Effects of Relacorilant on Body Weight and Body Composition in Patients With Endogenous Hypercortisolism in the Phase 3 GRACE and GRADIENT Studies

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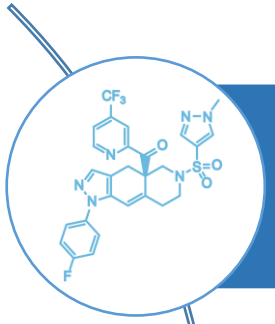
grace STUDY

GRADIENT STUDY

The views expressed in this educational program are those of the faculty and do not necessarily represent the views of the Endocrine Society.

Relacorilant: In Development for the Treatment of Endogenous Hypercortisolism



A selective GR modulator

- Structurally different from mifepristone (nonsteroidal)
- Decreases excess cortisol activity by competing with cortisol for binding to the GR

Highly selective: No PR, MR, or AR activity

- Avoids unwanted PR effects (eg, endometrial hypertrophy, vaginal bleeding)

Unique downstream effects

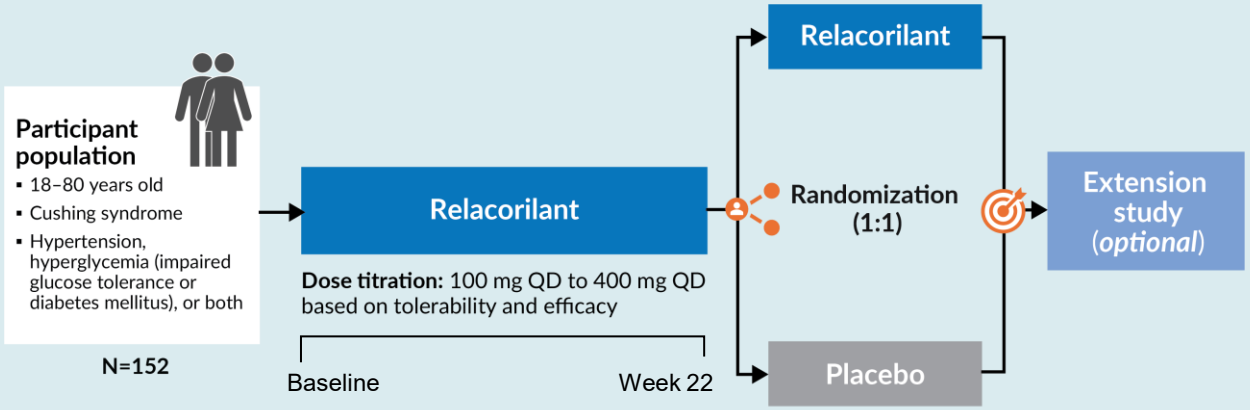
- No clinically significant impact on ACTH levels
- No clinically significant rise in cortisol levels

