A Comprehensive Safety Assessment of Relacorilant: Insights From Phase 2 and Phase 3 Trials in Patients With Endogenous Hypercortisolism

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BACKGROUND

- Relacorilant is a selective glucocorticoid receptor (GR) modulator in development for endogenous hypercortisolism (Cushing syndrome) treatment[1]
- Relacorilant is highly selective for the GR and modulates cortisol activity through competitive binding to the GR[1-3]
- Having no affinity for the progesterone receptor (PR) or other steroid hormone receptors, relacorilant has no off-target PR-related effects, such as endometrial hypertrophy and vaginal bleeding[1-5]
- The phase 3 GRACE study in adults with any type of endogenous hypercortisolism showed that relacorilant significantly improved hypertension, meeting its primary endpoint[1]
  - Patients treated with relacorilant also showed clinically and statistically significant improvements in other cardiometabolic manifestations of cortisol excess, such as hyperglycemia, weight, and body composition[1]
  - Relacorilant was well tolerated, and no new safety signals were identified in the study[1]

AIM

- To comprehensively characterize the safety profile of relacorilant by examining treatment-emergent adverse event (TEAE) data from phase 2 and 3 studies conducted in patients with endogenous hypercortisolism

METHODS

- An integrated safety analysis was conducted using data from 4 studies in patients with hypercortisolism treated with relacorilant:
  - A phase 2 single-arm, open-label, 12- to 16-week dose-finding study (NCT02804750)[5]
  - GRACE: a phase 3 study with a 22-week open-label relacorilant treatment phase followed by a double-blind, placebo-controlled, 12-week randomized-withdrawal phase (NCT03697109)[1]
  - GRADIENT: a phase 3, randomized, double-blind, placebo-controlled 22-week study (NCT04308590)[6]
  - An open-label extension (OLE) study (NCT03604198) that included patients from the above phase 2 and 3 studies[7]
- All studies evaluated relacorilant in adults aged 18–80 years with endogenous hypercortisolism and hypertension, hyperglycemia, or both[1,5-7]
- In all studies, patients were treated with relacorilant 100–400 mg once daily[1,5-7]
- TEAEs were defined as adverse events with onset after the first dose of study drug or existing events that worsened after the first dose during the study and up to 28 days after the last dose of study drug
- TEAEs were reported using Medical Dictionary for Regulatory Activities version 26.0
- Data were summarized using descriptive statistics

RESULTS

Patient Characteristics and Relacorilant Exposure

- Data were evaluated from a total of 324 patients (data cutoff date for the analysis: January 8, 2025)
- Patient characteristics at parent study and OLE baseline from the phase 2, GRACE, and GRADIENT studies are shown in **Table 1**
- Median (range) duration of exposure to relacorilant was 85 days (4–113) in the phase 2 study, 160 days (15–234) in the open-label portion of GRACE, and 150 days (9–397) in GRADIENT
  - In the OLE, median (range) duration of relacorilant exposure for patients enrolled from the GRACE and GRADIENT studies was 447 days (1–1,967) and 259 days (19–1,266), respectively

Table 1. Patient Characteristics and Demographics at Baseline: Parent Studies and OLE

