MON-696: RESULTS FROM GRACE, A PHASE 3 DOUBLE-BLIND, RANDOMIZED-WITHDRAWAL STUDY OF THE SELECTIVE GLUCOCORTICOID RECEPTOR MODULATOR RELACORILANT FOR THE TREATMENT OF ENDOGENOUS HYPERCORTISOLISM (CUSHING SYNDROME)

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Potential conflicts of interest exist. Refer to the Meeting App.

Summary & Conclusions

- Relacorilant, a selective glucocorticoid receptor (GR) modulator, was designed to decrease excess cortisol activity at the GR and improve the clinical signs and symptoms of endogenous Cushing syndrome (CS)
- GRACE was the largest prospective, interventional phase 3 study to date in patients with CS of all etiologies and uncontrolled hypertension and/or hyperglycemia
- Significant improvements in hypertension, hyperglycemia, and other manifestations of cortisol excess were observed in the open-label phase, along with a favorable safety profile
- GRACE met its primary endpoint of loss of hypertension control in the randomized-withdrawal phase (odds ratio 0.17 for relacorilant vs placebo; *P*=0.02)
- Due to relacorilant's unique mechanism of action in the corticotroph cells of the pituitary gland, the observed efficacy was seen without increases in cortisol concentrations and associated hypokalemia
  - No cases of drug-induced irregular vaginal bleeding associated with endometrial hyperplasia
  - No cases of independently confirmed QT prolongation
  - No adrenal insufficiency
- Consistent with its known safety profile, relacorilant was well-tolerated in both phases of GRACE
  - Adverse events were mostly mild-to-moderate in severity, and consistent with glucocorticoid withdrawal, which may occur with any treatment for CS
  - No differences in adverse events were observed in the randomized-withdrawal phase between relacorilant and placebo

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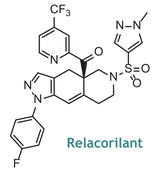
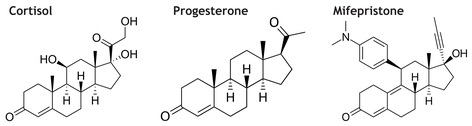
Relacorilant: In Development for the Treatment of Cushing Syndrome

- A selective glucocorticoid receptor modulator (SGRM)
  - Modulates cortisol activity by competing with cortisol for binding to the glucocorticoid receptor
- Highly selective: No activity at the progesterone, mineralocorticoid, or androgen receptors
  - Structurally different from mifepristone
  - Avoids unwanted progesterone receptor effects (eg, endometrial hypertrophy, vaginal bleeding)





- Unique downstream effects
  - No clinically significant impact on ACTH, resulting in no clinically significant rise in cortisol levels

ACTH, adrenocorticotropic hormone.

Patient Demographics & Baseline Characteristics

Mean (SD)	Hypertension only (n=31)	Hyperglycemia only (n=50)	Hypertension & hyperglycemia (n=71)	Overall (N=152)
Age, yrs	43.5 (11.6)	54.1 (13.7)	50.9 (12.6)	50.4 (13.2)
Female, n (%)	24 (77.4)	42 (84.0)	61 (85.9)	127 (83.6)
Weight, kg	95.2 (25.5)	91.1 (21.4)	95.0 (26.6)	93.8 (24.7)
BMI, kg/m^2	33.4 (7.5)	34.8 (7.9)	35.3 (9.6)	34.7 (8.6)
Waist circumference, cm	112.8 (17.4)	114.4 (14.7)	116.1 (20.4)	114.9 (18.0)
ACTH dependent, n (%)	23 (74.2)	39 (78.0)	56 (78.9)	118 (77.6)
Plasma ACTH, pg/mL	67.7 (34.0) (n=23)	74.9 (85.0) (n=39)	78.1 (69.9) (n=56)	74.9 (69.8) (n=118)
24-h UFC, µg/d	191.2 (221.8) (n=18)	148.0 (136.3) (n=26)	257.9 (407.1) (n=39)	209.0 (308.3) (n=83)
ACTH independent, n (%)	8 (25.8)	11 (22.0)	15 (21.1)	34 (22.4)
Plasma ACTH, pg/mL	7.3 (4.8) (n=8)	20.0 (26.6) (n=11)	10.0 (6.2) (n=15)	12.7 (16.2) (n=34)
24-h UFC, µg/d	108.3 (88.9) (n=6)	68.7 (67.9) (n=7)	61.3 (30.5) (n=8)	77.2 (64.0) (n=21)
Mean 24-h SBP, mm Hg	138.1 (9.4) (n=30)	124.6 (9.0) (n=47)	141.6 (11.0) (n=71)	135.5 (12.6) (n=148)
Mean 24-h DBP, mm Hg	90.8 (5.7) (n=30)	76.0 (7.3) (n=47)	88.1 (7.6) (n=71)	84.8 (9.4) (n=148)
HbA1c, %	5.4 (0.5)	7.1 (1.6)	7.2 (1.6)	6.8 (1.6)

Comorbidities at baseline shown. BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; SD, standard deviation; UFC, urinary free cortisol. Normal ranges: ACTH, 0–45.3 pg/mL; UFC, ≤45 µg/d (women), ≤60 µg/d (men).

