LCI699, a Potent 11β-hydroxylase Inhibitor, Normalizes Urinary Cortisol in Patients With Cushing's Disease: Results From a Multicenter, Proof-of-Concept Study

Xavier Bertagna, Rosario Pivonello, Maria Fleseriu, Yiming Zhang, Paul Robinson, Ann Taylor, Catherine E. Watson, Mario Maldonado, Amir H. Hamrahian, Marco Boscaro, and Beverly M. K. Biller

Department of Endocrinology (X.B.), Centre de Référence des Maladies Rares de la Surrénale, Hôpital Cochin, Faculté de Médecine Paris Descartes, Université Paris 5, Paris 75014, France; Dipartimento di Medicina Clinica e Chirurgia (R.P.), Università Federico II di Napoli, IT-80131, Naples, Italy; Department of Medicine and Neurological Surgery (M.F.), Northwest Pituitary Center, Oregon Health and Science University, Portland, Oregon 97239-3098; Novartis Pharmaceuticals Corporation (Y.Z.), East Hanover, New Jersey 07936; Novartis Pharmaceuticals UK Limited (P.R.), Horsham, West Sussex, RH12 5AB, United Kingdom; Novartis Institutes for BioMedical Research (A.T., C.E.W.), Cambridge, Massachusetts 02139; Clinical Development (M.M.), Oncology Business Unit, Novartis Pharma AG, CH-4002 Basel, Switzerland; Department of Endocrinology, Diabetes, and Metabolism (A.H.H.), Cleveland Clinic Foundation, Cleveland, Ohio 44106; Division of Endocrinology (M.B.), Polytechnic University of Marche, 60121 Ancona, Italy; and Neuroendocrine Clinical Center (B.M.K.B.), Massachusetts General Hospital, Boston, Massachusetts 02114

Introduction: The clinical features and increased mortality associated with Cushing's syndrome result from a chronic excess of circulating cortisol. As LCI699 potently inhibits 11β-hydroxylase, which catalyzes the final step of cortisol synthesis, it is a potential new treatment for Cushing's disease, the most common cause of endogenous Cushing's syndrome.

Methods: Adult patients with moderate-to-severe Cushing's disease (urinary free cortisol [UFC] levels $>1.5 \times$ ULN [upper limit of normal]) received oral LCI699 for 10 weeks in this proof-of-concept study. LCI699 was initiated at 4 mg/d in two equal doses; the dose was escalated every 14 days to 10, 20, 40, and 100 mg/d until UFC normalized, whereupon the dose was maintained until treatment ended (day 70). The primary endpoint was UFC $\leq$ ULN or a $\geq$50% decrease from baseline at day 70.

Results: Twelve patients were enrolled and completed the study. Baseline UFC ranged over 1.6–17.0 $\times$ ULN. All 12 patients achieved UFC $\leq$ ULN or a $\geq$50% decrease from baseline at day 70; 11 (92%) had normal UFC levels at that time. After treatment discontinuation (day 84), UFC was $>$ULN in 10 patients with available measurements. Mean 11-deoxycortisol, 11-deoxycorticosterone, and adrenocorticotropic hormone levels increased during treatment and declined after discontinuation. Mean systolic and diastolic blood pressure decreased from baseline by 10.0 and 6.0 mmHg, respectively. LCI699 was generally well tolerated; most adverse events (AEs) were mild or moderate. The most common AEs included fatigue (7/12), nausea (5/12), and headache (3/12). No serious drug-related AEs were reported.

Conclusions: LCI699 was efficacious and well tolerated in patients with Cushing's disease enrolled in this proof-of-concept study. **(*J Clin Endocrinol Metab* 99: 1375–1383, 2014)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.
Copyright © 2014 by the Endocrine Society
Received May 3, 2013. Accepted November 27, 2013.
First Published Online December 11, 2013

For editorial see page 1157

Abbreviations: AEs, adverse events; BP, blood pressure; CV, coefficient of variation; HbA_{1c}, glycosylated hemoglobin; LC-MS/MS, liquid chromatography–tandem mass spectrometry; SAE, serious adverse event; UFC, urinary free cortisol; ULN, upper limit of normal.