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

Relacorilant Phase 3 Clinical Development Program

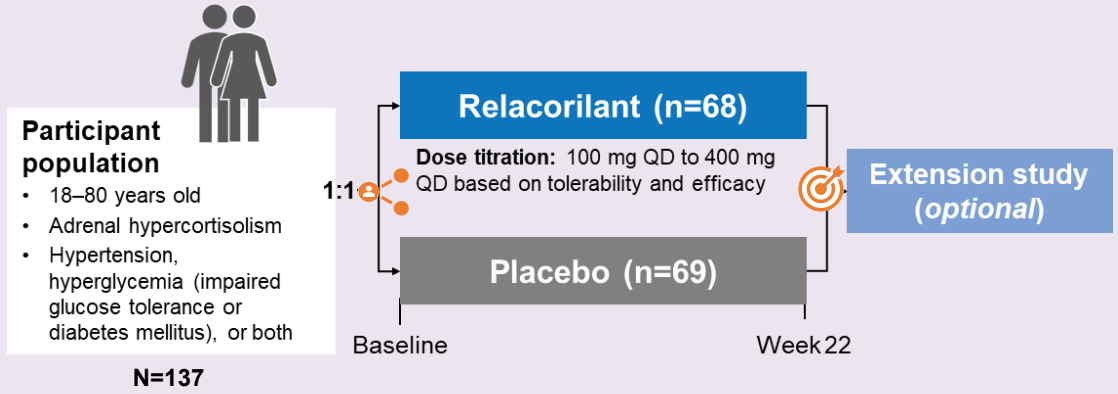
GRACE STUDY

Patients with pituitary, ectopic, or adrenal hypercortisolism



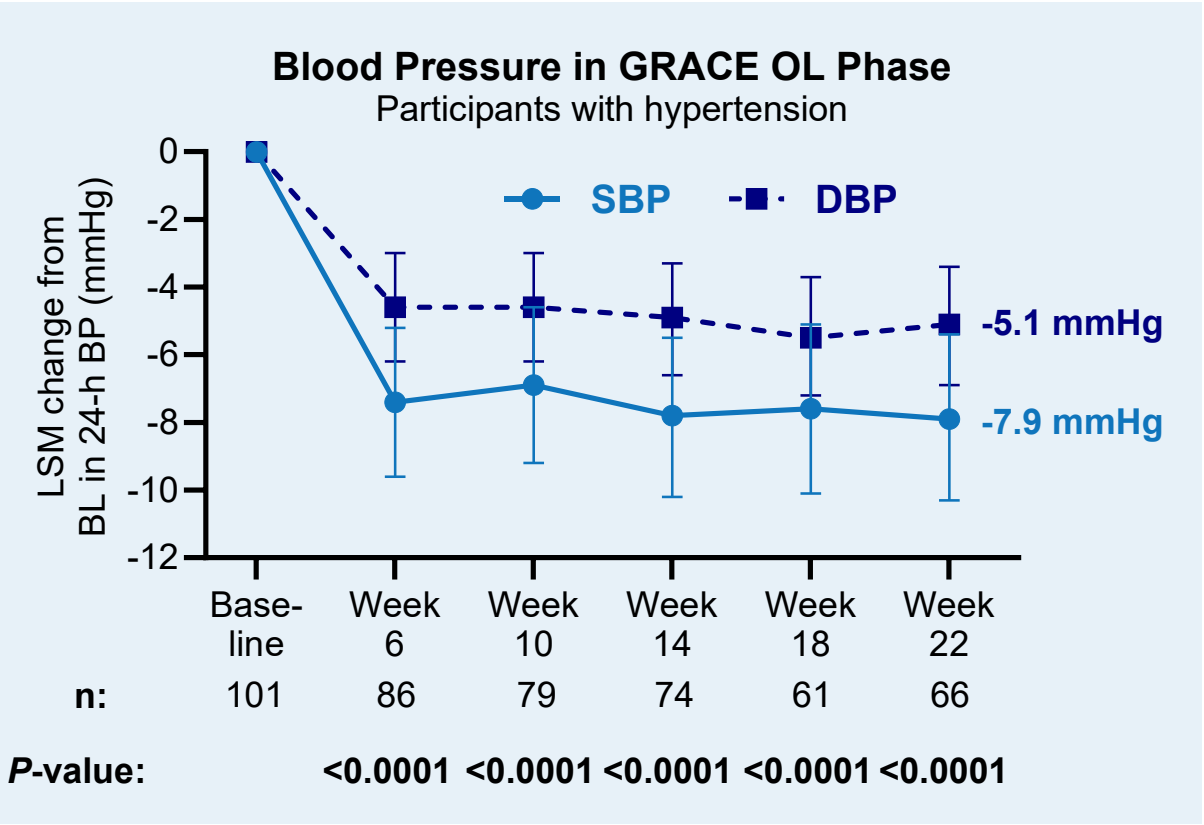
GRADIENT STUDY

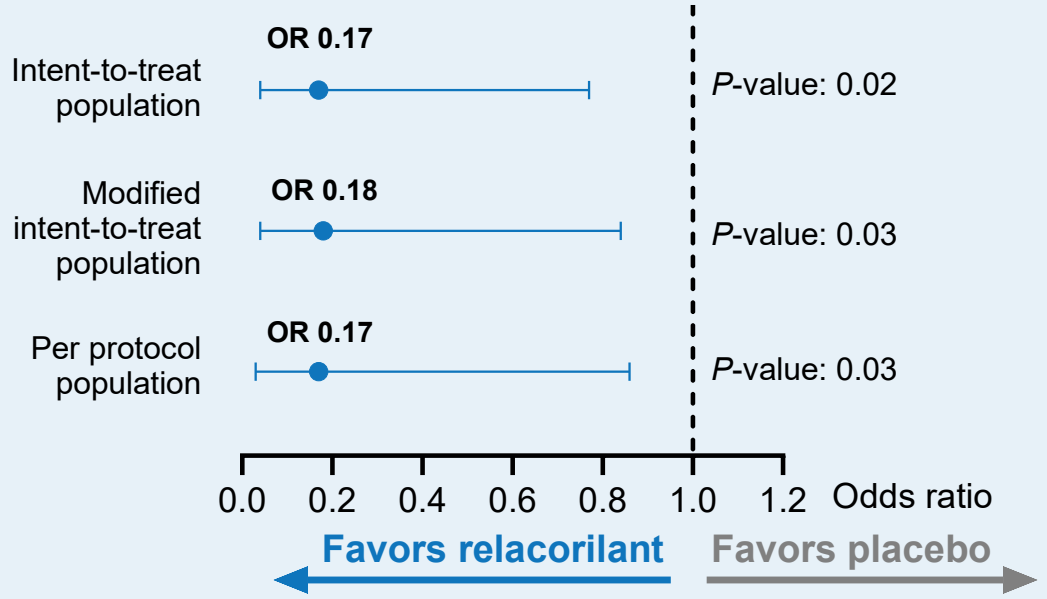
Patients with adrenal hypercortisolism



NCT03697109 (GRACE), NCT04308590 (GRADIENT). QD, every day.

Pivotal GRACE Study: **Rapid and Sustained Improvements in Blood Pressure** With Relacorilant[1]





1. Pivonello R, et al. Presented at: 8th Heart in Diabetes Conference; June 7–9, 2024; Philadelphia, PA. Error bars: 95% CI. LSM and CI calculated using a linear mixed model for repeated measures (MMRM). Wilcoxon rank sum test p-values for the mean change from baseline shown. Blood