Endogenous Hypercortisolism
Long-term Extension
Study

Relacorilant Improved Blood Pressure and Maintained Other Cardiometabolic Improvements in Long-term Study in Patients With Endogenous Hypercortisolism (Cushing Syndrome)

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Speaker Disclosures

Contracted Research

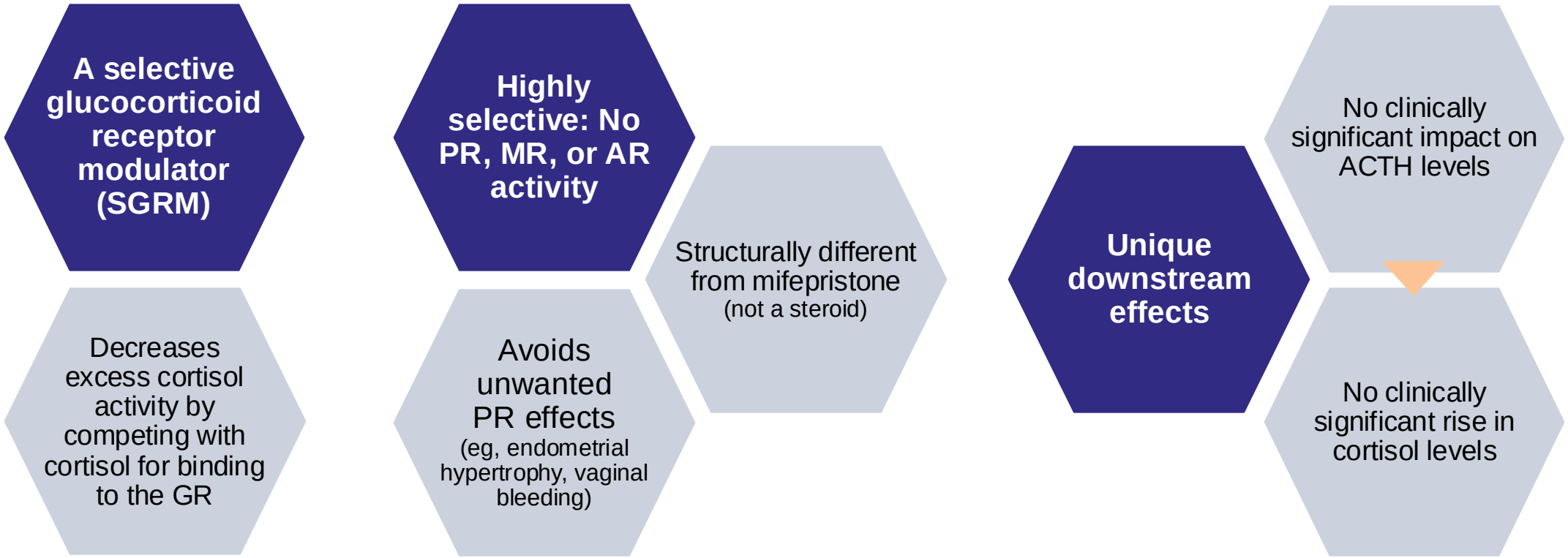
- Neurocrine Biosciences/Diurnal LTD
- Spruce Biosciences
- Corcept Therapeutics
- Crinetics Pharmaceuticals
- Recordati Rare Diseases
- Adrenas Therapeutics
- Mineralys Pharmaceuticals

Consultant

- Quest Diagnostics
- Corcept Therapeutics
- Xeris Pharmaceuticals
- Crinetics Pharmaceuticals
- Novo Nordisk
- Neurocrine Biosciences/Diurnal LTD
- Recordati Rare Diseases
- H Lundbeck A/S
- Sparrow Pharmaceuticals

Endogenous Hypercortisolism Long-term Extension Study

Relacorilant: In Development for the Treatment of Endogenous Hypercortisolism (Cushing Syndrome)



ACTH, adrenocorticotropic hormone; AR, androgen receptor; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; PR, progesterone receptor.

The Relacorilant Long-term Extension Study

NCT03604198

Relacorilant parent studies

Phase 3 studies:

grace STUDY

GRADIENT STUDY

Phase 2 Study

Endogenous Hypercortisolism Long-term Extension Study

Dose titration phase → **Maintenance phase**

Relacorilant QD → **Relacorilant QD**

Only for patients rolling over from a placebo design

Dose titration: 100 mg QD to 400 mg QD based on tolerability and efficacy

Median duration of treatment: 362 days
Maximum duration of treatment: 6.3 years
(as of 8 September 2024)

