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Relacorilant Maintained Hypertension Improvement in Long-term Follow-up of Patients With Endogenous Hypercortisolism (Cushing Syndrome)

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INTRODUCTION

- Relacorilant is a selective glucocorticoid receptor modulator (SGRM) in development for the treatment of endogenous hypercortisolism (Cushing syndrome)
  - Modulates cortisol activity by competing with cortisol for binding to the glucocorticoid receptor (GR)[1-3]
  - Highly selective for the GR, with no affinity for the progesterone receptor (PR) or other steroid hormone receptors (**Figure 1**)[1]
- In the phase 3 GRACE study in adults with endogenous hypercortisolism, relacorilant resulted in significant improvements in hypertension, meeting the study's primary endpoint (**Figure 2**)[3]
  - In the placebo-controlled, randomized withdrawal (RW) phase (**Figure 3**), patients who continued on relacorilant were 5.9× more likely to maintain hypertension response vs those who were switched to placebo (odds ratio, 0.17; *P*=0.02)[3]
  - Relacorilant was observed to have similar effects at the GR as the nonselective GR antagonist mifepristone but without PR-related off-target effects, such as endometrial hypertrophy and vaginal bleeding[1-5]
  - Relacorilant also has no clinically significant impact on adrenocorticotropic hormone (ACTH) levels, resulting in no increase in clinically significant cortisol levels[5,6]
  - Relacorilant was well-tolerated, with no new safety signals identified[3]

Figure 1. Relacorilant

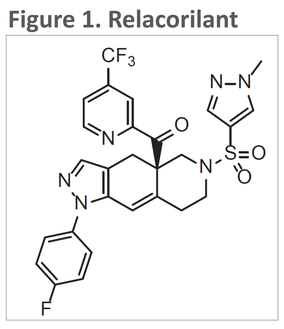
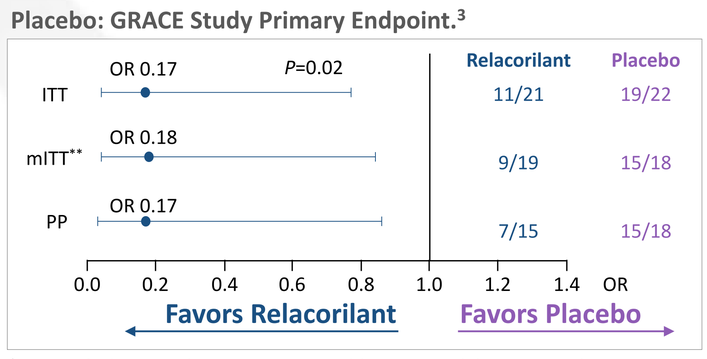


Figure 2. Loss of Hypertension Response* in Patients Randomized to Continue Relacorilant Treatment or Switch to Placebo: GRACE Study Primary Endpoint.[3]



*Prespecified criteria: hypertension control (patients with hypertension): ≥5 mm Hg decrease in mean systolic and/or diastolic blood pressure, without worsening of either, based on 24-h ambulatory blood pressure monitoring (ABPM). **mITT included all patients in the ITT population with at least one post-randomization efficacy assessment for the primary efficacy endpoint. ITT, intent to treat; mITT, modified ITT; OR, odds ratio; PP, per protocol.*

