Efficacy and Safety of the Selective Glucocorticoid Receptor Modulator, Relacorilant (up to 400 mg/day), in Patients With Endogenous Hypercortisolism: Results From an Open-Label Phase 2 Study

Rosario Pivonello, MD, PhD[1]; Atil Y. Kargi, MD[2]; Noel Ellison, MS[3]; Andreas Moraitis, MD[4]; Massimo Terzolo, MD[5]

[1]Università Federico II di Napoli, Naples, Italy; [2]University of Miami Miller School of Medicine, Miami, FL, USA; [3]Trialwise, Inc, Houston, TX, USA; [4]Corcept Therapeutics, Menlo Park, CA, USA; [5]Internal Medicine 1 - San Luigi Gonzaga Hospital, University of Turin, Orbassano, Italy

INTRODUCTION

- Relacorilant is a highly selective glucocorticoid receptor modulator under investigation for the treatment of all etiologies of endogenous Cushing syndrome (CS)
  - Relacorilant reduces the effects of cortisol, but unlike mifepristone, does not bind to progesterone receptors (**Table 1**)[1]

Table 1. Glucocorticoid Receptor and Progesterone Receptor Binding Affinity With Mifepristone and Relacorilant

	Inhibitory Constant (Ki)	
GR Antagonist	GR	PR
Mifepristone	1.0 nM	1.0 nM
Relacorilant	0.5 nM	>1000 nM

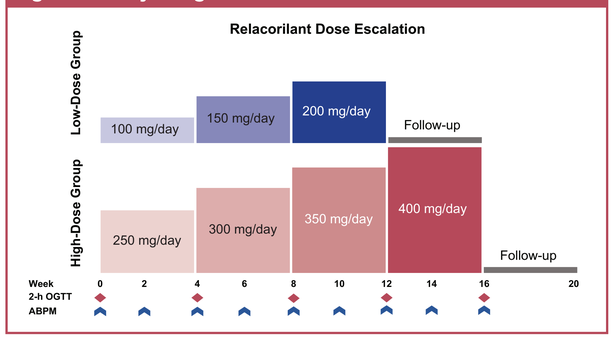
Note: Smaller Ki values indicate greater binding affinity.
GR, glucocorticoid receptor; PR, progesterone receptor.

- The objectives of this phase 2 study were to:
  - Assess the efficacy and safety of relacorilant in patients with endogenous CS
  - Evaluate the impact of a reduction in cortisol activity with relacorilant on cortisol excess and related comorbidities

METHODS

- This multicenter, open-label study (www.clinicaltrials.gov NCT02804750) included 2 relacorilant dosing groups: a low-dose group and a high-dose group (**Figure 1**)

Figure 1. Study Design



ABPM, ambulatory blood pressure monitoring; OGTT, oral glucose tolerance test.

STUDY PARTICIPANTS

Table 2. Key Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• 18-80 years old	• Severe, uncontrolled T2DM (HbA1c >12%) or HTN (BP >170/100 mmHg)
• Confirmed biochemical diagnosis of endogenous CS per Endocrine Society guidelines[2]	• Uncontrolled, clinically significant hypothyroidism or hyperthyroidism
• ≥2 clinical signs/symptoms of CS[a]	• Severe renal insufficiency (GFR ≤29 mL/min)
• Hyperglycemia and/or uncontrolled HTN at baseline[b]	• Abnormal LFTs (total bilirubin >1.5×ULN or ALT/AST >3×ULN)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CS, Cushing syndrome; T2DM, type 2 diabetes mellitus; LFTs, liver function tests; GFR, glomerular filtration rate; HTN, hypertension; ULN, upper limit of normal;.

[a]Cushingoid appearance, increased body weight, proximal muscle weakness, low bone mineral density, psychiatric symptoms, easy bruising, or skin changes.

[b]Hyperglycemia defined as impaired glucose tolerance (2-h oral glucose tolerance test [OGTT] plasma glucose value 140-199 mg/dL) or T2DM (fasting plasma glucose >126 mg/dL and a 2-h plasma glucose ≥200 mg/dL after a 75-g OGTT); uncontrolled HTN defined as mean systolic BP (SBP) of ≥130 mmHg and/or mean diastolic BP (DBP) ≥85 mmHg based on 24-h ambulatory blood pressure monitoring.

EFFICACY ANALYSES

- Key efficacy assessments were the evaluation of blood pressure in the hypertensive subgroup and glucose tolerance in the impaired glucose tolerance (IGT)/type 2 diabetes mellitus (T2DM) subgroup
  - Response in hypertension defined as a decrease of ≥5 mmHg in either mean systolic blood pressure (SBP) or diastolic blood pressure (DBP) from baseline
  - Response in IGT/T2DM defined by one of the following:
    - Decrease in HbA1c ≥0.5% from baseline
    - Normalization in 2-h oral glucose tolerance test (OGTT) glucose (<140 mg/dL) or decrease of ≥50 mg/dL from baseline
    - Decrease in total daily insulin dose of ≥25% or daily sulfonylurea dose by ≥50% from baseline
- Secondary (exploratory) endpoints included changes in body weight, area under the concentration-time curve for glucose ($AUC_{glucose}$) and fructosamine, liver function tests, osteocalcin, coagulation factors, depression, and quality of life (QoL)

