Medical Treatment of Hypercortisolism with Relacorilant: Final Results of the Phase 3 GRACE Study

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SUMMARY & CONCLUSIONS

- Relacorilant is a selective glucocorticoid receptor (GR) modulator in development for the treatment of endogenous hypercortisolism
- GRACE was a phase 3, randomized-withdrawal (RW) study assessing the efficacy and safety of relacorilant in patients with hypercortisolism and hypertension and/or hyperglycemia (diabetes/impaired glucose tolerance [IGT])
- Significant improvements in hypertension, hyperglycemia, and other manifestations of cortisol excess were observed throughout the treatment with relacorilant
- Due to relacorilant's specificity for the GR and its unique mechanism of action, the observed efficacy was seen:
  - Without cases of relacorilant-induced irregular vaginal bleeding with endometrial hypertrophy
  - Without increases in cortisol concentrations and relacorilant-induced hypokalemia
  - Without reported cases of adrenal insufficiency
  - Without independently confirmed QT prolongation

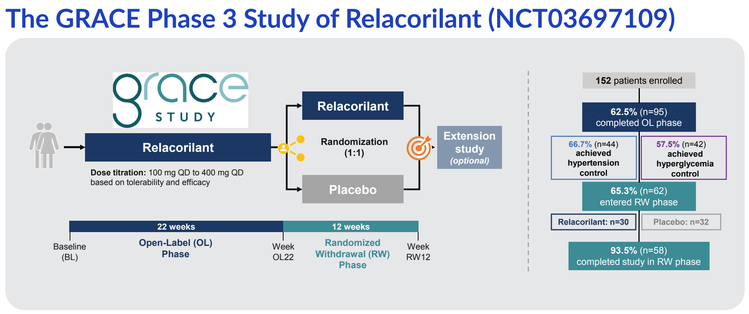
INTRODUCTION

Relacorilant: In Development for the Treatment of Cushing Syndrome

- A selective glucocorticoid receptor modulator (SGRM)
  - Decreases excess cortisol activity by competing with cortisol for binding to the GR
- 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 adrenocorticotropic hormone (ACTH) levels, resulting in no clinically significant rise in cortisol levels

METHODS

The GRACE Phase 3 Study of Relacorilant (NCT03697109)



- **Patient population**
  - 18—80 years of age
  - Cushing syndrome
  - Hypertension, hyperglycemia (IGT or diabetes mellitus [DM]), 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
  - Patients with hypertension and hyperglycemia who do not meet response criteria for both must meet the respective response criteria without worsening of the other comorbidity
- Hypertension control (in patients with hypertension) defined as:
  - ≥5 mm Hg decrease in mean systolic blood pressure (SBP) and/or diastolic blood pressure (DBP), without worsening of either (by 24-h ambulatory blood pressure monitoring [ABPM])
- Hyperglycemia control **defined as:**
  - Patients with IGT:
    - 2-h oral glucose tolerance test (oGTT) glucose normalized (<140 mg/dL)
  - Patients with diabetes (at least one of):
    - HbA1c decrease by ≥0.5%
    - 2-h oGTT glucose normalization (<140 mg/dL) or decrease by ≥50 mg/dL, and/or
    - Total daily insulin dose decrease by ≥25% and HbA1c unchanged or decreased

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Disclosures

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OPEN-LABEL RESULTS

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	219.5 (260.5) (n=23)	164.5 (162.1) (n=39)	231.1 (353.4) (n=56)	206.8 (284.5) (n=118)
ACTH independent, n (%)	8 (25.8)	11 (22.0)	15 (21.1)	34 (22.4)
Plasma ACTH[a], 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	98.0 (81.2) (n=8)	84.4 (73.7) (n=11)	96.2 (156.8) (n=15)	92.8 (116.3) (n=34)
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)

Data updated based on database lock; analysis date 5 July 2024. [a]Median ACTH was <5 pg/mL (hypertension only); 9 pg/mL (hyperglycemia only, hypertension and hyperglycemia, and overall). ACTH, adrenocorticotropic hormone; BMI, body mass index; DBP, diastolic blood pressure; OL, open-label phase; SBP, systolic blood pressure; SD, standard deviation; UFC, urinary free cortisol.

