

Relacorilant Provides Significant Benefit Across Cardiometabolic Outcomes in Global Statistical Tests of the Placebo-controlled, Randomized-withdrawal GRACE Trial in Cushing Syndrome

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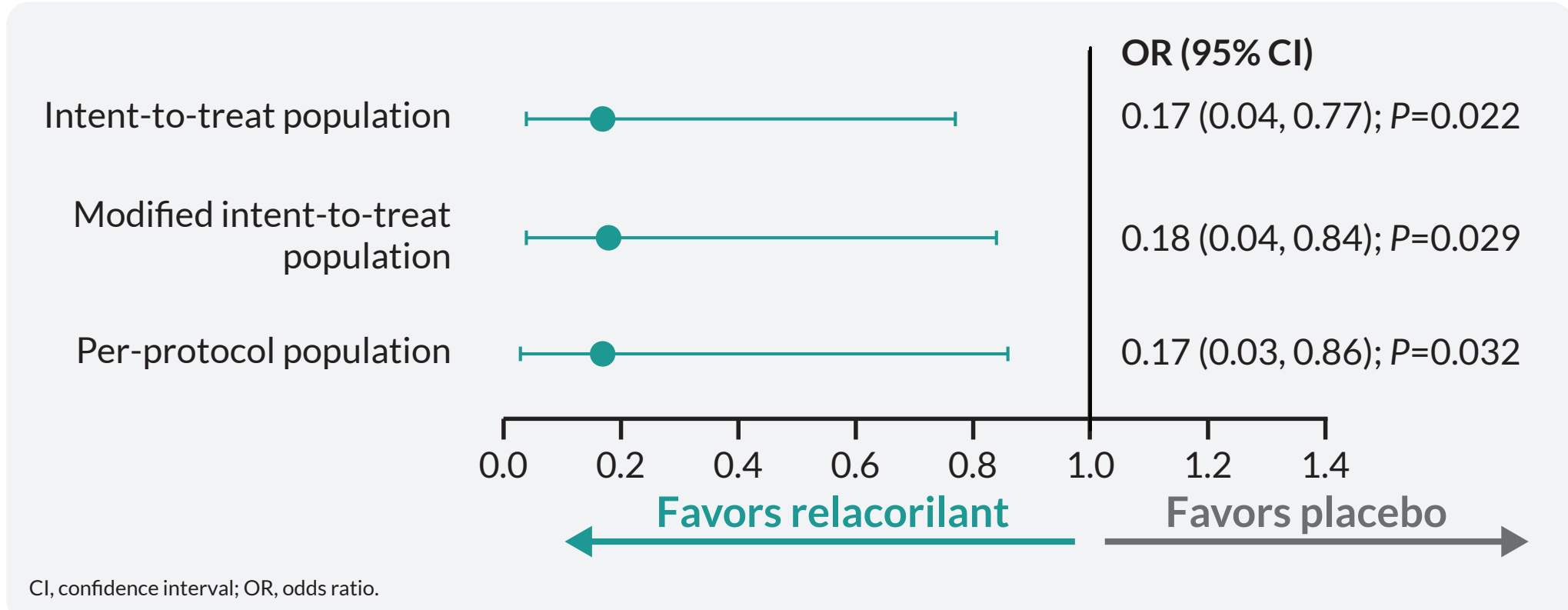
SUMMARY AND CONCLUSIONS

- In the phase 3 GRACE study, patients with Cushing syndrome treated with relacorilant were 5.9 times more likely to maintain hypertension response than those treated with placebo in the randomized-withdrawal phase, meeting the trial's primary endpoint
- Global statistical test (GST) analyses integrating measures of hypertension, hyperglycemia, and obesity in the GRACE study showed that relacorilant provided a statistically significant overall treatment benefit across the combined cardiometabolic endpoints compared with placebo
- Significant GST results were observed using both placebo-washout and missing-at-random multiple imputation methods, demonstrating robustness to different missing data assumptions
- These findings extend and support the primary results of the phase 3 GRACE study, reinforcing the clinical significance and broad cardiometabolic benefits of relacorilant treatment for patients with Cushing syndrome

