

Efficacy and Safety of Relacorilant in Individuals With Adrenal Hypercortisolism: Results From the Phase 3 GRACE and GRADIENT Studies

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SUMMARY AND CONCLUSIONS

- Relacorilant resulted in clinically and statistically significant treatment benefits in participants with adrenal hypercortisolism in the phase 3 GRACE and GRADIENT studies
- Compared with placebo, relacorilant treatment:
- Significantly reduced systolic and diastolic blood pressure in participants with hypertension
- Improved fasting glucose and glucose area under the curve in participants with hyperglycemia
- Resulted in significant weight loss
- Across studies, relacorilant was well-tolerated in participants with adrenal hypercortisolism¹⁻⁵
- There were no cases of adrenal insufficiency or vaginal bleeding associated with endometrial hypertrophy, and no cases of drug-induced hypokalemia or QT interval prolongation^{1,3,5}

BACKGROUND AND OBJECTIVE

Figure 1. Relacorilant

 Relacorilant, a selective glucocorticoid receptor (GR) modulator (Figure 1) that reduces excess cortisol activity at the GR, is being investigated for the treatment of endogenous hypercortisolism^{6,7}

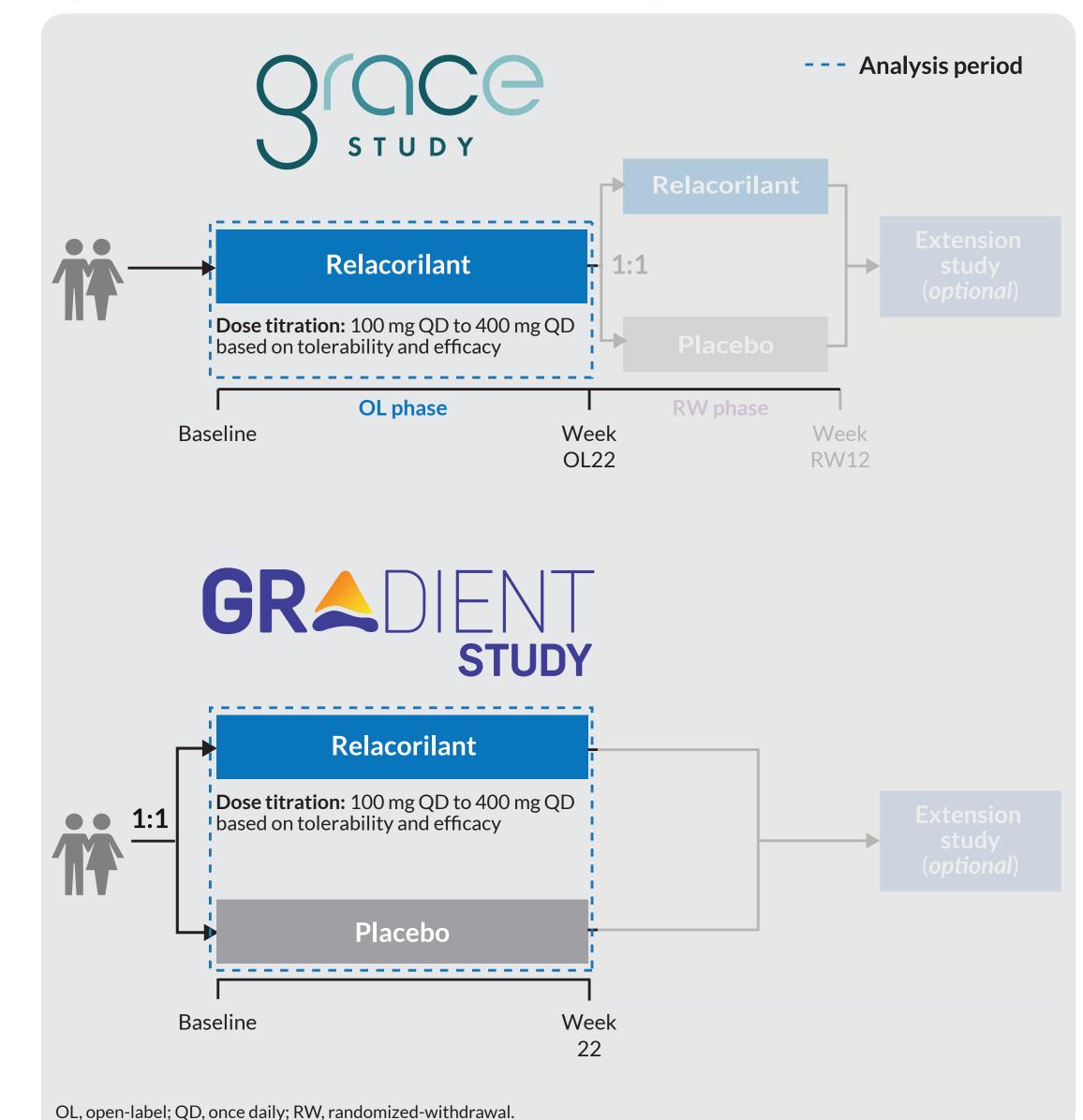
vaginal bleeding¹⁻⁵

- Exhibits high GR selectivity, with no activity at other hormone receptors (eg, progesterone, mineralocorticoid, androgen)^{6,7}
 Structurally different from mifepristone,
- a nonselective GR antagonist^{6,7}
 Avoids undesirable off-target progesterone receptor effects, such as endometrial hypertrophy and
- In the phase 3 GRACE study (NCT03697109), relacorilant treatment improved the signs and symptoms of endogenous hypercortisolism^{1,5}
- In the open-label (OL) phase, relacorilant treatment significantly reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline to week 22 (mean change: SBP, -7.9 mmHg; DBP, -5.1 mmHg; both P<0.0001) in participants with hypertension¹
- The phase 3 GRADIENT study (NCT04308590) investigated the efficacy and safety of relacorilant treatment in individuals with adrenal hypercortisolism³