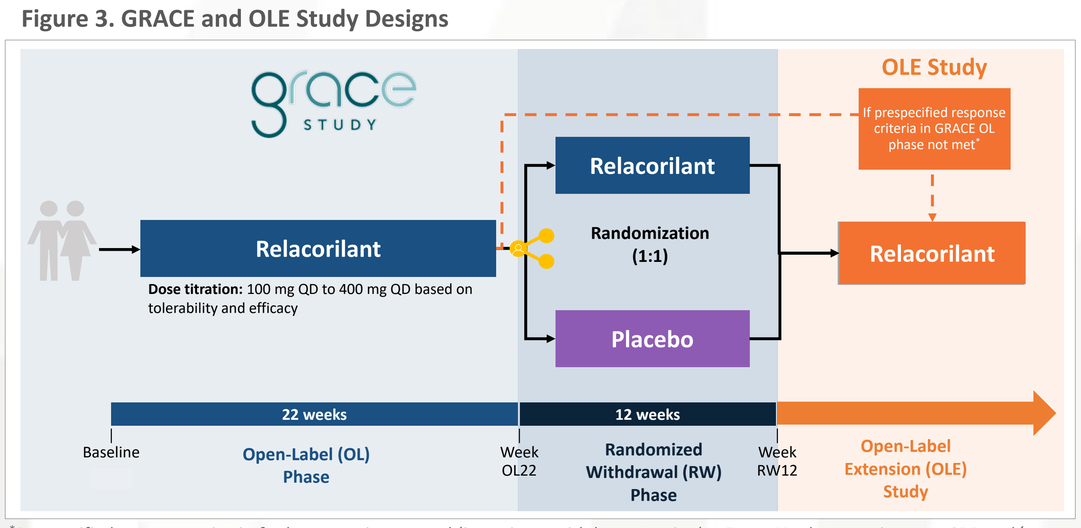
AIM

Here, we report the first interim analysis of the longer-term impact of relacorilant on hypertension in patients participating in the GRACE study who entered the open-label extension (OLE) study.

METHODS

- The GRACE study (NCT03697109) was a phase 3 study with 2 parts (**Figure 3**):
  1) A 22-week open-label (OL) phase, in which adults aged 18–80 years with endogenous hypercortisolism and hypertension (n=31), hyperglycemia (impaired glucose tolerance or diabetes mellitus; n=50), or both (n=71) received relacorilant 100 mg to 400 mg QD based on tolerability and efficacy
  2) Those who completed the OL phase and met the prespecified response criteria were randomized 1:1 to continue relacorilant or be switched to placebo for 12 weeks (RW phase)
- Patients who completed the GRACE RW phase and those who completed the GRACE OL phase but did not enter the RW phase due to not meeting the prespecified response criteria were eligible to continue relacorilant in the OLE study (NCT03604198)
  - Relacorilant was discontinued during the transition period between studies in some patients

Figure 3. GRACE and OLE Study Designs



Prespecified response criteria for hypertension control (in patients with hypertension): ≥5 mm Hg decrease in mean SBP and/or DBP, without worsening of either, based on 24-h ABPM. Prespecified criteria for hyperglycemia control have been presented elsewhere.[3] DBP, diastolic blood pressure; SBP, systolic blood pressure.

- The starting relacorilant dose in the OLE was:
  - For patients who completed the GRACE RW phase: 100 mg QD titrated up to 400 mg based on tolerability
  - For patients who completed only the GRACE OL phase: the dose received at last study visit in the OL phase
- Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were longitudinally measured by 24-hour ambulatory blood pressure (BP) monitoring
- Wilcoxon signed rank test was used for detecting significant changes compared with baseline

