# MEDICAL TREATMENT OF HYPERCORTISOLISM WITH RELACORILANT: FINAL RESULTS OF THE PHASE 3 GRACE STUDY

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## Summary & Conclusions

- Relacorilant is a selective glucocorticoid receptor modulator in development for the treatment of endogenous hypercortisolism
- GRACE was a phase 3, randomized-withdrawal (RW) study to assess the efficacy and safety of relacorilant in patients with hypercortisolism and hypertension and/or hyperglycemia (diabetes/impaired glucose tolerance)
- Significant improvements in hypertension, hyperglycemia, and other manifestations of cortisol excess were observed throughout the treatment with relacorilant
- Due to relacorilant's specificity for the GR and its unique mechanism of action, the observed efficacy was seen:
  - Without cases of relacorilant-induced irregular vaginal bleeding with endometrial hypertrophy
  - Without increases in cortisol concentrations and relacorilant-induced hypokalemia
  - Without reported cases of adrenal insufficiency
  - Without independently confirmed QT prolongation

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HiD presentation

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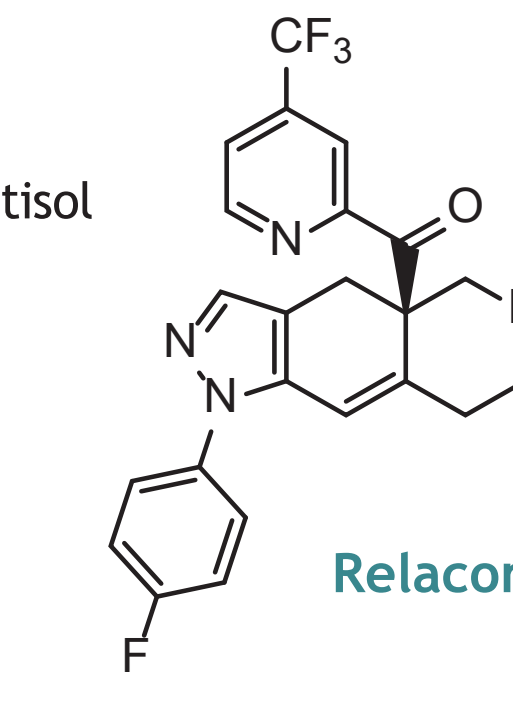
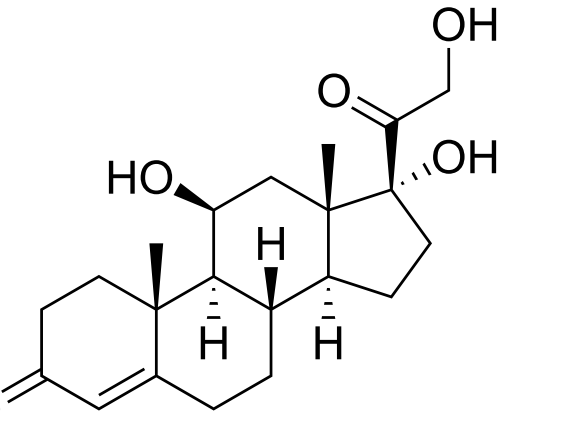
## Relacorilant: In Development for the Treatment of Cushing Syndrome



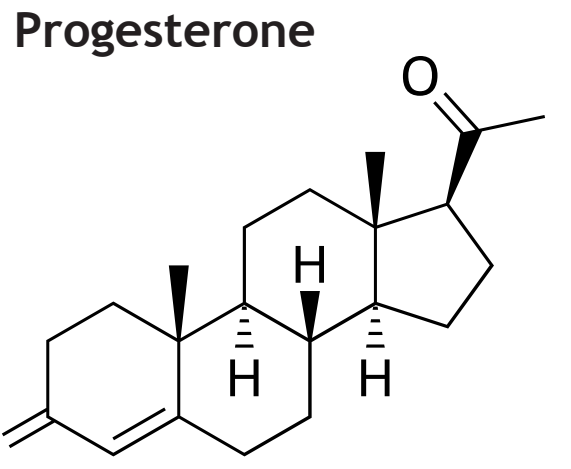
Relacorilant

- A selective glucocorticoid receptor modulator (SGRM)
  - Decreases excess cortisol activity by competing with cortisol for binding to the GR
- Highly selective: No activity at the progesterone, mineralocorticoid, or androgen receptors
  - Structurally different from mifepristone
  - Avoids unwanted progesterone receptor effects (eg, endometrial hypertrophy, vaginal bleeding)

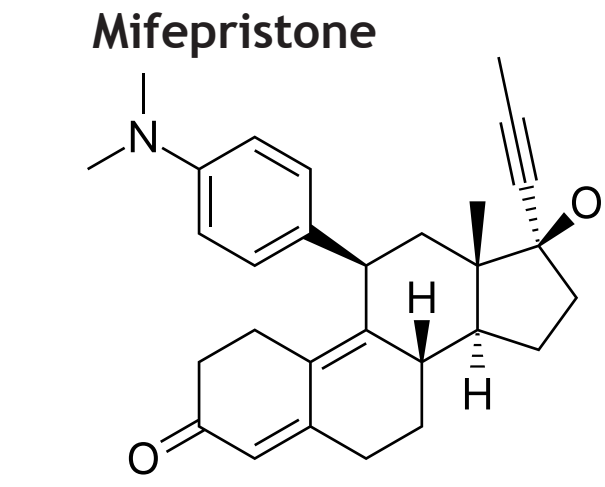
Cortisol



Progesterone



Mifepristone



- Unique downstream effects
  - No clinically significant impact on ACTH levels, resulting in no clinically significant rise in cortisol levels

ACTH, adrenocorticotropic hormone.