	Phase 2 study		GRACE				GRADIENT		
				Randomized withdrawal					
	Parent study (N=35)	OLE (n=3)	Open label (N=152)	Relacorilant (n=30)	Placebo (n=32)	OLE (n=53)	Relacorilant (n=68)	Placebo (n=69)	OLE (n=69)
Age, y, mean (SD)	48.6 (13.4)	43.0 (20.1)	50.4 (13.2)	46.6 (11.0)	48.8 (14.4)	50.5 (12.5)	62.5 (9.1)	63.0 (9.0)	61.3 (9.8)
Female, n (%)	25 (71.4)	3 (100)	127 (83.6)	22 (73.3)	26 (81.3)	43 (81.1)	50 (73.5)	49 (71.0)	51 (73.9)
Weight, kg, mean (SD)	96.9 (27.5)	76.9 (19.9)	93.8 (24.7)	93.3 (27.4)	88.6 (21.1)	88.8 (22.1)	89.6 (20.5)	85.9 (20.9)	89.8 (23.8)
BMI, kg/m², mean (SD)	35.3 (9.7)	31.2 (7.2)	34.7 (8.6)	33.2 (7.6)	32.6 (6.5)	33.1 (7.8)	33.0 (7.5)[a]	32.3 (8.0)	33.2 (8.4)
Waist circumference, cm, mean (SD)	115.5 (20.9)	108.5 (19.1)	114.9 (18.0)	113.8 (17.7)	108.9 (17.1)	110.1 (17.8)	108.2 (16.0)	106.4 (14.8)	107.8 (17.6)
Ethnicity Hispanic, n (%)	3 (8.6)	1 (33.3)	28 (18.4)	5 (16.7)	5 (15.6)	10 (18.9)	4 (5.9)	6 (8.7)	2 (2.9)
Race, n (%)									
White	35 (100)	3 (100)	121 (79.6)	22 (73.3)	28 (87.5)	43 (81.1)	63 (92.6)	65 (94.2)	67 (97.1)
Black	0	0	18 (11.8)	3 (10.0)	4 (12.5)	4 (7.5)	3 (4.4)	1 (1.4)	0
Missing/Other	0	0	13 (8.6)	5 (16.7)	0	6 (11.3)	2 (2.9)	3 (4.3)	2 (2.9)
Endogenous hypercortisolism etiology, n (%)									
ACTH-dependent	28 (80.0)	2 (66.7)	118 (77.6)	26 (86.7)	23 (71.9)	40 (75.5)	0	0	0
ACTH-independent	7 (20.0)	1 (33.3)	34 (22.4)	4 (13.3)	9 (28.1)	13 (24.5)	68 (100)	69 (100)	69 (100)
Hypertension only, n (%)	7 (20.0)	1 (33.3)	31 (20.4)	11 (36.7)	10 (31.3)	15 (28.3)	20 (29.4)	21 (30.4)	21 (30.4)
Hyperglycemia only, n (%)	12 (34.3)	1 (33.3)	50 (32.9)	8 (26.7)	8 (25.0)	17 (32.1)	26 (38.2)	27 (39.1)	29 (42.0)
Hypertension and hyperglycemia, n (%)	16 (45.7)	1 (33.3)	71 (46.7)	11 (36.7)	14 (43.8)	21 (39.6)	22 (32.4)	21 (30.4)	19 (27.5)

[a]n=67.
ACTH, adrenocorticotropic hormone; BMI, body mass index; OLE, open-label extension; SD, standard deviation.

TEAEs

- Across all studies, most TEAEs were mild to moderate in severity and nonserious (**Tables 2-5**)
- When adjusted for the duration of exposure, the incidence of TEAEs did not increase with longer cumulative exposure to relacorilant
- TEAEs that led to permanent discontinuation of the study drug were mostly mild to moderate in severity, without apparent dose-dependent trends
  - Nausea, peripheral edema, and fatigue were among the TEAEs that led to discontinuation in ≥1 patient

Table 2. Summary of TEAEs[a] in the Phase 2, GRACE, GRADIENT, and OLE Studies

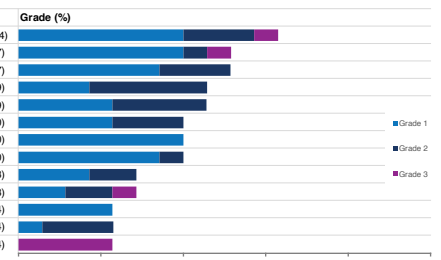
	Phase 2 study		GRACE				GRADIENT		
				Randomized withdrawal					
Category, n (%)	Relacorilant (N=35)	OLE (n=3)	Open label (N=152)	Relacorilant (n=30)	Placebo (n=32)	OLE (n=53)	Relacorilant (n=68)	Placebo (n=69)	OLE (n=69)
Patients reporting ≥1 TEAE	33 (94.3)	3 (100)	147 (96.7)	30 (100)	27 (84.4)	53 (100)	67 (98.5)	60 (87.0)	69 (100)
Patients reporting ≥1 TESAE	4 (11.4)	2 (66.7)	29 (19.1)	9 (30.0)	1 (3.1)	27 (50.9)	15 (22.1)	4 (5.8)	21 (30.4)
TEAE by CTCAE grade									
Grade 1 (mild)	8 (22.9)	0	22 (14.5)	3 (10.0)	12 (37.5)	3 (5.7)	7 (10.3)	23 (33.3)	12 (17.4)
Grade 2 (moderate)	15 (42.9)	1 (33.3)	88 (57.9)	15 (50.0)	13 (40.6)	21 (39.6)	43 (63.2)	31 (44.9)	31 (44.9)
Grade 3 (severe)	10 (28.6)	2 (66.7)	34 (22.4)	12 (40.0)	2 (6.3)	21 (39.6)	15 (22.1)	6 (8.7)	22 (31.9)
Grade 4 (life-threatening)	0	0	1 (0.7)	0	0	3 (5.7)	1 (1.5)	0	2 (2.9)
Grade 5 (fatal)	0	0	2 (1.3)	0	0	5 (9.4)	1 (1.5)	0	2 (2.9)
TEAEs related to study drug	27 (77.1)	3 (100)	133 (87.5)	28 (93.3)	16 (50.0)	52 (98.1)	56 (82.4)	32 (46.4)	57 (82.6)
TEAEs leading to study drug discontinuation	9 (25.7)	0	24 (15.8)	3 (10.0)	2 (6.3)	11 (20.8)	13 (19.1)	2 (2.9)	14 (20.3)
TEAEs requiring dose change[b]	8 (22.9)	2 (66.7)	81 (53.3)	22 (73.3)	1 (3.1)	37 (69.8)	45 (66.2)	10 (14.5)	51 (73.9)
Fatal TEAEs[c]	0	0	2 (1.3)	0	0	5 (9.4)	1 (1.5)	0	2 (2.9)