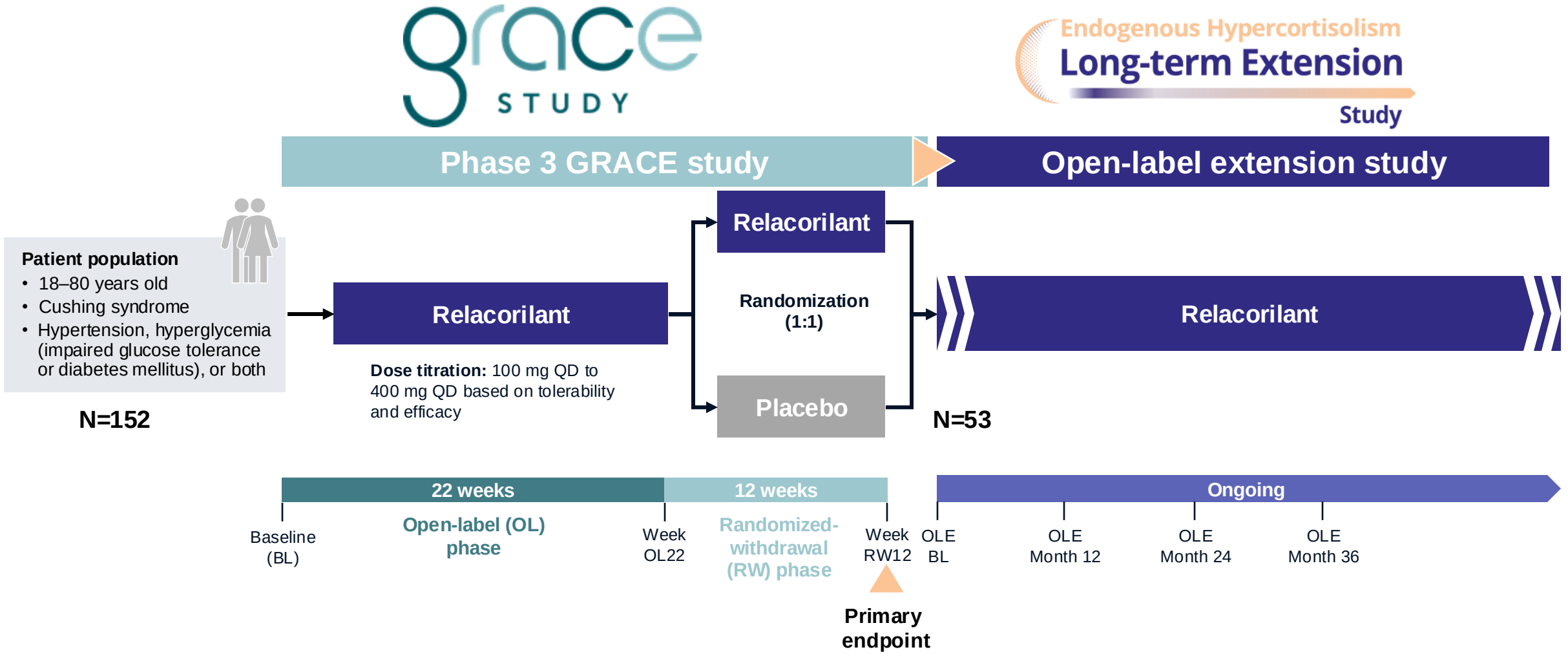
N=116

Patient population
- 18–80 years old
- Cushing syndrome
- Hypertension, hyperglycemia (impaired glucose tolerance or diabetes mellitus), or both

Long-term, open-label extension study

QD, once daily. Phase 2 Study, open-label phase 2 study of relacorilant in patients with Cushing syndrome (NCT02804750). GRACE, NCT03697109; GRADIENT, NCT04308590. Data cutoff date: 8 September 2024.

Longitudinal Assessments in Patients who Participated in the Phase 3 GRACE & Extension Studies



GRACE: NCT03697109. BL, baseline; OL, open label; OLE, open-label extension; QD, every day; RW, randomized withdrawal.

