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Continued Improvements in Hypertension and Diabetes During Long-Term Osilodrostat Therapy in Patients With Cushing's Disease: A Pooled Analysis From the Phase III LINC 3 and LINC 4 Studies

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INTRODUCTION

- Hypertension and diabetes mellitus are common, potentially serious comorbidities in patients with Cushing's syndrome[1]
  - Control of cortisol is a primary treatment goal in the management of Cushing's syndrome and may alleviate these comorbidities[1]
- Osilodrostat, a potent oral 11β-hydroxylase inhibitor, provided rapid and sustained cortisol normalization over long-term treatment in patients with Cushing's disease in two Phase III studies (LINC 3, NCT02180217; LINC 4, NCT02697734), with improvements in clinical manifestations of hypercortisolism[2–5]
- Using pooled data from LINC 3 and LINC 4, we assessed long-term changes in BP and markers of glucose homeostasis (FPG and HbA_{1c}) in patients with hypertension and diabetes, respectively, at baseline

CONCLUSIONS

- **Many patients with Cushing's disease and comorbid hypertension or diabetes showed improvements in BP and glycemic control during osilodrostat treatment**
  - **BP decreased over time, irrespective of whether patients were treated with antihypertensives during the study**
  - **Most patients with high SBP or DBP at baseline had normotensive levels as early as week 12**
  - **In patients with hypertension at baseline, BP decreased in those with complete or partial mUFC control at week 72**
  - **Some patients had improved glycemic control during the study, and many were able to reduce the dose of, or stop taking, their antidiabetic medication**
- **Comorbidities should be closely monitored in patients with Cushing's disease treated with osilodrostat**
  - **Adjustments in concomitant medications are required for some patients taking osilodrostat as cortisol levels decline, including those with improving hypertension or diabetes**
- **Improvements in BP and glycemic control were maintained or further improved in most patients with long-term osilodrostat therapy**

METHODS

- Scan the QR code for details of the LINC 3 and LINC 4 study designs
- Individual patient data from LINC 3 and LINC 4 were pooled for all patients with data at baseline and weeks 12, 48 and 72, excluding periods in which patients were randomized to placebo
- Baseline hypertension was defined as prior diagnosis, taking antihypertensive medication and/or SBP >130/DBP >90 mmHg
- Baseline diabetes was defined as prior diagnosis, taking antidiabetic medication, HbA_{1c} ≥6.5% and/or FPG ≥126 mg/dL
- No formal statistical hypothesis testing was performed; all analyses are descriptive

RESULTS

Patient population

- Overall, 210 patients were included in the analyses (LINC 3, n=137; LINC 4, n=73)

Baseline characteristics in patients with and without hypertension at baseline

	Patients with hypertension at baseline (N=174)	Patients without hypertension at baseline (N=36)
Age, median (min–max), years	41.0 (19–70)	35.0 (19–55)
Sex, %		
Male	23.0	8.3
Female	77.0	91.7
mUFC, µg/24 h [nmol/24 h]		
Mean (SD)	307.5 (501.49) [848.8 (1384.12)]; 6.2 × ULN (10.0)	217.8 (372.91) [601.1 (1029.22)]; 4.4 × ULN (7.5)
Median (min–max)	156.3 (8–3483) [431.4 (21–9612)]; 3.1 × ULN (0.2–69.7)	116.7 (24–2072) [322.2 (67–5720)]; 2.3 × ULN (0.5–41.4)
Weight, mean (SD), kg	80.6 (20.97)	76.3 (19.57)
SBP, mean (SD), mmHg	135.3 (14.90)	113.2 (8.79)
DBP, mean (SD), mmHg	86.5 (10.41)	74.6 (7.58)
FPG, mean (SD), mg/dL	99.0 (26.78)*	92.3 (22.14)†
HbA_{1c}, mean (SD), %	6.0 (0.94)	5.7 (0.75)