## Open-label: Patient Demographics & Baseline Characteristics

| Mean (SD) | Hypertension only (n=31) | Hyperglycemia only (n=50) | Hypertension & hyperglycemia (n=71) | Overall (N=152) |
|---|---|---|---|---|
| Age, yrs | 43.5 (11.6) | 54.1 (13.7) | 50.9 (12.6) | 50.4 (13.2) |
| Female, n (%) | 24 (77.4) | 42 (84.0) | 61 (85.9) | 127 (83.6) |
| Weight, kg | 95.2 (25.5) | 91.1 (21.4) | 95.0 (26.6) | 93.8 (24.7) |
| BMI, kg/m² | 33.4 (7.5) | 34.8 (7.9) | 35.3 (9.6) | 34.7 (8.6) |
| Waist circumference, cm | 112.8 (17.4) | 114.4 (14.7) | 116.1 (20.4) | 114.9 (18.0) |
| ACTH dependent, n (%) | 23 (74.2) | 39 (78.0) | 56 (78.9) | 118 (77.6) |
| Plasma ACTH, pg/mL | 67.7 (34.0) (n=23) | 74.9 (85.0) (n=39) | 78.1 (69.9) (n=56) | 74.9 (69.8) (n=118) |
| 24-h UFC, µg/d | 219.5 (260.5) (n=23) | 164.5 (162.1) (n=39) | 231.1 (353.4) (n=56) | 206.8 (284.5) (n=118) |
| ACTH independent, n (%) | 8 (25.8) | 11 (22.0) | 15 (21.1) | 34 (22.4) |
| Plasma ACTH[a], pg/mL | 7.3 (4.8) (n=8) | 20.0 (26.6) (n=11) | 10.0 (6.2) (n=15) | 12.7 (16.2) (n=34) |
| 24-h UFC, µg/d | 98.0 (81.2) (n=8) | 84.4 (73.7) (n=11) | 96.2 (156.8) (n=15) | 92.8 (116.3) (n=34) |
| Mean 24-h SBP, mm Hg | 138.1 (9.4) (n=30) | 124.6 (9.0) (n=47) | 141.6 (11.0) (n=71) | 135.5 (12.6) (n=148) |
| Mean 24-h DBP, mm Hg | 90.8 (5.7) (n=30) | 76.0 (7.3) (n=47) | 88.1 (7.6) (n=71) | 84.8 (9.4) (n=148) |
| HbA1c, % | 5.4 (0.5) | 7.1 (1.6) | 7.2 (1.6) | 6.8 (1.6) |

Data updated based on database lock; analysis date 5 July 2024. [a]Median ACTH was <5 pg/mL (hypertension only); 9 pg/mL (hyperglycemia only, hypertension and hyperglycemia, and overall). ACTH, adrenocorticotropic hormone; BMI, body mass index; DBP, diastolic blood pressure; OL, open-label phase; SBP, systolic blood pressure; SD, standard deviation; UFC, urinary free cortisol.

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## Author disclosures

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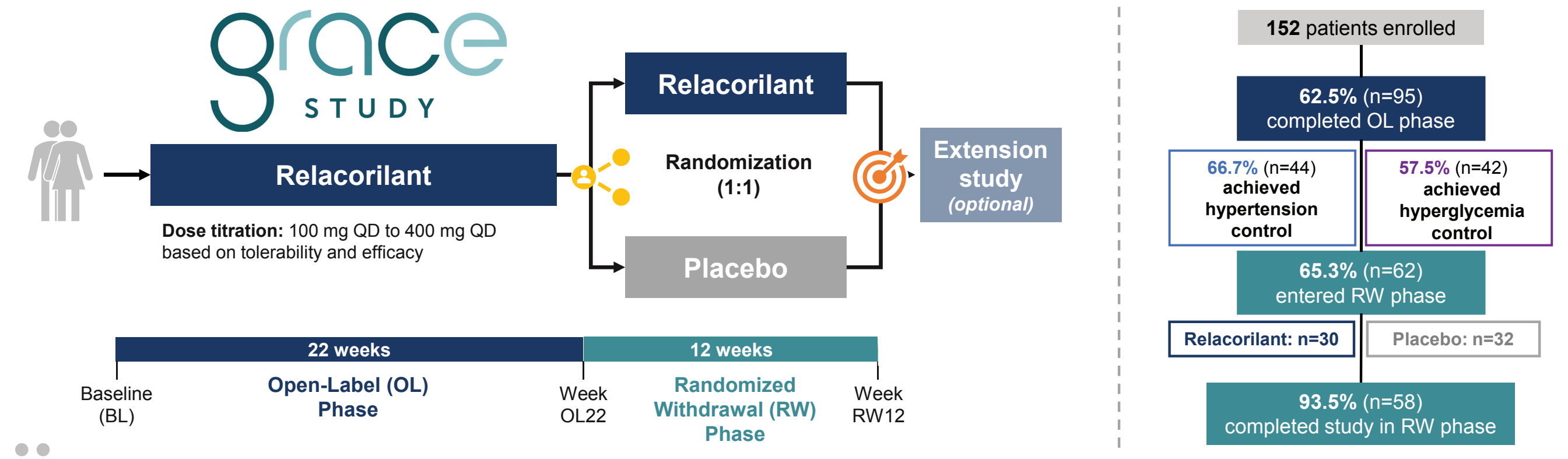
## The GRACE Phase 3 Study of Relacorilant (NCT03697109)



### Patient population

- 18—80 years
- Cushing syndrome
- Hypertension, hyperglycemia (impaired glucose tolerance or diabetes mellitus), or both

### Endpoints

- <u>Primary:</u> Loss of hypertension control (at visit RW12), safety
- <u>Secondary & exploratory:</u> Control of hyperglycemia and other cortisol-related comorbidities

### Eligibility for randomization

Those who completed the open-label phase and met response criteria at visit OL22[a]:

**Hypertension control** (in patients with hypertension)

- ≥5 mm Hg decrease in mean SBP and/or DBP, without worsening of either (by 24-h ABPM)