Patient Demographics & Baseline Characteristics

Extension Study: All participants

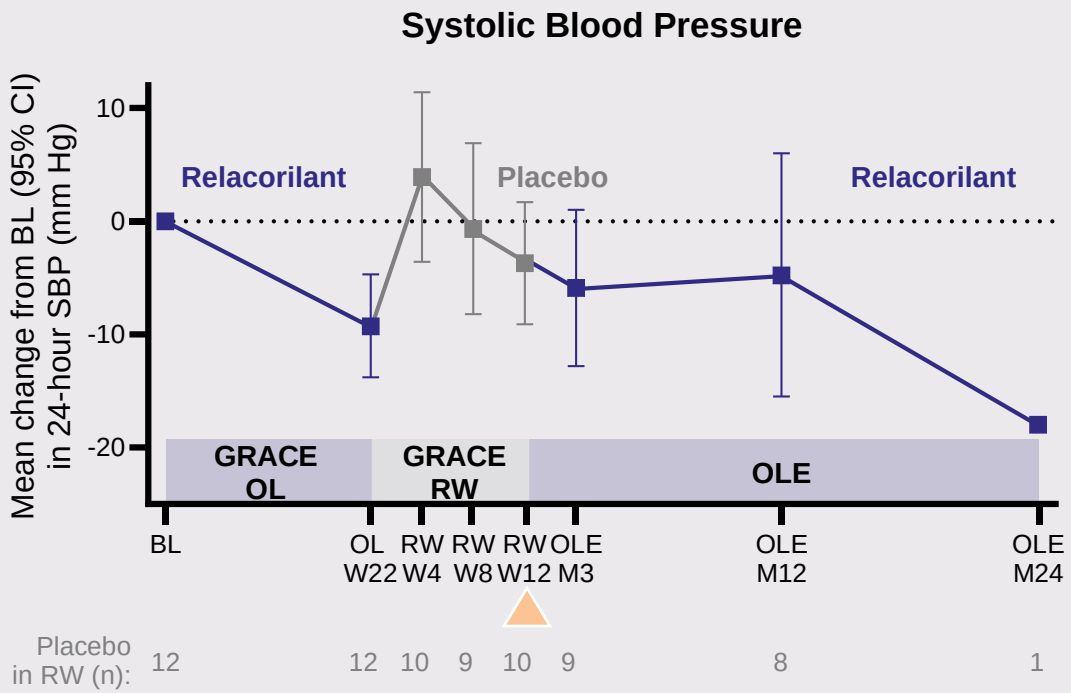
Mean (SD)	Hypertension only (n=35)	Hyperglycemia only (n=12)	Hypertension & hyperglycemia (n=69)	Overall (N=116)
Age, yrs	54.7 (11.6)	50.8 (15.7)	58.2 (12.4)	56.4 (12.7)
Female, n (%)	28 (80.0)	12 (100.0)	50 (72.5)	90 (77.6)
Weight, kg	89.4 (22.6)	75.8 (16.1)	88.5 (22.9)	87.6 (22.4)
BMI, kg/m²	32.9 (8.5)	28.7 (6.2)	32.8 (6.9)	32.4 (7.4)
Waist circumference, cm	105.6 (18.7)	102.0 (25.8)	109.9 (16.2)	107.8 (18.0)
ACTH-dependent, n (%)	12 (34.3)	5 (41.7)	25 (36.2)	42 (36.2)
Plasma ACTH, pg/mL [n] 24-h UFC, µg/d [n]	76.3 (46.1) [12] 143.7 (118.3) [12]	110.3 (131.2) [4] 117.2 (99.2) [4]	116.2 (100.0) [24] 446.1 (1067.8) [24]	103.6 (90.3) [40] 322.5 (837.1) [40]
ACTH-independent, n (%)	23 (65.7)	7 (58.3)	44 (63.8)	74 (63.8)
Plasma ACTH, pg/mL [n] 24-h UFC, µg/d [n]	9.0 (5.8) [21] 53.8 (38.5) [6]	7.7 (1.9) [7] 54.7 (NE) [1]	10.2 (5.2) [43] 232.7 (279.0) [8]	9.6 (5.2) [71] 149.3 (219.0) [15]
Mean 24-h SBP (mm Hg) [n]	134.2 (16.0) [24]	126.0 (NE) [1]	133.0 (11.9) [45]	133.3 (13.3) [70]
Mean 24-h DBP (mm Hg) [n]	83.8 (10.2) [24]	73.0 (NE) [1]	80.6 (9.4) [45]	81.6 (9.8) [70]
HbA1c (%) [n]	5.6 (0.4) [30]	6.1 (0.6) [10]	6.6 (1.4) [62]	6.3 (1.2) [102]