ULN for mUFC = 50 µg/24 h [138 nmol/24 h]. *n=165; †n=35

Baseline characteristics in patients with and without diabetes at baseline

	Patients with diabetes at baseline (N=84)	Patients without diabetes at baseline (N=126)
Age, median (min–max), years	42.5 (19–69)	38.0 (19–70)
Sex, %		
Male	17.9	22.2
Female	82.1	77.8
mUFC, µg/24 h [nmol/24 h]		
Mean (SD)	322.0 (534.47) [888.7 (1475.14)]; 6.4 × ULN (10.7)	272.3 (445.26) [751.5 (1228.92)]; 5.4 × ULN (8.9)
Median (min–max)	156.3 (8–3483) [431.4 (21–9612)]; 3.1 × ULN (0.2–69.7)	139.2 (17–3440) [384.3 (47–9494)]; 2.8 × ULN (0.3–68.8)
Weight, mean (SD), kg	83.8 (21.72)	77.3 (19.74)
FPG, mean (SD), mg/dL	110.7 (32.26)*	89.7 (17.10)†
HbA_{1c}, mean (SD), %	6.5 (1.05)	5.5 (0.50)
SBP, mean (SD), mmHg	133.1 (15.76)	130.6 (16.69)
DBP, mean (SD), mmHg	83.6 (10.81)	85.1 (11.01)

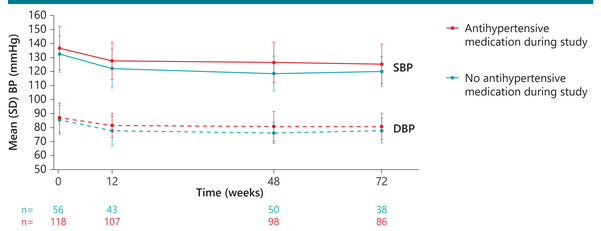
ULN for mUFC = 50 µg/24 h [138 nmol/24 h]. *n=77; †n=123

1. Many patients were classified as having hypertension or diabetes at baseline

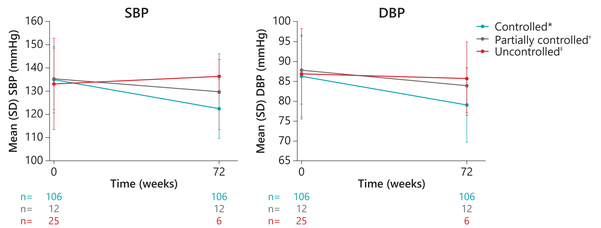
83% (174/210) of patients were classified as having hypertension
- Mean baseline SBP/DBP: 135.3/86.5 mmHg
- 54% of all patients (114/210) were taking antihypertensive medication

40% (84/210) of patients were classified as having diabetes
- Mean baseline FPG and HbA_{1c}: 110.7 mg/dL and 6.5%, respectively
- 22% of all patients (46/210) were taking antidiabetic medication

2. BP was reduced irrespective of whether patients with hypertension at baseline were taking antihypertensive medication during the study



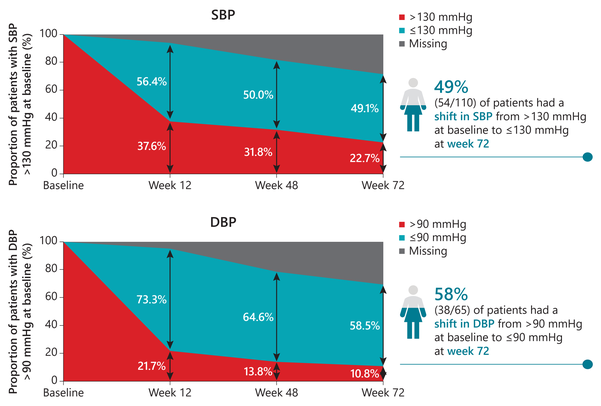
3. Patients with hypertension at baseline who achieved complete or partial mUFC control at week 72 had decreased SBP and DBP



