I farmaci ad azione surrenalica: METIRAPONE ed OSILODROSTAT

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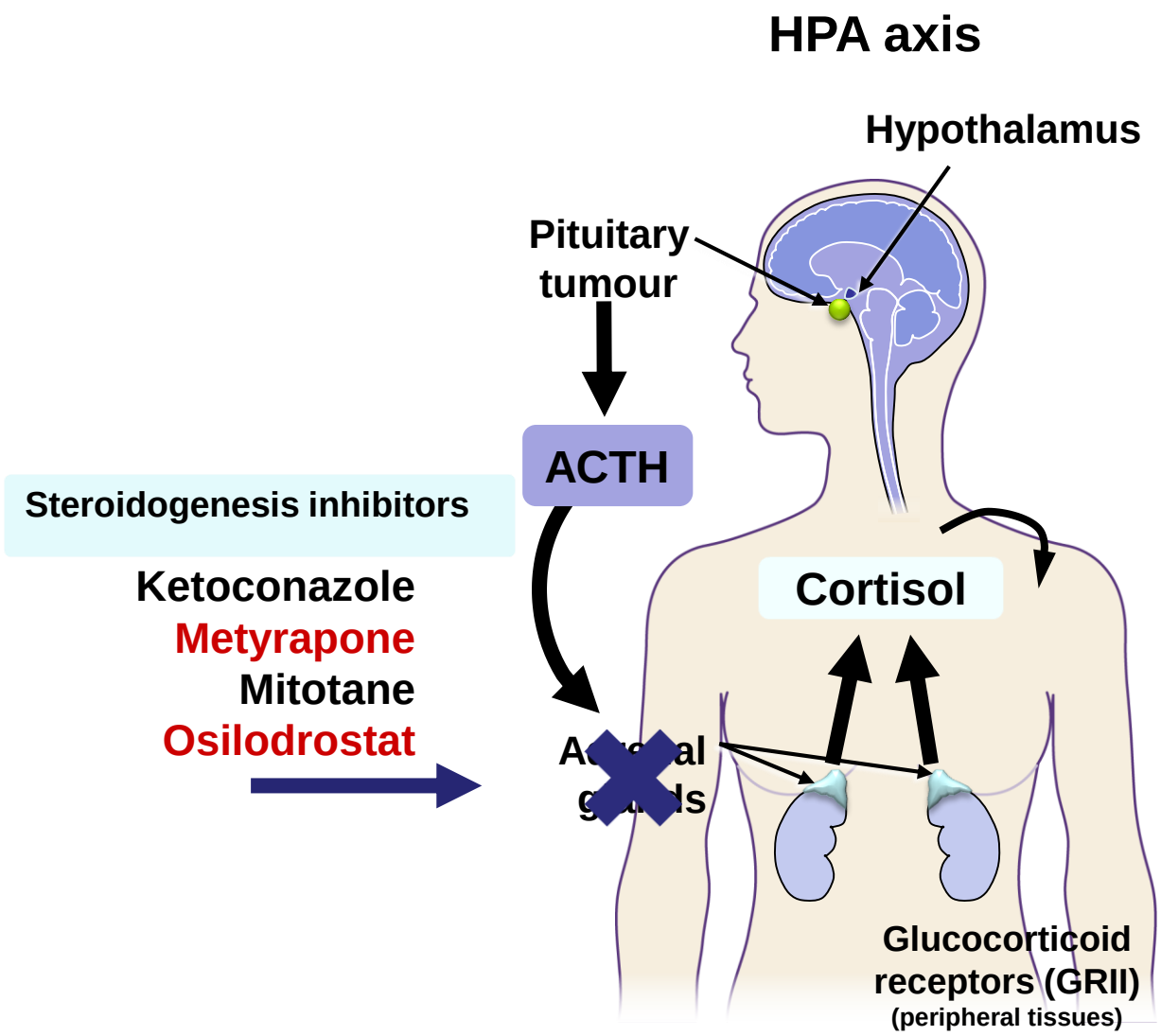
Treatment algorithm for current management of CD

Pivonello R *et al* *Endocrine Reviews* 2015;36:385-486

Adrenal-directed therapy



Adrenal-directed drugs:

- Steroidogenesis inhibitors
  - Reduce cortisol levels through inhibition of adrenal steroid synthesis

- Can be used for both short- and long-term management
  - Between administration and effect of radiotherapy
  - To lower cortisol levels in patients if surgery is delayed

- Do not target the underlying corticotroph tumour
- Side effects

Biller BMK *et al. J Clin Endocrinol Metab* 2008;93:2454–2462;
Baudry C *et al. Eur J Endocrinol* 2012;167:473–481

Goals of medical therapy

- Effective medical therapy would:
  - Normalize biochemical changes with minimal morbidity
  - Restore normal secretory dynamics to the HPA axis
  - Lower ACTH secretion
  - Reduce tumour volume
  - Reverse clinical features
  - Result in long-term control without recurrence