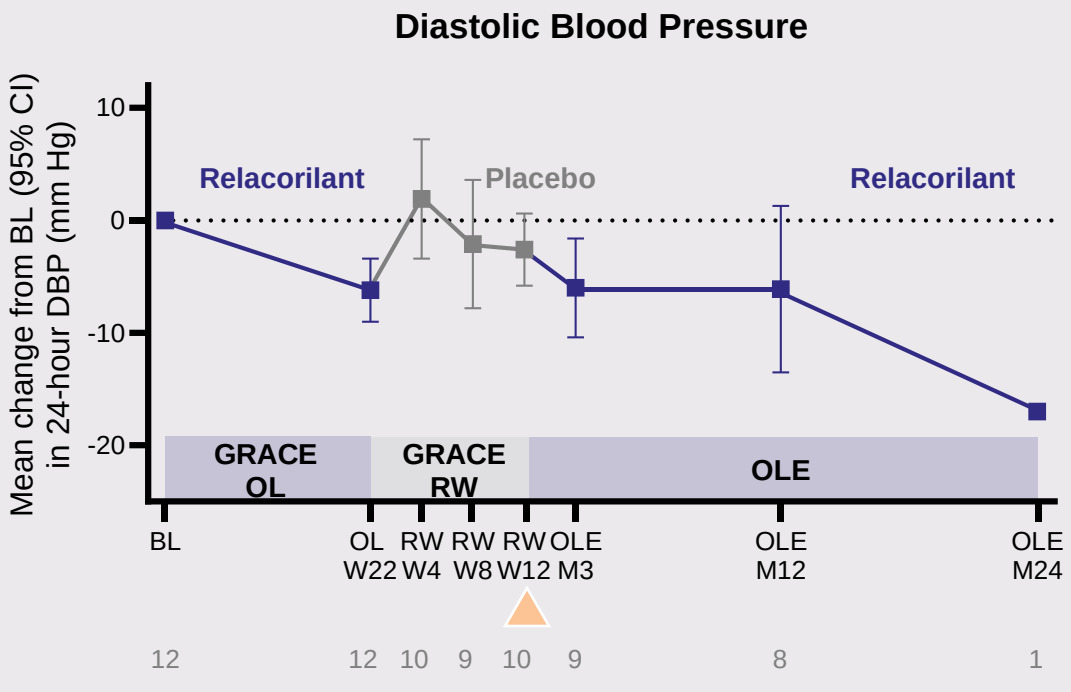
ACTH, adrenocorticotropic hormone; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; NE, not evaluable; SBP, systolic blood pressure;UFC, urinary-free cortisol.

Endogenous Hypercortisolism Long-term Extension Study

Longitudinal Blood Pressure Improvements in GRACE Patients who Continued in the Extension Study

Patients with hypertension who received placebo in the GRACE RW phase





All patients in the OLE received relacorilant.