[a]Patients reporting >1 adverse event are counted only once using the highest CTCAE grade per dose level and using the closest relationship to study drug per dose level. [b]Includes dose reductions and dose interruptions. [c]Not related to relacorilant treatment.
CTCAE, Common Terminology Criteria for Adverse Events; OLE, open-label extension; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Table 3. TEAEs Occurring in ≥10% of Patients in the Phase 2 Study

Phase 2 study (N=35)

TEAE	n (%)	Grade (%)
Back pain	11 (31.4)	
Headache	9 (25.7)	
Peripheral edema	9 (25.7)	
Pain in extremity	8 (22.9)	
Nausea	8 (22.9)	
Arthralgia	7 (20.0)	
Diarrhea	7 (20.0)	
Dizziness	7 (20.0)	
Dyspepsia	5 (14.3)	
Myalgia	5 (14.3)	
Fatigue	4 (11.4)	
Abdominal pain	4 (11.4)	
Hypertension	4 (11.4)	

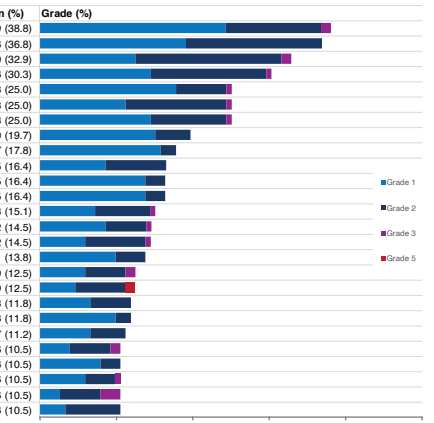


TEAE, treatment-emergent adverse event.

Table 4. TEAEs Occurring in ≥10% of Patients in the GRACE Study

GRACE (N=152)

TEAE	n (%)	Grade (%)
Peripheral edema	59 (38.8)	
Nausea	56 (36.8)	
Pain in extremity	50 (32.9)	
Back pain	46 (30.3)	
Headache	38 (25.0)	
Arthralgia	38 (25.0)	
Fatigue	38 (25.0)	
Diarrhea	30 (19.7)	
Skin hyperpigmentation	27 (17.8)	
Upper abdominal pain	25 (16.4)	
Constipation	25 (16.4)	
Dizziness	25 (16.4)	
Myalgia	23 (15.1)	
Vomiting	22 (14.5)	
Paresthesia	22 (14.5)	
Asthenia	21 (13.8)	
Muscular weakness	19 (12.5)	
COVID-19	19 (12.5)	
Abdominal pain	18 (11.8)	
Decreased appetite	18 (11.8)	
Peripheral swelling	17 (11.2)	
Peripheral neuropathy	16 (10.5)	
Acne	16 (10.5)	
Urinary tract infection	16 (10.5)	
Hypotension	16 (10.5)	
Insomnia	16 (10.5)	

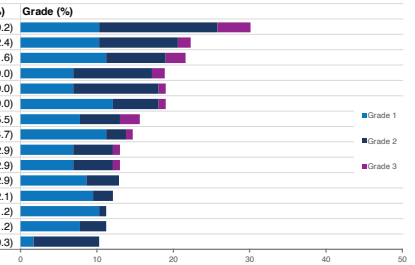


TEAE, treatment-emergent adverse event.