**Hyperglycemia control**

Patients with <u>impaired glucose tolerance:</u>

- 2-h oGTT glucose normalized (<140 mg/dL)

Patients with <u>diabetes</u> (at least one of):

- HbA1c decrease by ≥0.5%
- 2-h oGTT glucose normalization (<140 mg/dL) or decrease by ≥50 mg/dL, and/or
- Total daily insulin dose decrease by ≥25% and HbA1c unchanged or decreased

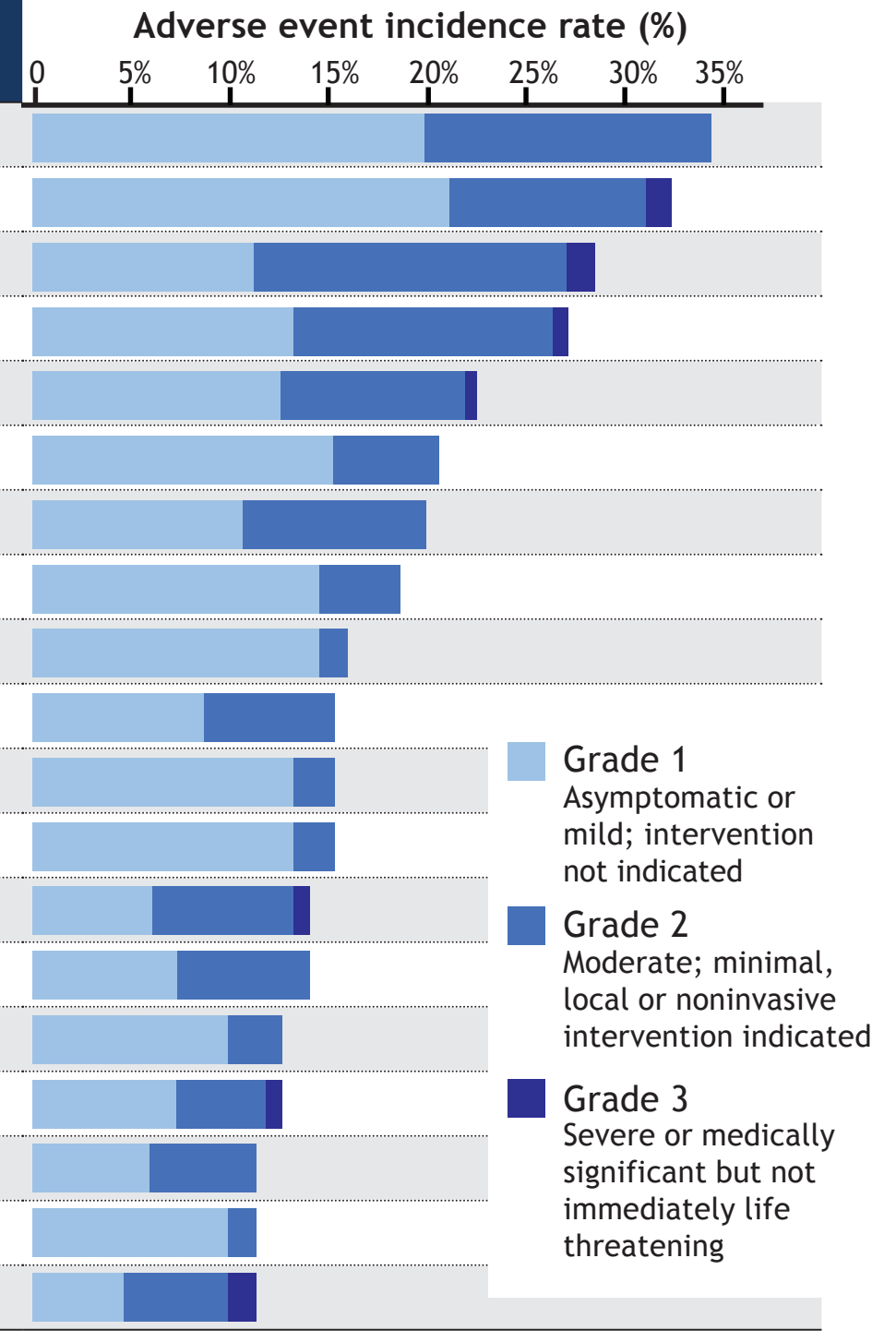
[a]Patients with hypertension and hyperglycemia who do not meet the response criteria for both must meet the respective response criteria without worsening of the other comorbidity. ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; oGTT, oral glucose tolerance test; SBP, systolic blood pressure.

## Open-label Results: Favorable Safety Profile

- The majority of AEs were mild to moderate in severity
- No new safety signals were identified
- The frequency of serious adverse events was low with no dose-dependent pattern
- Due to relacorilant's specificity for the GR and its unique mechanism of action, the observed efficacy was seen:
  - Without cases of relacorilant-induced irregular vaginal bleeding with endometrial hypertrophy
  - Without increases in cortisol concentrations and relacorilant-induced hypokalemia
  - Without reported cases of adrenal insufficiency
  - Without independently confirmed QT prolongation