ACTH, adrenocorticotropic hormone;
HPA, hypothalamic–pituitary–adrenal

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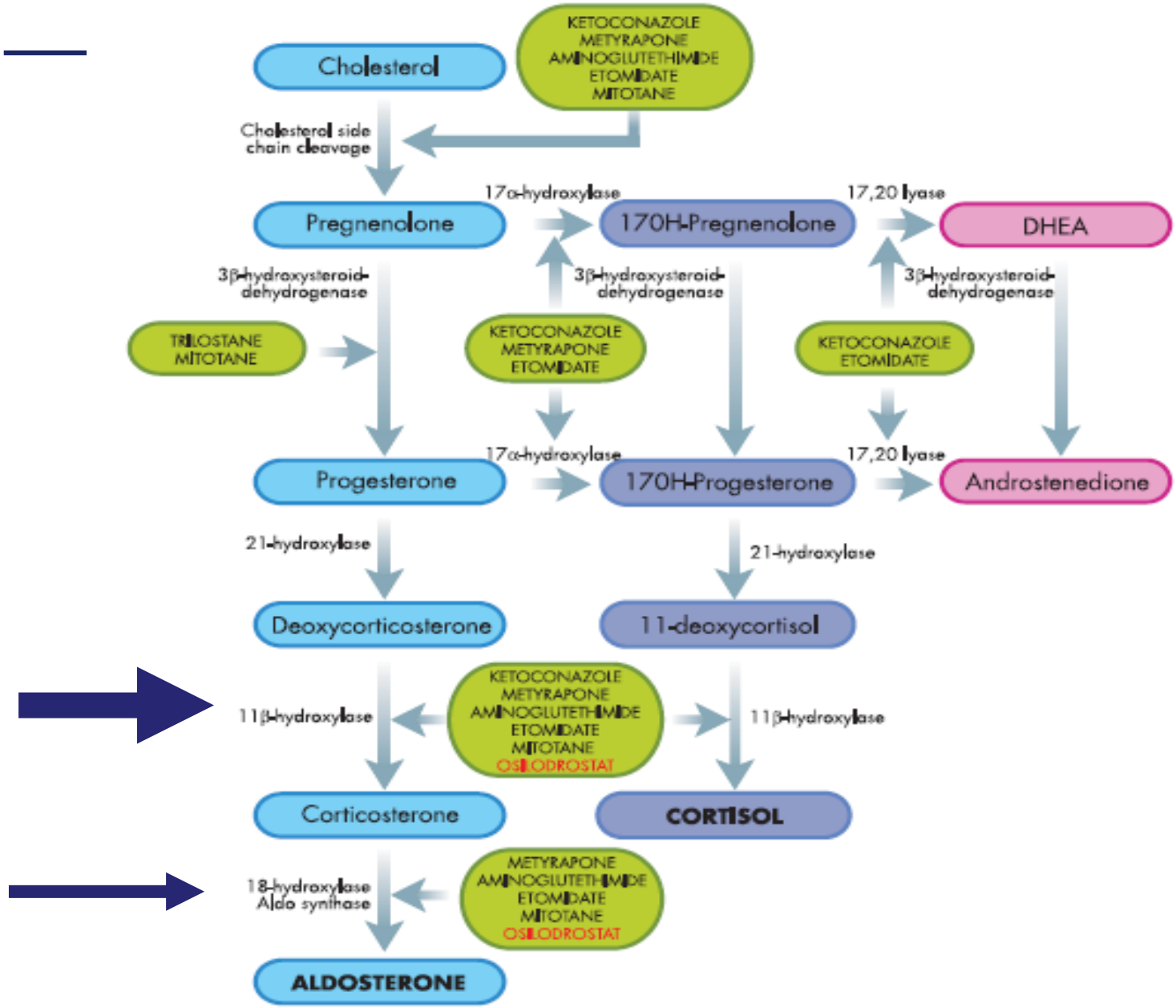
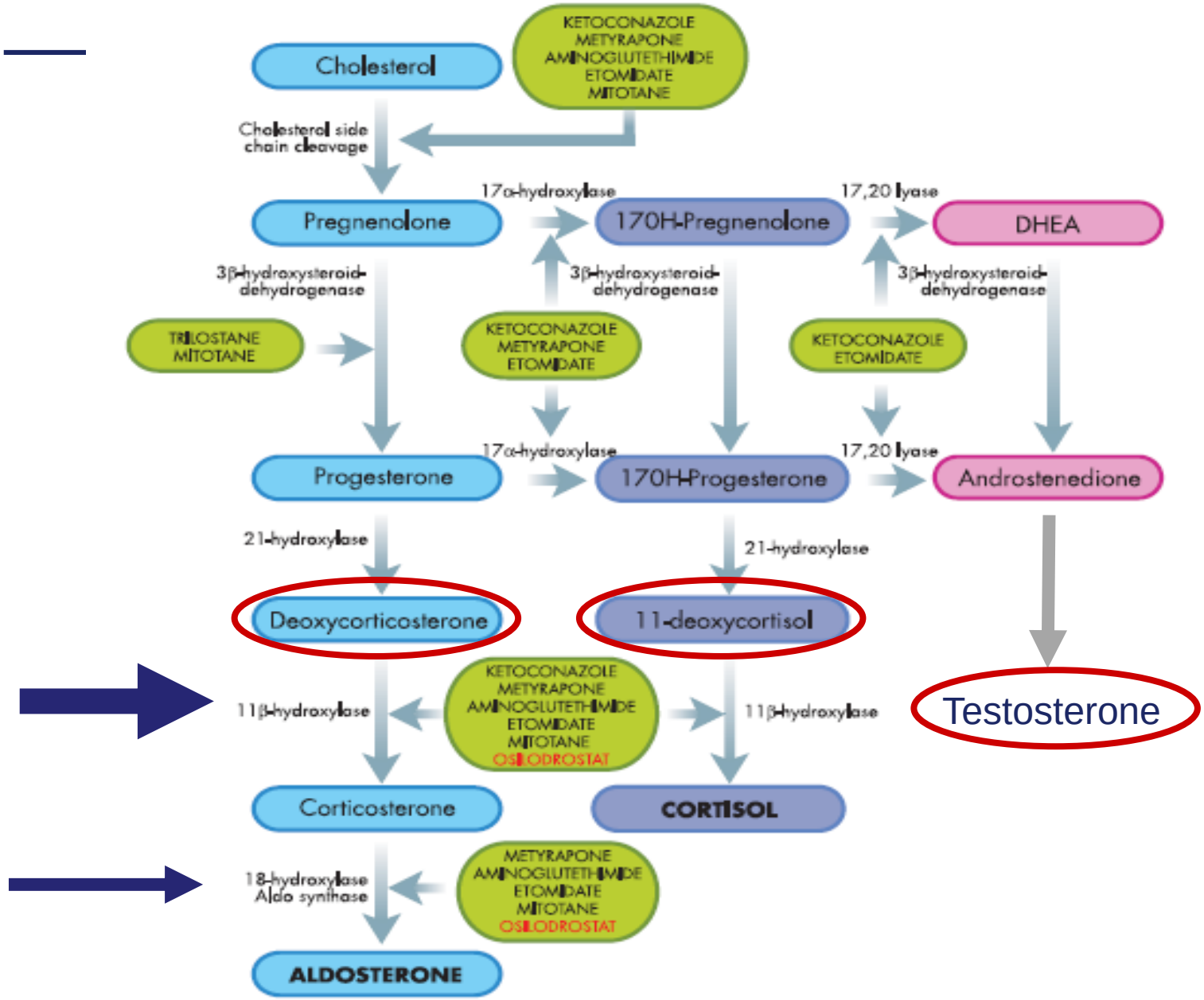
Site of action of adrenal-directed drugs



Pivonello R *et al* *Endocr Rev 2015 36(4)385-486*

Site of action of adrenal-directed drugs



Pivonello R *et al* *Endocr Rev 2015 36(4)385-486*

Metyrapone

Indicated in EU for the management of patients with ENDOGENOUS CUSHING'S SYNDROME

Results of the main studies evaluating the outcome of Metyrapone in CD

First author, Year	N° of patients	Drug dose (mg/d)	Follow-up (months)	Remission rate (%)	Escape (% of the total population)	Escape (% of the initially responsive population)
Jeffcoat , 1977	13 (9 RT)	R:500-4000;	R:2-66; M:18,2;m:11	100	0	0
Thoren, 1985	9 (8 RT, 1 BA)	R:1000-3000; M:1777,8 m:1500	R:0,6-6,5; M:1,9;m:1,2	77,8	NA	NA
Verhelst, 1991 (short-term study)	53	R:500-6000;	R:0,25-4;	75,4	na	na
Verhelst, 1991 (long-term study)	24 (24RT)	R:750-4000; m:750	R:3-140; m:27	83,3	4,2*	4,8*
Valassi, 2012	23 (CS)	R:750-1000; (initial dose)	R:1-30,7; m:4	56,5	13	18,7
Van den Bosch, 2014	22	R:1000-6000; M:2477,2; m:2000	R:1,7-11,6; M:5,9; m:5,8	45,4	NA	NA
Total	**120**	**R:500-6000; M:2127,5;m:1750**	**R:0,25-66; M:8,7;m:5,5**	**R:45,4-100; M:71;m:75,5**	**R:0-13; M:5,7;m:4,2**	**R:0-18,7; M:7,8;m:4,8**