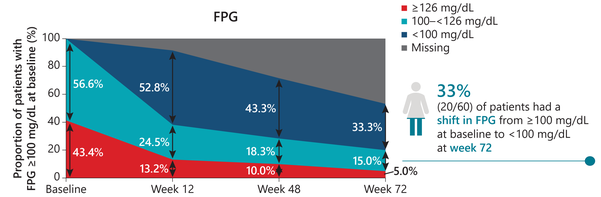
Complete mUFC control: mUFC ≤ULN; partial mUFC control: mUFC >ULN but ≥50% decrease from baseline; uncontrolled: >ULN and <50% reduction from baseline

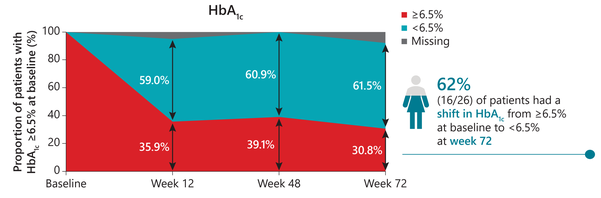
- The magnitude of the reduction in SBP and DBP in patients with hypertension at baseline did not appear to be affected by baseline mUFC severity (scan QR code for data)
- There was a weak correlation between change in SBP and DBP and change in mUFC from baseline to week 72 (r=0.2 [*P*=0.048] and r=0.22 [*P*=0.028], respectively)

4. Most patients with SBP >130 mmHg or DBP >90 mmHg at baseline had SBP ≤130 mmHg or DBP ≤90 mmHg, respectively, from as early as week 12 of osilodrostat treatment



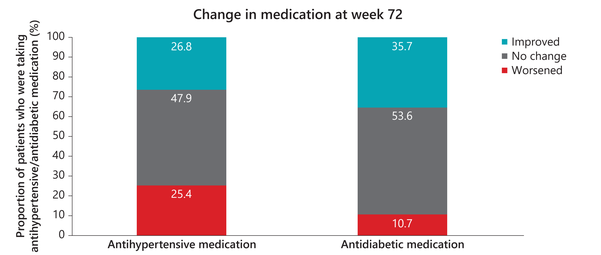
5. Many patients with FPG ≥100 mg/dL or diabetic HbA_{1c} levels at baseline had improved glycemic control as early as week 12 of osilodrostat treatment





- There were reductions in mean weight, waist circumference and BMI during the study in patients with and without hypertension at baseline (scan QR code for data)
- Mean 11-deoxycorticosterone levels increased during the study in those with and without hypertension at baseline
  - Mean (SD) levels at baseline were 2834.6 (5549.63) pmol/L (n=18) and 484.0 pmol/L (n=1), respectively
  - Corresponding values at week 72 were 4004.6 (3377.51) pmol/L (n=100) and 4344.1 (3821.85) pmol/L (n=20)
- Mean potassium levels remained largely unchanged and within the normal range in those with and without hypertension at baseline
  - Mean (SD) levels at baseline were 4.1 (0.37) mmol/L (n=174) and 4.2 (0.35) mmol/L (n=35), respectively
  - Corresponding values at week 72 were 4.1 (0.40) mmol/L (n=118) and 4.1 (0.28) mmol/L (n=23)

6. Some patients were able to reduce the dose of, or stop taking, antihypertensive and/or antidiabetic medication during the study



Improved: reduced dose or stopped baseline medication; no change: no change in dose of baseline medication or initiation of any new medication; worsened: increased dose of baseline medication or started new medication

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ABBREVIATIONS

BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; mUFC, mean urinary free cortisol; SBP, systolic blood pressure; SD, standard deviation; ULN, upper limit of normal

DISCLOSURES

The studies were sponsored by Novartis Pharma AG; however, as of July 12, 2019, osilodrostat is an asset of Recordati AG.