### Adverse events occurring in ≥10% of patients

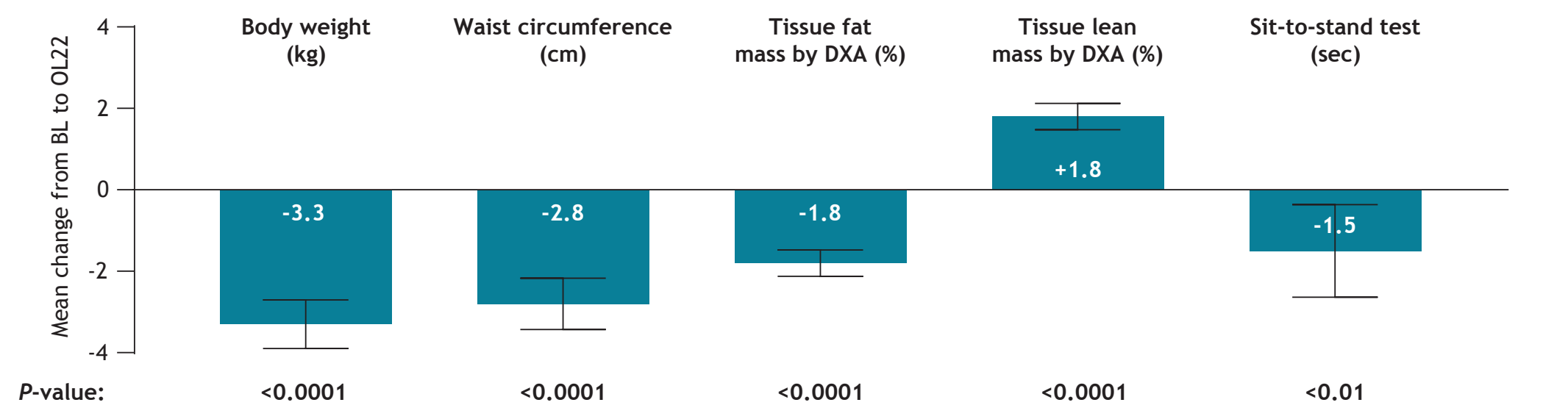
| Adverse event, n (%) | Relacorilant (n=152) |
|---|---|
| Nausea | 52 (34.2) |
| Edema peripheral | 50 (32.9) |
| Pain in extremity | 43 (28.3) |
| Back pain | 41 (27.0) |
| Fatigue | 34 (22.4) |
| Headache | 31 (20.4) |
| Arthralgia | 30 (19.7) |
| Diarrhea | 28 (18.4) |
| Skin hyperpigmentation | 24 (15.8) |
| Abdominal pain upper | 23 (15.1) |
| Constipation | 23 (15.1) |
| Dizziness | 23 (15.1) |
| Paresthesia | 21 (13.8) |
| Myalgia | 21 (13.8) |
| Asthenia | 19 (12.5) |
| Vomiting | 19 (12.5) |
| Abdominal pain | 17 (11.2) |
| Decreased appetite | 17 (11.2) |
| Muscular weakness | 17 (11.2) |



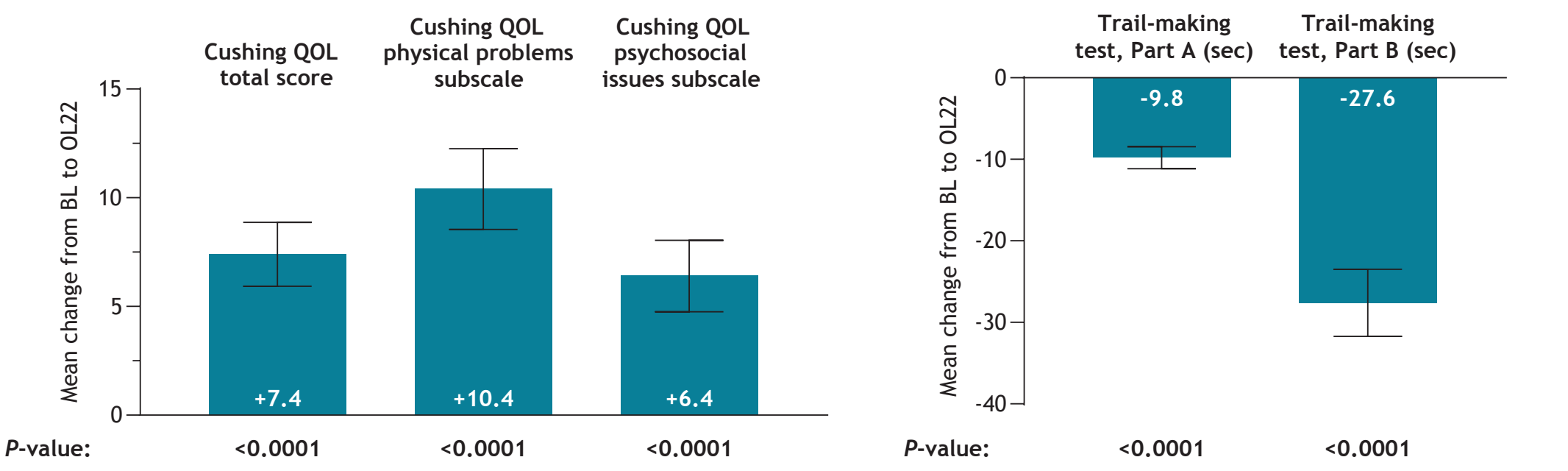
Data updated based on database lock; analysis date 5 July 2024. TEAEs and CTCAE grade shown. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; OL, open label; TEAE, treatment-emergent adverse event.

