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Relacorilant Treatment Improves Glycemic Control Among Individuals With Cushing Syndrome (Endogenous Hypercortisolism) and Hyperglycemia on Glucagon-Like Peptide-1 Receptor Agonists: Insights From a Phase 3 Study

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SUMMARY AND CONCLUSIONS

- **In the phase 3 GRACE study, relacorilant treatment led to a near 1% reduction in hemoglobin A1c (HbA1c) for the participant subgroup with Cushing syndrome and hyperglycemia who were taking glucagon-like peptide-1 receptor agonists (GLP-1 RAs) or dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RAs**
- **The mean baseline HbA1c of 8.5% for this subgroup indicates suboptimal glycemic control despite treatment with these agents**
- **Relacorilant treatment also resulted in significant reductions in weight and waist circumference in these participants while preserving lean body mass percentage**
- **These results suggest that addressing excess cortisol activity with relacorilant can provide benefit beyond that achieved with GLP-1 RAs or GIP/GLP-1 RAs alone in individuals with Cushing syndrome and hyperglycemia receiving these medications**

BACKGROUND AND OBJECTIVE

- Relacorilant is an oral, investigational, selective glucocorticoid receptor (GR) modulator that regulates excess cortisol activity to treat Cushing syndrome[1,2]:
  - Competitively and reversibly binds to the GR[1,2]
  - Structurally different from the GR antagonist mifepristone[1,2]
  - Highly selective for the GR and does not bind to the progesterone receptor (PR) or other hormone receptors, thus avoiding unwanted PR-mediated effects like endometrial hypertrophy and vaginal bleeding[1,3]
- In the phase 3 GRACE study, adults with Cushing syndrome and hypertension with or without hyperglycemia treated with relacorilant showed improved blood pressure, glycemic control, and body weight from baseline in the open-label (OL) phase[4]
- GRACE achieved its primary endpoint: significantly more participants who were switched to placebo during the randomized-withdrawal (RW) phase lost hypertension control compared with those who stayed on relacorilant (odds ratio 0.17 for relacorilant vs placebo; *P*=0.02)[4]
- A subgroup of GRACE study participants had hyperglycemia despite use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) or dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RAs
- Excess cortisol may diminish the efficacy of these diabetes treatments by increasing gluconeogenesis, disrupting the incretin system (including GLP-1 signaling), increasing appetite, and impairing beta cell function[5]
- This analysis investigated relacorilant in the subgroup of GRACE study participants with hyperglycemia taking GLP-1 RAs or GIP/GLP-1 RAs

RESULTS

Efficacy

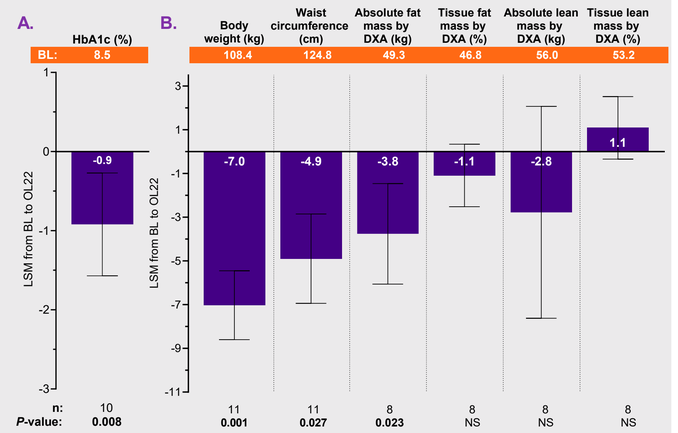
- Of the 152 participants in the OL phase, 28 had hyperglycemia despite use of GLP-1 RAs or GIP/GLP-1 RAs (**Table 1**)
  - Baseline mean HbA1c, weight, and waist circumference were 8.5%, 108.4 kg, and 124.8 cm, respectively
  - The tissue lean mass percentage at baseline was 53.2%
- Relacorilant treatment resulted in a significant reduction in HbA1c from baseline to week OL 22 (-0.9%; 95% confidence interval, -1.6 to -0.3; *P*=0.008; **Figure 2**)
- Significant reductions from baseline to OL week 22 were also seen for body weight, waist circumference, and absolute fat mass, whereas lean body mass was preserved (**Figure 2**)

Table 1. Baseline Characteristics of GRACE Participants Taking GLP-1 RAs or GIP/GLP-1 RAs (OL Phase)

	Relacorilant (n=28)
Age, y, median (range)	52.5 (44–60)
Female, n (%)	26 (92.9)
Weight, kg, mean (SD)	108.4 (21.6)
BMI, kg/m^2, mean (SD)	40.6 (8.3)
Waist circumference, cm, mean (SD)	124.8 (15.3)
Absolute fat mass, kg, mean (SD) [n]	49.3 (11.6) [22]
Percent tissue fat mass, %, mean (SD) [n]	46.8 (5.5) [22]
Absolute lean mass, kg, mean (SD) [n]	56.0 (12.6) [22]
Percent tissue lean mass, %, mean (SD) [n]	53.2 (5.5) [22]
Glucose parameters	
HbA1c, %, mean (SD) [n]	8.5 (1.7) [27]
Fasting plasma glucose, mg/dL, mean (SD) [n]	166.1 (77.8) [26]

BMI, body mass index; HbA1c, hemoglobin A1c; SD, standard deviation.

