Open-label Extension Study Evaluating the Safety and Efficacy of Long-term Use of Relacorilant in Patients With Endogenous Hypercortisolism (Cushing Syndrome): Interim Analysis Results

P-3

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Corin Badiu[1], Richard Auchus[2], Irina Bancos[3], Ulrich Dischinger[4], Amir H. Hamrahian[5], Alexandra Kautzky Willer[6], Miguel Angel Mangas-Cruz[7], Cary Mariash[8], John Parker[9], Rosario Pivonello[10], Aurelian Emil Ranetti[11], Gadi Shlomai[12], Jeffrey Botbyl[13], Andreas G. Moraitis[13], Katherine A. Araque[13]

[1]"Carol Davila" University of Medicine and Pharmacy and National Institute of Endocrinology, Bucharest, Romania. [2]University of Michigan, Ann Arbor, MI, USA. [3]Mayo Clinic, Rochester, MN, USA. [4]Hospital of Würzburg, Würzburg, Germany. [5]Johns Hopkins University, Baltimore, MD, USA. [6]Medizinische Universität Wien, Wien, Austria. [7]Hospital Universitario Virgen del Rocio, Sevilla, Spain. [8]Indiana University, Carmel, IN, USA. [9]Accellacare Clinical Research, Wilmington Health Endocrinology, Wilmington, NC, USA. [10]Università Federico II di Napoli, Naples, Italy. [11]Central Military University Emergency Hospital "Carol Davila", Bucharest, Romania. [12]Sheba Medical Center, Tel Aviv Faculty of Medicine, Ramat Gan, Israel. [13]Corcept Therapeutics Incorporated, Redwood City, CA, USA.

SUMMARY & CONCLUSIONS

- Relacorilant is a selective glucocorticoid receptor modulator in development for the treatment of endogenous hypercortisolism (Cushing syndrome [CS]) of all etiologies
- The presented ongoing open-label phase 2/3 extension study investigates the long-term safety and efficacy of relacorilant treatment in patients with endogenous CS
- This interim analysis provides support for the long-term tolerability and efficacy of relacorilant in patients with endogenous CS
- Relacorilant led to improvement and/or long-term maintenance of clinical and cardiometabolic benefit

INTRODUCTION

- Relacorilant (CORT125134) is a selective glucocorticoid receptor modulator in development for the treatment of endogenous hypercortisolism (Cushing syndrome [CS])
  - Relacorilant modulates cortisol activity by competing with cortisol for binding to the glucocorticoid receptor (GR)
  - It has similar antagonistic effects at the GR as the FDA-approved GR antagonist mifepristone but has no activity at the progesterone receptor or other steroid hormone receptors[1]
- Relacorilant's safety and efficacy in patients with CS of any etiology have been assessed in one phase 2 and two phase 3 studies[2–4]
  - The phase 3 GRACE study met its primary endpoint (loss of response with respect to hypertension: odds ratio [OR] 0.17 for relacorilant vs placebo, *P*=0.02)[3,4]
  - Patients receiving relacorilant were 5.9x more likely to maintain hypertension response than those who were switched to placebo
  - Due to relacorilant's specificity for the GR and its unique mechanism of action, the observed efficacy was seen[3,4]:
    - Without cases of relacorilant-induced irregular vaginal bleeding and endometrial hypertrophy
    - Without increases in cortisol concentration and relacorilant-induced hypokalemia
    - Without reported cases of adrenal insufficiency
    - Without QT prolongation (independently confirmed)

AIM

- Here, we present results from an interim analysis of the ongoing phase 2/3 extension study (NCT03604198), which aims to evaluate relacorilant's long-term safety and therapeutic effect

METHODS

- Patients are eligible to enter the single-arm open-label extension (OLE) if they completed a Corcept-sponsored parent study of relacorilant in patients with CS (NCT02804750, NCT03697109, NCT04308590) and, in the investigator's opinion, may benefit from treatment with relacorilant
- In some patients, relacorilant is discontinued during the transition period between parent study and OLE
  - For those entering the OLE from an open-label study, if roll-over occurs within 4 weeks, the OLE starting dose is the dose last received in the parent study
  - For all others, including those who completed a placebo-controlled parent study, the OLE starting dose is 100 mg daily titrated up to 400 mg daily based on tolerability
- Dose titration up or down during the OLE is allowed based on tolerability
- Safety, as well as changes in blood pressure (by ambulatory blood pressure monitoring [ABPM]), glucose parameters, and other cortisol-related comorbidities, are being assessed throughout the study
- Data cutoff date for the interim analysis: 8 April 2024

RESULTS

Patient Characteristics and Baseline Demographics

- 53 patients were enrolled in the OLE and received at least 1 dose of relacorilant
- Comorbidities were assessed at the beginning of the respective parent study
  - 17 (31.5%) had hypertension
  - 5 (9.3%) had hyperglycemia (impaired glucose tolerance [IGT] or type 2 diabetes mellitus [T2DM])
  - 31 (59.3%) had both hypertension and hyperglycemia
- The median duration of treatment at the time of the interim analysis was 53.1 weeks (range: 4.6–307.9)

Table 1.