pressure measured by ABPM. Intent-to-treat population (ITT), participants randomized in the double-blind RW phase who received at least one dose of study drug post randomization. Modified ITT population, participants in the ITT population who had at least one post-randomization efficacy assessment. Per protocol population, participants in the modified ITT population who completed the study without an important protocol deviation. ABPM, ambulatory blood pressure monitoring; BL, baseline; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; LSM, least squares mean; OL, open label; OR, odds ratio; RW, randomized withdrawal; SBP, systolic blood pressure.

Focus today: Effects of relacorilant on

glucose measures, body weight, & body composition

in the 22-week treatment phases of GRACE & GRADIENT

Baseline Characteristics in GRACE and GRADIENT

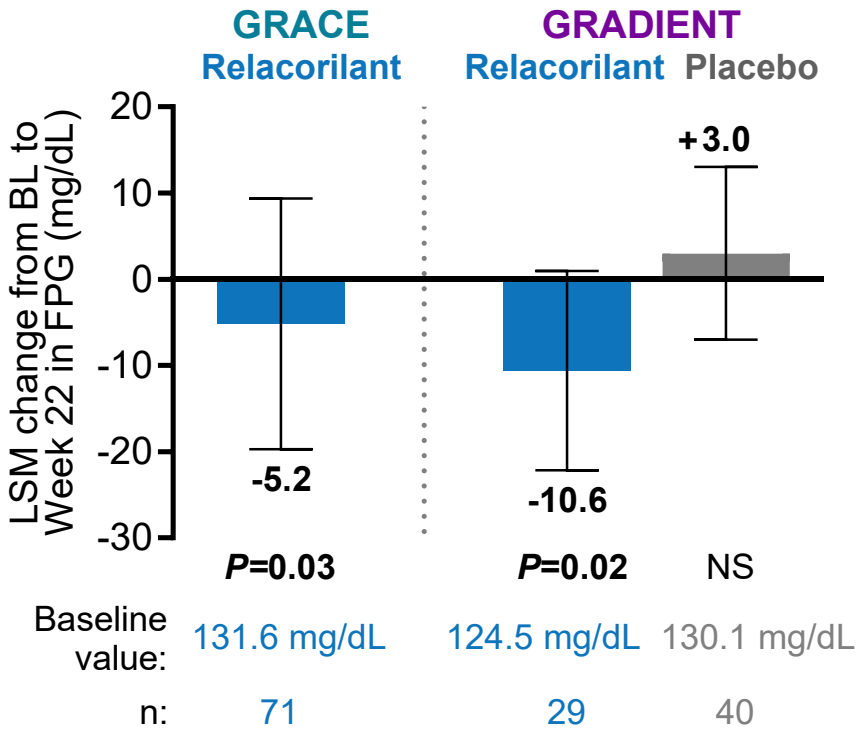
	GRACE		GRADIENT			
	Relacorilant		Relacorilant		Placebo	
	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n
Age, years	50.4 ± 13.2	152	62.5 ± 9.11	68	63.0 ± 9.0	69
Female, n (%)	127 (83.6%)	—	50 (73.5%)	—	49 (71.0%)	—
Etiology, n (%) ACTH-independent ACTH-dependent	 34 (22.4%) 118 (77.6%)	—	 68 (100%) 0	—	 69 (100%) 0	—
Body weight, kg	93.8 ± 24.7	152	89.6 ± 20.5	68	85.9 ± 20.9	69
Tissue fat mass by DXA, %	46.4 ± 8.4	131	44.1 ± 8.3	38	42.6 ± 8.8	37
Tissue lean mass by DXA, %	53.6 ± 8.4	131	53.7 ± 7.8	38	55.1 ± 8.5	37
Systolic blood pressure, mmHg	135.5 ± 12.6	148	132.4 ± 12.2	66	131.0 ± 11.5	66
Diastolic blood pressure, mmHg	84.8 ± 9.4	148	78.4 ± 9.2	66	78.7 ± 9.4	66
HbA1c, %	6.8 ± 1.6	152	6.2 ± 1.0	65	6.4 ± 1.1	68

