Efficacy and Safety of Relacorilant in Patients With Adrenal Hypercortisolism: Results From a Phase 3 Study

Amir H. Hamrahian,[1] Carmen Aresta,[2] Corin Badiu,[3] Irina Bancos,[4] Ulrich Dischinger,[5] Aleksandra Gilis-Januszewska,[6] Miguel Ángel Mangas Cruz,[7] John C. Parker,[8] Rosario Pivonello,[9] Aurelian-Emil Ranetti,[10] Sergio Rovner,[11] Francisco José Tinahones Madueño,[12] Gadi Shlomai,[13] Austin L. Hand,[14] Andreas G. Moraitis[14]

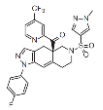
[1]Division of Endocrinology, Diabetes and Metabolism, Johns Hopkins University, Baltimore, MD, USA; [2]Istituto Auxologico Italiano, IRCCS, Milan, Italy; [3]"Carol Davila" University of Medicine and Pharmacy and National Institute of Endocrinology, Bucharest, Romania; [4]Division of Endocrinology and Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA; [5]Department of Internal Medicine, Division of Endocrinology and Diabetes, University Hospital of Würzburg, Würzburg, Germany; [6]Chair and Department of Endocrinology, Jagiellonian University, Medical College, Kraków, Poland; [7]Hospital Universitario Virgen del Rocio, Sevilla, Spain; [8]Accellacare Clinical Research, Wilmington Health Endocrinology, Wilmington, NC, USA; [9]Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Diabetologia, Andrologia e Nutrizione Università Federico II di Napoli, Naples, Italy; [10]Central Military University Emergency Hospital "Carol Davila," Bucharest, Romania; [11]Frontier Medical Center, El Paso, TX, USA; [12]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [13]Institute of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Tel Aviv Faculty of Medicine, Ramat Gan, Israel; [14]Corcept Therapeutics Incorporated, Redwood City, CA, USA

Contact: Andreas G. Moraitis (amoraitis@corcept.com)

INTRODUCTION

- Relacorilant is a selective glucocorticoid receptor (GR) modulator in development for the treatment of all types of endogenous hypercortisolism (**Figure 1**)
  - Competes with cortisol for binding to the GR to modulate cortisol activity[1-3]
  - Highly selective for the GR, with no affinity for the progesterone receptor (PR) or other steroid hormone receptors[1]
- Relacorilant has similar effects at the GR as the nonselective GR antagonist mifepristone but without the PR-associated off-target effects (eg, endometrial hypertrophy and vaginal bleeding)[1-5]
- Relacorilant also has no clinically significant impact on adrenocorticotropic hormone (ACTH) levels, resulting in no clinically significant increase in cortisol levels[5,6]
- In the phase 3 GRACE study (NCT03697109) in adults with endogenous hypercortisolism, relacorilant resulted in significant and sustained improvements in hypertension, meeting the study's primary endpoint.[3,7] Relacorilant was also well tolerated, with no new safety signals identified[3]
- Here, we report the results of the phase 3 GRADIENT study (NCT04308590) assessing the safety and efficacy of relacorilant in patients with adrenal hypercortisolism

Figure 1. Relacorilant



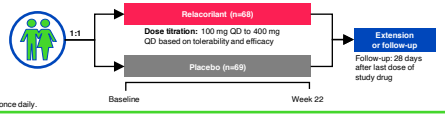
AIM

- GRADIENT assessed the safety and efficacy of relacorilant for the treatment of hypercortisolism in patients with cortisol-secreting adrenal adenomas or hyperplasia, with the primary objective of evaluating blood pressure control
- GRADIENT evaluated the impact of relacorilant on other cortisol excess-related comorbidities, including glycemic parameters and body composition