RESULTS

- A total 35 patients were enrolled at 19 centers in the United States, Italy, United Kingdom, Hungary, and Netherlands
- Baseline characteristics are shown in **Tables 3** and **4**

Table 3. Demographic and Clinical Characteristics at Baseline

	Overall Study Population[a] (N=35)
Age, yr (mean ± SD)	48.6 ± 13.37
Female sex, n (%)	25 (71.4)
White race, n (%)	35 (100)
Weight, kg (mean ± SD)	96.9 ± 27.54
BMI, kg/m^2 (mean ± SD)	35.3 ± 9.75
Etiology of CS, n (%)	
ACTH-dependent: CD or ectopic	28 (80.0)
Adrenal	7 (20.0)
CS comorbidity, n (%)	
IGT/Diabetes only	12 (34.3)
Hypertension only	7 (20.0)
IGT/Diabetes and hypertension	16 (45.7)
Cushing QoL (mean ± SD)	41.3 ± 19.81
Fructosamine, µmol/L (mean ± SD)	220.6 ± 28.48
2-h OGTT plasma glucose, mmol/L (mean ± SD)	11.3 ± 4.97
$AUC_{glucose}$, h·mmol/L (mean ± SD)	23.58 ± 8.807
HbA1c, % (mean ± SD)	6.31 ± 1.266
Osteocalcin, µg/L (mean ± SD)	11.67 ± 8.54
SBP, mmHg (mean ± SD)	132.41 ± 12.045
DBP, mmHg (mean ± SD)	83.46 ± 8.152

ACTH, adrenocorticotropic hormone; AUC, area under the curve; BMI, body mass index; CD, Cushing disease; CS, Cushing syndrome; DBP, diastolic blood pressure; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; QoL, quality of life; SBP, systolic blood pressure.

[a]Includes all patients who received at least 1 dose of study medication.

Table 4. Biochemistry at Baseline

	ACTH-dependent (n=28)	Adrenal (n=7)	Overall[a] (N=35)
ACTH (pg/mL)	66.4 ± 28.23	5.0 ± 1.00	54.1 ± 35.36
24-h UFC (µg/24 h)	203.44 ± 219.60	224.65 ± 296.91	207.68 ± 232.22
Late-night salivary cortisol (µg/dL)	0.35 ± 0.33	0.30 ± 0.27	0.34 ± 0.32

Data presented as mean±standard deviation.

ACTH, adrenocorticotropic hormone; UFC, urinary free cortisol.

Normal laboratory ranges: ACTH: 5-45 pg/mL; UFC: <50 µg/24 h; late-night salivary cortisol: ≤0.09 µg/dL.

[a]Includes all patients who received at least 1 dose of study medication.

IMPACT ON HYPERTENSION

- In patients with hypertension (n=23), 41.7% (5/12) and 63.6% (7/11) in the low-dose and high-dose groups, respectively, were responders (**Table 5**)

Table 5. Summary of Responder Analysis in Patients at Last Observation

	Low-Dose Group Responder, n/N (%)	High-Dose Group Responder, n/N (%)
HTN	5/12 (41.67)	7/11 (63.64)
IGT/T2DM	2/13 (15.38)	6/12 (50.00)

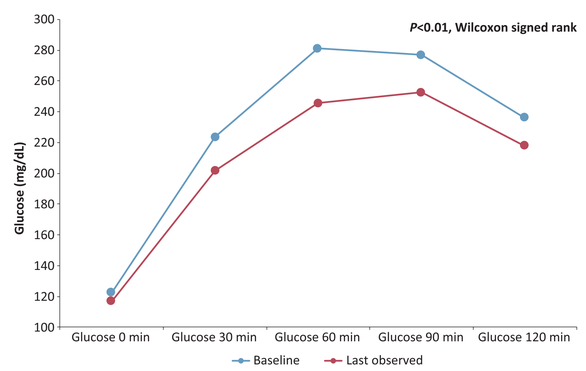
IGT, impaired glucose tolerance; HTN, hypertension; T2DM, type 2 diabetes mellitus.

Note: Data are from the modified per-protocol population defined as all patients who received at least 1 dose of study medication and had non-missing post-baseline data, with exclusions at specific visits per patient based on clinical judgment and/or major or important protocol deviations that were applied on a visit and outcome level rather than patient level.