Mean ± SD shown unless otherwise noted. ACTH, adrenocorticotropic hormone; DXA, dual-energy X-ray absorptiometry; HbA1c, hemoglobin A1c; SD, standard deviation.

Relacorilant **Improved Glycemic Measures** in Both Studies

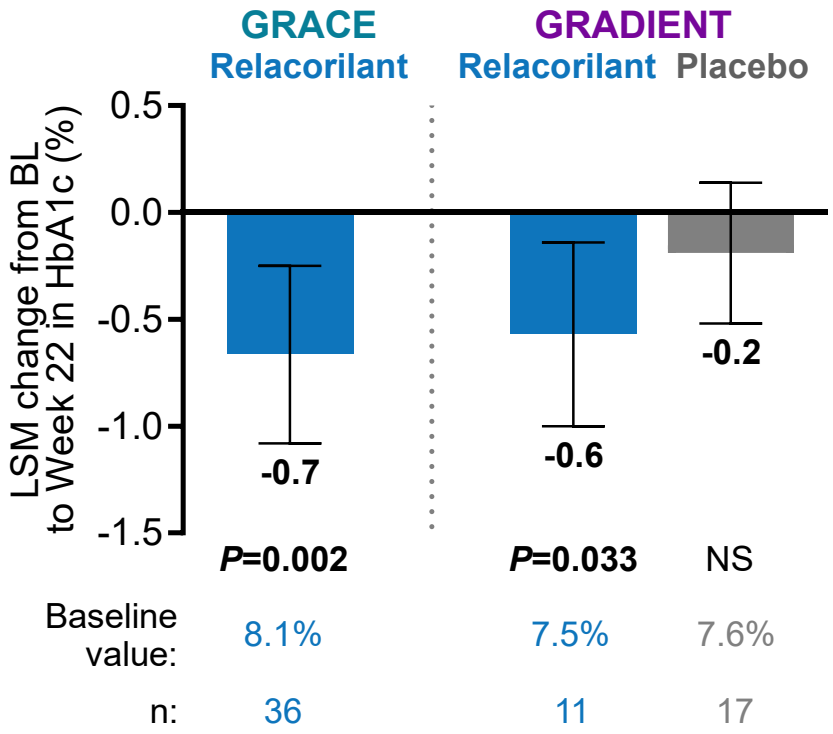
Fasting Plasma Glucose

Participants with IGT/DM



HbA1c

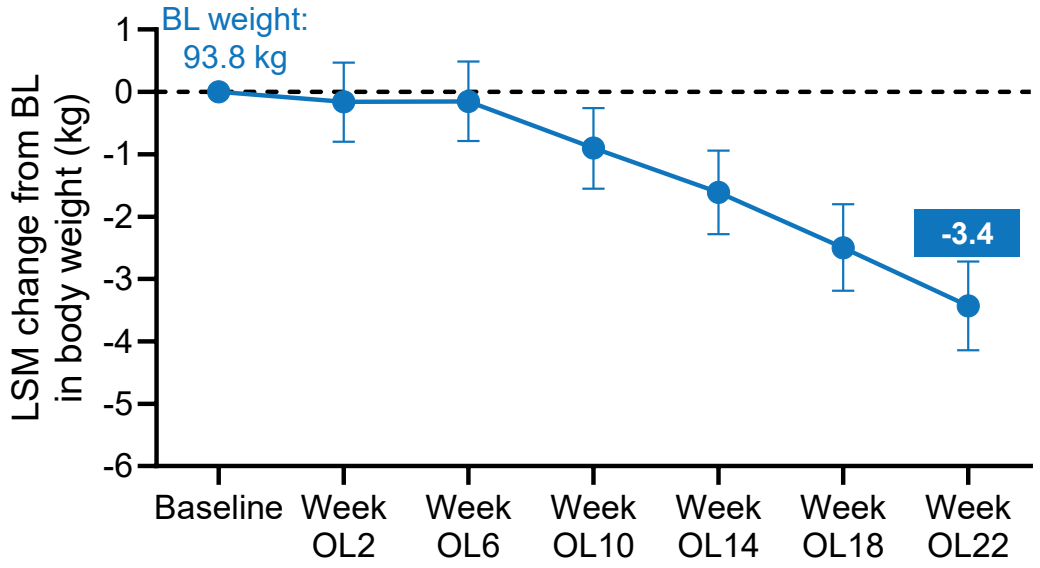
Participants with DM and BL HbA1c ≥6.5%



Error bars: 95% CIs. *P*-values from a Wilcoxon signed rank test for detecting significant changes compared to baseline. LSM and CI from a mixed model for repeated measures.
BL, baseline; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; IGT, impaired glucose tolerance; LSM, least squares mean; NS, not significant (P>0.05).

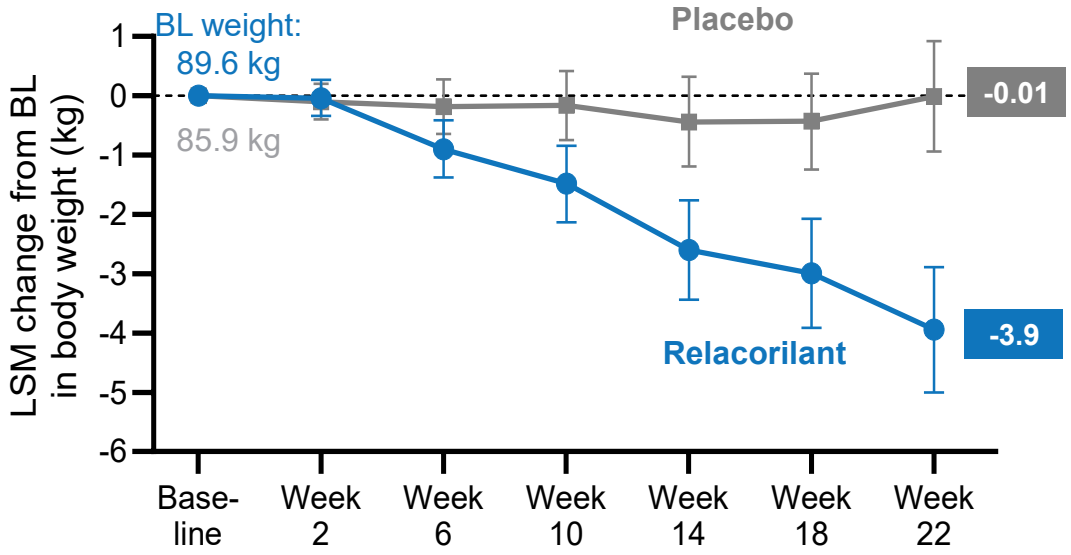
Relacorilant Resulted in **Consistent Weight Loss** In Both Studies

GRACE: Body weight
All participants



Relacorilant (n):	151	148	141	138	121	106	97
***P*-value:**		NS	NS	**0.0045**	**0.0002**	**<0.0001**	**<0.0001**