RESULTS

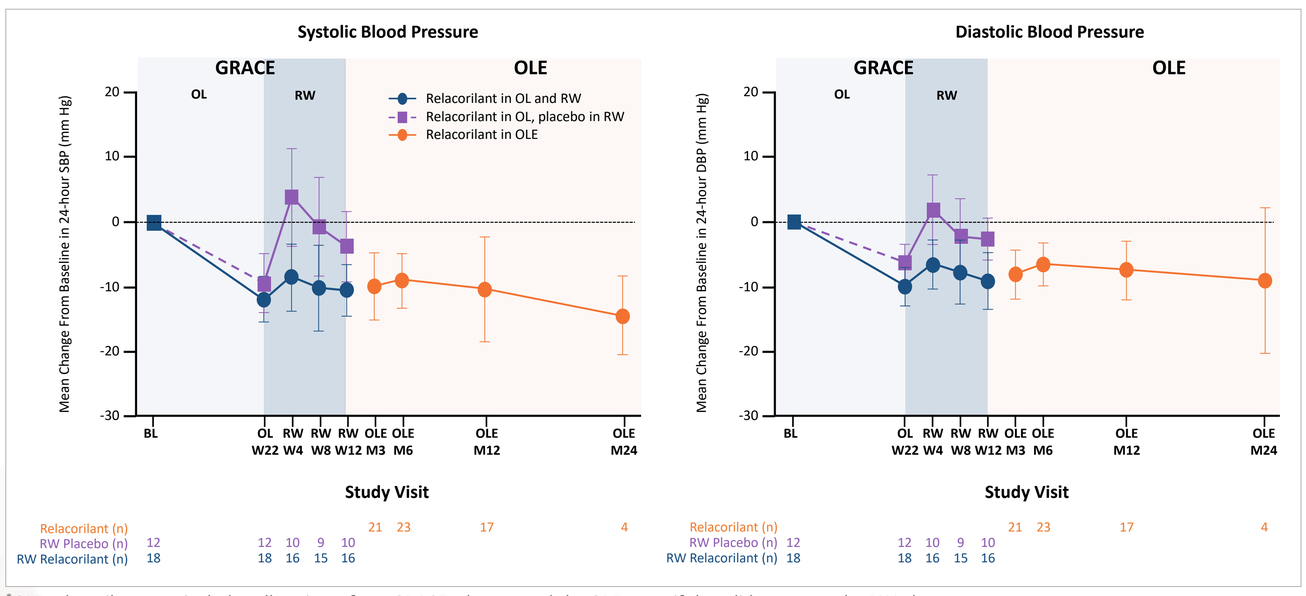
Patients

- Baseline demographic and clinical characteristics of patients for the full GRACE cohort have been presented previously[3,7]
- 51 patients from GRACE were enrolled in and received ≥1 dose of relacorilant in the OLE

Hypertension Control

- Relacorilant treatment resulted in long-term improvement in hypertension (**Figure 4**)
  - Patients treated continuously with relacorilant in GRACE and the OLE maintained hypertension control throughout
  - Patients switched to placebo in the GRACE RW phase had a deterioration in BP control followed by improvement after resumption of relacorilant in the OLE
  - Three of the 4 patients who completed the GRACE OL phase without meeting the hypertension response criteria and had available data in the OLE experienced hypertension response during the OLE
- Patients with hypertension at baseline (n=36) had clinically and statistically significant reductions from OL baseline to OLE month 12 in mean SBP (-10.2 mm Hg [95% confidence interval [CI]: -18.3, -2.2; *P*<0.01]) and DBP (-7.4 mm Hg [95% CI: -11.9, -2.9; *P*<0.01])

Figure 4. Mean Change From Baseline in Blood Pressure in Patients With Hypertension at Baseline*

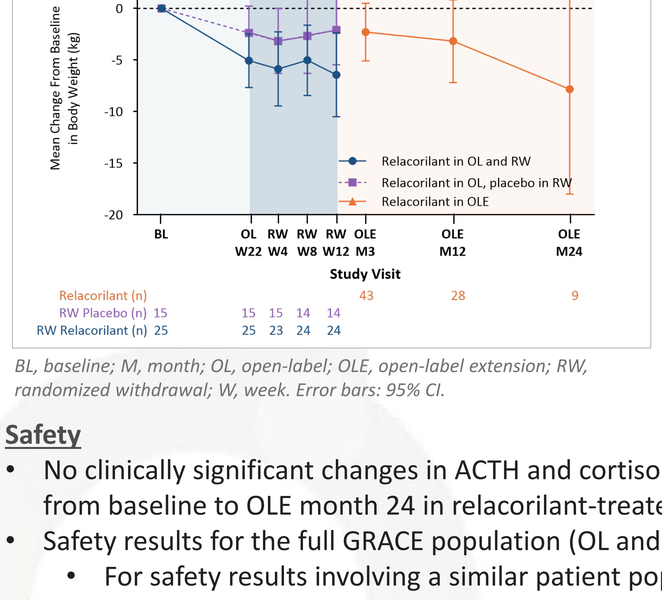


OLE relacorilant arm includes all patients from GRACE who entered the OLE, even if they did not enter the RW phase.
BL, baseline; CI, confidence interval; DBP, diastolic blood pressure; M, month; OL, open-label; OLE, open-label extension; RW, randomized withdrawal; SBP, systolic blood pressure; W, week. Error bars: 95% CI.