Favorable Safety Profile

- The majority of adverse events (AEs) were mild to moderate in severity
- No new safety signals were identified
- The frequency of serious adverse events was low with no dose-dependent pattern
- Due to relacorilant's specificity for the GR and its unique mechanism of action, the observed efficacy was seen:
  - Without cases of relacorilant-induced irregular vaginal bleeding with endometrial hypertrophy
  - Without increases in cortisol concentrations and relacorilant-induced hypokalemia
  - Without reported cases of adrenal insufficiency
  - Without independently confirmed QT prolongation

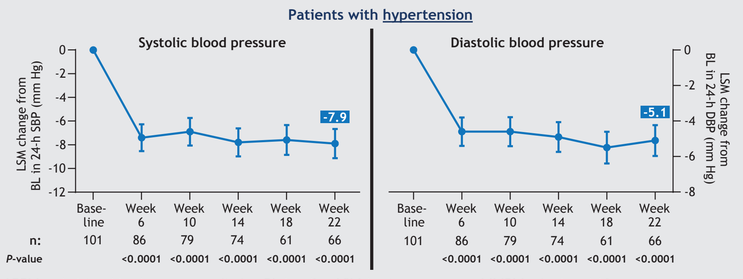
Adverse events occurring in ≥10% of patients

Adverse event, n (%)	Relacorilant (n=152)	Adverse event incidence rate (%) 0 5% 10% 15% 20% 25% 30% 35%
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)	
Paresthesia	21 (13.8)	
Myalgia	21 (13.8)	
Asthenia	19 (12.5)	
Vomiting	19 (12.5)	
Abdominal pain	17 (11.2)	
Decreased appetite	17 (11.2)	
Muscular weakness	17 (11.2)	

Grade 1 Asymptomatic or mild; intervention not indicated
Grade 2 Moderate; minimal, local or noninvasive intervention indicated
Grade 3 Severe or medically significant but not immediately life threatening

Data updated based on database lock; analysis date 5 July 2024. TEAEs and CTCAE grade shown. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; OL, open label; TEAE, treatment-emergent adverse event.

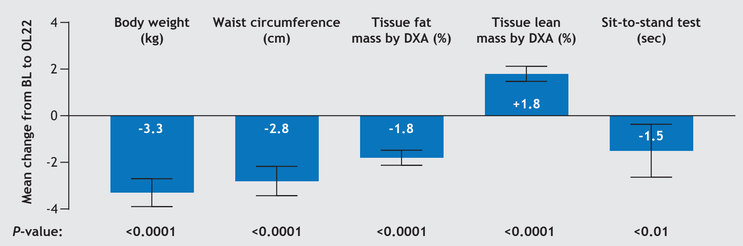
Rapid & Sustained Improvements in Systolic & Diastolic Blood Pressure With Relacorilant



ABPM, ambulatory blood pressure monitoring; 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.

Improvements in Other Symptoms of Cushing Syndrome

Significant improvements in body composition with relacorilant



BL, baseline; DXA, dual energy X-ray absorptiometry; OL, open label; QOL, quality of life. Error bars: Standard deviation. Wilcoxin rank sum test P-values for the mean change from baseline shown.

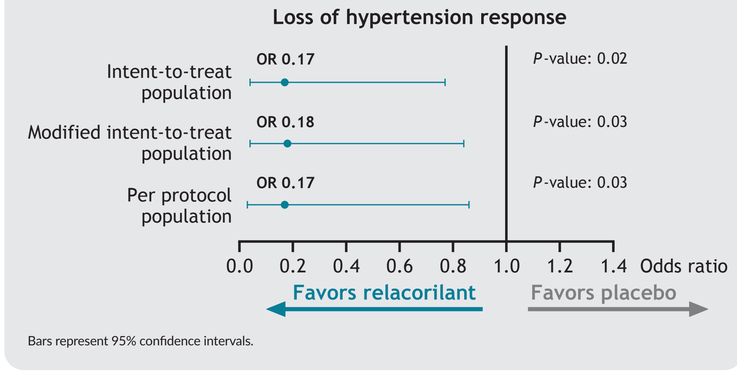
Rapid & Sustained Improvements in Hyperglycemia With Relacorilant

- Among patients with hyperglycemia, significant least-squares mean (LSM) changes in glucose area under the curve ($AUC_{glucose}$) occurred from baseline to visit OL14 (-2.1 h*mmol/L; *P*=0.002; n=77), OL18 (-2.7 h*mmol/L; *P*=0.0001; n=69) and OL22 (-2.7 h*mmol/L; *P*=0.0002; n=69)
- Greater improvement in glucose parameters occurred with relacorilant in hyperglycemia responders from baseline to visit OL22:
  - LSM change in HbA1c was -0.7% (*P*<0.0001; n=37) for patients with IGT/DM and -0.9% (*P*<0.0001; n=29) for patients with DM
  - LSM change in fasting plasma glucose (FPG) was -25.2 mg/dL (*P*=0.006; n=37) for patients with IGT/DM and -30.2 mg/dL (*P*=0.01; n=29) for patients with DM
  - LSM change in 2-h oGTT was -85.0 mg/dL (*P*<0.0001; n=37) for patients with IGT/DM and -88.8 mg/dL (*P*<0.0001; n=29) for patients with DM

RANDOMIZED WITHDRAWAL RESULTS

Primary Endpoint Met: Hypertension

- In the randomized-withdrawal phase, significantly more patients receiving placebo lost hypertension control than those who continued to receive relacorilant
  - Odds ratio 0.17 for relacorilant vs placebo (*P*=0.02)
  - Patients receiving relacorilant were 5.9× more likely to maintain hypertension response



Bars represent 95% confidence intervals.