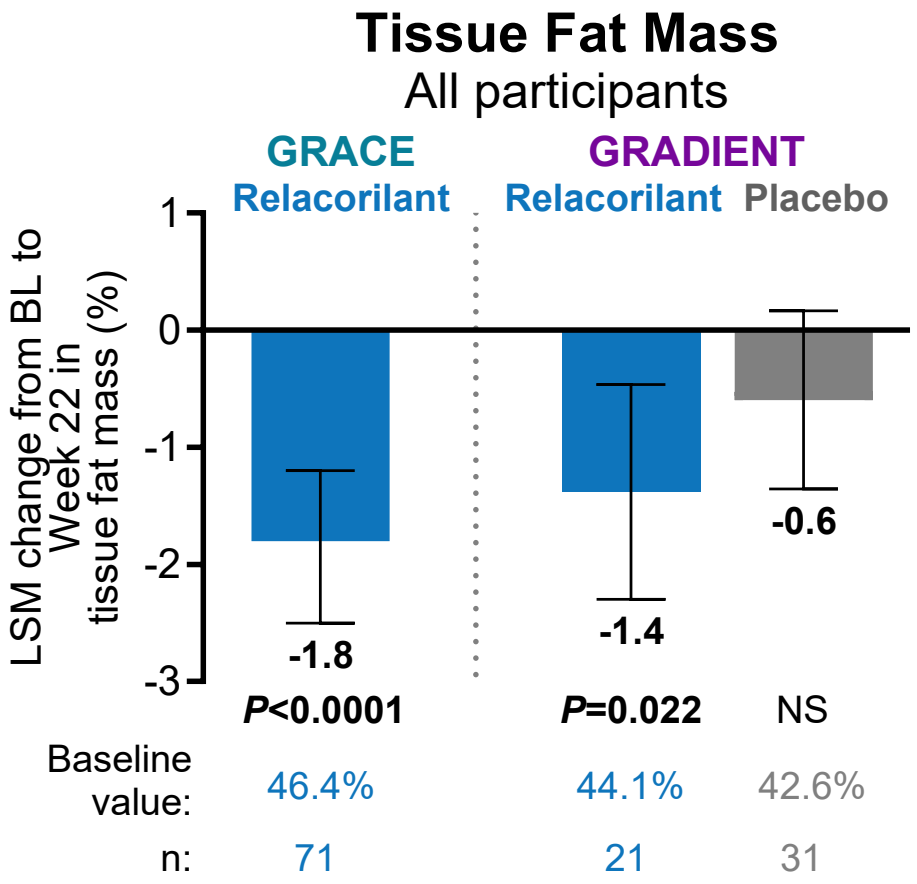
GRADIENT: Body weight
All participants

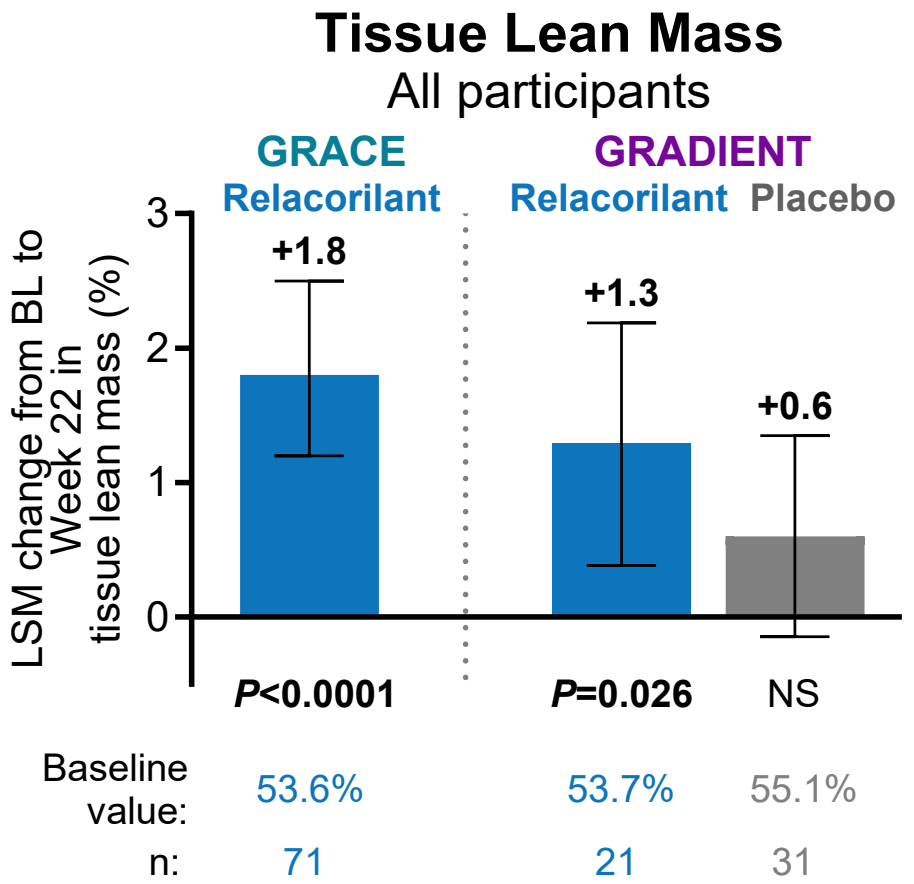


Relacorilant (n):	68	67	58	51	49	43	45
Placebo (n):	69	69	68	66	64	64	62
***P*-value**							
Relacorilant:		NS	**0.0027**	**0.0016**	**<0.0001**	**<0.0001**	**<0.0001**
Placebo:		NS	NS	NS	NS	NS	NS

Error bars: 95% CI. *P*-values from a Wilcoxon signed rank test for detecting significant changes compared to baseline. LSM and CI from a mixed model for repeated measures.
BL, baseline; CI, confidence interval; LSM, least-squares mean; NS, not significant (P>0.05); OL, open-label.