Table 5. TEAEs Occurring in ≥10% of Patients in the GRADIENT Study

GRADIENT (N=116[a])

TEAE	n (%)	Grade (%)
Back pain	35 (30.2)	
Pain in extremity	26 (22.4)	
Arthralgia	25 (21.6)	
Fatigue	22 (19.0)	
Upper abdominal pain	22 (19.0)	
Nausea	22 (19.0)	
Abdominal pain	18 (15.5)	
Dizziness	17 (14.7)	
Diarrhea	15 (12.9)	
Asthenia	15 (12.9)	
COVID-19	15 (12.9)	
Peripheral edema	14 (12.1)	
Headache	13 (11.2)	
Myalgia	13 (11.2)	
Peripheral neuropathy	12 (10.3)	



[a]Cumulative number of patients who ever received relacorilant during GRADIENT or the OLE, including patients who may have received placebo during GRADIENT. OLE, open-label extension; TEAE, treatment-emergent adverse event.

Additional Safety Data and TEAEs of Special Interest

- Across the 3 parent studies and the OLE, 77.1% to 100% of patients had ≥1 TEAE considered related to relacorilant
  - The most frequently reported TEAEs (≥20%) considered related to relacorilant included back pain, pain in extremity, nausea, diarrhea, and peripheral edema
- Across all studies, including the OLE, there were 10 fatal TEAEs: acute myocardial infarction/myocardial ischemia (3), COVID-19 (2), chronic cardiac failure, cardiac arrest, pneumonia, lung adenocarcinoma, and cellulitis gangrenous. The deaths occurred between study days 33 and 878
  - No patterns were detected across fatalities, and no deaths were considered related to relacorilant
- Most cases of peripheral neuropathy were mild to moderate in severity, did not result in treatment discontinuation, and were reported in patients who had underlying chronic hyperglycemia
  - 34.2% of patients in the GRACE open-label phase, 17.6% of patients treated with relacorilant in GRADIENT, and 5.7% of patients in the phase 2 study reported a peripheral neuropathy event
  - 28.3% of patients from GRACE and 33.3% of patients from GRADIENT reported a new peripheral neuropathy event in the OLE
- Hyperpigmentation was reported by 16.4% of patients in the GRACE open-label phase, 1.5% of patients treated with relacorilant in GRADIENT, and 5.7% of patients in the phase 2 study. Few events led to dose changes or treatment discontinuation
  - In GRACE, hyperpigmentation events were reported 2 to 3 times more frequently among non-White patients compared with White patients; however, the comparison is limited by the small numbers of non-White patients (Black patients, n=18; patients of other races, n=12)
- There were no cases of excessive GR antagonism or adrenal insufficiency, TEAEs associated with activity at the PR (ie, vaginal bleeding associated with endometrial hypertrophy), drug-induced hypokalemia, new onset or exacerbation of hypertension, or drug-induced QT interval prolongation
- No patients met Hy's law criteria for potential drug-induced liver injury

ACKNOWLEDGEMENTS

- The authors want to thank all those who are participating in these studies: The study patients and their families, the Investigators, and the Sponsor team
- This study is sponsored by Corcept Therapeutics Incorporated. Medical writing assistance was provided by Valerie Hilliard, PhD, CMPP of Corcept, and R&R Healthcare Communications

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CONCLUSIONS

- Relacorilant was well tolerated in patients with endogenous hypercortisolism and demonstrated an acceptable and consistent safety profile
  - Most TEAEs reported by patients treated with relacorilant were mild to moderate in severity, and the frequency of serious TEAEs was low
  - Consistent with its high selectivity for the GR, patients treated with relacorilant reported no TEAEs associated with other hormone receptors
  - There were no cases of excessive GR antagonism, adrenal insufficiency, or vaginal bleeding associated with endometrial hypertrophy
  - There were no cases of drug-induced hypokalemia, new onset or exacerbation of hypertension, or QT interval prolongation
  - No patients met Hy's law criteria for potential drug-induced liver injury
- Certain frequently reported TEAEs, such as musculoskeletal symptoms, abdominal pain, nausea, and fatigue, likely reflect glucocorticoid withdrawal, which occurs with any surgical or pharmacologic treatment for hypercortisolism, and can be indicative of clinical benefit[8]
  - These events often improved or resolved with continued treatment and did not worsen with dose escalation