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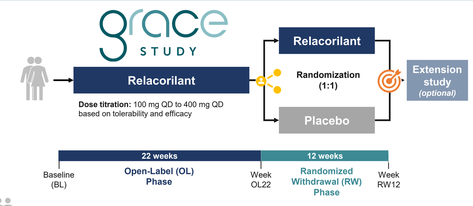
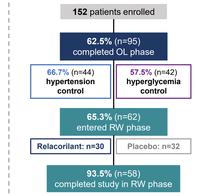
The GRACE Phase 3 Study of Relacorilant (NCT03697109)





Patient population

- 18–80 years
- Cushing syndrome
- Hypertension, hyperglycemia (impaired glucose tolerance or diabetes mellitus), or both

Endpoints

- **Primary:** Loss of hypertension control (at visit RW12), safety
- **Secondary & exploratory:** Control of hyperglycemia and other cortisol-related comorbidities

Eligibility for randomization

Those who completed the open-label phase and met response criteria at visit OL22:

Hypertension control (in patients with hypertension)
≥5 mm Hg decrease in mean SBP and/or DBP, without worsening of either (by 24-h ABPM)

Hyperglycemia control (in patients with hyperglycemia)
Impaired glucose tolerance: 2-h oGTT glucose normalized (<140 mg/dL)

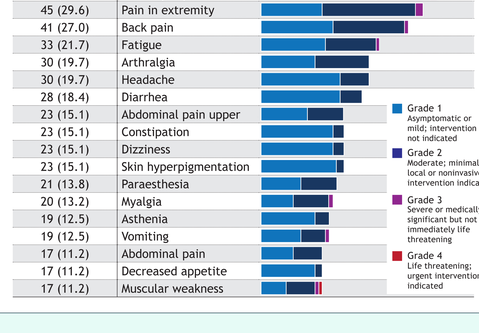
Diabetes: HbA1c decreased by ≥0.5%, AND/OR 2-h oGTT glucose normalized or decreased by ≥50 mg/dL, AND/OR total daily insulin dose decreased ≥25% and HbA1c unchanged/decreased

ABPM, ambulatory blood pressure monitoring; oGTT, oral glucose tolerance test; OL, open label; RW, randomized withdrawal.

Open-label Results: Favorable Safety Profile

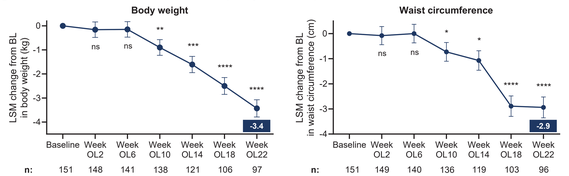
- The majority of adverse events were mild to moderate in severity
- No new safety concerns were identified
- The frequency of serious adverse events was low with no dose-dependent pattern
- Due to relacorilant's unique mechanism of action, the observed efficacy was seen without increases in cortisol concentrations and relacorilant-induced hypokalemia
- In addition, no cases of relacorilant-induced irregular vaginal bleeding with endometrial hypertrophy were seen, nor were there any instances of adrenal insufficiency or independently-confirmed QT prolongation

Treatment-emergent adverse events occurring in ≥10% of patients.



Open-label Results: Improvements in Other Symptoms of Cushing Syndrome

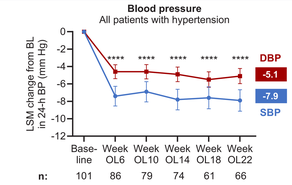
Body weight and waist circumference (all patients)

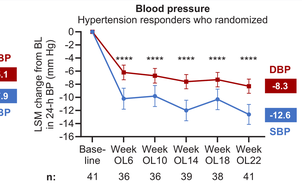


Mean (SD)	Baseline	Visit OL22	Change from BL to OL22	*P*-value
Fat mass by DXA, %	46.4 ± 8.4; n=131	43.9 ± 7.6; n=76	−1.8 ± 2.7; n=71	<0.0001
Lean mass by DXA, %	53.6 ± 8.4; n=131	56.1 ± 7.6; n=76	+1.8 ± 2.7; n=71	<0.0001
Sit-to-stand test, total time, sec	16.4 ± 11.5; n=141	14.1 ± 9.0; n=89	−1.5 ± 10.5; n=85	0.0032
Cushing QoL (normalized total score)	41.9 ± 19.8; n=151	49.7 ± 21.1; n=99	+7.4 ± 14.6; n=99	<0.0001
Trail-making test				
Part A: Total time to complete, sec	41.9 ± 19.8; n=147	31.8 ± 15.9; n=95	−9.8 ± 13.0; n=94	<0.0001
Part B: Total time to complete, sec	102.7 ± 59.9; n=146	73.3 ± 38.6; n=95	−27.6 ± 39.7; n=93	<0.0001