BACKGROUND AND OBJECTIVE

- Endogenous hypercortisolism, or Cushing syndrome, is a heterogeneous, multisystemic condition in which excess cortisol activity causes a broad spectrum of complications, including hypertension, hyperglycemia, visceral obesity, dyslipidemia, cognitive dysfunction, and osteoporosis¹⁻³
- Relacorilant is an oral, investigational, selective glucocorticoid receptor modulator designed to reduce excess cortisol activity by competitively binding to the glucocorticoid receptor⁴
- In the phase 3 GRACE study, patients with Cushing syndrome treated with relacorilant were 5.9 times more likely to maintain hypertension response than those treated with placebo in the randomized-withdrawal (RW) phase, meeting the trial's primary endpoint (**Figure 1**)⁴
- Patients treated with relacorilant also maintained improvements in hyperglycemia and weight relative to those treated with placebo in the RW phase, although the between-group differences were not statistically significant⁴
 - The duration of the RW phase may have been too short to provide definitive evidence of treatment effect for these measures
- Given the heterogeneity and multiple organ systems involved in hypercortisolism, a single clinical endpoint may not capture the totality of treatment effect
- Global statistical tests (GST) can mitigate this issue by capturing treatment effect across diverse outcomes in a single analysis
- Because blood pressure, glucose area under curve (AUC_{glucose}), and body weight improved significantly in the study's open-label (OL) phase, we conducted a GST integrating changes to these outcomes to test the broader cardiometabolic treatment benefit of relacorilant versus placebo in the RW phase of the GRACE study