- In participants with hypertension, SBP improved significantly from baseline to week 22 with relacorilant treatment (mean change -6.6 mmHg; P=0.012) but not with placebo (mean change -2.7 mmHg; P=NS); the difference between arms was not statistically signficant³
- In the subgroup of participants with ≥2 abnormal cortisol tests (abnormal dexamethasone suppression test [DST] + elevated latenight salivary cortisol [LNSC] and/or urinary free cortisol [UFC]) at baseline, relacorilant significantly decreased SBP and DBP from baseline to week 22 vs placebo (least-squares mean [LSM] difference: SBP, -10.4; DBP, -7.9; both P<0.05)³
- The objective of this pooled data analysis was to evaluate the efficacy and safety of relacorilant in GRACE and GRADIENT study participants with adrenal hypercortisolism who had ≥2 abnormal cortisol tests

METHODS

- GRACE comprised a 22-week, OL phase of relacorilant treatment followed by a 12-week, double-blind, placebo-controlled randomized withdrawal phase (Figure 2)
- GRADIENT was a 22-week, randomized, double-blind study of relacorilant compared with placebo (Figure 2)
- In both studies:
- Participants were aged 18–80 years who had endogenous hypercortisolism and hypertension, hyperglycemia (impaired glucose tolerance or diabetes mellitus), or both
- Relacorilant was titrated from 100 mg to 400 mg once daily based on tolerability and efficacy
- In GRACE, in addition to the presence of clinical signs and symptoms, hypercortisolism was defined as ≥2 of:
- UFC greater than the upper limit of normal (ULN) in ≥2 complete 24-hour tests
- LNSC >ULN in ≥2 tests
- >1.8 µg/dL serum cortisol on either the 1-mg overnight or 2-mg 48-hour DST
- In GRADIENT, hypercortisolism was defined as:
- >1.8 μg/dL serum cortisol on either the 1-mg overnight or 2-mg 48-hour DST
- Suppressed or low (≤15 pg/mL) early-morning adrenocorticotropic hormone (ACTH) levels
- Radiologically confirmed benign adrenal lesion
- GRADIENT participants also underwent UFC and LNSC testing to collect samples for study pharmacodynamic assessments