BL, baseline; DXA, dual energy X-ray absorptiometry; LSM, least-mean square; QoL, quality of life; SE, standard error. Error bars: SE of the mean. LSM and SE calculated using a linear MMRM. Wilcoxon rank sum test *P*-values for the mean change from BL shown. ns, not significant (*P*≥0.05); *, *P*<0.05; **, *P*<0.01; ***, *P*<0.001; ****, *P*≤0.0001. Cushing QoL range: 0–100.

Open-label Results: Rapid & Sustained Improvements in Systolic & Diastolic Blood Pressure





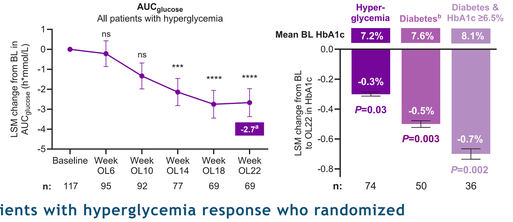
- Statistically significant and clinically meaningful reductions in blood pressure were seen from week 6
- In those who met hypertension response criteria and entered the randomized-withdrawal phase, blood pressure improvements were even greater
- Among the 78 patients who received anti-hypertensive medications during the open-label phase, 17 (21.8%) had their anti-hypertensive medications discontinued or decreased by week OL22

BL, baseline; LSM, least-squares mean; MMRM, mixed model for repeated measures; SE, standard error. Blood pressure measured by ABPM. Error bars: SE of the mean. LSM and SE calculated using a linear MMRM. Wilcoxon rank sum test *P*-values for the mean change from BL shown. ****, *P*<0.0001.

Open-label Results: Improvements in Hyperglycemia Across Several Glycemic Measures

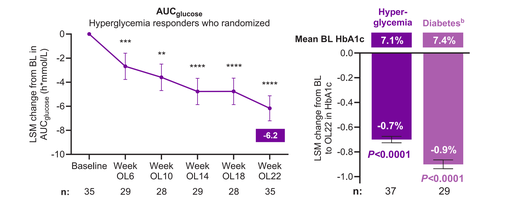
Patients with hyperglycemia

- $AUC_{glucose}$, HbA1c, and oGTT glucose significantly reduced
  - Greater HbA1c reductions were observed in those with higher baseline HbA1c
  - Fasting plasma glucose and 2-h oGTT glucose were also significantly reduced from BL to visit OL22 (mean [SD])
    - » Patients with hyperglycemia: −12.4 (45.2) mg/dL (*P*=0.03) and −38.1 (83.4) mg/dL (*P*=0.0002)
    - » Patients with diabetes: −17.7 (53.6) mg/dL (*P*=0.04) and −51.1 (91.0) mg/dL (*P*<0.0001)



Patients with hyperglycemia response who randomized

- Greater improvements were observed in those who met hyperglycemia response criteria and entered the randomized withdrawal phase
  - In responders with baseline hyperglycemia, mean (SD) fasting plasma glucose dropped by −25.2 (54.0) mg/dL (*P*=0.006) and 2-h oGTT glucose by −85.0 (73.7) mg/dL (*P*<0.0001)



[a]Mean change in $AUC_{glucose}$: −3.3 h*mmol/L. [b]Diabetes defined as fasting plasma glucose ≥126 mg/dL, 2-h oGTT plasma glucose ≥200 mg/dL, or HbA1c ≥6.5%). $AUC_{glucose}$, glucose area under the curve; BL, baseline; HbA1c, hemoglobin A1c; LSM, least-squares mean; oGTT, oral glucose tolerance test; SD, standard deviation; SE, standard error. Error bars: SE of the mean. LSM and SE calculated using a linear MMRM. Wilcoxon rank sum test *P*-values for the mean change from BL shown. ns, not significant (*P*≥0.05); **, *P*<0.01; ***, *P*<0.001; ****, *P*≤0.0001.

Primary Endpoint Met: Loss of Hypertension Control

- In the randomized-withdrawal phase, significantly more patients who switched to placebo lost hypertension control compared to those who continued to receive relacorilant (odds ratio 0.17 for relacorilant vs placebo, *P*=0.02; intent-to-treat population)
  - Patients receiving relacorilant were 5.9× more likely to maintain hypertension response achieved during the open-label phase compared to patients receiving placebo
  - Sensitivity analyses in the modified intent-to-treat and per-protocol populations confirmed the significant difference between relacorilant and placebo (odds ratios 0.18 and 0.17, both *P*=0.03)
- No clinically meaningful differences in adverse events observed between the relacorilant and placebo arms