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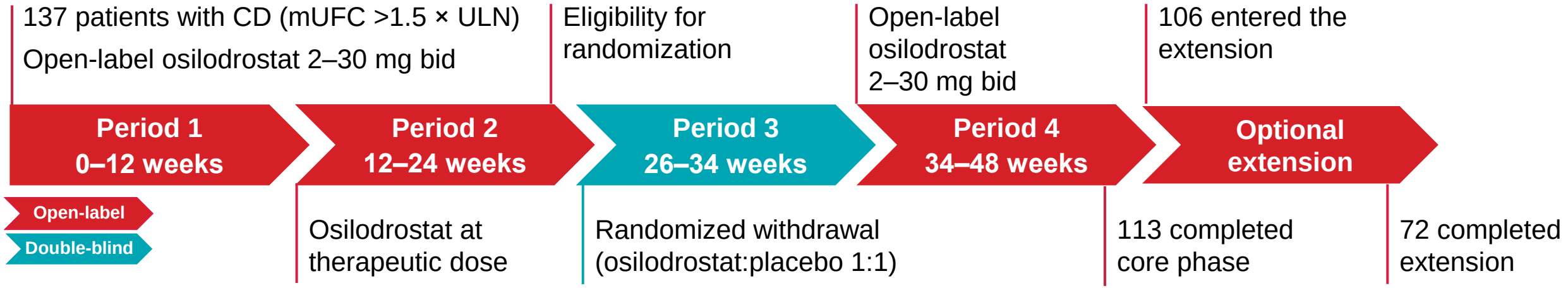
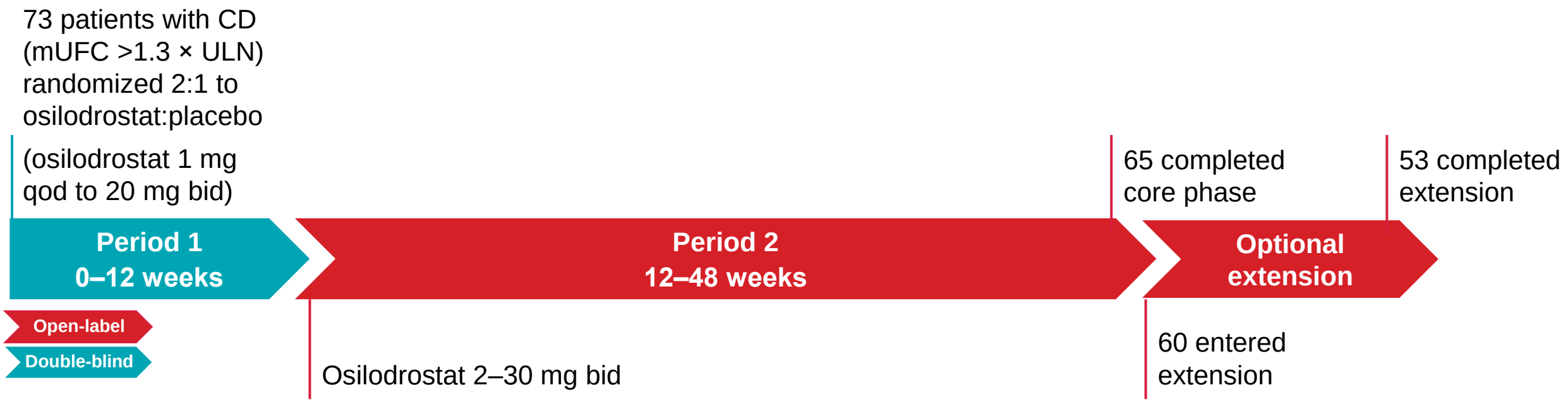
QR code content