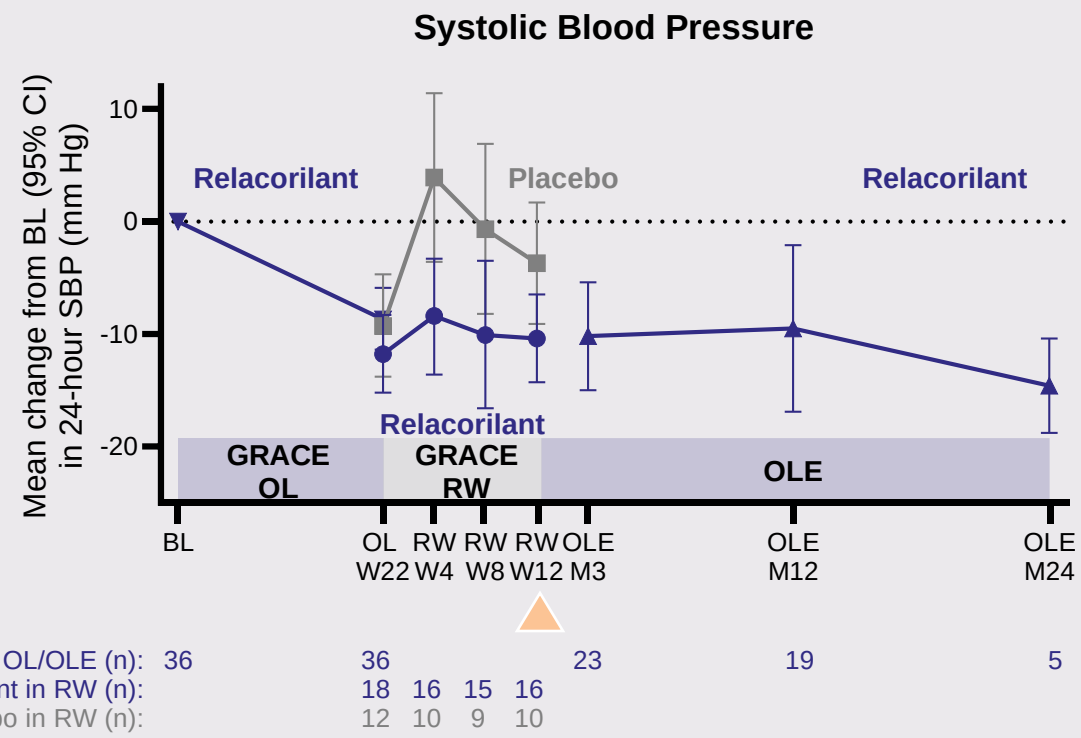
▲ GRACE primary endpoint

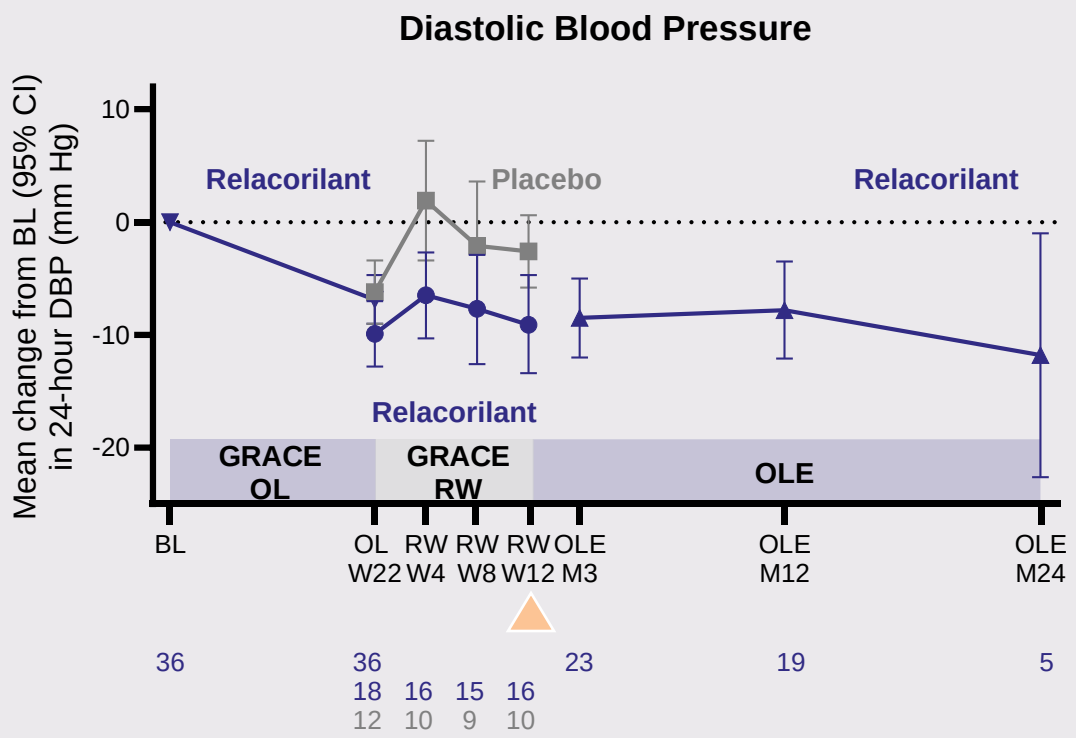
BL, baseline; CI, confidence interval; DBP, diastolic blood pressure; M, month; OL, open-label; OLE, open-label extension; RW, randomized withdrawal; SBP, systolic blood pressure; W, week. Patients with hypertension with or without hyperglycemia.

Endogenous Hypercortisolism Long-term Extension Study

Longitudinal Blood Pressure Improvements in GRACE Patients who Continued in the Extension Study

Patients with hypertension who participated in the GRACE & extension studies





The OLE arm includes all patients from GRACE who entered the OLE, even if they did not enter the RW phase. All patients in the OLE received relacorilant.