Figure 2. GRACE and GRADIENT Study Designs



- The analysis included the GRACE subgroup with adrenal hypercortisolism (n=34) and the GRADIENT subgroup with ≥2 abnormal cortisol tests (DST and at least 1 of UFC and/or LNSC; relacorilant, n=26; placebo, n=27)
- Relacorilant data from the 22-week periods in both studies were pooled and compared with GRADIENT placebo data
- The Wilcoxon signed rank test was used for detecting within-group significant changes from baseline
- LSM and 95% confidence intervals were estimated using the mixed-model for repeated measures, including fixed effect for visit, with participant as a random effect fit using restricted (or residual) maximum likelihood
- The Kenward and Roger method was used for calculating the denominator degrees of freedom for tests of fixed effects and an unstructured covariance matrix was used to model within-participant error

Select baseline characteristics for the GRACE and GRADIENT study populations with adrenal hypercortisolism and 2 abnormal cortisol tests are shown in Table 1

Table 1. Baseline Characteristics in GRACE and GRADIENT Participants With Adrenal Hypercortisolism

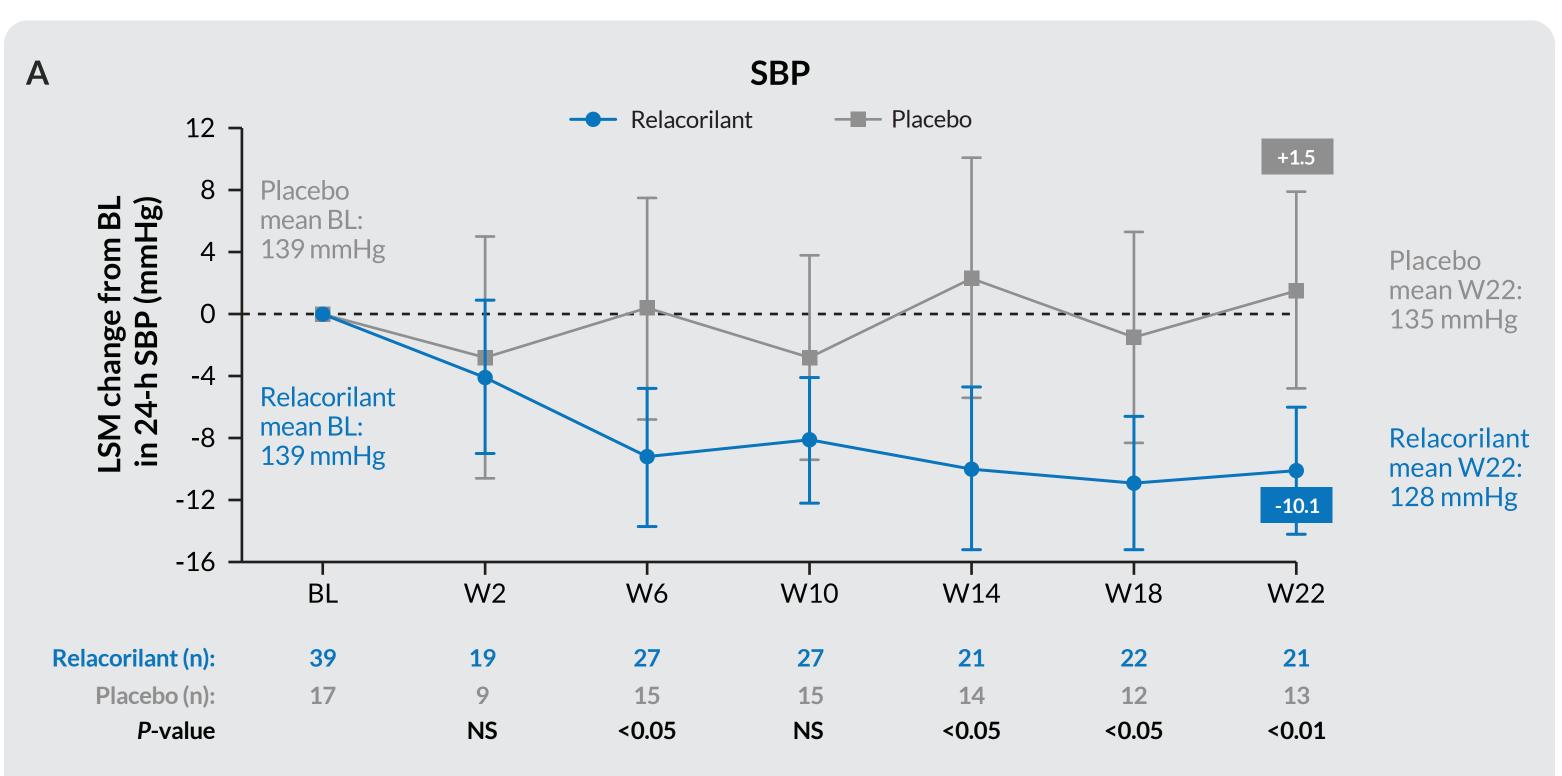
	GRACE ^a (n=34)	GRADIENT ^b (n=53)	Pooled Population (Relacorilant Arms Only) (n=60)	Pooled Population (Placebo) (n=27)
ITT population				
Weight, kg, mean (SD)	90.6 (22.7)	86.2 (17.9)	88.6 (19.9)	86.4 (20.2)
Waist circumference, cm, mean (SD)	114.7 (17.7)	106.3 (13.8)	110.9 (16.8)	106.6 (13.4)
Participants with hypertension with or without hyperglycemia				
24-hour SBP, mmHg, mean (SD) [n]	138.3 (7.7) [23]	139.0 (10.2) [33]	139.1 (8.9) [39]	137.8 (10.2) [17]
24-hour DBP, mmHg, mean (SD) [n]	87.6 (6.7) [23]	83.9 (8.7) [33]	86.4 (7.8) [39]	83.2 (8.6) [17]
Participants with hyperglycemia with or without hypertension				
HbA1c, %, mean (SD) [n]	6.6 (1.0) [26]	6.7 (1.0) [37]	6.5 (1.0) [44]	6.9 (1.1) [19]
AUC _{glucose} , hr*mmol/L, mean (SD) [n]	25.1 (5.5) [26]	24.6 (6.6) [38]	23.6 (5.2) [45]	27.6 (7.4) [19]
2-hour oGTT plasma glucose, mmol/L, mean (SD) [n]	12.6 (3.7) [26]	12.4 (4.3) [38]	11.8 (3.7) [45]	13.7 (4.5) [19]