Other Efficacy Endpoints

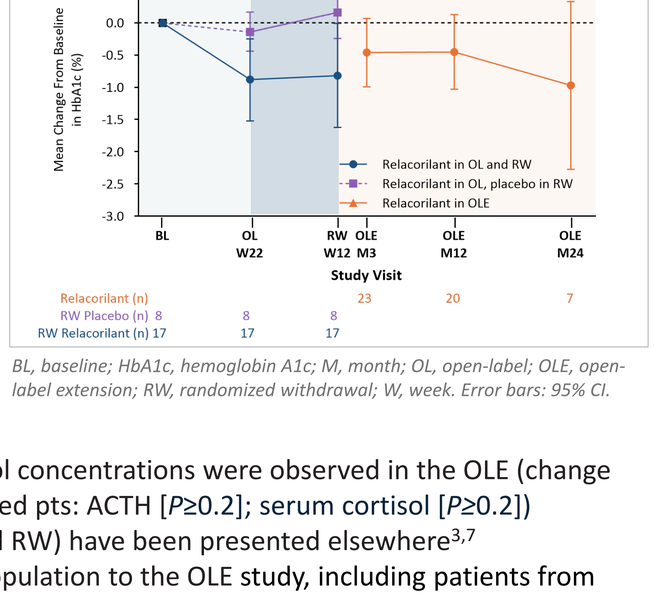
- Relacorilant treatment led to a signification reduction in body weight (*P*<.0001) and a significant improvement in hemoglobin A1c (HbA1c; *P*=0.03) in the GRACE OL phase;[7] this trend continued into the OLE phase (**Figure 5; Figure 6**)
- These results followed a similar pattern to that seen with BP control, with patients treated continuously with relacorilant in GRACE and the OLE seeing benefits throughout their time on study

Figure 5. Mean Change From Baseline in Body Weight



BL, baseline; M, month; OL, open-label; OLE, open-label extension; RW, randomized withdrawal; W, week. Error bars: 95% CI.

Figure 6. Mean Change From Baseline in HbA1c in Patients With Hyperglycemia at Baseline



BL, baseline; HbA1c, hemoglobin A1c; M, month; OL, open-label; OLE, open-label extension; RW, randomized withdrawal; W, week. Error bars: 95% CI.

Safety

- No clinically significant changes in ACTH and cortisol concentrations were observed in the OLE (change from baseline to OLE month 24 in relacorilant-treated pts: ACTH [*P*≥0.2]; serum cortisol [*P*≥0.2])
- Safety results for the full GRACE population (OL and RW) have been presented elsewhere[3,7]
  - For safety results involving a similar patient population to the OLE study, including patients from additional parent studies, see AACE MENA 2024 poster #P211

CONCLUSIONS

- As early as week 6 of treatment, relacorilant resulted in clinically and statistically significant improvement in blood pressure in patients with endogenous hypercortisolism and hypertension
- This early hypertension control with relacorilant was maintained throughout the GRACE OL and RW phases and long-term treatment through month 12 of the OLE
- In the GRACE OL phase, relacorilant treatment significantly improved the weight gain often observed in patients with endogenous hypercortisolism, and this trend continued in the OLE
- Relacorilant significantly reduced HbA1c during the GRACE OL phase, and this trend continued during the OLE study

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PRESENTER'S DISCLOSURES
Aleksandra Gilis-Januszewska has nothing to disclose.

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