RT:previous or concomitant radiotherapy; BA: bilateral adrenalectomy; R: range; M:mean:m:median; NA: not available; na: not applicable; *: for studies remission rate of the global population and escape rate of the long-term population have been considered for the calculation of total range, mean and median; **: results in overall population of patients with CS; £:results in the entire female population; $:results in entire population of patients treated with ketokonazole and metyrapone either as monotherapy or in combination

Pivonello R et al Endocr Rev 2015; 36(4):385-486

Metyrapone: A recent study in CS

First author, Year	N° of patients	Drug dose (mg/d)	Follow-up (months)	Remission rate (%)	Escape (% of the total population)	Escape (% of the initially responsive population)
Daniel, E . 2016	164 as monotherapy	R:250-4000;	R:0.1-132; M:3;	43-76%	0	0

Overall more than 80% of patients showed an improvement in levels of circulating cortisol with over 50% achiving eucortisolemia when on monotherapy (assessed cortisol day-curve)

Metyrapone: pharmacokinetics aspects

Rapid absorption:

- Peak plasma concentration within 1-hours (extensive intra-individual variations)
- Maximum 11 beta-hydroxylase block reached at 2-4 hours after administration

Metabolism

- Liver metabolism

Excretion:

- Half-life :~ 2 hours
- Excretion: bile and then urinary

Schöneshöfer et al., J Endocrinol Invest. 1980
Verhelst et al., Clin Endocrinol. 1991
Adlin et al., Endocrinology.1966

Metyrapone: dose and administration

Management

- Severity of hypercortisolism
- Dose response
- Patients tolerability
- Cortisol levels reached
- 4-6 daily doses
- Max dose: 6000 mg/day (24 tablets/day)

Daily dose		Cortisol monitoring and dose adjustments
Start	Mild disease: 750 mg/day (250-1000 mg/day) Severe disease: up to 1500 mg/day	After few days to maintain the levels of cortisol to the target values or to reach max tolerated dose. Adjustments every 1-4 weeks
Maintenance	1500-2000 mg/day	Every 1-2 months when cortisol is close to standard levels

Daniel et al., J Clin Endocrinol Metab , 2015
Pivonello R et al ,Endocr Rev 2015;

Metyrapone: dose and administration

- **Serum cortisol measurements:**
- Average levels of 5-6 samples during the day
- **UFC levels**
- Use a reliable method, such as spectrometric (preferable) or specific RIA method, without cross reactivity with precursors. To avoid the risk of :
  - Over-estimation of cortisol levels
  - Over -treatment
  - Failure to diagnose adrenal insufficiency

Two alternative schemes:

- Titration (or one block)
- Block-and-replace: dose increase + Corticosteroid replacement therapy if:
  - Quick dose increase need
  - Cyclic Cushing's disease patients

UFC: Urinary Free Cortisol;
RIA: radioimmunoassay

Metyrapone: special populations

- **Pediatric population:**
- Limited data and no specific dose guidelines
- **Elderly patients:**
- Adults dose

- **Women:**
- Not recommended in reproductive age women not using contraception
- During pregnancy: monitor blood pressure and adequately treat hypertension
- Lactation: not recommended during treatment with Metyrapone

Metyrapone: adverse events

Common adverse events:

- Dizziness
- Sweating
- Headache
- Nausea, vomiting
- Hypertension, hypokalemia, aedema
- Hirsutism

Rare adverse events:

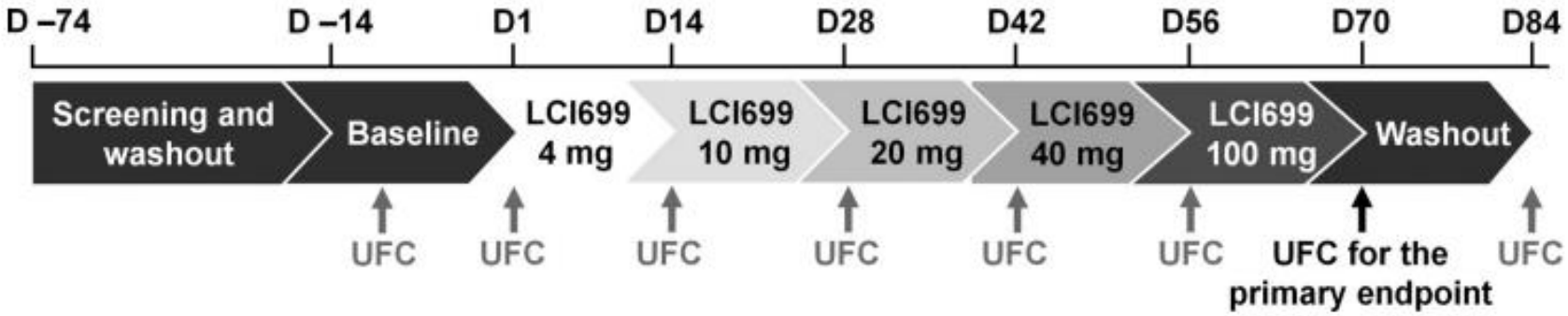
- Adrenal insufficiency
- Abdominal pain
- Atopic dermatitis