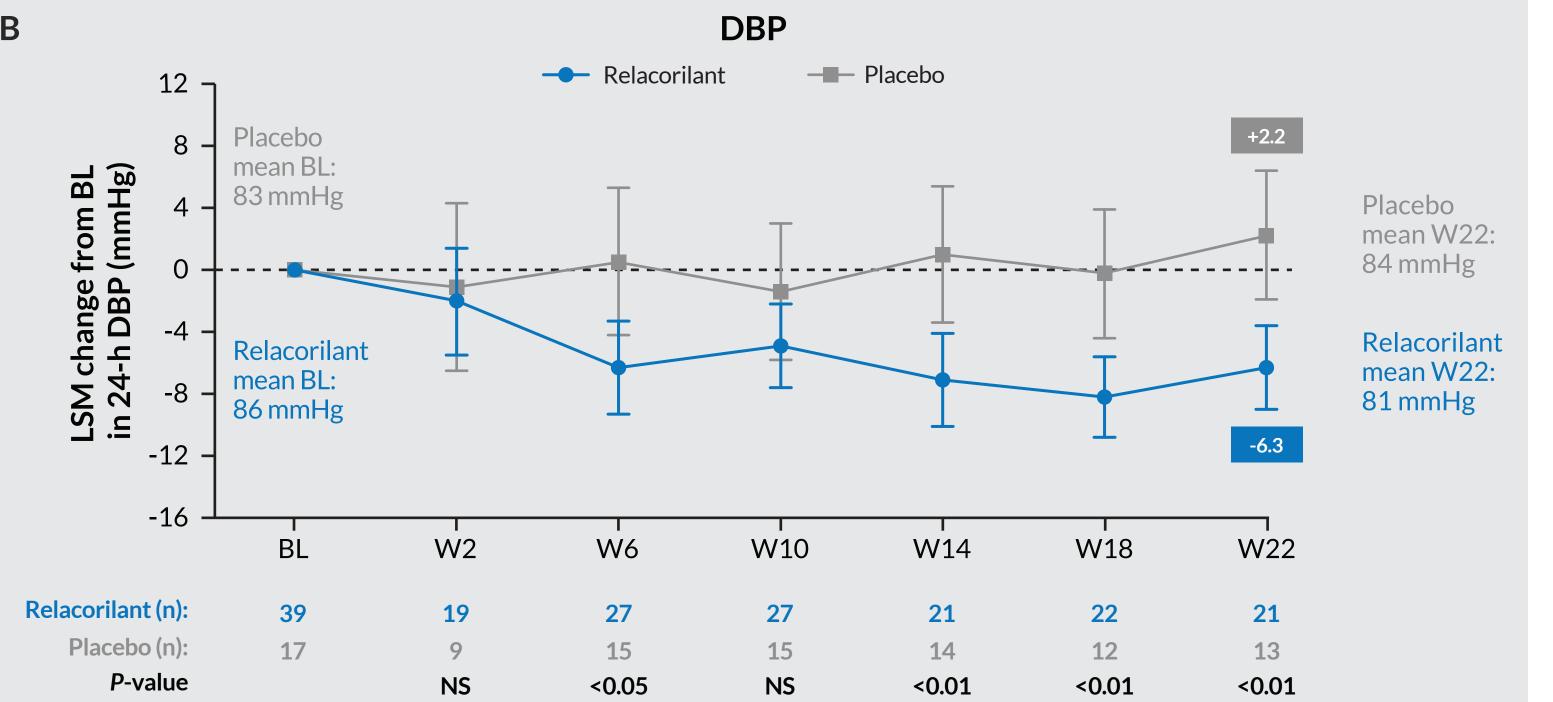
^aReceived relacorilant. ^bReceived relacorilant or placebo. AUC, area under the curve; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; ITT, intent to treat; oGTT, oral glucose tolerance test; SBP, systolic blood pressure; SD, standard deviation.

Blood Pressure

• In the pooled analysis in participants with hypertension with or without hyperglycemia, relacorilant significantly decreased SBP and DBP measured by 24-hour ambulatory blood pressure monitoring (-10.1 and -6.3 mmHg, respectively) vs placebo (+1.5 and +2.2 mmHg, respectively; both P<0.01) (**Figure 3**)

Figure 3. Change From Baseline for A) SBP and B) DBP in GRACE and GRADIENT Participants With Adrenal Hypercortisolism and Hypertension With or Without Hyperglycemia





