Impact of Relacorilant on Blood Pressure and Antihypertensive Medication Burden in Patients With Hypercortisolism and Hypertension: Results From the GRACE Study

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Abstract 0097

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SUMMARY AND CONCLUSIONS

- In the GRACE study, participants who had endogenous hypercortisolism and hypertension with or without hyperglycemia were receiving multiple antihypertensive medications at baseline
- In participants with hypertension, rapid and sustained improvements in blood pressure were observed with relacorilant treatment during the open-label phase
- Blood pressure improvements were maintained with relacorilant during the randomized-withdrawal phase, whereas blood pressure deteriorations occurred in the placebo arm
- Relacorilant treatment also resulted in antihypertensive medication decreases/discontinuations for a proportion of participants with hypertension

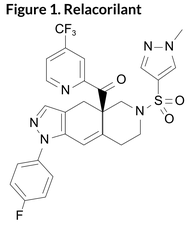
ABSTRACT

In the phase 3 GRACE study (NCT03697109) in adults with endogenous hypercortisolism and hypertension, hyperglycemia, or both, relacorilant significantly improved blood pressure (BP), meeting the primary endpoint. We report on the impact of relacorilant on BP and antihypertensive medication use among study participants with hypertension. GRACE comprised a 22-week, open-label (OL) phase of relacorilant 100–400 mg once daily followed by a 12-week, double-blind, placebo-controlled randomized-withdrawal phase. Hypertension was defined as mean systolic blood pressure (SBP) 135–170 mm Hg and/or diastolic blood pressure (DBP) 85–110 mm Hg. Among participants with hypertension at OL baseline (n=102), mean SBP and DBP were 141 and 89 mm Hg, respectively, and 76% (78/102) were taking ≥1 antihypertensive medication. The most common (≥15%) antihypertensive classes were calcium channel blockers (31%), angiotensin-converting enzyme (ACE) inhibitors (26%), angiotensin II receptor blockers (ARBs) (25%), beta blockers (22%), and aldosterone antagonists (20%). Relacorilant significantly improved BP from baseline to week 22 (P<0.0001), and 19% (15/78) of those taking antihypertensive medications discontinued and/or decreased use by week 22 or their early termination visit. Medication reductions were most common with aldosterone antagonists (10%) and ARBs (8%). Complete discontinuation was highest for loop diuretics (31%) and calcium channel blockers (19%), followed by aldosterone antagonists (10%), ACE inhibitors (7%), beta blockers (5%), and ARBs (4%). In summary, in GRACE, relacorilant improved BP and resulted in antihypertensive medication decreases/discontinuations for participants with hypertension.

BACKGROUND

- Relacorilant is an investigational selective glucocorticoid receptor (GR) modulator (**Figure 1**) designed to modulate excess cortisol activity at the GR to treat the manifestations of endogenous hypercortisolism (HC)[1,2]
  - Highly selective for the GR, with no activity at the progesterone, mineralocorticoid, or androgen receptors; structurally different from the nonselective GR antagonist mifepristone[1-3]
  - Avoids unwanted off-target progesterone receptor effects (eg, endometrial hypertrophy, vaginal bleeding)[3-6]
- Relacorilant has been shown to be effective in treating the signs and symptoms of endogenous hypercortisolism in individuals with hyperglycemia, hypertension, or both in a phase 2 and 2 phase 3 studies[3-6]
- An interim analysis of an ongoing open-label (OL) extension study showed that long-term use of relacorilant led to clinically significant and durable cardiometabolic improvements and was well tolerated in participants with hypercortisolism treated for 6+ years[6]
- The observed efficacy was seen without reported cases of relacorilant-induced hypokalemia, adrenal insufficiency, vaginal bleeding associated with endometrial hypertrophy, or QT interval prolongation

