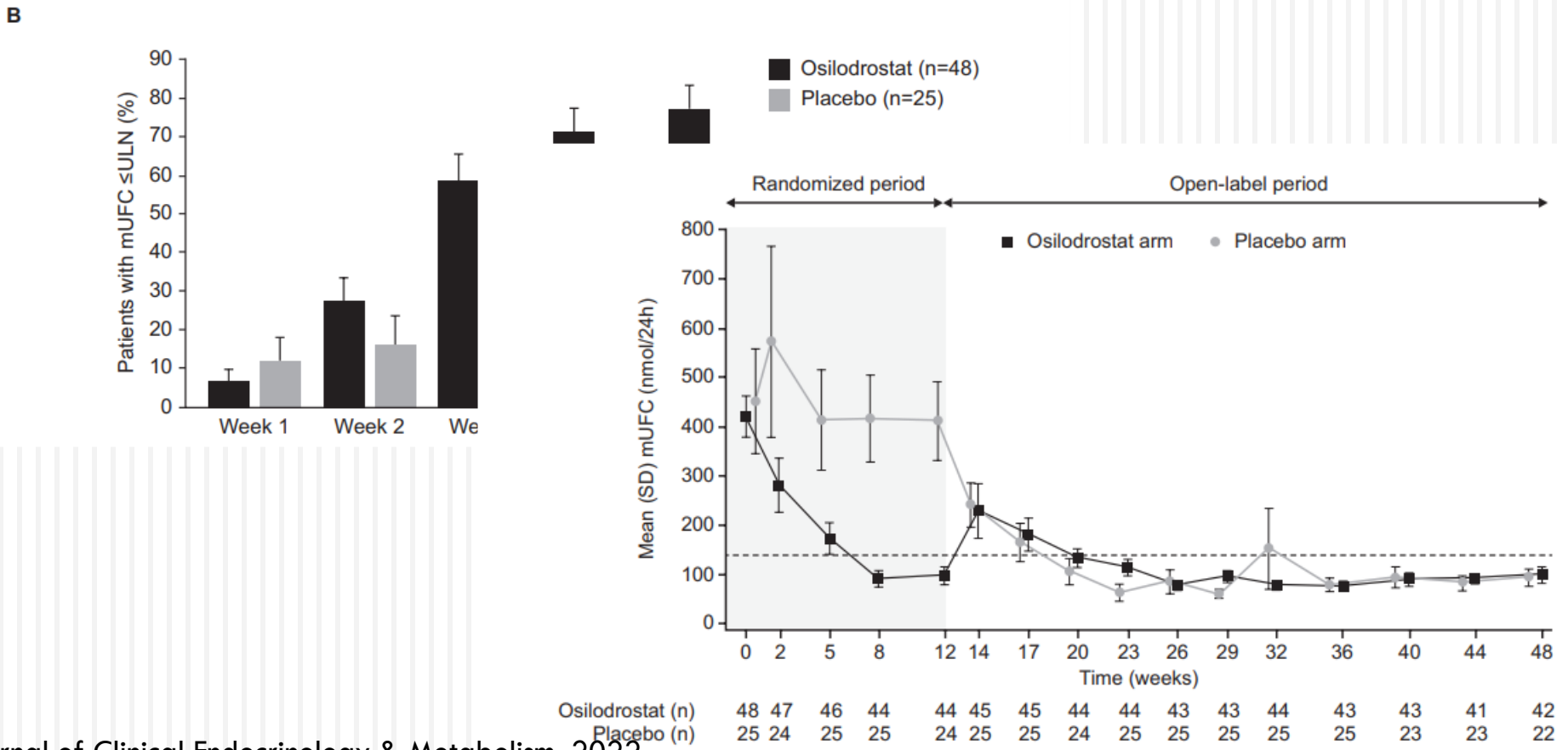

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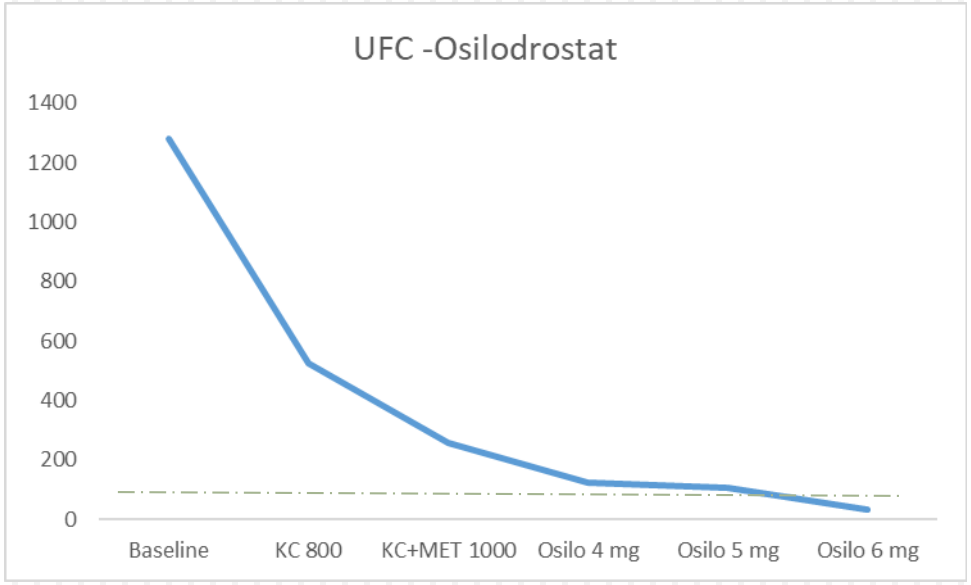
Case study - continued

- 8/2021-10/2021 – UFC -**1065-1492** (-75)
- 11/2021-12/2021 – 800 mg **Ketoconazole**, Nexium, UFC – **511, 537** (-75)
- 2/2022 – 800 mg **Ketokonazole** + 1000 mg **Metyrapone**, Nexium, UFC – **255**
- 4/2022 – **Osilodrostat (Isturisa)** - 2 mg x 2/day, UFC – **122**
- 5/2022 – **Osilodrostat** - 2+3 mg/day, UFC – **108** (-75)
- 7/2022 – 3 ng x 2/ day – UFC – **34** (-75) (urine volume – 600 cc)



Levoketoconazole vs. Osilodrostat

- No head to head study
- LINC 4 (osilodrostat) – mean baseline UFC -3.1x ULN;
- LINC 3 (Osilodrostat) – mean baseline UFC – 7.3 x ULN
- SONICS (levoketoconazole) – mean UFC – 4.9 x ULN
- LOGICS (Levoketoconazole) – mean UFC – 5.4 X ULN

- LINC 4 – 77% normalized UFC among the 44 completers
- LINC 3 – 53% normalized UFC among 137 patients
- SONICS – 62% normalized UFC among the 55 completers
- LOGICS – 65% normalized UFC before randomization

Summary

- Cushing syndrome is a serious and life-threatening disease
- Pituitary-directed and adrenal-directed medications are available for patients with active disease following unsuccessful surgery
- Adrenal-directed drugs are more potent (50% remission rate) and can be given as combined treatment
- However, up to 25% of patients with Cushing experience resistance to medical treatment
- New medications, approved recently – levoketoconazole, osilodrostat – showed better efficacy for hypercortisolism control with a good safety profile
- Treatment with these drugs should be considered for patients with active disease resistant to the cu