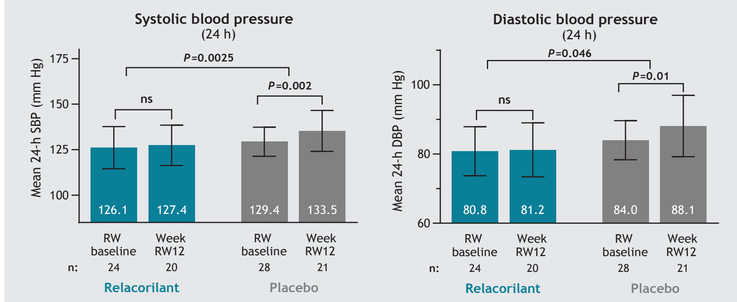
Patient demographics and characteristics entering randomized-withdrawal period

Mean (SD)	Relacorilant (n=30)	Placebo (n=32)
Age, yrs	46.6 (11.0)	48.8 (14.4)
Female, n (%)	22 (73.3)	26 (81.3)
Weight, kg	93.3 (27.4)	88.6 (21.1)
BMI, kg/m^2	33.3 (7.6)	32.6 (6.5)
Waist circumference, cm	113.8 (17.7)	108.9 (17.1)
ACTH dependent, n (%)	26 (86.7)	23 (71.9)
Plasma ACTH, pg/mL 24-h UFC, µg/d	91.7 (85.7) 257.1 (449.1)	71.7 (74.7) 301.3 (287.9)
ACTH independent, n (%)	4 (13.3)	9 (28.1)
Plasma ACTH, pg/mL 24-h UFC, µg/d	5.9 (2.3) 66.9 (36.8)	10.0 (9.0) 142.2 (194.1)

ACTH, adrenocorticotropic hormone; BMI, body mass index; SD, standard deviation; UFC, urinary free cortisol.

Improvements in Blood Pressure, Glycemic Measures, and Body Composition Maintained With Relacorilant

Blood pressure: All patients with available ABPM data



ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; ns, not significant (P≥0.05); RW, randomized withdrawal; SBP, systolic blood pressure. Blood pressure measured by ABPM. Error bars: Standard deviation. Wilcoxon rank sum test *P*-values for the observed mean within each treatment arm shown.

Glycemic measures

	Relacorilant (n=30)	Placebo (n=32)
Change from RW baseline to week RW12 in:		
$AUC_{glucose}$ (in patients with hyperglycemia at study entry), h*mmol/L		
n	15	19
Mean (SD)	+1.1 (4.7)	+4.9 (6.1)
Wilcoxon signed rank sum *P*-value[a]	ns	**0.0003**
HbA1c (in patients with hyperglycemia at study entry), %		
n	16	19
Mean (SD)	+0.1 (0.8)	+0.3 (0.6)
Wilcoxon signed rank sum *P*-value[a]	ns	**0.03**
HbA1c (in patients with diabetes at study entry), %		
n	13	13
Mean (SD)	+0.1 (0.8)	+0.4 (0.6)
Wilcoxon signed rank sum *P*-value[a]	ns	**0.04**

$AUC_{glucose}$, glucose area under the curve; HbA1c, hemoglobin A1c; ns, not significant (P≥0.05); RW, randomized withdrawal. Wilcoxon rank sum test *P*-values for the observed mean within each treatment arm shown. [a]Wilcoxon signed-rank test P-values within each treatment arm.

- At the end of the RW phase, patients who switched to placebo experienced significant increases in $AUC_{glucose}$ and HbA1c
- In contrast, glycemic measures were maintained in patients who continued to receive relacorilant

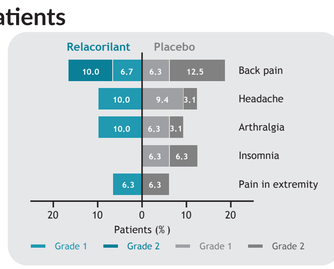
Body composition

- Similar trends observed across measures of body composition (body weight, waist circumference, tissue fat mass, tissue lean mass)
  - Those who switched to placebo experienced a deterioration in body composition
  - In contrast, trends toward further improvement were observed in the relacorilant arm

Favorable Safety Profile

Adverse events occurring in ≥5% of patients

n (%)	Relacorilant (n=30)	Placebo (n=32)
Back pain	5 (16.7)	6 (18.8)
Headache	3 (10.0)	4 (12.5)
Arthralgia	3 (10.0)	3 (9.4)
Insomnia	0	4 (12.5)
Pain in extremity	2 (6.7)	2 (6.3)



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