Relacorilant **Reduced Fat Mass & Increased Lean Mass** In Both Studies



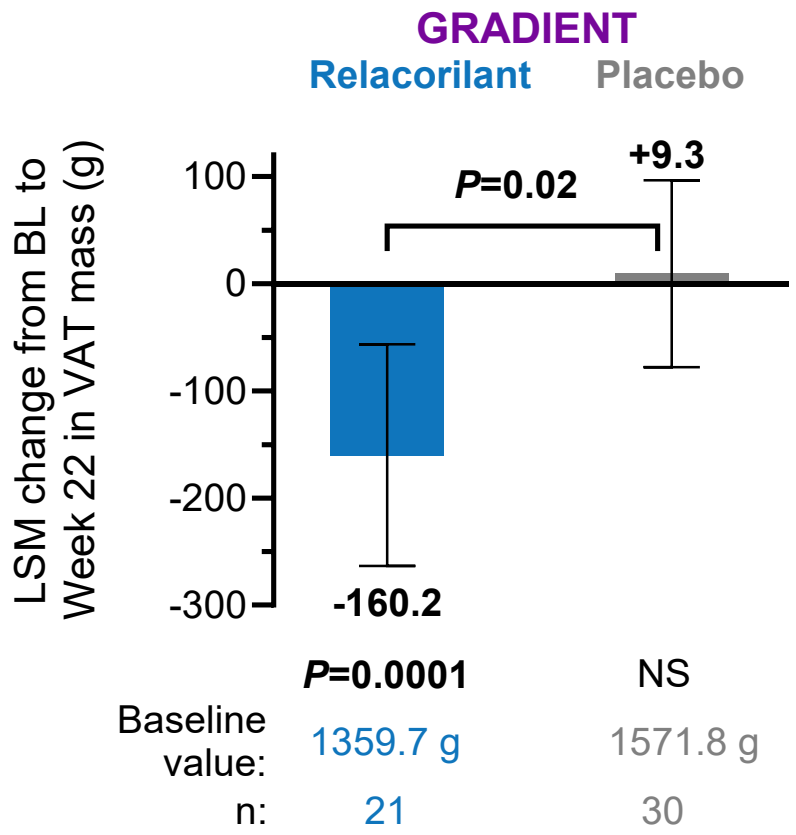


Results shown are based on DXA scans. In GRACE, DXA scans were locally read, while they were centrally read in GRADIENT. Error bars: 95% CI. Wilcoxon signed rank test was used for detecting significant changes compared to baseline. LSM and 95% CI from a mixed model for repeated measures (GRACE) and from an ANCOVA model (GRADIENT) BL, baseline; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; LSM, least-squares mean; NS, not significant (P>0.05).