IMPACT ON IGT/T2DM

- In patients with IGT/T2DM (n=25), 15.4% (2/13) and 50.0% (6/12) of the low-dose group and the high-dose group, respectively, met the overall response criteria (**Table 5**)

Figure 2. Results of OGTT Tests in Patients With IGT/T2DM



SECONDARY ENDPOINTS

- 6 of 17 patients (35.3%) lost weight in the low-dose group (mean loss, 2.2 kg)
- 9 of 15 patients (60.0%) lost weight in the high-dose group (mean loss, 5.1 kg)
- Statistically significant improvements from baseline were observed in various secondary endpoints (**Figure 2**; **Table 6**)

Table 6. Significant Improvements in Selected Secondary Endpoints

Parameter	Results	*P*-Value
$AUC_{glucose}$ (h·mmol/L)	Decreased	0.0214
Fructosamine (µmol/L)	Decreased	0.0021
ALT (U/L)	Decreased	<0.0001
AST (U/L)	Decreased	0.0013
Serum osteocalcin (µg/L)	Increased	0.0097
Absolute eosinophils (10^9/L)	Increased	0.006
aPTT (sec)	Increased	0.0456
Factor VIII (%)	Decreased	0.0219
Platelet count (10^9/L)	Decreased	<0.0001
BDI-II Total score	Decreased	0.0044
Cushing QoL score	Increased	0.0024
Trail-Making Test Part A—Total time to complete test (sec)	Decreased	0.003
Trail-Making Test Part B—Total time to complete test (sec)	Decreased	<0.0001

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; AUC, area under the curve; BDI, Beck Depression Inventory; QoL, quality of life.

Note: *P*-values for the mean change from baseline to last observation in the modified intent-to-treat (mITT) population are from the Wilcoxon signed rank test. The mITT population was defined as patients who received at least 1 dose of study medication and had non-missing post-baseline data.

SAFETY

- **Table 7** shows frequency of TEAEs; all were categorized as ≤Grade 3 in severity
- Five serious TEAEs were reported in 4 patients in the high-dose group (pilonidal cyst, myopathy, polyneuropathy, myocardial infarction, and hypertension)
- No drug-induced cases of hypokalemia or abnormal vaginal bleeding were noted
- No clinically significant changes in plasma ACTH or serum cortisol from baseline were observed (modified intent-to-treat population)

Table 7. TEAEs by Preferred Term

TEAE, n (%)	Low-Dose Group (n=17)	High-Dose Group (n=18)	Overall Population[a] (N=35)
Patients reporting ≥1	15 (88.24)	18 (100)	33 (94.29)
TEAE occurring in ≥20% of patients in the overall population			
Back pain	4 (23.53)	7 (38.89)	11 (31.43)
Headache	4 (23.53)	5 (27.78)	9 (25.71)
Edema peripheral	4 (23.53)	5 (27.78)	9 (25.71)
Nausea	3 (17.65)	5 (27.78)	8 (22.86)
Pain in extremity	4 (23.53)	4 (22.22)	8 (22.86)
Diarrhea	4 (23.53)	3 (16.67)	7 (20.00)
Dizziness	3 (17.65)	4 (22.22)	7 (20.00)

TEAE, treatment emergent adverse events.

[a]Includes all patients who received at least 1 dose of study medication.

CONCLUSIONS

- Results from the phase 2 study of relacorilant showed clinically significant improvement in cortisol excess related comorbidities, including hypertension, blood glucose control, weight, hypercoagulopathy, neuropsychiatric symptoms, and QoL
- Differences in response rates between groups suggest a dose response
- As expected, a higher rate of TEAEs was observed in the high-dose group, possibly due to cortisol withdrawal symptoms due to the forced titration trial design, and unmasking of underlying comorbidities of patients in the trial
  - In the phase 3 trial, patients will begin treatment at 100 mg/d for 2 weeks, a dose designed to make dose escalation more gradual and enhance tolerability and treatment persistence
- Relacorilant did not cause clinically significant increases in cortisol levels in patients with CS, unlike the substantial increases noted with mifepristone[3]
  - This finding may explain the absence of mineralocorticoid receptor-mediated hypokalemia in patients treated with relacorilant and the higher response rates in hypertension compared with response observed in the study with mifepristone
- Relacorilant offers the clinical benefit of potent glucocorticoid modulation without the undesirable progesterone receptor-mediated effects (eg, vaginal bleeding)

REFERENCES

1. Hunt H, et al. *Clin Pharmacol Drug Dev.* 2018;7(4):408-21.
2. Nieman LK, et al. *J Clin Endocrinol Metab.* 2008;93(5):1526-40.
3. Fleseriu M, et al. *J Clin Endocrinol Metab.* 2012;97(6):2039-49.

ACKNOWLEDGMENTS

Funding for editorial, design, and production support for this poster was provided by Corcept Therapeutics to MedVal Scientific Information Services, LLC, Princeton, NJ. The authors developed and revised the poster and provided approval of the final version.

DISCLOSURES

RP: Consultant, Novartis, Pfizer, Viropharma-Shire, Ferring, Italfarmaco, Ipsen; Speaker, Novartis, Viropharma-Shire, Research, Novartis, Viropharma-Shire, Corcept Therapeutics; Grant support, Novartis, Pfizer, Viropharma-Shire, IBSA.

AYK: Consultant, Strongbridge; Research, Corcept Therapeutics.

NE: Consultant, Trialwise, Corcept Therapeutics, Pentara.

AM: Employee, Corcept Therapeutics.

MT: Consultant, HRA Pharma; Research, Corcept Therapeutics.

Presented at the American Association of Clinical Endocrinologists Annual Congress, April 24-28, 2019, Los Angeles, CA