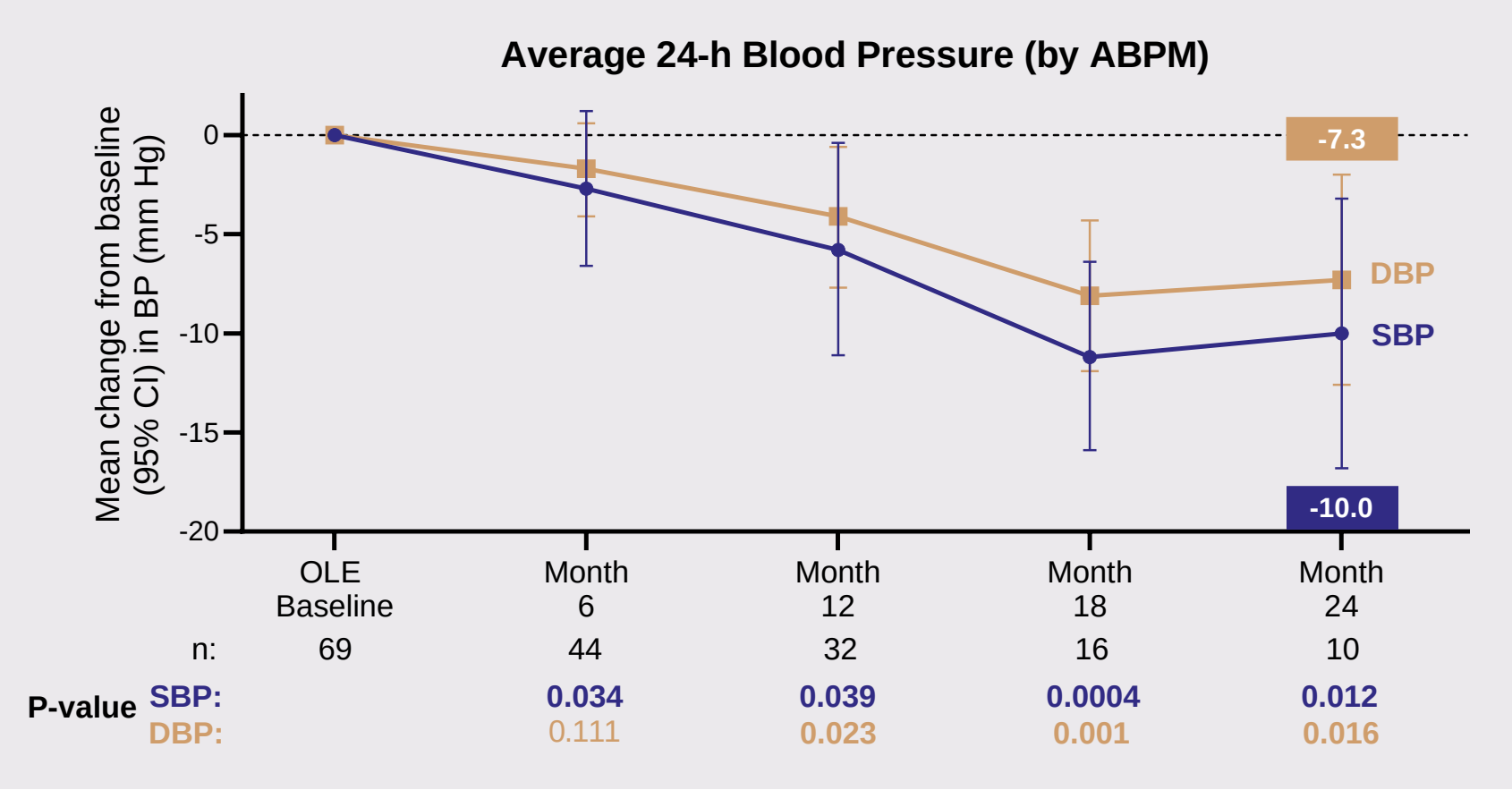
▲ GRACE primary endpoint

BL, baseline; CI, confidence interval; DBP, diastolic blood pressure; M, month; OL, open-label; OLE, open-label extension; RW, randomized withdrawal; SBP, systolic blood pressure; W, week. Patients with hypertension with or without hyperglycemia.