Pivonello R et al Endocr Rev 2015; 36(4):385-486

Osilodrostat

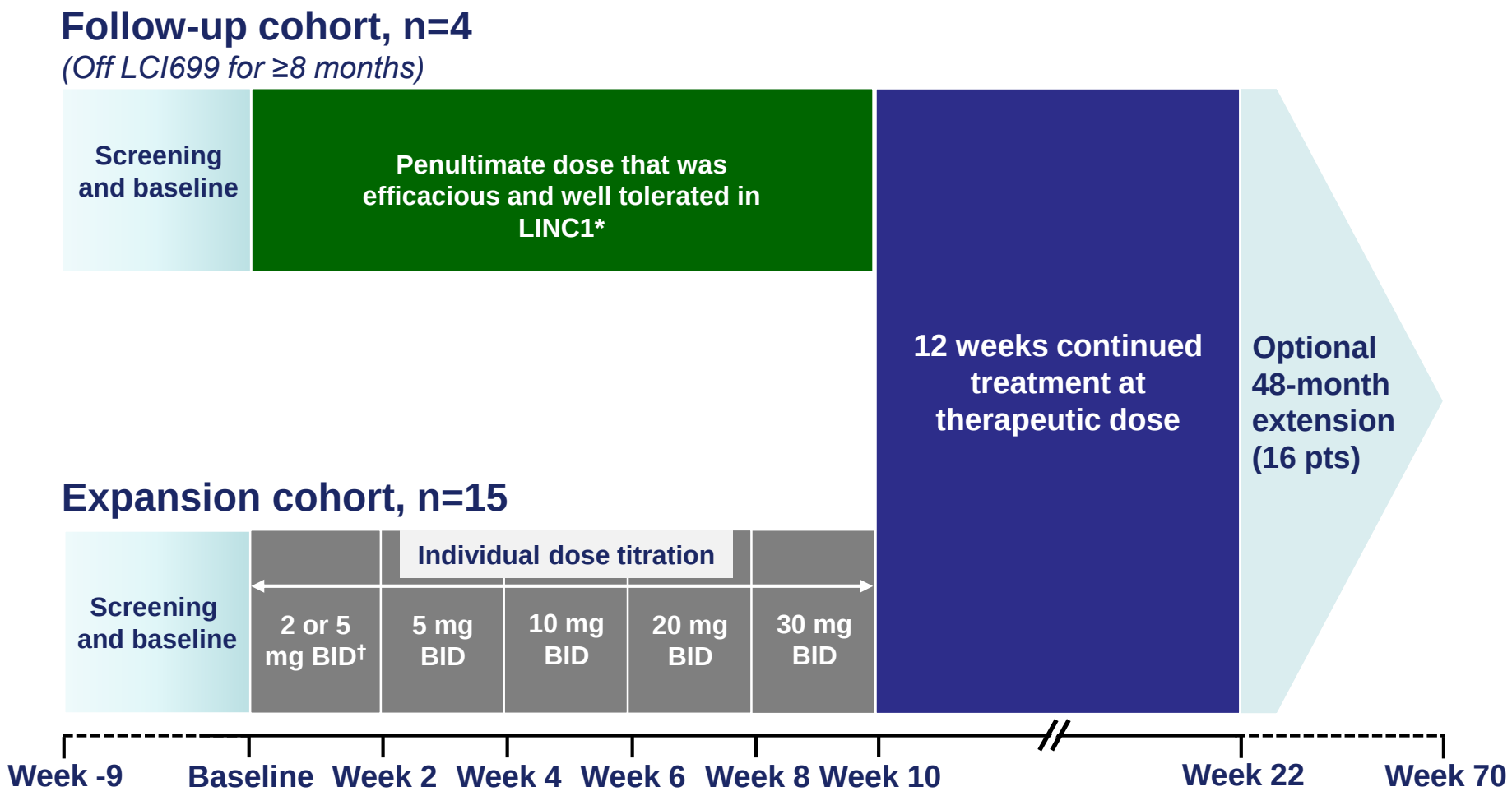
In phase III in CD

LINC 1 – proof-of-concept Study



- LINC 1, showed normal UFC in 11 of 12 patients with Cushing's disease after 10 weeks of LCI699

LINC 2 – Study Background and Key Eligibility Criteria

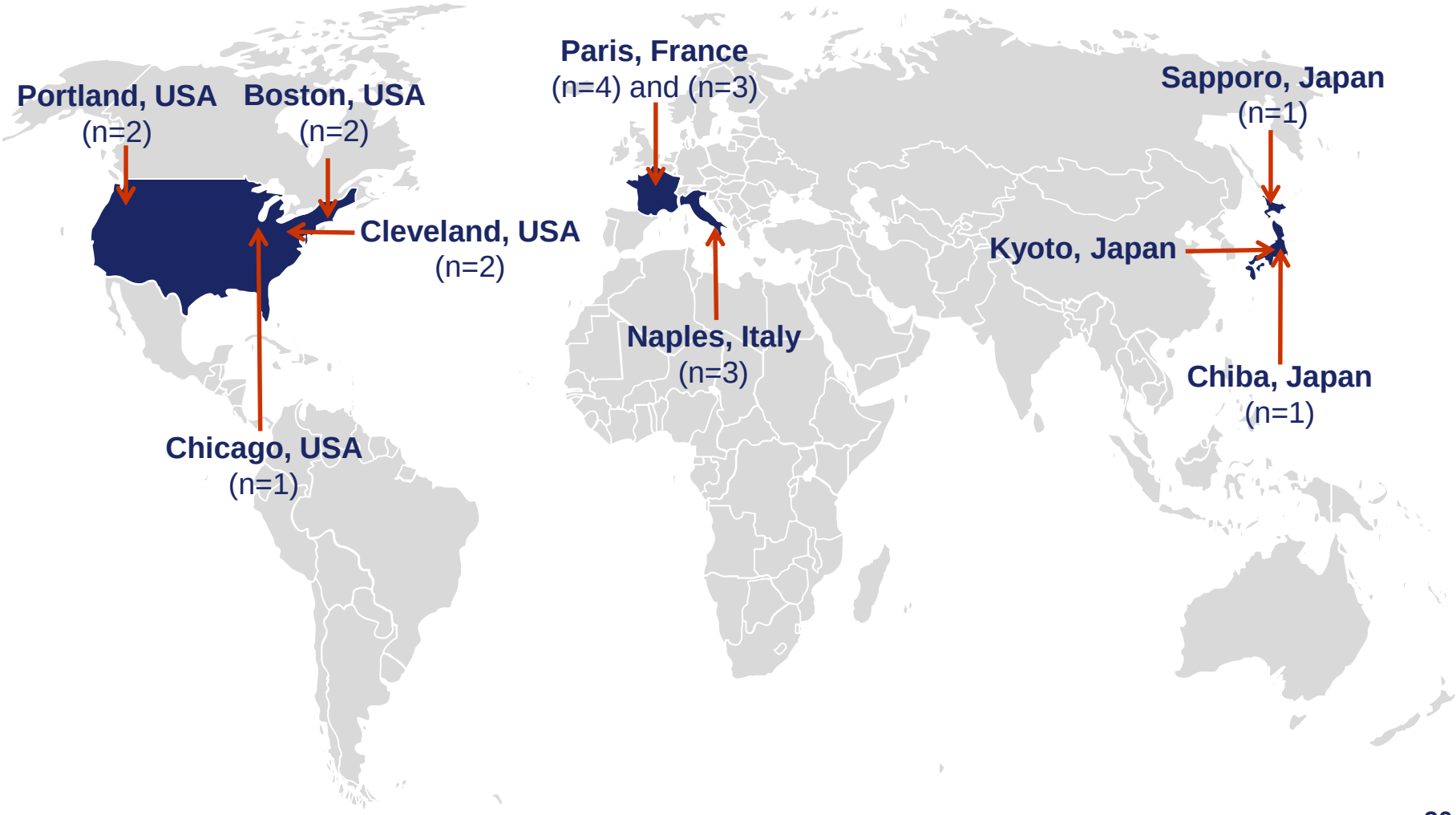


BID, twice daily; BL, baseline; UFC, urinary-free cortisol; ULN, upper limit of normal.