METHODS

- GRADIENT was a double-blind, placebo-controlled study in which individuals aged 18–80 years with cortisol-secreting adrenal adenoma(s) or hyperplasia and hyperglycemia, uncontrolled systolic hypertension, or both were randomized (1:1) to relacorilant or placebo for 22 weeks (**Figure 2**)
  - Patients had >1.8 µg/dL serum cortisol on either 1-mg overnight or 2-mg 48-hour dexamethasone suppression test (DST), suppressed or low (≤15 pg/mL) early-morning ACTH levels, and a radiologically confirmed benign adrenal lesion
  - Systolic hypertension was defined as blood pressure average of ≥130 to ≤170 mm Hg based on 24-hour ambulatory blood pressure monitoring (ABPM)
  - Hyperglycemia was defined as type 2 diabetes (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%) or impaired glucose tolerance (oGTT plasma glucose ≥140 mg/dL and <200 mg/dL at 2 hours)
- Relacorilant was titrated from 100 mg to 400 mg once daily based on tolerability and efficacy
- The primary endpoints were mean change from baseline to week 22 in 24-hour systolic blood pressure by ABPM for relacorilant versus placebo in patients with hypertension, as well as safety and tolerability
- Secondary and exploratory endpoints included changes in hyperglycemia and body weight/composition
- The Wilcoxon signed-rank test was used for detecting significant changes compared with baseline, and a linear mixed model for repeated measures was used to detect differences between placebo and relacorilant

Figure 2. GRADIENT Study Schema



QD, once daily.

RESULTS

Baseline Characteristics

- Baseline characteristics are shown in **Table 1**
- Of the 137 patients randomized to relacorilant or placebo, 41 patients (30%) had hypertension only, 53 patients (39%) had hyperglycemia only, and 43 patients (31%) had both

Table 1. Baseline Patient Characteristics

	Relacorilant (n=68)	Placebo (n=69)
Age, y, median (range)	63.5 (40–79)	64.0 (37–78)
Female, n (%)	50 (73.5)	49 (71.0)
Weight, kg, mean (SD)	89.6 (20.5)	85.9 (20.9)
BMI, kg/m², mean (SD)	33.0 (7.5)	32.3 (8.0)
Waist circumference, cm, mean (SD)	108.2 (16.0)	106.4 (14.8)
Plasma ACTH, pmol/L, median (range) [n]	2.0 (1–7) [67]	2.0 (1–8) [68]
24-hour UFC, µg/dL, median (range) [n]	20.4 (0.0–154.5) [65]	25.6 (0.4–178.7) [66]
LNSC, ng/dL, median (range) [n]	53.0 (50.0–30,500.0) [62]	50.0 (50.0–6,143.0) [64]
Hypertension with or without hyperglycemia, n (%)	42 (61.8)	42 (60.9)
SBP, mm Hg, mean (SD) [n][a]	138.8 (9.4) [41]	135.8 (11.2) [42]
DBP, mm Hg, mean (SD) [n][a]	82.3 (8.7) [41]	82.2 (8.2) [42]
Hyperglycemia[b] with or without hypertension, n (%)	48 (70.6)	48 (69.6)
HbA1c, %, mean (SD) [n]	6.5 (1.1) [45]	6.7 (1.2) [47]
2-hour plasma glucose, mg/dL, mean (SD) [n]	214.1 (103.1) [47]	215.0 (75.2) [46]
$AUC_{glucose}$, h*mmol/L, mean (SD) [n]	23.9 (8.6) [47]	25.0 (6.1) [46]

[a]Based on average 24-hour ambulatory blood pressure monitoring.
[b]Impaired glucose tolerance or type 2 diabetes.
ACTH, adrenocorticotropic hormone; $AUC_{glucose}$, glucose area under the curve; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; LNSC, late-night salivary cortisol; SBP, systolic blood pressure; SD, standard deviation; UFC, urinary free cortisol.