## Open-label Results: Improvements in Other Symptoms of Cushing Syndrome

### Significant improvements in body composition with relacorilant



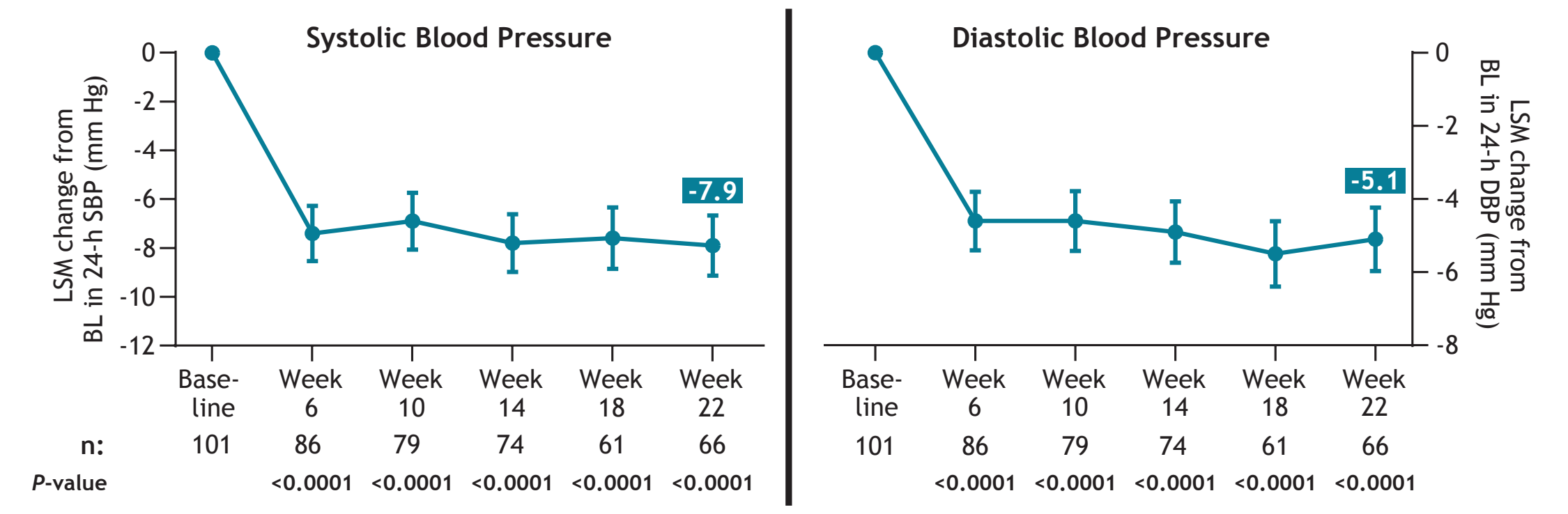
### Significant improvement in quality of life and cognitive assessments with relacorilant



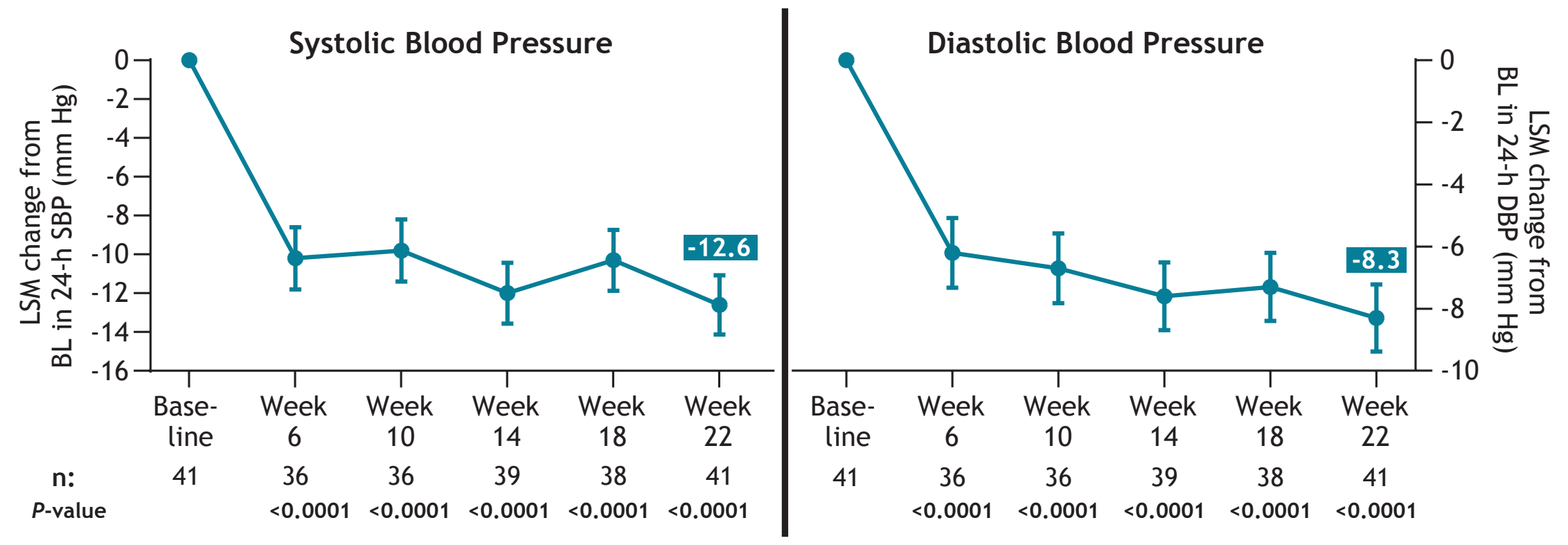
BL, baseline; DXA, dual energy X-ray absorptiometry; OL, open label; QOL, quality of life. Error bars: Standard deviation. Wilcoxin rank sum test *P*-values for the mean change from baseline shown.

## Open-label Results: Rapid & Sustained Improvements in Systolic & Diastolic Blood Pressure With Relacorilant

Patients with <u>hypertension</u>



Patients with hypertension who <u>met hypertension response criteria & entered the RW</u>