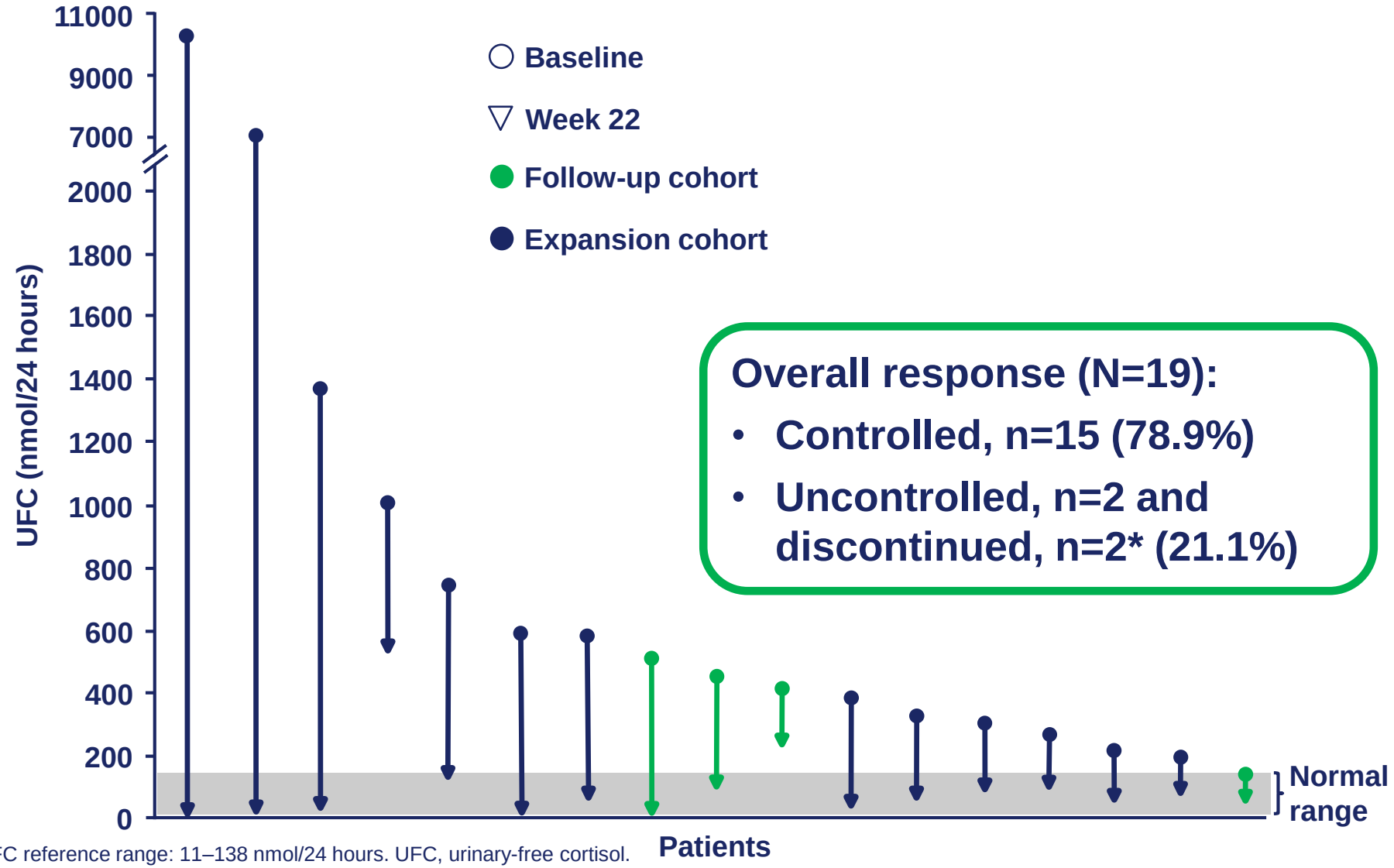
*Dose could be up-titrated within 1 week. Additional dose titrations were allowed up to week 10 and between weeks 10 and 22 as needed based on efficacy and tolerability. †Patients with baseline UFC ≤3 × ULN started at 2 mg BID; those with baseline UFC >3 × ULN started at 5 mg BID.

Study Sites

- Study sites in this international multicenter trial included



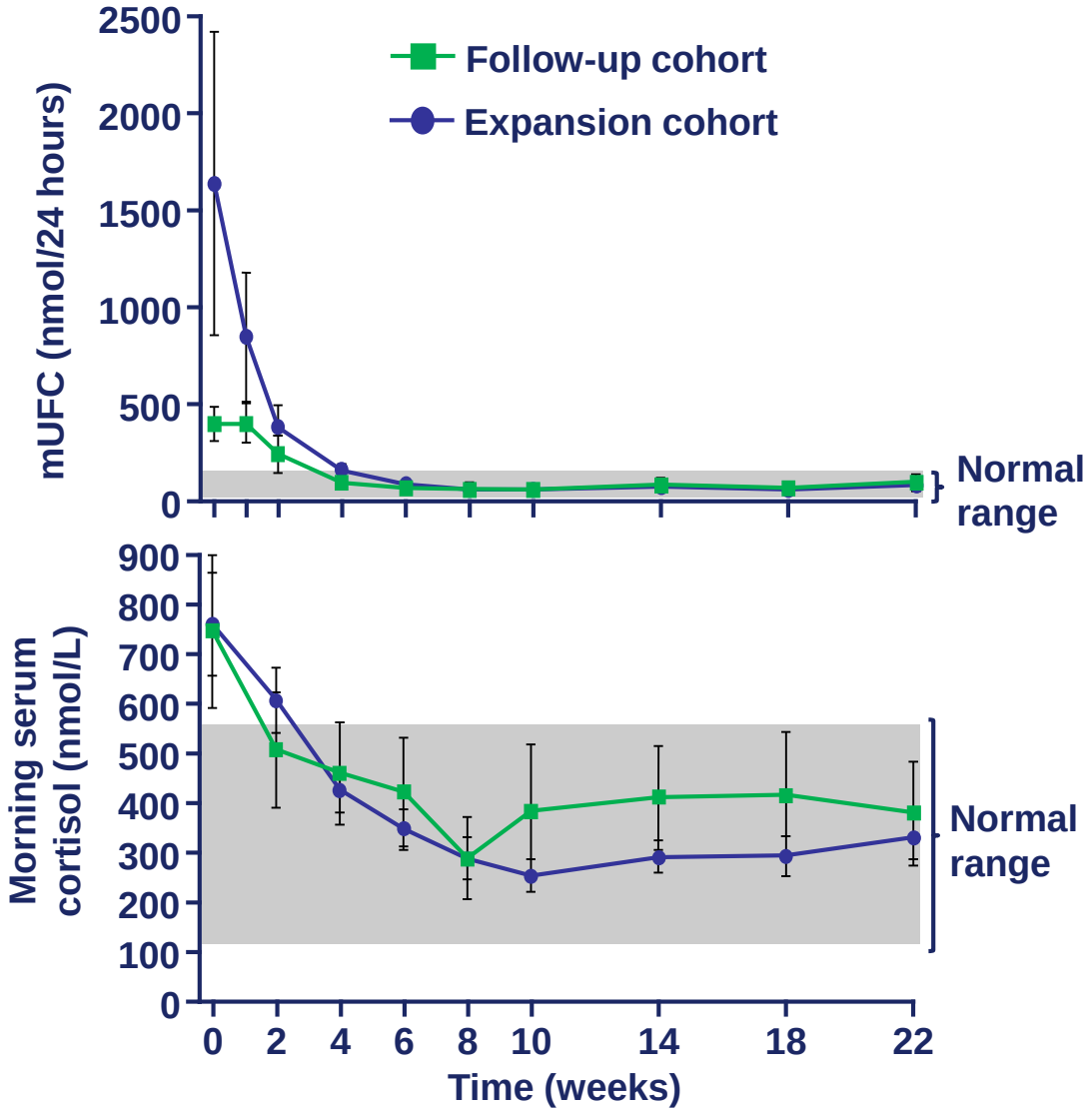
Absolute Changes in UFC From Baseline in Patients Who Completed 22 Weeks of LCI699



UFC reference range: 11–138 nmol/24 hours. UFC, urinary-free cortisol.