Downloaded from https://academic.oup.com/jcem/article/99/4/1375/2537458 by guest on 19 April 2024

Cushing's syndrome is characterized by a chronic excess of cortisol secretion, which results in numerous clinical features that are associated with a higher mortality compared with the general population if not appropriately treated (1). The most common cause of endogenous Cushing's syndrome is Cushing's disease (~70%), which is caused by an ACTH-secreting pituitary tumor (2, 3).

The treatment goals for Cushing's disease are to decrease elevated cortisol levels—ideally reverting to normal pituitary–adrenal axis function—and to reverse the signs and symptoms of chronic hypercortisolism. First-line treatment is transsphenoidal surgery to remove the pituitary tumor (3). Although pituitary surgery is currently the only therapeutic option that can fulfill all the treatment aims, it is not always successful and relapses may occur after successful initial surgery (4). Alternative treatment options are therefore necessary and include pituitary radiotherapy, bilateral adrenalectomy, and medical therapy. Pasireotide (Signifor) is a multireceptor-targeted somatostatin analog that acts directly on the tumoral corticotroph cells. It is currently the only medical therapy approved in the European Union and the United States for the treatment of Cushing's disease and is licensed for use in patients for whom surgery is not an option or has failed (5, 6). Mifepristone (Korlym), which is a glucocorticoid receptor antagonist, is approved in the United States for the control of hyperglycemia secondary to hypercortisolism in patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed, or are not candidates for, surgery (7). Other commonly used medical therapies include the dopamine receptor agonist cabergoline (8, 9), which inhibits ACTH oversecretion and is currently approved for the treatment of hyperprolactinemia, and the steroidogenesis inhibitors metyrapone (10), ketoconazole (11, 12), and mitotane (13–15). Although a number of medical therapies are available, not all patients will respond, and the available evidence for agents used off-label is limited to retrospective studies. New medical therapies with improved efficacy and safety profiles would therefore be valuable for the treatment of Cushing's disease.

LCI699 is a potent inhibitor of 11β-hydroxylase (CYP11B1), the enzyme that catalyzes the final step of cortisol synthesis, and has a half-life of ~4 hours (16). LCI699 also inhibits aldosterone synthase (CYP11B2) and has previously been shown to decrease blood pressure (BP) in patients with essential hypertension and primary aldosteronism (17, 18). The mechanism of action of LCI699 is similar to that of metyrapone, which has been used to treat patients with Cushing's syndrome for many years (10, 19). However, metyrapone is less potent against 11β-hydroxylase than LCI699 (in vitro IC_{50} of ~7.5 nM vs 2.5 nM for LCI699; Novartis Pharma AG, unpublished data, 2013) and has a shorter half-life (<2 hours [20]).

Owing to its inhibitory effect on 11β-hydroxylase and data demonstrating suppression of baseline and ACTH-stimulated plasma cortisol levels (18), LCI699 is currently under investigation as a potential new treatment for Cushing's syndrome. This open-label, proof-of-concept, single-arm, multicenter study was conducted to assess the safety/tolerability and efficacy of LCI699 in patients with Cushing's disease (LINC 1 study, **LCI IN C**ushing's; clinicaltrials.gov identifier NCT01331239).

Patients and Methods

Patient population and study design

Adult patients aged 18–75 years with Cushing's disease were enrolled at six centers in Italy, France, and the United States. Inclusion criteria were moderate-to-severe Cushing's disease, as confirmed by urinary free cortisol (UFC) levels >1.5 times the upper limit of normal (ULN) based on the mean of at least two 24-hour urine samples collected within 14 days; a morning plasma ACTH level above the lower limit of normal; and evidence of a pituitary origin of the excess ACTH (based on a history of magnetic resonance imaging confirmation of pituitary adenoma ≥6 mm with a positive dynamic test; or history of inferior petrosal sinus gradient >3 after corticotropin-releasing hormone stimulation; or determined histologically in patients with previous pituitary surgery). Patients were excluded if they had undergone major surgery within 1 month before screening; poorly controlled diabetes mellitus as evidenced by glycosylated hemoglobin (HbA_{1c}) >9%; or compression of the optic chiasm. The study was conducted in accordance with the Declaration of Helsinki, and an independent ethics committee, or institutional review board, for each study site approved the study protocol. All patients provided written informed consent to participate in the trial.