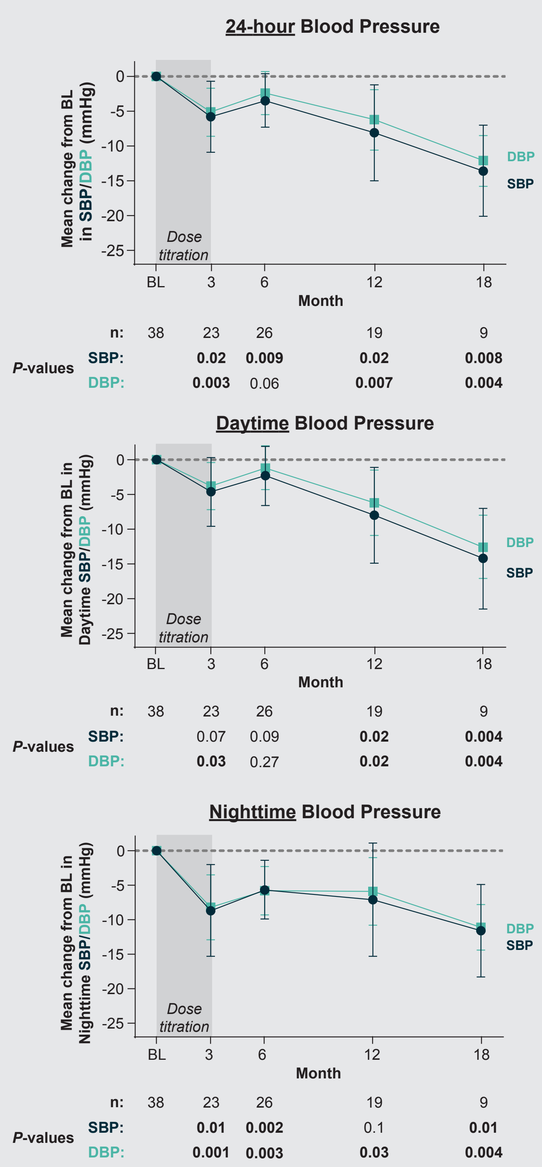
	Total (N=53)
Age (years), mean (SD)	50.4 (12.5)
Female, n (%)	44 (83.0)
Weight (kg), mean (SD)	85.5 (20.8)
Body mass index (kg/m²), mean (SD)	32.0 (6.4)
Waist circumference (cm), mean (SD)	108.6 (18.0)
HbA1c (%), mean (SD)	6.3 (1.7)
24-h SBP (mmHg), mean (SD)	134.8 (11.87)
24-h DBP (mmHg), mean (SD)	85.7 (8.50)
Etiology, n (%)	
ACTH-dependent (pituitary, ectopic)	39 (73.6)
ACTH-independent (adrenal)	14 (26.4)
Plasma ACTH (pg/mL), mean (SD)	
ACTH-dependent	109.9 (92.1)
ACTH-independent	12.7 (9.0)
24-h urinary-free cortisol (µg/day), mean (SD)	
ACTH-dependent	334.5 (869.2)
ACTH-independent	169.5 (229.4)
Late-night salivary cortisol (ng/dL), mean (SD)	
ACTH-dependent	423.3 (725.9)
ACTH-independent	292.5 (337.7)
Pituitary tumor size,[a] n (%)	
Not visible	11 (35.5)
Microadenoma	15 (48.4)
Macroadenoma	5 (16.1)

[a]In patients with Cushing Disease and evaluable MRI scans at baseline (n=31). Pituitary MRI scans were centrally read. ACTH, adrenocorticotropic hormone; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; SD, standard deviation.

Clinically and Statistically Significant Reductions in Blood Pressure

- In patients with hypertension with or without hyperglycemia (n=38), clinically and statistically significant reductions from baseline in mean 24-hour, daytime, and nighttime blood pressure were observed

Figure 1.