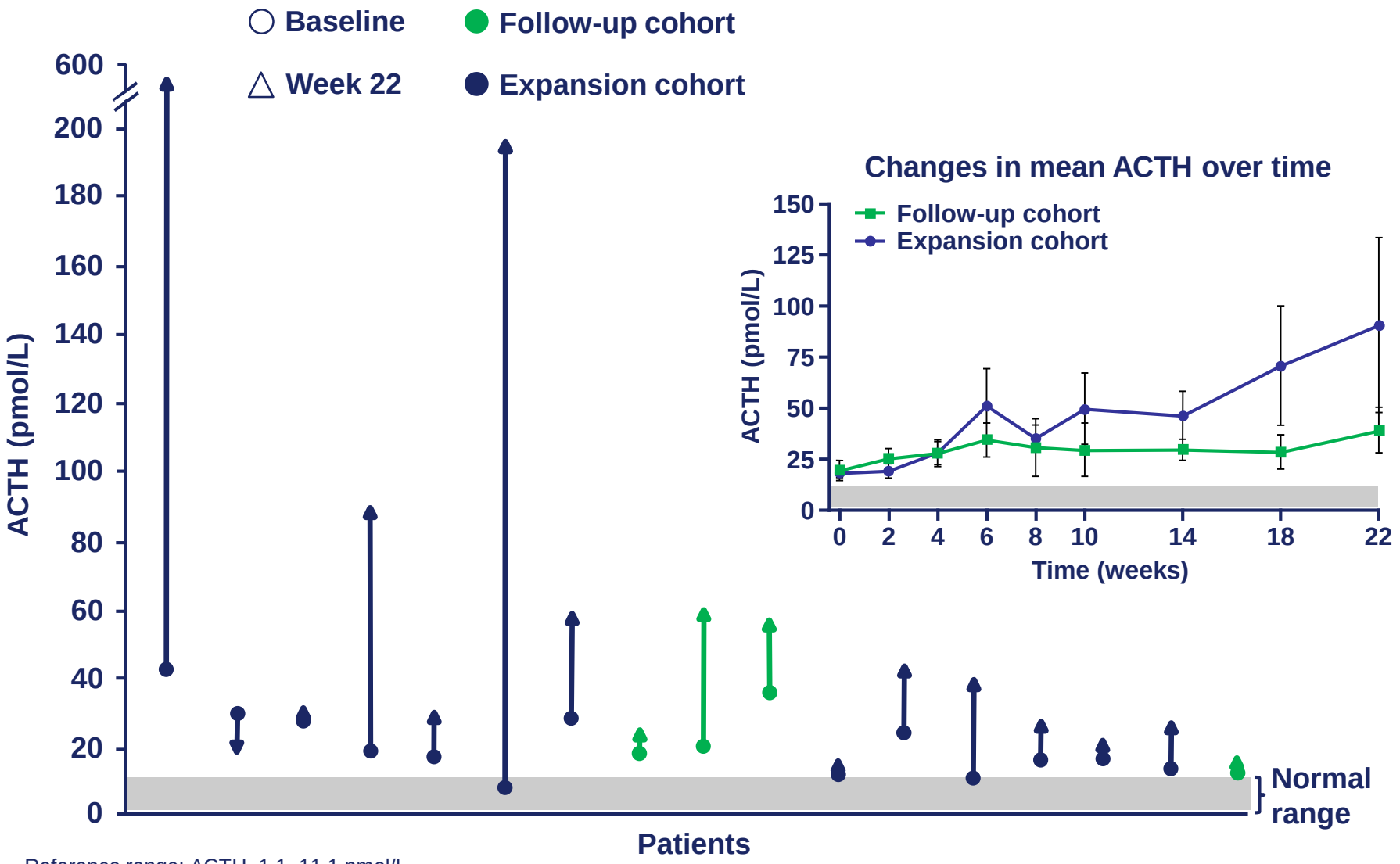
*discontinued during the first 10 weeks, 1 non-treatment-related administrative issue and 1 because AE; grade 3 papular rash; 1 might have experienced an "escape"

Mean Cortisol Levels Over Time After 22 Weeks of LCI699 Treatment



All data are mean±SE. Reference ranges: UFC, 11–138 nmol/24 hours; serum cortisol, 127–567 nmol/L.
mUFC, mean UFC; SE, standard error; UFC, urinary-free cortisol.

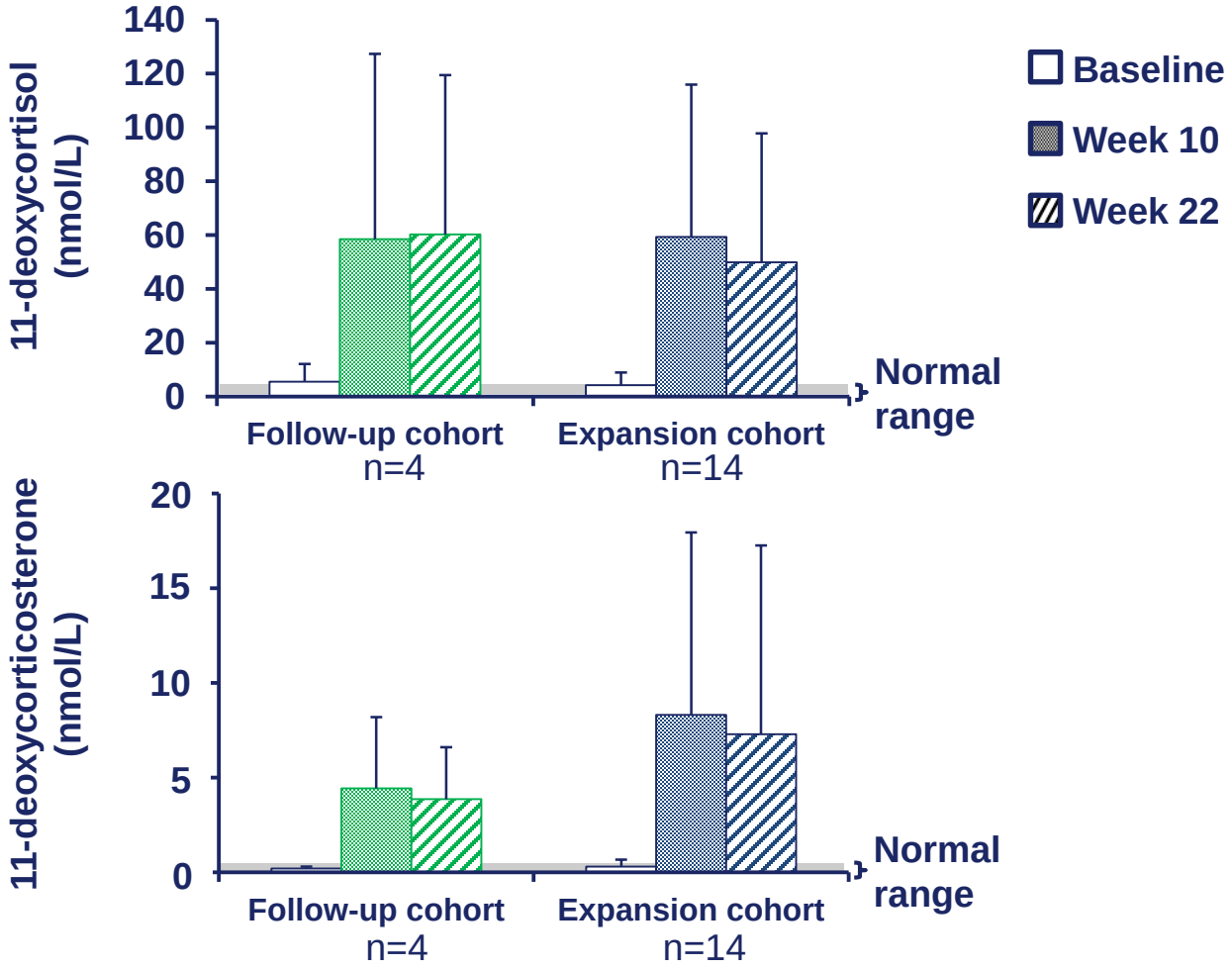
Absolute Changes in ACTH From Baseline in Patients Who Completed 22 Weeks of LCI699