Blood Pressure

- In patients with hypertension, systolic blood pressure improved significantly from baseline to week 22 with relacorilant treatment but not with placebo (**Table 2**)
  - The difference between arms was not statistically significant

Table 2. Change in Systolic and Diastolic Blood Pressure[a] in Patients With Hypertension

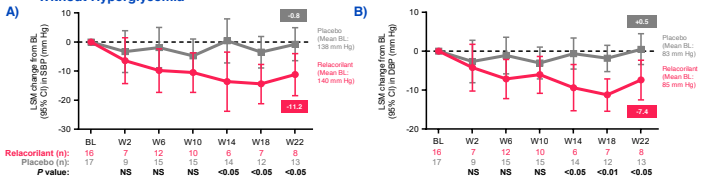
	Baseline, mean (SD)		Change from baseline to week 22, mean (SD)			Difference from placebo, LSM (SE)	
	Relacorilant (n=41)	Placebo (n=42)	Relacorilant (n=21)	Placebo (n=30)	*P*	Relacorilant	*P*
SBP, mm Hg	138.8 (9.4)	135.8 (11.2)	-6.6 (10.5)	-2.1 (12.7)	**0.012**	-2.67 (3.3)	**NS**
DBP, mm Hg	82.3 (8.7)	82.2 (8.2)	-4.1 (7.7)	-1.7 (7.2)	**NS**	-1.9 (1.8)	**NS**

[a]Based on average 24-hour ambulatory blood pressure monitoring.
DBP, diastolic blood pressure; LSM, least-squares mean; NS, not significant; SBP, systolic blood pressure; SD, standard deviation; SE, standard error.

- A subgroup analysis was conducted in study participants who had two abnormal tests: elevated late-night salivary cortisol or urinary free cortisol in addition to post-DST cortisol >1.8 µg/dL (relacorilant, n=26; placebo, n=27)
- Among individuals with hypertension with or without hyperglycemia in this subgroup (relacorilant, n=16; placebo, n=17):
  - Relacorilant, but not placebo, significantly decreased systolic blood pressure as measured by 24-hour ABPM from baseline to week 22 (*P*<0.05; **Figure 3**), with a significant least-squares mean (LSM) difference between arms of -10.4 (95% confidence interval [CI], -19.7 to -1.2; *P*<0.05)
    - The difference between relacorilant and placebo for diastolic blood pressure was also significant at week 22 (LSM, -7.9; 95% CI, -14.4 to -1.5; *P*<0.05)

Blood Pressure (continued)

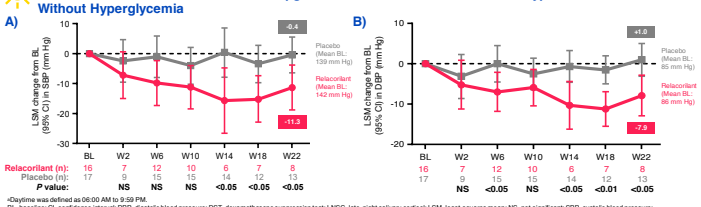
Figure 3. Change From Baseline to Week 22 in 24-h ABPM A) Systolic and B) Diastolic Blood Pressure in Patients With Post-DST Cortisol >1.8 µg/dL and Elevated LNSC or UFC and Hypertension With or Without Hyperglycemia



ABPM, ambulatory blood pressure monitoring; BL, baseline; CI, confidence interval; DBP, diastolic blood pressure; DST, dexamethasone suppression test; LNSC, late-night salivary cortisol; LSM, least-squares mean; NS, not significant; SBP, systolic blood pressure; UFC, urinary free cortisol; W, week.

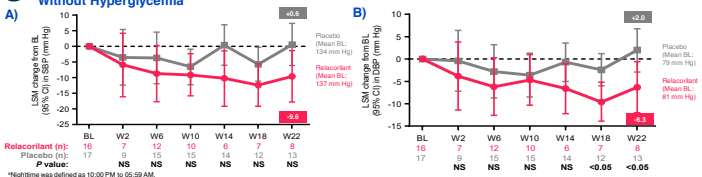
- Relacorilant resulted in significant decreases from baseline to week 22 in daytime systolic and diastolic blood pressure (**Figure 4**) and nighttime diastolic blood pressure (all *P*<0.05; **Figure 5**)
  - The LSM difference between relacorilant and placebo for daytime and nighttime systolic blood pressure at week 22 was -10.9 (95% CI, -20.6 to -1.2; *P*<0.05) and -10.2 (95% CI, -20.9 to 0.5; *P*=not significant), respectively
  - The LSM difference between the relacorilant and placebo arms for daytime and nighttime diastolic blood pressure at week 22 was -8.8 (95% CI, -15.4 to -2.3) and -8.2 (95% CI, -15.7 to -0.7), respectively (both *P*<0.05)