Figure 2. Changes in A) HbA1c and B) Body Composition From Baseline to OL Week 22 With Relacorilant Treatment in GRACE Study Participants Taking GLP-1 RAs or GIP/GLP-1 RAs



Error bars: 95% confidence interval. Wilcoxon rank sum test *P*-values for the mean change from baseline shown.
BL, baseline; DXA, dual energy X-ray absorptiometry; HbA1c, hemoglobin A1c; LSM, least squares mean; NS, not significant; OL, open-label.

Safety

- Adverse events in GRACE were generally mild to moderate
- In the OL phase, the most frequent treatment-emergent adverse events (TEAEs) in the subgroup taking GLP-1 RAs or GIP/GLP-1 RAs were nausea, peripheral edema, and pain in the extremities (**Table 2**)
- Grade ≥3 TEAEs and serious TEAEs during the OL phase occurred in 32.1% and 28.6%, respectively, of participants taking GLP-1 RAs or GIP/GLP-1 RAs vs 24.3% and 19.1%, respectively, of participants in the overall study
- No transaminase elevations >3× ULN were observed in this subgroup, and no participants met Hy's Law criteria
- The observed safety profile of relacorilant was consistent with its GR specificity and mechanism of action, and no new safety signals were identified in this subgroup

Table 2. TEAEs Occurring in ≥15% of Participants Taking GLP-1 RAs or GIP/GLP-1 RAs (OL Phase)

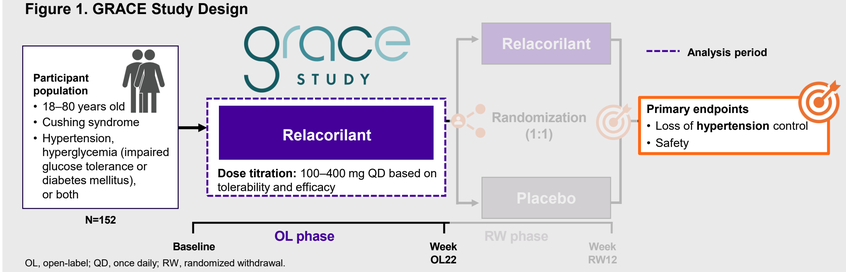
TEAE, n (%)	GIP/GLP-1 RA subgroup (n=28)	All participants (N=152)
Nausea	13 (46.4)	52 (34.2)
Peripheral edema	10 (35.7)	50 (32.9)
Pain in extremity	9 (32.1)	43 (28.3)
Dizziness	8 (28.6)	23 (15.1)
Constipation	7 (25.0)	23 (15.1)
Headache	7 (25.0)	31 (20.4)
Abdominal pain	5 (17.9)	17 (11.2)
Abdominal pain upper	5 (17.9)	23 (15.1)
Diarrhea	5 (17.9)	28 (18.4)
Paresthesia	5 (17.9)	21 (13.8)
Asthenia	5 (17.9)	19 (12.5)
Fatigue	5 (17.9)	34 (22.4)
Pain	5 (17.9)	13 (8.6)
Back pain	5 (17.9)	41 (27.0)

GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; TEAE, treatment-emergent adverse event.

METHODS

- GRACE consisted of a 22-week OL phase of relacorilant 100–400 mg once daily, followed by a 12-week, double-blind, placebo-controlled, RW phase (**Figure 1**)
- Eligible participants had ≥2 clinical symptoms of Cushing syndrome and biochemical confirmation based on the presence of ≥2 of the following[4]:
  - Urinary free cortisol > upper limit of normal (ULN) in ≥2 complete 24-hour tests
  - Late-night salivary cortisol > ULN on ≥2 tests
  - >1.8 µg/dL morning serum cortisol on either the 1-mg overnight or 2-mg 48-hour dexamethasone suppression test
- Hyperglycemia was defined as[4]:
  - Diabetes mellitus: fasting plasma glucose ≥126 mg/dL and/or oral glucose tolerance test (oGTT) plasma glucose ≥200 mg/dL at 2 hours or hemoglobin A1c (HbA1c) ≥6.5%
  - Impaired glucose tolerance: plasma glucose 140–199 mg/dL at the 2-hour oGTT time point

Figure 1. GRACE Study Design



OL, open-label; QD, once daily; RW, randomized withdrawal.

- This exploratory analysis included participants taking a GLP-1 RA or GIP/GLP-1 RA prior to and for ≥80% of the OL phase
- Least squares mean changes from baseline to OL week 22 in HbA1c, weight, waist circumference, and body composition were analyzed using a mixed model for repeated measures (MMRM)
  - MMRM estimates included a fixed effect for visit, with participant as a random effect fit using restricted maximal likelihood
  - The Kenward and Roger method was used for calculating the denominator degrees of freedom for tests of fixed effects, and a compound symmetry covariance matrix was used to model within-participant error
- Body composition parameters were measured by dual-energy X-ray absorptiometry

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PRESENTER DISCLOSURE

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