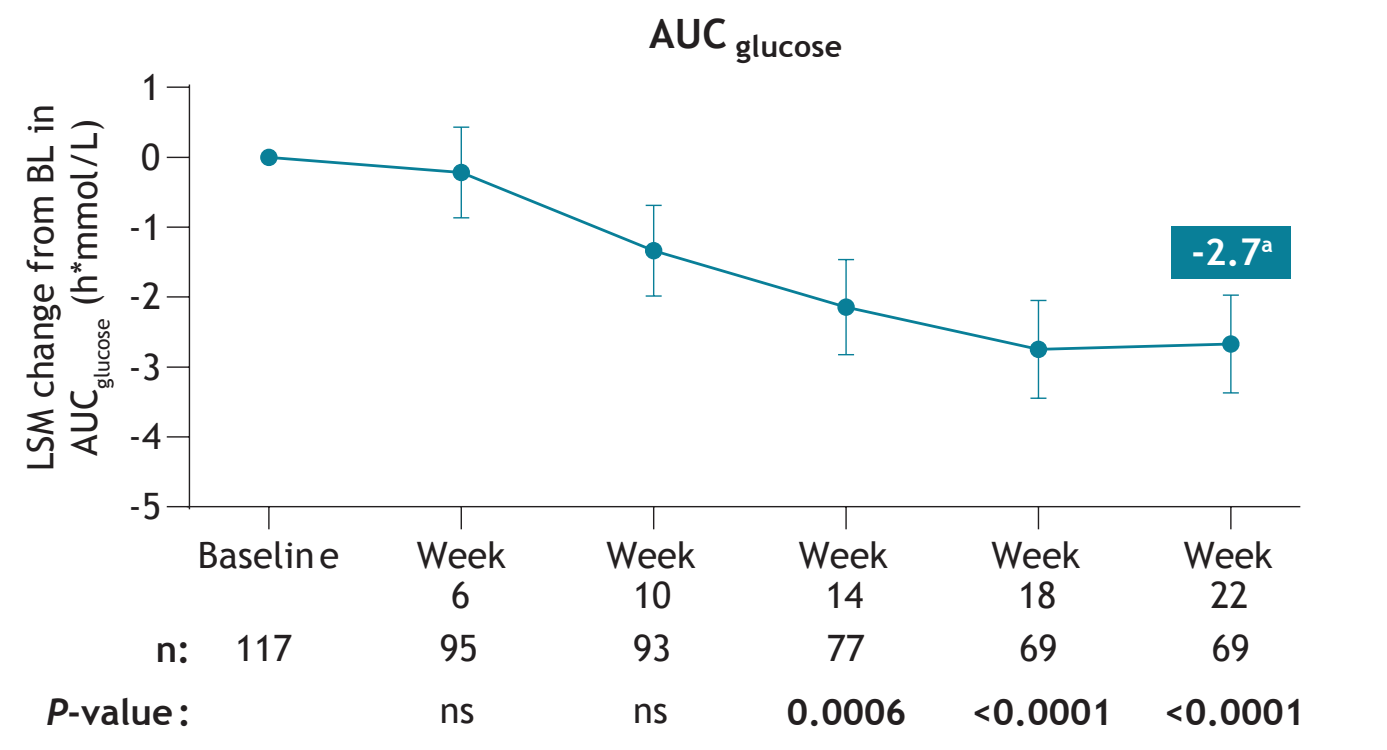


ABPM, ambulatory blood pressure monitoring; BL, baseline; LSM, least-squares mean; MMRM, mixed model for repeated measures; SE, standard error. Blood pressure measured by ABPM. Error bars: SE of the mean. LSM and SE calculated using a linear MMRM. Wilcoxon rank sum test *P*-values for the mean change from BL shown.

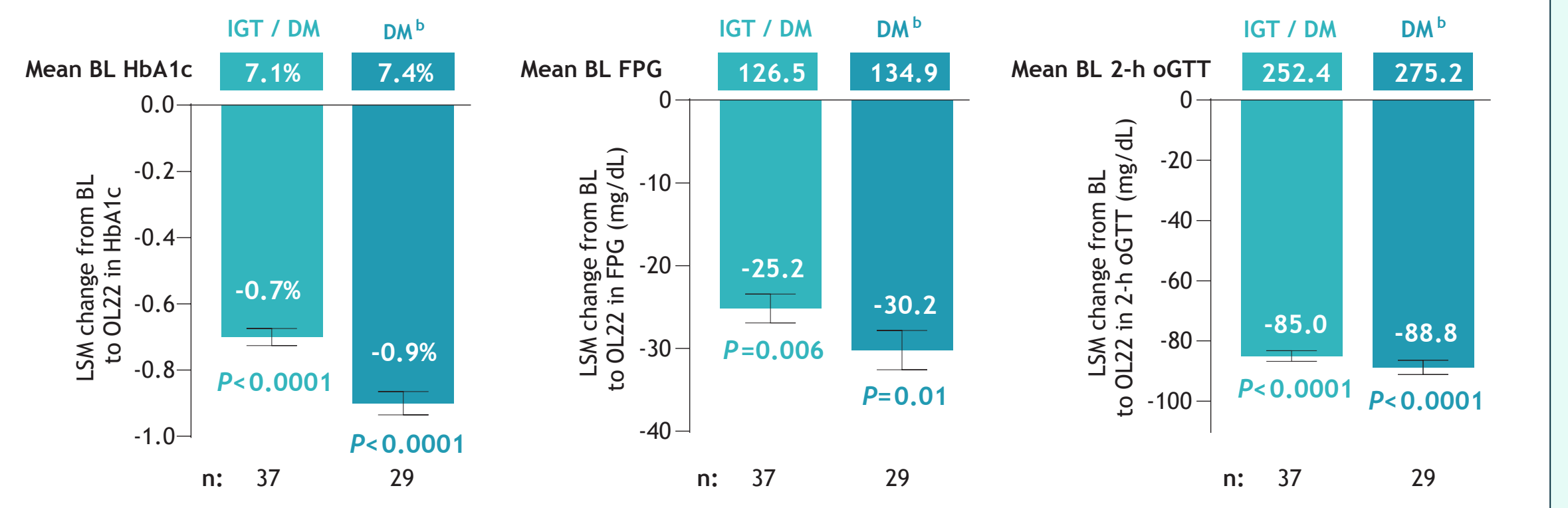
## Open-label Results: Rapid and Sustained Improvements in Hyperglycemia With Relacorilant

### Rapid and sustained improvements in $AUC_{glucose}$ with relacorilant

Patients with hyperglycemia (IGT or DMb)