Endogenous Hypercortisolism Long-term Extension Study

Blood Pressure Continued to Improve in the Extension Study

Extension study patients with hypertension: All participants

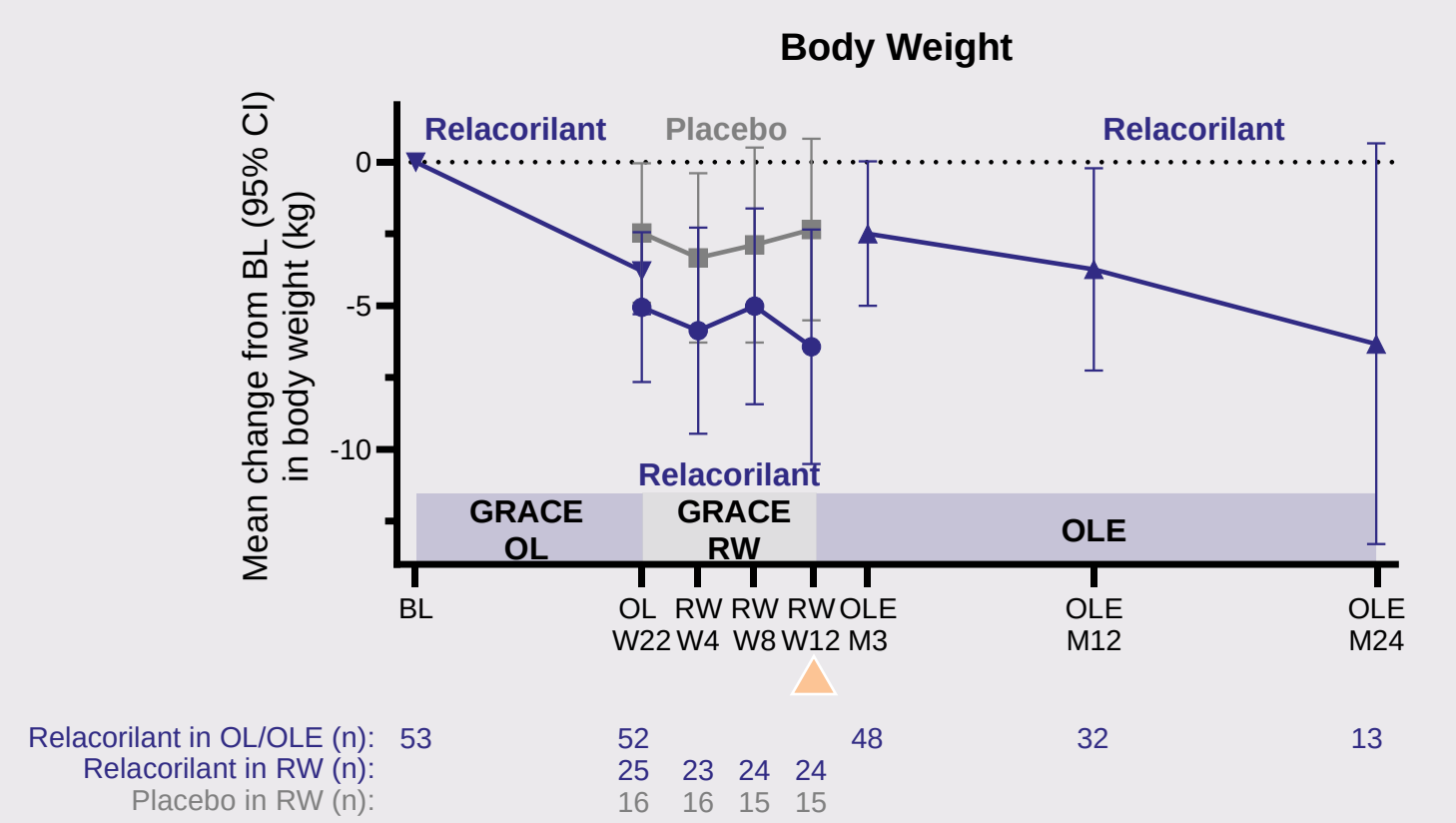


ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; OLE, open-label extension study; SBP, systolic blood pressure.
Patients with hypertension with or without hyperglycemia.

Endogenous Hypercortisolism Long-term Extension Study

Weight Reductions Maintained in the Extension Study

Patients who participated in the GRACE & extension studies



The OLE arm includes all patients from GRACE who entered the OLE, even if they did not enter the RW phase. All patients in the OLE received relacorilant.