Figure 1. Loss of Hypertension Response: GRACE Study Primary Endpoint⁴



METHODS

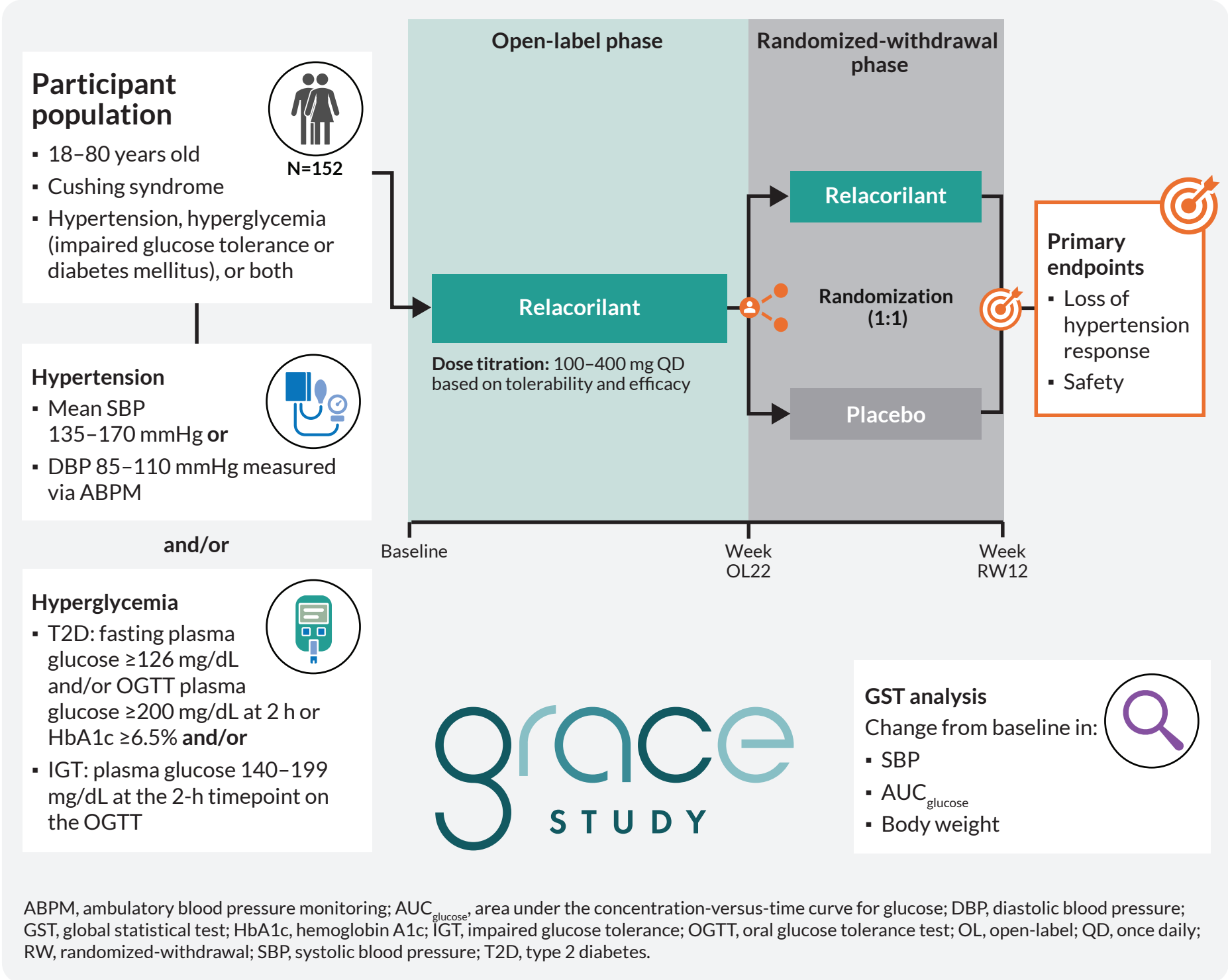
GRACE Study

- The GRACE study enrolled patients with hypertension and/or hyperglycemia and ≥ 2 clinical symptoms of Cushing syndrome with biochemical confirmation based on the presence of ≥ 2 of the following⁴:
 - Urinary free cortisol > upper limit of normal (ULN) in ≥ 2 complete 24-hour collections
 - Late-night salivary cortisol above ULN on ≥ 2 tests
 - Morning serum cortisol >1.8 $\mu\text{g/dL}$ on either the 1-mg overnight or 2-mg 48-hour dexamethasone suppression test
- After a 22-week OL titration phase of oral relacorilant, participants who met the response criteria for hypertension, hyperglycemia, or both were eligible to enter a double-blind, placebo-controlled, 12-week RW phase (**Figure 2**)⁴

Statistical Analysis

- An analysis of covariance (ANCOVA) model was applied to evaluate the treatment effect of relacorilant compared with that of placebo for each of the 3 endpoints at week 12
- The post hoc GST analysis assessed results in the intent-to-treat population for change from baseline at week 12 of the RW phase for the continuous endpoints of:
 - Systolic blood pressure (SBP) measured by ambulatory blood pressure monitoring
 - AUC_{glucose} following 75 g oral glucose
 - Body weight
- To evaluate a global treatment effect across these 3 distinct endpoints simultaneously, the O'Brien ordinary least squares (OLS) approach was used to construct the GSTs⁵
 - This method pools data across endpoints while accounting for their multivariate correlation structure
 - Because O'Brien's test lacks mechanisms to incorporate covariates in the model, the multivariate framework proposed by Dallow et al.⁶ was followed as an extension of O'Brien's OLS method, allowing inclusion of baseline values and stratification factors in a linear mixed model structure
- To assess robustness of the GSTs, 2 imputation methods were used for all missing values: 1) missing at random (MAR) and 2) placebo-washout multiple imputation

Figure 2. GRACE Study Design



References

1. Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2016;4(7):611–629. 2. Bhatt D, et al. Presented at: American College of Cardiology; March 28–30, 2026. 3. Samson SL, et al. *Endocr Pract*. 2026;32(4):473–518. 4. Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026;14(4):291–304. 5. O'Brien PC. *Biometrics*. 1984;40(4):1079–1087. 6. Dallow NS, et al. *Pharm Stat*. 2008;7(1):53–68.