Figure 1. Relacorilant



OBJECTIVES

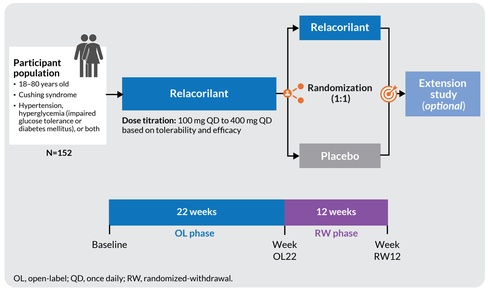
- To assess the impact of relacorilant on blood pressure (BP) and antihypertensive medication use among GRACE study participants with hypertension

METHODS

Study Design and Procedures

- The phase 3 GRACE study consisted of 2 parts (**Figure 2**):
  - A 22-week OL phase, in which adults aged 18–80 years with endogenous hypercortisolism and hypertension, hyperglycemia (impaired glucose tolerance or diabetes mellitus), or both received relacorilant 100–400 mg once daily based on tolerability and efficacy
  - A randomized-withdrawal (RW) phase, in which participants 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

Figure 2. GRACE Phase 3 Study



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

- Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by 24-hour ambulatory BP monitoring
- Hypertension was defined as mean SBP 135–170 mm Hg and/or mean DBP 85–110 mm Hg
- The Wilcoxon signed rank test was used for detecting significant changes in BP compared with baseline
- The data in Figure 3 and P-values in Figure 5 for the comparison between treatment arms are from a mixed model for repeated measures

RESULTS

Open-Label Phase

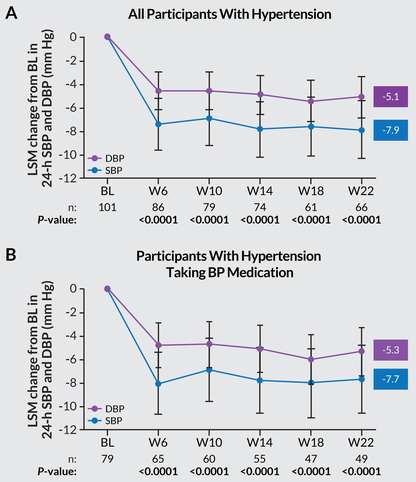
- During the OL phase, all patients received 100 and 200 mg of relacorilant, 89.2% received 300 mg, and 53.9% received 400 mg
- Among participants with hypertension at OL baseline (n=102), 76% (78/102) were taking ≥1 antihypertensive medication (**Table 1**)
  - Calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors were used by >25% of participants taking antihypertensives
- Relacorilant significantly improved BP from baseline to week 22 (P<0.0001) (**Figure 3**)

Table 1. Demographics and Characteristics for Participants With Hypertension: OL Baseline

	Participants (n=102)
Age, years, mean (SD)	48.6 (12.7)
Female, n (%)	85 (83.3)
Weight, kg, mean (SD)	95.1 (26.1)
BMI, kg/m^2, mean (SD)	34.7 (9.0)
Waist circumference, cm, mean (SD)	115.1 (19.5)
HbA1c, mean (%)	6.7 (1.6)
24-h SBP, mm Hg, mean (SD) [n]	140.6 (10.6) [101]
24-h DBP, mm Hg, mean (SD) [n]	88.9 (7.2) [101]
Most common concomitant antihypertensive medications, n (%)	
Calcium channel blockers	32 (31.4)
ACE inhibitors	27 (26.5)
ARBs	25 (24.5)
Beta blockers	22 (21.6)
Aldosterone antagonists	20 (19.6)
Loop diuretics	13 (12.7)
≥1 BP medication, n (%)	78 (76.5)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; OL, open-label; SBP, systolic blood pressure; SD, standard deviation.

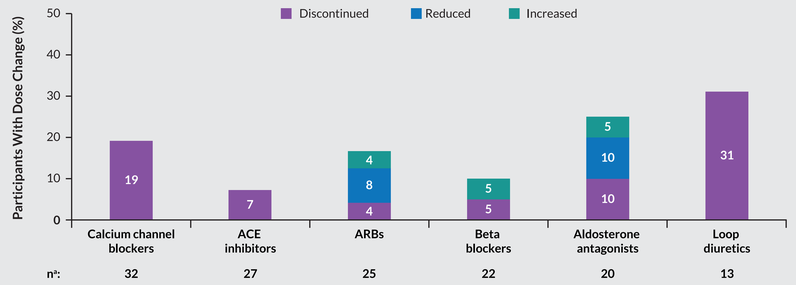
Figure 3. Changes in 24-Hour ABPM From Baseline With Relacorilant During the OL Phase Among A) All Participants With Hypertension and B) Those Taking Antihypertensives



Error bars: 95% confidence intervals.
ABPM, ambulatory blood pressure monitoring; BL, baseline; BP, blood pressure; DBP, diastolic blood pressure; LSM, least-squares mean; OL, open-label; SBP, systolic blood pressure; W, week.