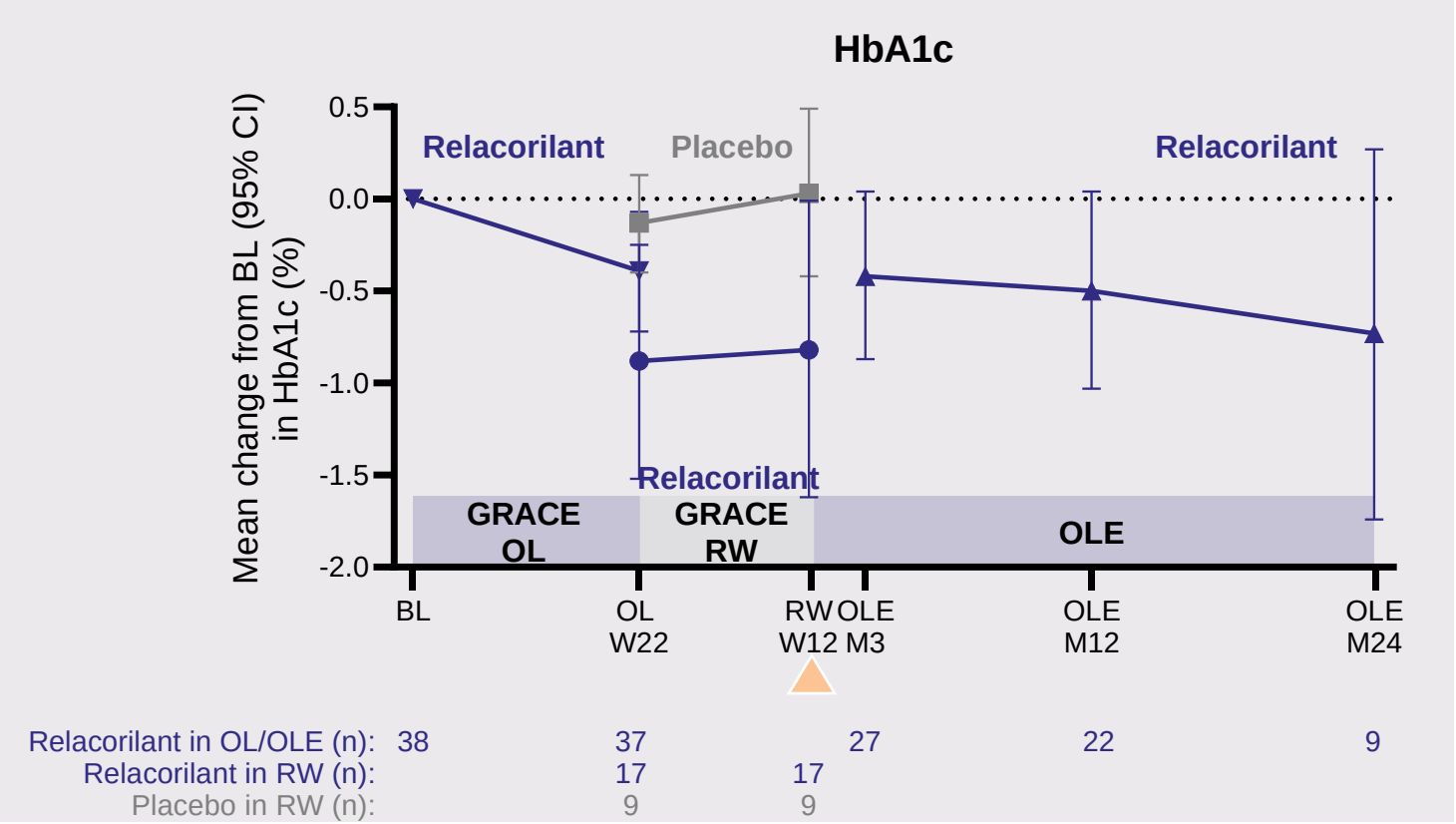
▲ GRACE primary endpoint

BL, baseline; CI, confidence interval; M, month; OL, open-label; OLE, open-label extension; RW, randomized withdrawal; W, week.

Endogenous Hypercortisolism Long-term Extension Study

Improvements in HbA1c Maintained in the Extension Study

Patients with hyperglycemia who participated in the GRACE & extension studies



The OLE arm includes all patients from GRACE who entered the OLE, even if they did not enter the RW phase. All patients in the OLE received relacorilant.

▲ GRACE primary endpoint

BL, baseline; CI, confidence interval; HbA1c, hemoglobin A1c; M, month; OL, open-label; OLE, open-label extension; RW, randomized withdrawal; W, week.
Patients with hyperglycemia with or without hypertension.

Endogenous Hypercortisolism Long-term Extension Study

Extension Study: Adverse Events Occurring in ≥10% of Patients

n (%)	Relacorilant (N=116)
Pain in extremity	27 (23.3%)
Arthralgia	25 (21.6%)
Back pain	21 (18.1%)
COVID-19	20 (17.2%)
Peripheral edema	17 (14.7%)
Nausea	16 (13.8%)
Headache	13 (11.2%)

- Relacorilant's **safety profile** in the extension study was **consistent with the parent studies** (GRACE, GRADIENT, phase 2)
  - The majority of adverse events 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

Extension Study: Adverse Event Summary

n (%)	Relacorilant (N=116)
Patients reporting at least one TEAE (any grade)	109 (94.0)
Patients reporting at least one grade ≥3 TEAE	44 (37.9)
TEAEs resulting in:	
Dose interruption	47 (40.5)
Dose reduction	32 (27.6)
Permanent withdrawal	20 (17.2)
Serious TEAEs	37 (31.9)
Treatment-related serious TEAEs	3 (2.6)
TEAEs leading to death[a] (none relacorilant related)	6 (5.2)

- 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**

[a]Deaths due to pneumonia, COVID-19, necrotizing cellulitis, cardiac arrest, myocardial infarction, and cardiogenic shock and myocardial ischemia.
GR, glucocorticoid receptor; TEAE, treatment-emergent adverse event.

Summary & Conclusions

- Relacorilant showed **clinically significant and durable cardiometabolic improvements** and was well-tolerated in patients with hypercortisolism treated for 6+ years
  - **Blood pressure continued to improve** during the extension study
  - **Improvements in weight and glycemic measures** were **maintained**
- Due to relacorilant's **specificity for the glucocorticoid receptor** 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**

Thanks to all Those who Contributed to the Extension and GRACE Studies!

The investigators & their teams

- Dr. Lisa Abbott *(GRACE)*
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- Dr. Carmen Aresta *(Extension, GRACE)*
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- Dr. Margaret Wierman *(GRACE)*
- Dr. Carol Wysham *(Extension)*
- Dr. Tamer G. Yacoub *(Extension)*
- Dr. Kevin Yuen *(GRACE)*

The study patients and their families.

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