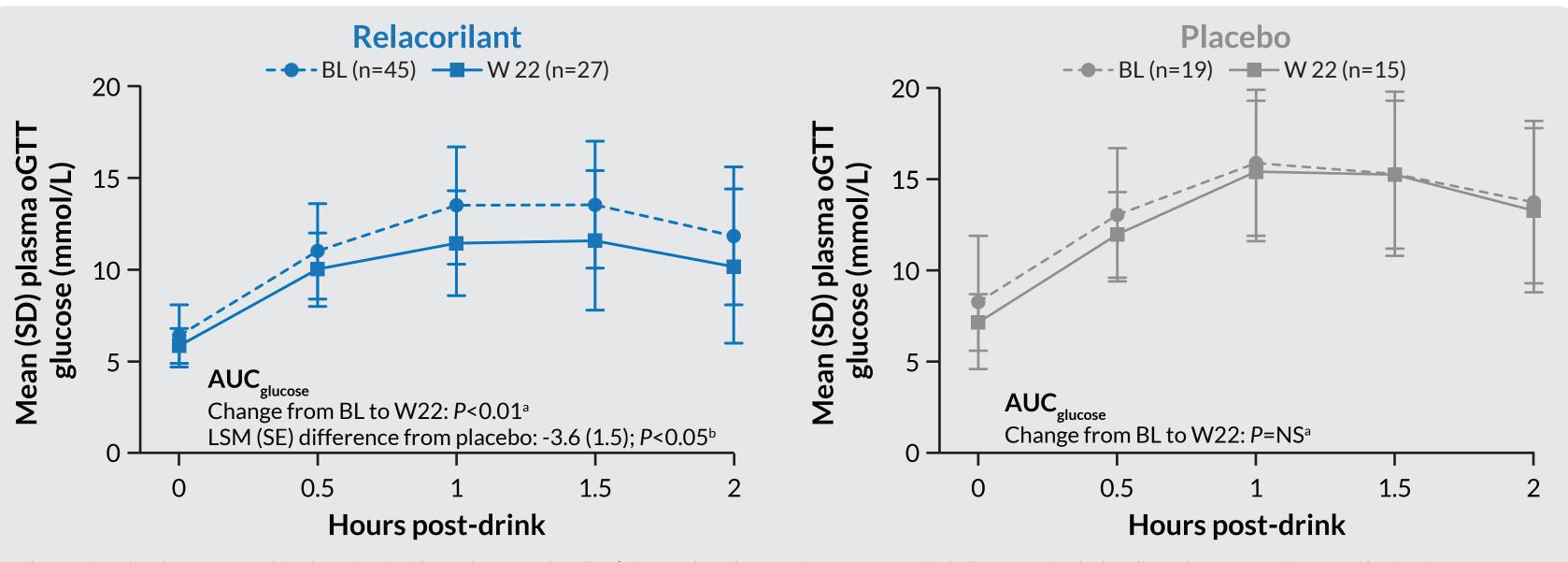
LSMs, 95% CIs, and P-values are from an MMRM, including terms for the baseline value as a covariate, stratification factor at randomization and fixed effects for study, treatment, visit and the treatment by visit interaction, with participants within treatment arm as a random effect, fit using REML. BL, baseline; CI, confidence interval; DBP, diastolic blood pressure; LSM, least-squares mean; MMRM, mixed-model for repeated measures; NS, not significant; REML, restricted maximum likelihood; SBP, systolic blood pressure; W, week.

RESULTS

Hyperglycemia

- In individuals with hyperglycemia, relacorilant significantly improved fasting glucose and glucose area under the curve (AUC_{glucose})
 (-0.7 mmol/L and -2.4 hr*mmol/L, respectively) vs placebo (+0.4 mmol/L and +1.3 hr*mmol/L, respectively; both P<0.05)
- Improvements in fasting glucose and AUC_{glucose} were observed even though participants in the relacorilant pooled arm had very well-controlled hyperglycemia (mean hemoglobin A1c, 6.5%)
- Changes from baseline to week 22 for plasma oral glucose tolerance test results for relacorilant and placebo are shown in Figure 4

Figure 4. Change From Baseline for oGTT Results in GRACE and GRADIENT Participants With Adrenal Hypercortisolism and Hyperglycemia With or Without Hypertension