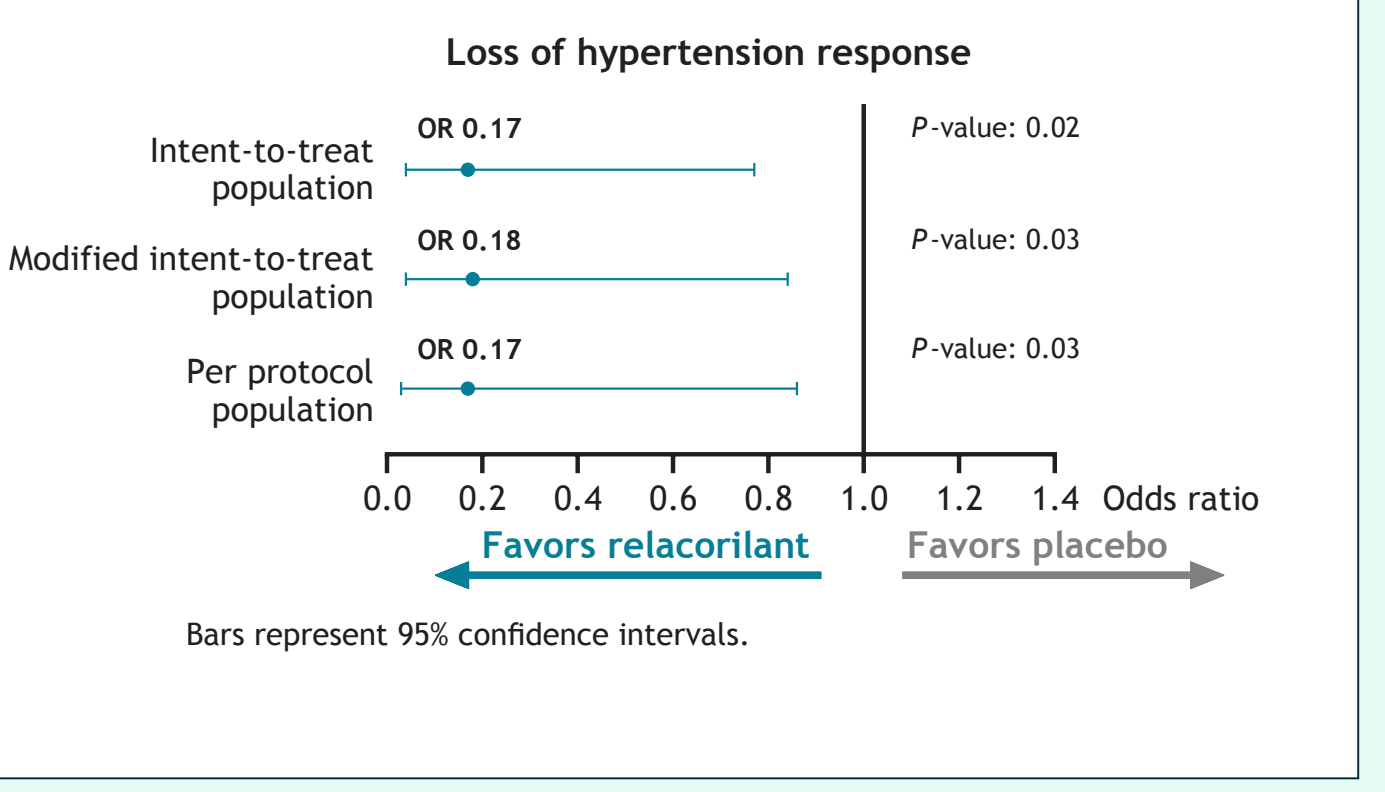
### Greater improvement in glucose parameters with relacorilant in hyperglycemia responders



[a]Mean change from baseline to visit OL 22: -3.3 h*mmol/L. [b]Diabetes defined as fasting plasma glucose ≥126 mg/dL, 2-h oGTT plasma glucose ≥200 mg/dL, or HbA1c ≥6.5%. $AUC_{glucose}$, glucose area under the curve; BL, baseline; DM, diabetes mellitus; FPG, fasting plasma glucose hemoglobin A1c; HbA1c, hemoglobin A1c; IGT, impaired glucose tolerance; LSM, least squares mean; ns, not significant ($P≥0.05$); oGTT, oral glucose tolerance test; SE, standard error. Error bars: SE of the mean. LSM and SE calculated using a linear mixed model for repeated measures (MMRM). Wilcoxon rank sum test *P*-values for the mean change from baseline shown.

## Primary Endpoint Met: Hypertension

- In the randomized-withdrawal phase, significantly more patients receiving placebo lost hypertension control compared to those who continued to receive relacorilant
  - Odds ratio 0.17 for relacorilant vs placebo (*P*=0.02)
  - Patients receiving relacorilant were 5.9× more likely to maintain hypertension response



Bars represent 95% confidence intervals.