LINC 3 and LINC 4 study designs

LINC 3

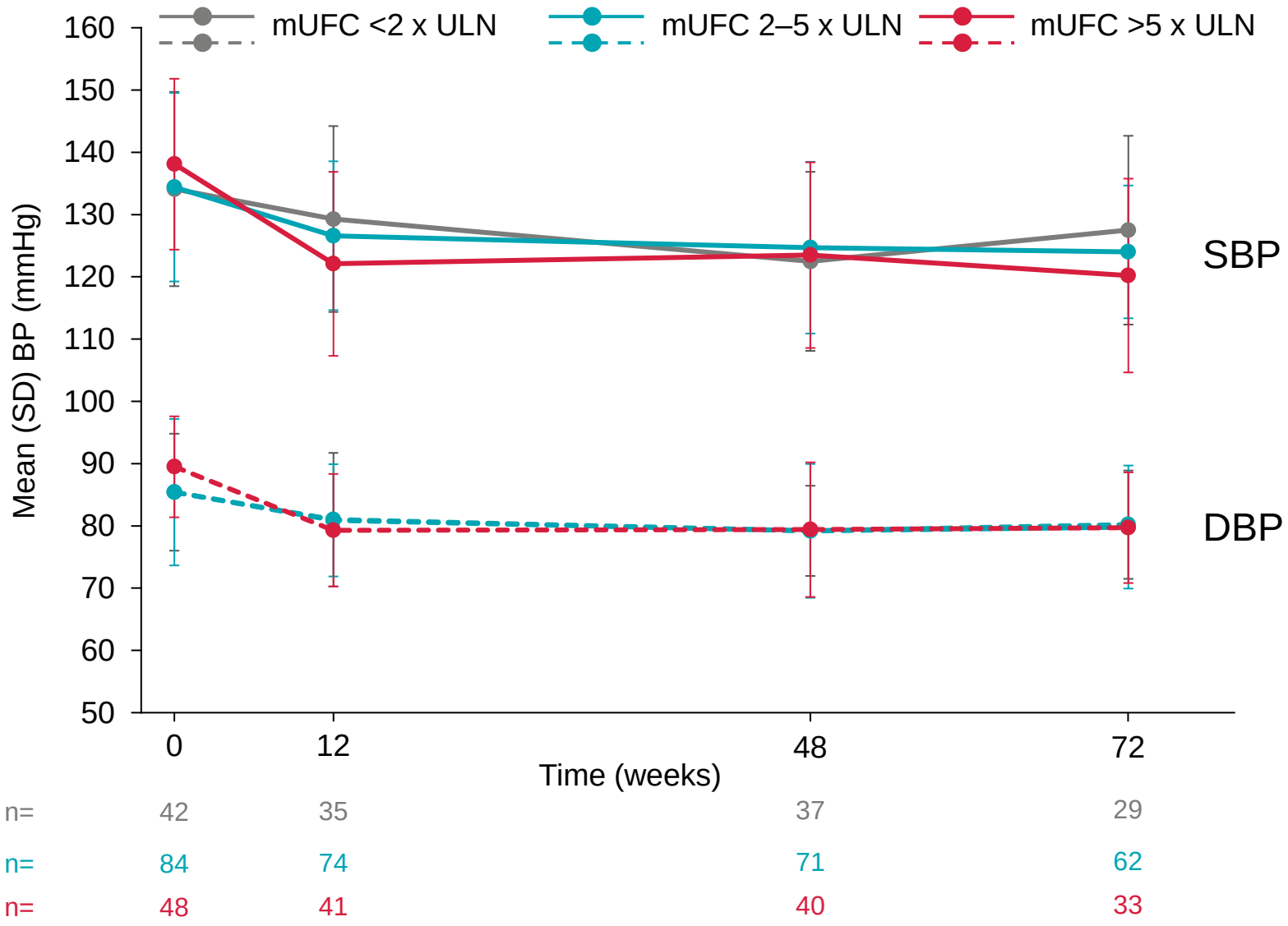


LINC 4



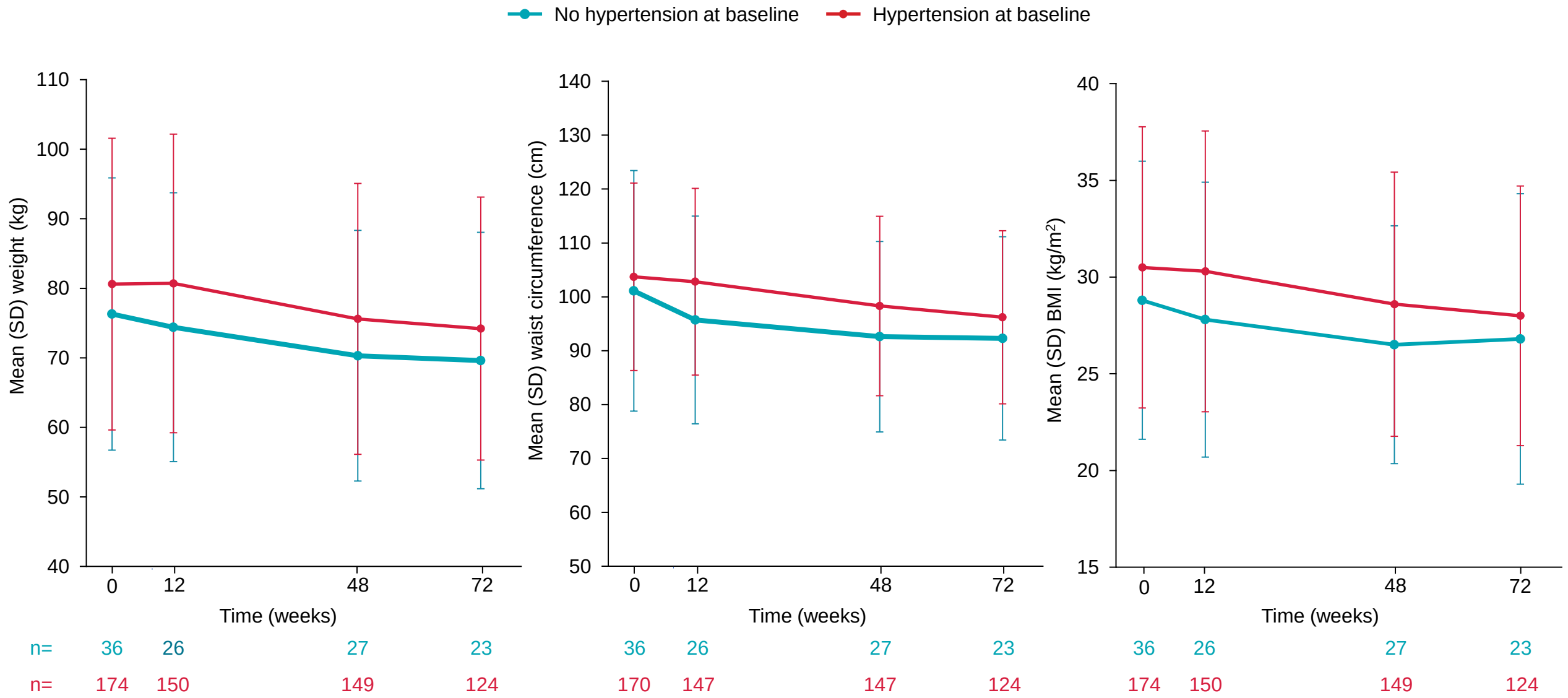
bid, twice daily; CD, Cushing's disease; mUFC, mean urinary free cortisol; qod, every other day; ULN, upper limit of normal

Mean (SD) blood pressure in patients with hypertension during osilodrostat treatment according to baseline mUFC levels



BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation

Mean (SD) body weight, waist circumference and BMI during osilodrostat treatment in patients with and without hypertension at baseline



BMI, body mass index