Figure 4. Change From Baseline to Week 22 in Daytime[a] A) Systolic and B) Diastolic Blood Pressure in Patients With Post-DST Cortisol >1.8 µg/dL and Elevated LNSC or UFC and Hypertension With or Without Hyperglycemia



[a]Daytime was defined as 06:00 AM to 9:59 PM.
BL, baseline; CI, confidence interval; DBP, diastolic blood pressure; DST, dexamethasone suppression test; LNSC, late-night salivary cortisol; LSM, least-squares mean; NS, not significant; SBP, systolic blood pressure; UFC, urinary free cortisol; W, week.

Figure 5. Change From Baseline to Week 22 in Nighttime[a] A) Systolic and B) Diastolic Blood Pressure in Patients With Post-DST Cortisol >1.8 µg/dL and Elevated LNSC or UFC and Hypertension With or Without Hyperglycemia



[a]Nighttime was defined as 10:00 PM to 05:59 AM.
BL, baseline; CI, confidence interval; DBP, diastolic blood pressure; DST, dexamethasone suppression test; LNSC, late-night salivary cortisol; LSM, least-squares mean; NS, not significant; SBP, systolic blood pressure; UFC, urinary free cortisol; W, week.

Glycemic Parameters

- Among patients with hyperglycemia with or without hypertension, fasting glucose, HbA1c, and glucose area under the curve improved from baseline to week 22 with relacorilant, with significant LSM differences at week 22 vs placebo for these parameters (all *P*<0.05; **Table 3**)

Table 3. Results for Glucose Metabolism Parameters From Baseline to Week 22 for Relacorilant Versus Placebo in Patients With Hyperglycemia With or Without Hypertension

	Relacorilant (n=48)	Placebo (n=48)
Fasting plasma glucose, mg/dL, mean (SD)		
Baseline	125.8 (68.8)	123.4 (38.7)
Week 22	102.1 (21.2)	124.1 (45.4)
Change from baseline to week 22, mean (SD)	-12.7 (24.5)	5.3 (30.2)
P value	**0.0026**	**NS**
LSM difference relacorilant vs placebo (SE)	-22.2 (6.9)	
P value	**0.0022**	
HbA1c, %, mean (SD)		
Baseline	6.5 (1.1)	6.7 (1.2)
Week 22	6.3 (0.7)	6.6 (0.9)
Change from baseline to week 22, mean (SD)	-0.2 (0.6)	0.1 (0.7)
P value	**NS**	**NS**
LSM difference relacorilant vs placebo (SE)	-0.3 (0.1)	
P value	**0.0188**	
$AUC_{glucose}$, h*mmol/L, mean, (SD)		
Baseline	23.9 (8.6)	25.0 (6.1)
Week 22	21.1 (6.2)	25.0 (7.4)
Change from baseline to week 22, mean (SD)	-1.3 (3.8)	0.9 (6.1)
P value	**0.0365**	**NS**
LSM difference relacorilant vs placebo (SE)	-2.6 (1.3)	
P value	**0.0459**	

$AUC_{glucose}$, glucose area under the curve; HbA1c, hemoglobin A1c; LSM, least-squares mean; NS, not significant; SD, standard deviation; SE, standard error.