RESULTS

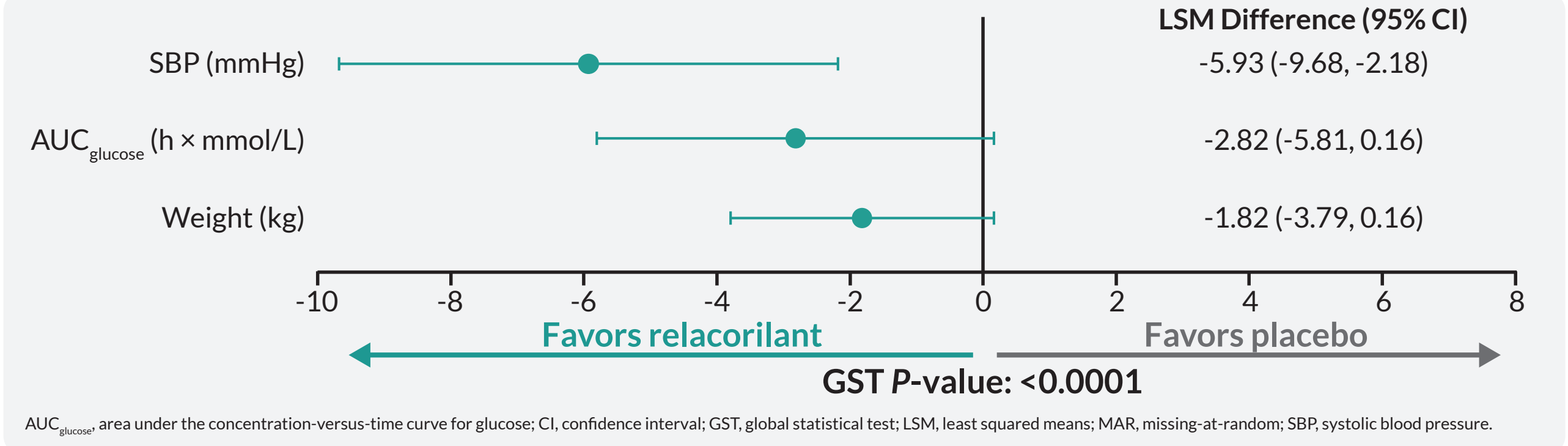
Table 1. Baseline Demographics of Participants in the RW Phase of GRACE

	Relacorilant n=30	Placebo n=32
Age, y, mean (SD)	46.6 (11.0)	48.8 (14.4)
Female, n (%)	22 (73.3)	26 (81.3)
Ethnicity not Hispanic or Latino, n (%)	25 (83.3)	27 (84.4)
Race, n (%)		
Black	3 (10.0)	4 (12.5)
Native Hawaiian or other Pacific Islander	1 (3.3)	0
White	22 (73.3)	28 (87.5)
Other	4 (13.3)	0
Weight, kg, mean (SD)	93.3 (27.4)	88.6 (21.1)
BMI, kg/m ² , mean (SD)	33.2 (7.6)	32.6 (6.5)
Waist circumference, cm, mean (SD)	113.8 (17.7)	108.9 (17.1)
ACTH dependent, n (%)	26 (86.7)	23 (71.9)
24-h SBP, mmHg, mean (SD) [n]	133.7 (12.0) [29]	136.7 (11.1) [32]
24-h DBP, mmHg, mean (SD) [n]	86.4 (9.1) [29]	86.7 (8.7) [32]
HbA1c, %, mean (SD) [n]	6.6 (1.8) [30]	6.3 (1.4) [32]
AUC_{glucose} , h $\times$ mmol/L, mean (SD) [n]	21.9 (9.8) [29]	20.6 (7.3) [31]

ACTH, adrenocorticotropic hormone; AUC_{glucose} , area under the concentration-versus-time curve for glucose; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; RW, randomized-withdrawal; SBP, systolic blood pressure; SD, standard deviation.