Reference range: ACTH, 1.1–11.1 pmol/L.

ACTH, adrenocorticotropic hormone.

Changes in Other Hormone Levels of the HPA Axis During LCI699 Treatment



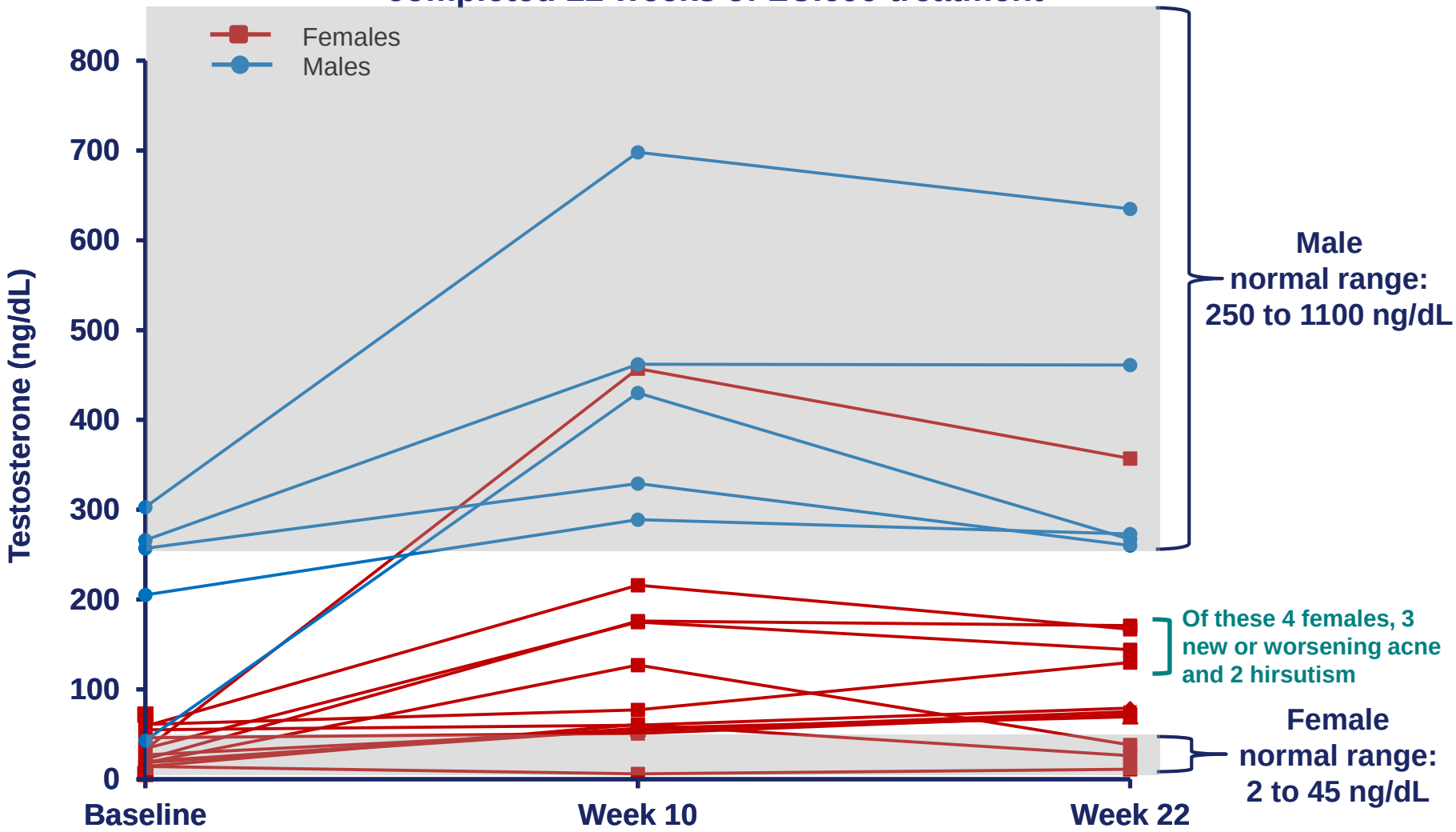
All data are mean±SD.

Reference ranges: 11-deoxycortisol, ≤3.92 nmol/L;11-deoxycorticosterone, 0.045–0.393 nmol/L.

HPA, hypothalamic-pituitary-adrenal; SD, standard deviation.

Changes in Testosterone Levels in Individual Patients

Testosterone was above normal in 9 of 12 women who completed 22 weeks of LCI699 treatment