- At last modification, 19% (15/78) of those taking antihypertensive medications discontinued use and/or had a dose reduction, whereas 9% (7/78) switched antihypertensive medication or had a dose increase
  - In the 7 participants for whom antihypertensive therapy was intensified, 1 switched medications, 1 had a new medication added, 3 switched medications and had a new medication added, and 2 had the dose of their current medication increased
- For the most common antihypertensive medication classes used at baseline, patterns of dose reduction, discontinuation, and dose increase are shown in **Figure 4**

Figure 4. Changes in Antihypertensive Medication Use/Dose in the OL Phase by Drug Class in Participants With Hypertension (n=102)



[a]Number of participants taking the medication at baseline.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; OL, open-label.

Randomized-Withdrawal Phase

- RW phase baseline characteristics for participants with hypertension are shown in **Table 2**

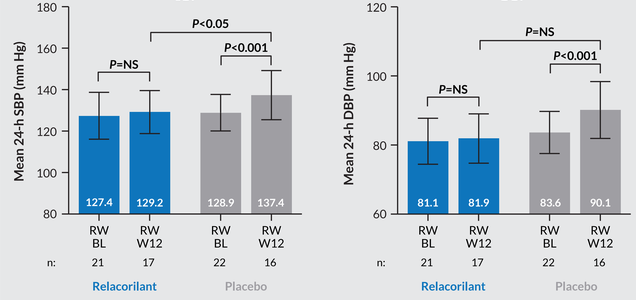
Table 2. Demographics and Characteristics for Participants With Hypertension: RW Baseline[a]

	Relacorilant (n=21)	Placebo (n=22)
Age, years, mean (SD)	46.1 (11.4)	49.0 (13.3)
Female, n (%)	15 (71.4)	20 (90.9)
Weight, kg, mean (SD)	93.7 (32.0)	85.0 (21.4)
BMI, kg/m^2, mean (SD)	32.5 (8.4)	31.6 (6.8)
Waist circumference, cm, mean (SD)	113.1 (20.5)	105.9 (16.7)
24-h SBP, mm Hg, mean (SD)	137.9 (11.0)	140.8 (10.6)
24-h DBP, mm Hg, mean (SD)	89.2 (7.0)	90.6 (5.5)

[a]Participants with hypertension with or without hyperglycemia who met the criteria for hypertension response in the open-label phase and who entered the RW phase.
BMI, body mass index; DBP, diastolic blood pressure; RW, randomized-withdrawal; SBP, systolic blood pressure; SD, standard deviation.

- Relacorilant resulted in significant improvements in BP, and the study's primary efficacy endpoint was met
  - In the placebo-controlled RW phase, participants with hypertension who continued to receive relacorilant were 5.9x more likely to maintain hypertension response (primary endpoint) compared with those who switched to placebo (odds ratio, 0.17; P=0.02)
- Compared with placebo, improvements in SBP and DBP with relacorilant in patients with hypertension were maintained during the RW phase (**Figure 5**)

Figure 5. Changes in 24-Hour ABPM During the RW Phase in Participants With Hypertension[a]



[a]Participants with hypertension with or without hyperglycemia who met the criteria for hypertension response in the open-label phase and who entered the RW phase.
Error bars: standard deviation.
ABPM, ambulatory blood pressure monitoring; BL, baseline; DBP, diastolic blood pressure; NS, not significant; RW, randomized-withdrawal; SBP, systolic blood pressure; W, week.

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Presenter Disclosures

Serge Jabbour reports: Consultant for Eli Lilly and Sanofi.