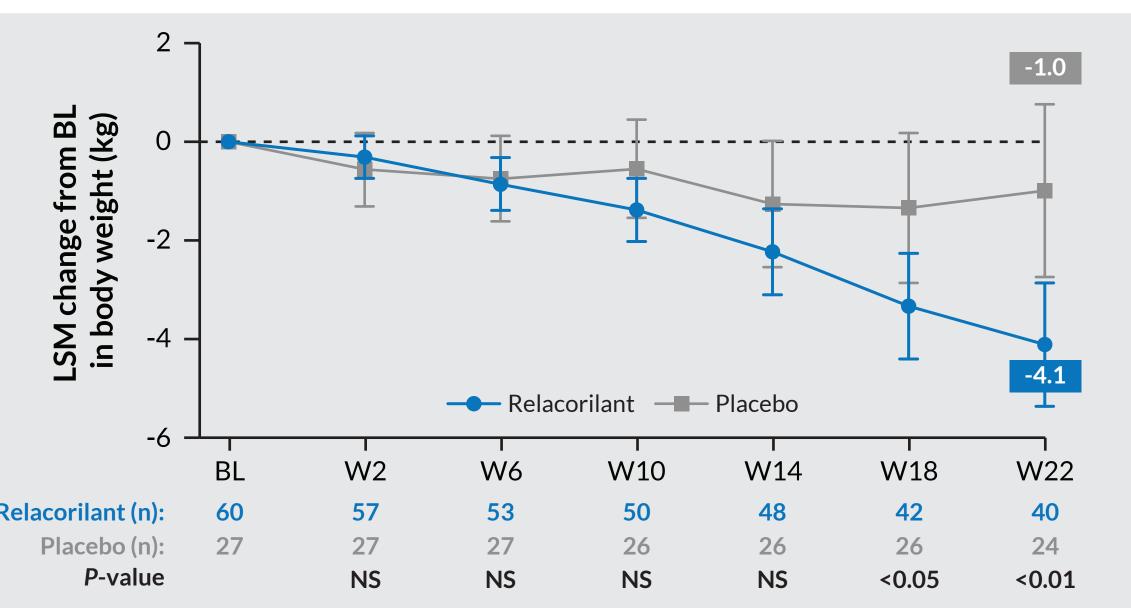


aWilcoxon signed rank test was used for detecting significant changes vs baseline. LSMs and P-values are from an MMRM, including terms for the baseline value as a covariate, stratification factor at randomization and fixed effects for study, treatment, visit and the treatment by visit interaction, with participants within treatment arm as a random effect, fit using REML. AUC, area under the curve; BL, baseline; LSM, least-squares mean; MMRM, mixed-model for repeated measures; NS, not significant; oGTT, oral glucose tolerance test; REML, restricted maximum likelihood; SD, standard deviation SE, standard error; W, week.

Body Weight

Participants treated with relacorilant experienced a statistically significant weight reduction (-4.1 kg) compared with those receiving placebo (-1.0 kg; P<0.01) (Figure 5)

Figure 5. Change From Baseline in Body Weight for GRACE and GRADIENT Participants With Adrenal Hypercortisolism



LSMs, 95% CIs, and P-values are from an MMRM, including terms for the baseline value as a covariate, stratification factor at randomization and fixed effects for study, treatment, visit and the treatment by visit interaction, with participants within treatment arm as a random effect, fit using REML. BL, baseline; CI, confidence interval; LSM, least-squares mean; MMRM, mixed-model for repeated measures; NS, not significant; REML, restricted maximum likelihood; W, week.

Safety

- Across relacorilant studies, the safety profile of relacorilant in participants with adrenal hypercortisolism was consistent with that in other endogenous hypercortisolism populations¹⁻⁵
- Across all participants and studies of relacorilant in hypercortisolism, adverse events were mostly mild-to-moderate in severity and no new safety signals were identified¹⁻⁵
- Due to relacorilant's specificity for the glucocorticoid receptor and its unique mechanism of action, the observed efficacy was seen:^{1,3,5}
- 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 relacorilant-induced QT prolongation

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Author Disclosures

Potential conflicts of interest may exist. Refer to the Meeting App.