Body Composition

- In the overall study population, relacorilant, but not placebo, resulted in significant weight loss (*P*<0.0001) and decreased visceral adipose fat mass and volume (both *P*=0.0001) from baseline to week 22 (**Table 4**)
  - Comparisons between relacorilant and placebo at week 22 were statistically significant for these parameters (all *P*<0.05)

Table 4. Results for Body Composition Parameters From Baseline to Week 22 for Relacorilant Versus Placebo in the Overall Study Population (ITT)

	Relacorilant (n=68)	Placebo (n=69)
Body weight, kg, mean, (SD)		
Baseline	89.6 (20.5)	85.9 (20.9)
Week 22	87.9 (22.8)	86.0 (21.0)
Change from baseline to week 22, mean (SD)	-3.6 (4.3)	-0.0 (3.4)
P value	**<0.0001**	**NS**
LSM difference relacorilant vs placebo (SE)	-3.9 (0.7)	
P value	**<0.0001**	
Visceral adipose tissue mass, g, mean (SD)		
Baseline	1,359.7 (726.4)	1,571.8 (981.8)
Week 22	1,242.3 (827.7)	1,579.0 (910.8)
Change from baseline to week 22, mean (SD)	-161.5 (182.3)	14.1 (256.0)
P value	**0.0001**	**NS**
LSM difference relacorilant vs placebo (SE)	-169.5 (68.8)	
P value	**0.0175**	
Visceral adipose tissue volume, mL, mean (SD)		
Baseline	1,452.9 (767.8)	1,674.8 (1,036.4)
Week 22	1,330.3 (877.6)	1,682.7 (961.6)
Change from baseline to week 22, mean (SD)	-173.3 (195.1)	15.3 (271.6)
P value	**0.0001**	**NS**
LSM difference relacorilant vs placebo (SE)	-182.3 (73.1)	
P value	**0.0163**	

ITT, intent to treat; LSM, least-squares mean; NS, not significant; SD, standard deviation; SE, standard error.

Safety and Tolerability

- 67 and 60 patients in the relacorilant and placebo groups, respectively, reported ≥1 treatment-emergent adverse event (TEAE), the majority of which were mild to moderate in severity
  - Nineteen (13.9%) patients (relacorilant, n=17; placebo, n=2) had TEAEs that resulted in withdrawal of study drug or premature withdrawal from the study
  - 1 death occurred during the study and was considered unrelated to relacorilant (acute myocardial infarction)
- Many of the most common TEAEs reported by patients treated with relacorilant (**Table 5**), including myalgia, fatigue, and abdominal discomfort, are consistent with cortisol withdrawal, which can occur in individuals with endogenous hypercortisolism after a rapid reduction in exposure to excess cortisol activity precipitated by surgery or medical therapy, particularly when individuals begin treatment[8]
- There were no reported cases of relacorilant-induced hypokalemia, adrenal insufficiency, vaginal bleeding associated with endometrial hypertrophy, or QT interval prolongation

Table 5. TEAEs Occurring in ≥10% of Patients

TEAE, n (%)	Relacorilant (n=68)	Placebo (n=69)
Back pain	21 (30.9)	9 (13.0)
Fatigue	16 (23.5)	10 (14.5)
Upper abdominal pain	14 (20.6)	3 (4.3)
Nausea	13 (19.1)	8 (11.6)
Pain in extremity	13 (19.1)	5 (7.2)
Abdominal pain	12 (17.6)	2 (2.9)
Dizziness	10 (14.7)	4 (5.8)
Diarrhea	9 (13.2)	6 (8.7)
Arthralgia	8 (11.8)	14 (20.3)
Asthenia	8 (11.8)	6 (8.7)
Headache	7 (10.3)	12 (17.4)

TEAE, treatment-emergent adverse event.

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CONCLUSIONS

- In GRADIENT, relacorilant led to clinically significant improvements in signs and symptoms of endogenous hypercortisolism, including improvements in blood pressure, hyperglycemia, and body weight/composition
  - Greater reductions in systolic blood pressure were observed with relacorilant treatment in the subgroup of patients with 2 abnormal cortisol tests
  - Relacorilant exhibited statistically significant improvements in hyperglycemia, weight loss, and decreased visceral adiposity in all patients
- Relacorilant was well tolerated, and many of the most common adverse events were consistent with cortisol withdrawal
- The safety profile of relacorilant was similar to that seen in previous trials in patients with endogenous hypercortisolism of all etiologies