Changes in Clinical and Laboratory Values at Week 22 of LCI699 Treatment

Parameter	Baseline (n = 19)	Week 22 (n = 17)	Absolute change from baseline	Percentage change from baseline
Weight, kg	85.1 ± 24.0	85.6 ± 26.2	–1.5 ± 3.8	–3.0 (–7, 6)
Body mass index, kg/m^2	30.7 ± 7.0	30.1 ± 7.9	–0.5 ± 1.4	–3.1 (–7, 7)
Systolic blood pressure,[a] mmHg	132.6 ± 11.6	131.9 ± 17.8	–1.0 ± 16.2	–0.5 (–20, 26)
Patients with baseline[b] hypertension (n = 13)	133.6 ± 13.1	133.5 ± 20.1	–0.8 ± 19.0	–4.9 (–20, 26)
Diastolic blood pressure,[a] mmHg	85.1 ± 6.5	86.0 ± 8.9	1.3 ± 9.7	2.4 (–15, 24)
Patients with baseline[b] hypertension (n = 13)	85.4 ± 7.5	86.8 ± 9.7	1.9 ± 11.2	2.4 (–15, 24)
Fasting plasma glucose, mg/dL	105.6 ± 49.0	81.2 ± 9.0	–14.9 ± 28.9	–10.2 (–58, 18)
Patients with baseline[b] diabetes mellitus (n = 8)	133.4 ± 67.2	82.7 ± 12.3	–33.3 ± 41.0	–21.4 (–58, –5)
HbA_{1c}, %	5.7 ± 0.7	5.5 ± 0.6	–0.2 ± 0.3	–2.2 (–11, 8)
Patients with baseline[b] diabetes mellitus (n = 8)	6.4 ± 0.5	6.0 ± 0.5	–0.3 ± 0.3	–5.5 (–11, 0)
Total cholesterol, mmol/L	5.3 ± 1.4	4.6 ± 0.8	–0.7 ± 1.4	–8.0 (–39, 70)
Patients with baseline[b] dyslipidemia (n = 6)	5.9 ± 1.8	5.2 ± 0.9	–0.7 ± 1.9	–12.6 (–39, 70)
HDL-cholesterol, mmol/L	1.7 ± 0.9	1.3 ± 0.4	–0.5 ± 0.8	–16.6 (–68, 11)
Patients with baseline[b] dyslipidemia (n = 6)	1.5 ± 0.5	1.3 ± 0.6	–0.2 ± 0.2	–13.7 (–34, 11)
LDL-cholesterol, mmol/L	3.3 ± 1.7	2.8 ± 0.6	–0.6 ± 1.6	–15.2 (–57, 350)
Patients with baseline[b] dyslipidemia (n = 6)	3.6 ± 1.9	3.1 ± 0.7	–0.5 ± 1.7	–17.8 (–48, 350)
Triglycerides, mmol/L	1.5 ± 0.6	1.3 ± 0.6	0 ± 0.4	–11.9 (–38, 65)
Patients with baseline[b] dyslipidemia (n = 6)	1.7 ± 0.7	1.7 ± 0.4	–0.1 ± 0.6	–7.8 (–29, 44)

Reported Adverse Events (Regardless of Relationship to Study Drug)

- AEs were reported in ≥5 patients in the combined cohorts
- Safety follow-up includes data of up to 50 weeks (median, 26.7 weeks)

	All patients (N=19)	
	All grades, n (%)	Grade 3/4, n (%)
Increased adrenal precursors	7 (36.8)	0
Increased ACTH	6 (31.6)	0
Increased testosterone	5 (26.3)	1 (5.3)
Nausea	6 (31.6)	0
Diarrhea	6 (31.6)	0
Asthenia	6 (31.6)	0
Adrenal insufficiency	6 (31.6)	1 (5.3)
Nasopharyngitis	5 (26.3)	0

2 of 19 patients discontinued from the study:
AEs (n=1*); administrative issue (n=1)

All AEs are as reported by the investigator.
*Patient discontinued at week 2: diarrhea, nausea, muscular weakness, malaise, and papule.
ACTH, adrenocorticotropic hormone; AE, adverse event.

Osilodrostat Versus Metyrapone

- Advantages of Osilodrostat include
  - Longer half-life, allowing twice-daily dosing
  - Higher potency against 11β-hydroxylase

	LCI699	Metyrapone
Administration	Oral	Oral
Half-life	~4 hours	<2 hours
IC_{50} against 11β-hydroxylase	2.5 nM	7.5 nM

- Advantages of Metyrapone
  - Indicated for **CS** in EU

IC_{50}, half-maximal inhibitory concentration.

Bertagna X, et al. *J Clin Endocrinol Metab.* 2014;99:1375–1383.

Conclusions

Metyrapone and Osilodrostat:

- Are able to control CS/CD in 50-80% of patients
- Are generally well tolerated
  - Most AEs were expected based on the mechanism of action and were consistent with those previously observed
- Metyrapone is indicated in EU for the management of patients with endogenous CS
- Osilodrostat is currently under evaluation in a large population of CD patients confirmatory phase III study (LINC 3)

MARCELLO ROSCIOLI

AE, adverse event; LINC, LCI699 IN Cushing's; UFC, urinary-free cortisol.

Bertagna X, et al. *J Clin Endocrinol Metab.* 2014;99:1375–1383.

Thank you

Annamaria Colao,

Rosario Pivonello

Chiara Simeoli

Monica De Leo

Davide Iacuaniello

Questions

LINC 2 – Study Background and Key Eligibility Criteria

- LINC 2 is an amended extension in 2 adult cohorts:
  - LINC 1 patients: if UFC >ULN off LCI699 (follow-up cohort, n=4)
  - Additional Cushing's disease patients: UFC >1.5 × ULN (expansion cohort, n=15)
- UFC based on mean of at least two 24-hour urine samples
  - After washout of other medications for Cushing's disease
  - Measured using LC-MS/MS in a central laboratory

Overall goal: assess efficacy and safety/tolerability of LCI699 in Cushing's disease over a longer period

LC-MS/MS, liquid chromatography–tandem mass spectrometry; LINC, LCI699 IN Cushing's; UFC, urinary-free cortisol; ULN, upper limit of normal.

Bertagna X, et al. *J Clin Endocrinol Metab.* 2014;99:1375–1383.

Study Objectives

- Effect of 10 and 22 weeks of LCI699 treatment on 24-hour assessments of UFC and other hormones of the HPA axis
  - Response was classified as follows:
    - Controlled – mean UFC ≤ULN
    - Partially controlled – mean UFC >ULN but with reduction of ≥50% from baseline
    - Uncontrolled – mean UFC >ULN and with reduction of <50% from baseline
- Safety/tolerability

HPA, hypothalamic-pituitary-adrenal; UFC, urinary-free cortisol; ULN, upper limit of normal.

Changes in Clinical and Laboratory Values at Week 22 of LCI699 Treatment

Parameter; median (range)	Baseline (N=19)	Week 22 (N=17)	Absolute change at week 22
Weight, kg	85 (62–143)	85 (60–148)	0
SBP, mm Hg	133 (116–156)	132 (108–174)	0
Patients with baseline HT (n=13)	135 (117–134)	134 (108–155)	-1
DBP, mm Hg	84 (69–102)	86 (72–103)	+2
Patients with baseline HT (n=13)	84 (69–102)	86 (72–103)	+3
Glucose, mg/dL (NR: 70–110)	97 (69–187)	81 (64–102)	-16
Patients with baseline DM (n=8)	118 (87–187)	83 (64–102)	-35
HbA_{1c}, % (NR: <6.4)	5.4 (4.6–7.0)	5.1 (4.5–6.4)	-0.3
Patients with baseline DM (n=8)	6.4 (5.7–6.9)	6.0 (5.1–6.0)	-0.4
Total cholesterol, mg/dL (NR: <199)	209 (153–325)	179 (140–237)	-30
HDL cholesterol, mg/dL (NR: 35–100)	70 (28–220)	50 (28–94)	-20
LDL cholesterol, mg/dL (NR: <129)	130 (37–330)	107 (72–157)	-22
Triglycerides, mg/dL (NR: <149)	138 (58–266)	118 (41–192)	-20

DBP, diastolic blood pressure; DM, diabetes mellitus; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; NR, normal range; SBP, systolic blood pressure.