Error bars: 95% confidence intervals. *P*-values: Wilcoxon signed rank test to evaluate if there is a significant change from to BL at each time point. Daytime: 6am–10pm; nighttime: 10pm–6am.
BL, baseline; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Bone and cortisol activity markers

- Statistically significant increases from baseline in osteocalcin were observed, along with numerical increases in alkaline phosphatase and no worsening in bone mineral density by dual-energy X-ray absorptiometry (DXA)

Table 2.

	Baseline	Month 6	CFB to Month 6	Month 12	CFB to Month 12
Serum osteocalcin (ng/mL)	12.7 ± 6.5 (n=49)	15.5 ± 9.1 (n=36)	**+2.0 ± 4.3** (n=34)	14.8 ± 7.4 (n=30)	**+1.6 ± 5.7** (n=28)
Alkaline phosphatase (U/L)	82.2 ± 34.6 (n=50)	87.5 ± 36.1 (n=38)	+1.4 ± 19.8 (n=36)	93.2 ± 58.6 (n=30)	+5.9 ± 30.6 (n=29)

Mean ± standard deviation shown. Bold print indicates statistically significant change from baseline (*P*<0.05). CFB, change from baseline.

Table 3.

	Baseline (n=14)	Month 12 (n=7)	CFB to Month 12 (n=5)
T-score			
Total lumbar spine	-1.39 ± 1.27	-0.39 ± 1.37	+0.11 ± 0.56
Total hip	-0.85 ± 0.62	-0.39 ± 0.95	-0.18 ± 0.12
Femoral neck	-1.10 ± 0.67	-0.88 ± 0.71	-0.17 ± 0.23
Z-score			
Total lumbar spine	-0.79 ± 1.21	0.49 ± 1.30	+0.16 ± 0.60
Total hip	-0.36 ± 0.62	0.25 ± 0.91	-0.12 ± 0.13
Femoral neck	-0.36 ± 0.47	0.00 ± 0.61	-0.13 ± 0.24

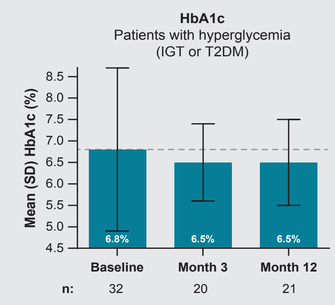
Mean ± standard deviation shown. CFB, change from baseline.

Improvement and/or Maintenance of Benefit in Other Cortisol-Related Comorbidities

Hyperglycemia

- Patients had well-controlled HbA1c at baseline because they rolled over from a parent study in which their hyperglycemia improved upon treatment with relacorilant
- Still, numerical reductions in HbA1c were observed in the OLE

Figure 2.



HbA1c, hemoglobin A1c; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus.

Pituitary tumor size

- At baseline, evaluable MRI scans were available in 31 patients with Cushing Disease
- In the majority of these patients, tumor volume decreased or remained unchanged throughout the OLE

Table 4.

n (%)	Baseline	Month 6	Month 12	Last observation
Not visible, scans available (n)	11	1	5	6
Increased	—	0	0	0
Decreased	—	0	0	0
Unchanged	—	1 (100)	5 (100)	6 (100)
Microadenoma, scans available (n)	15	1	10	11
Increased	—	0	4 (40)	3 (27.3)
Decreased	—	0	4 (40)	4 (36.4)
Unchanged	—	1 (100)	2 (20)	4 (36.4)
Macroadenoma, scans available (n)	5	1	0	2
Increased	—	0	0	0
Decreased	—	1 (100)	0	2 (100)
Unchanged	—	0	0	0

Increase/decrease defined as a 20% increase/decrease in tumor volume (mm^3) from baseline (defined as the last measurement available before or up to 6 weeks after day 1 in the OLE). OLE, open-label extension.

Relacorilant was Well Tolerated With an Adverse Event Profile Consistent With the Parent Studies

- The majority of treatment-emergent adverse events (TEAEs) were mild to moderate in severity (grade ≤2)
- The most common TEAEs (occurring in >15% of the study population) were arthralgia, peripheral edema, pain in extremity, and COVID-19
- The frequency of serious adverse events (SAEs) was low, and no new safety signals compared to the parent studies were identified
- There were no reports of relacorilant-induced hypokalemia, no reported cases of adrenal insufficiency, no clinically significant changes in ACTH and cortisol concentrations, no vaginal bleeding associated with endometrial hypertrophy, and no reports of QTcF prolongation

References

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