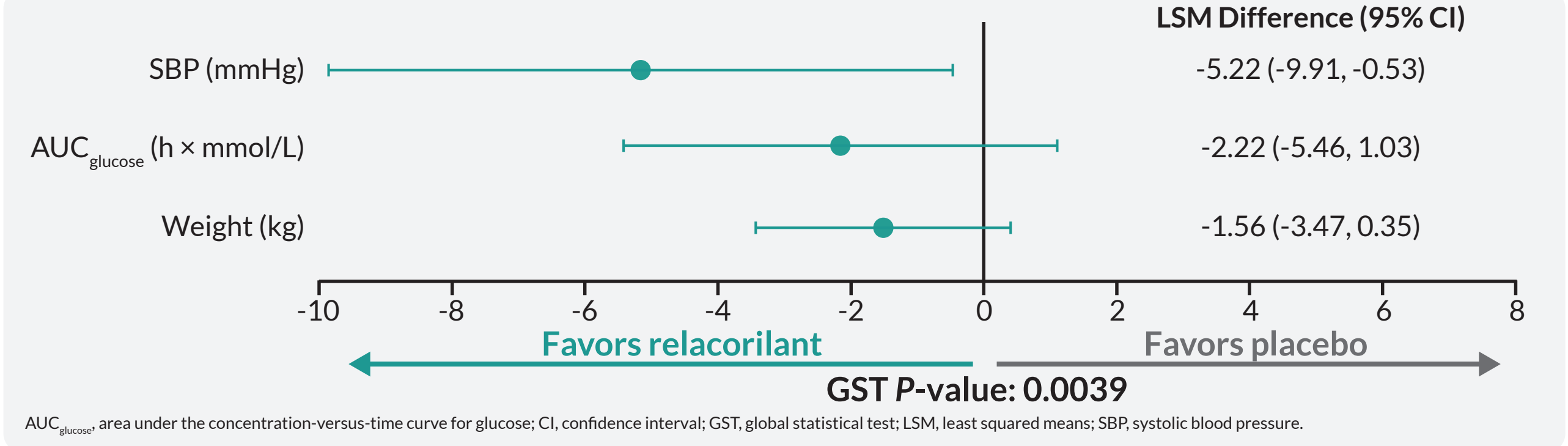
- Of the 152 participants who received relacorilant in the OL phase, 62 met the response criteria and entered the RW phase
- Demographics and baseline characteristics were well matched between the arms (**Table 1**)
- When MAR multiple imputation and ANCOVA were applied, the least squared means (LSM) differences between relacorilant and placebo were -5.93 mmHg for SBP, -2.82 h $\times$ mmol/L for AUC_{glucose} , and -1.82 kg for body weight (**Figure 3**)
- The GST for this analysis found a statistically significant treatment benefit for relacorilant vs placebo ($P<0.0001$) across the 3 efficacy outcomes

Figure 3. GST Analysis of Cushing Syndrome Outcomes for Relacorilant Versus Placebo: MAR Imputation Method



- Using placebo-washout multiple imputation and ANCOVA, the LSM difference between relacorilant and placebo was -5.22 mmHg for SBP, -2.22 h $\times$ mmol/L for AUC_{glucose} , and -1.56 kg for body weight (**Figure 4**)
- The GST for this analysis also found a statistically significant treatment benefit for relacorilant versus placebo ($P=0.0039$) across the 3 efficacy outcomes

Figure 4. GST Analysis of Cushing Syndrome Outcomes for Relacorilant Versus Placebo: Placebo-washout Imputation Method



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Presenter Disclosure

Austin Hand reports employment and stock ownership in Corcept Therapeutics, Inc.

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