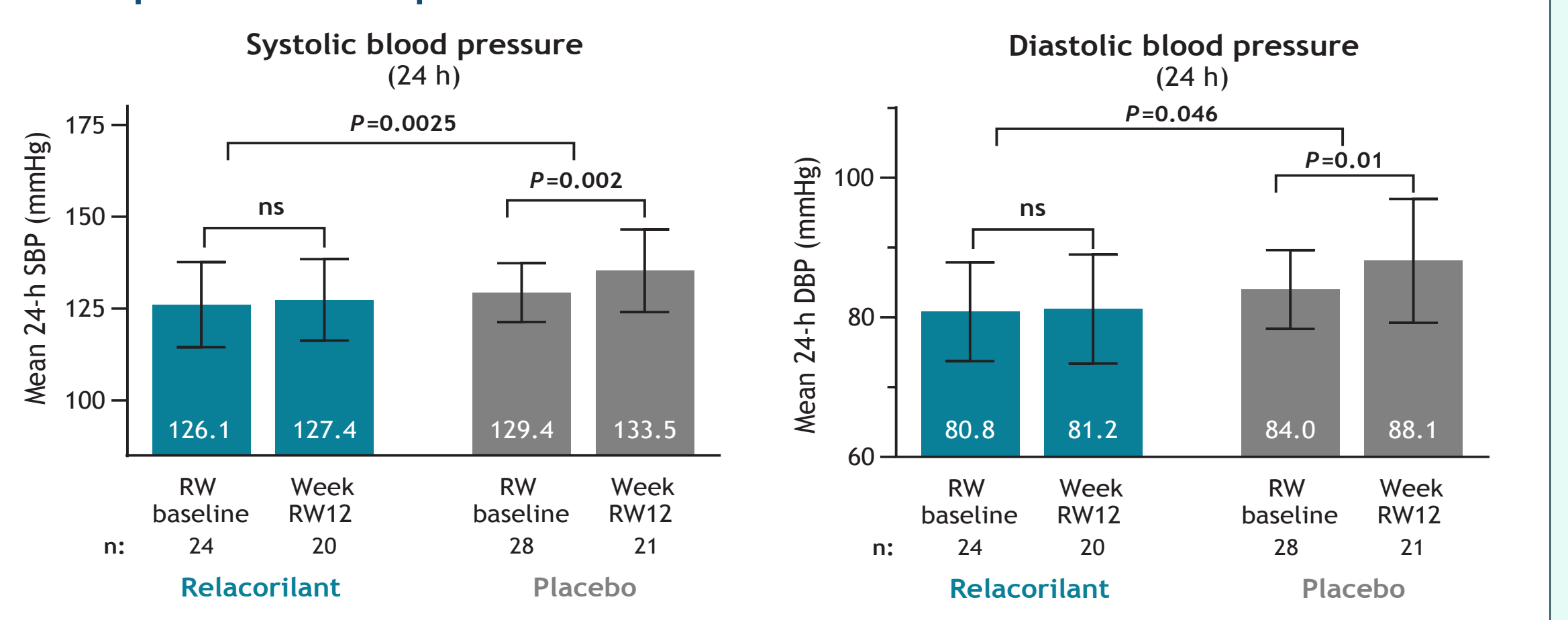
## Patient Demographics & Characteristics Entering Randomized-withdrawal Period

| Mean (SD) | Relacorilant (n=30) | Placebo (n=32) |
|---|---|---|
| Age, yrs | 46.6 (11.0) | 48.8 (14.4) |
| Female, n (%) | 22 (73.3) | 26 (81.3) |
| Weight, kg | 93.3 (27.4) | 88.6 (21.1) |
| BMI, kg/m² | 33.3 (7.6) | 32.6 (6.5) |
| Waist circumference, cm | 113.8 (17.7) | 108.9 (17.1) |
| ACTH-dependent, n (%) | 26 (86.7) | 23 (71.9) |
| Plasma ACTH, pg/mL<br>24-h UFC, µg/d | 91.7 (85.7)<br>257.1 (449.1) | 71.7 (74.7)<br>301.3 (287.9) |
| ACTH-independent, n (%) | 4 (13.3) | 9 (28.1) |
| Plasma ACTH, pg/mL<br>24-h UFC, µg/d | 5.9 (2.3)<br>66.9 (36.8) | 10.0 (9.0)<br>142.2 (194.1) |

ACTH, adrenocorticotropic hormone; BMI, body mass index; SD, standard deviation; UFC, urinary free cortisol.

## Randomized-withdrawal Results: Improvements in Blood Pressure, Glycemic Measures, & Body Composition Maintained With Relacorilant

### Blood pressure: All patients with available ABPM data



ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; ns, not significant ($P≥0.05$); RW, randomized withdrawal; SBP, systolic blood pressure. Blood pressure measured by ABPM. Error bars: Standard deviation. Wilcoxon rank sum test *P*-values for the observed mean within each treatment arm shown.

### 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 | | |
| n | 15 | 19 |
| Mean (SD) | +1.1 (4.7) | +4.9 (6.1) |
| Wilcoxon signed rank sum *P*-value[a] | ns | **0.0003** |
| **HbA1c** (in patients with hyperglycemia at study entry), % | | |
| n | 16 | 19 |
| Mean (SD) | +0.1 (0.8) | +0.3 (0.6) |
| Wilcoxon signed rank sum *P*-value[a] | ns | **0.03** |
| **HbA1c** (in patients with diabetes at study entry), % | | |
| n | 13 | 13 |
| Mean (SD) | +0.1 (0.8) | +0.4 (0.6) |
| Wilcoxon signed rank sum *P*-value[a] | ns | **0.04** |

$AUC_{glucose}$, glucose area under the curve; HbA1c, hemoglobin A1c; ns, not significant ($P≥0.05$); RW, randomized withdrawal. Wilcoxon rank sum test *P*-values for the observed mean within each treatment arm shown. [a]Wilcoxon signed-rank test *P*-values within each treatment arm.

- At the end of the RW phase, patients who switched to placebo, experienced significant increases in $AUC_{glucose}$ and HbA1c
- In contrast, glycemic measures were maintained in patients who continued to receive relacorilant

### Body composition

- Similar trends observed across measures of body composition (body weight, waist circumference, tissue fat mass, tissue lean mass)
  - Those who switched to placebo experienced a deterioration in body composition
  - In contrast, trends toward further improvement were observed in the relacorilant arm

## Randomized-withdrawal Results: Favorable Safety Profile

### Adverse events occurring in ≥5% of patients

| n (%) | Relacorilant (n=30) | Placebo (n=32) |
|---|---|---|
| Back pain | 5 (16.7) | 6 (18.8) |
| Headache | 3 (10.0) | 4 (12.5) |
| Arthralgia | 3 (10.0) | 3 (9.4) |
| Insomnia | 0 | 4 (12.5) |
| Pain in extremity | 2 (6.7) | 2 (6.3) |