Relacorilant **Reduced Visceral Adipose Tissue**, a Marker of Cardiovascular Risk, in GRADIENT

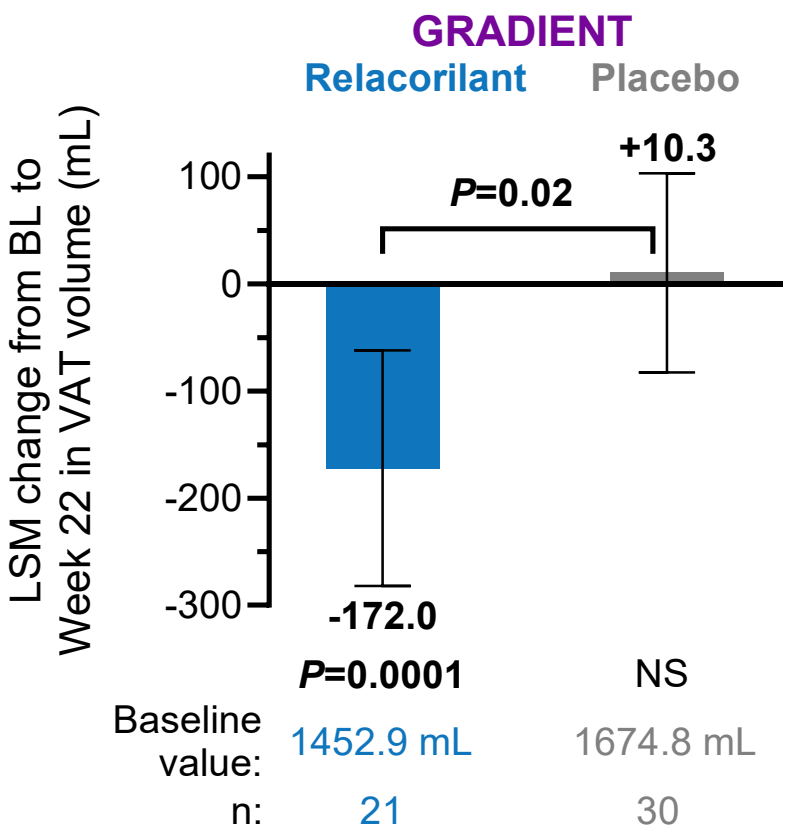
Visceral Adipose Tissue Mass

All participants



Visceral Adipose Tissue Volume

All participants



Visceral adipose tissue data not available in GRACE. Error bars: 95% CIs. *P*-values from a Wilcoxon signed rank test for detecting significant changes compared to baseline. LSM and CI from an ANCOVA model.
BL, baseline; CI, confidence interval; LSM, least-squares mean; VAT, visceral adipose tissue.

Safety: Most Common Adverse Events Were Consistent Across Both Studies (AEs Occurring in ≥15% in Either Study Arm)

GRACE	
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%)

GRADIENT		
n (%)	Relacorilant (n=68)	Placebo (n=69)
Back pain	21 (30.9%)	9 (13.0%)
Fatigue	16 (23.5%)	10 (14.5%)
Upper abdominal pain	14 (20.6%)	3 (4.3%)
Nausea	13 (19.1%)	8 (11.6%)
Pain in extremity	13 (19.1%)	5 (7.2%)
Abdominal pain	12 (17.6%)	2 (2.9%)
Arthralgia	8 (11.8%)	14 (20.3%)
Headache	7 (10.3%)	12 (17.4%)

Relacorilant was well tolerated across both studies. The most common AEs were consistent with cortisol withdrawal.

AE, adverse event.

Conclusions

1 Primary endpoint met in GRACE	Relacorilant treatment led to **clinically and statistically significant improvements in blood pressure and other signs and symptoms of hypercortisolism**[1]
2 Improvements in glycemic control	Despite well controlled hyperglycemia at baseline, relacorilant treatment improved fasting glucose and HbA1c in GRACE & GRADIENT
3 Improvements in body composition	Relacorilant led to **clinically and statistically significant improvements in body composition and body weight** in participants with endogenous hypercortisolism of pituitary, adrenal, and ectopic etiology • Improvements may occur as early as after 6–10 weeks of treatment
4 Preserved lean mass	Lean mass was preserved in both studies, in contrast to the reductions in lean mass reported with the most common classes of weight-loss agents
5 Favorable safety profile	Due to relacorilant's selectivity for the GR and unique downstream effects, no cases of relacorilant-induced hypokalemia, adrenal insufficiency, vaginal bleeding associated with endometrial hypertrophy, or QT interval prolongation were reported in these studies[1]

For results in participants with adrenal hypercortisolism from both studies, see poster SUN-463

1. Pivonello R, et al. Presented at: 8th Heart in Diabetes Conference; June 7–9, 2024; Philadelphia, PA, USA.

GR, glucocorticoid receptor.