Initially, there was a 60-day screening period to allow adequate washout of any prior medications that modified cortisol levels. After screening, there was a 10- to 14-day baseline period, a 10-week treatment period (days 1–70), and a 14-day washout period (days 71–84) (Figure 1). During the treatment period, LCI699 was given orally in two equal doses, one in the morning and one in the evening. Treatment dose was initiated at 4 mg/d and then escalated every 14 days to 10, 20, 40, and 100 (maximum allowed dose) mg/d. If UFC normalized during the escalation period, the dose was maintained at the effective level until the end of active treatment (day 70). If a patient's UFC had normalized but subsequently increased to above the ULN, dose escalation was resumed. The final evaluation was conducted 14 days after the last drug administration (day 84). Dose reductions during the treatment period were permitted for patients who were unable to tolerate the protocol-specified dose scheme, or for patients who experienced signs/symptoms of adrenal insufficiency. Patients were provided with an instruction sheet discussing the signs/symptoms of adrenal insufficiency and the details of rescue medications that could be taken.

Downloaded from https://academic.oup.com/jcem/article/99/4/1375/2537458 by guest on 19 April 2024

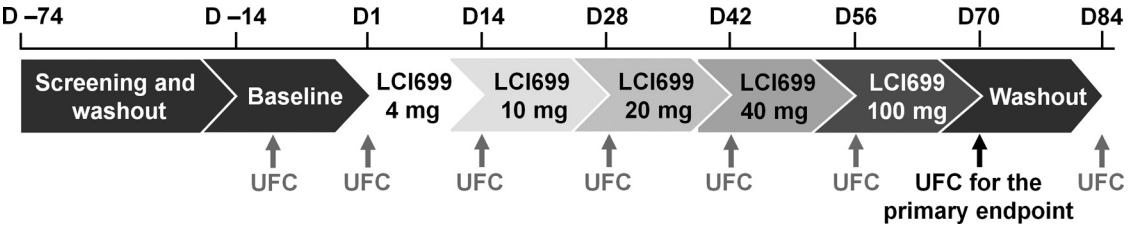

Figure 1. LINC 1 study design.

Primary endpoint: assessment of UFC

The primary endpoint was the proportion of patients with UFC ≤ ULN or who had a ≥50% decrease from baseline at day 70. For the primary endpoint, the mean UFC level from at least two 24-hour urine samples collected at baseline and within the 10th week of treatment was used. Otherwise, UFC was assessed from a single 24-hour urine sample taken on the penultimate day of each 14-day treatment period. UFC levels were measured at local laboratories that used different assays with different normal ranges; therefore, ULN values from each laboratory were used to normalize the data (ULN ranged from 42.4 to 135.0 μg/24 h). Two different techniques were used to measure UFC: an electrochemiluminescent immunoassay was used in Paris, France and Naples, Italy (both used Immulite 2000 Automated Chemiluminescent System, Siemens; coefficient of variation [CV] of 12%; cross-reactivity of 1.6% with 11-deoxycortisol), in Boston, MA, USA (Architect Cortisol assay, Abbott Laboratories; CV ≤20% for samples ≥3 to ≤35 μg/dL; cross-reactivity of 1.9% with 11-deoxycortisol), and in Ancona, Italy (Access Cortisol assay, Beckman Coulter; CV <12%; cross-reactivity of 17.8% with 11-deoxycortisol); liquid chromatography–tandem mass spectrometry (LC-MS/MS) was used in Portland, OR, USA (Quest Diagnostics; CV ≤20%; no known cross-reactivity with 11-deoxycortisol) and Cleveland, OH, USA (Cortisol Urine Free test, Arup Laboratories; CV <8.8%; cross-reactivity of 0.4% with 11-deoxycortisol).

Secondary endpoints: pharmacodynamic parameters

The key secondary endpoints were changes from baseline in various pharmacodynamic parameters to evaluate the impact of LCI699 on the hypothalamic–pituitary–adrenal and gonadal axes. Parameters evaluated included cortisol (in plasma); ACTH (plasma); 11-deoxycortisol (plasma); 11-deoxycorticosterone (plasma, urine); aldosterone (plasma, urine, saliva); renin (plasma); testosterone, estradiol, LH, and FSH (serum); insulin (serum); and HbA_{1c} (whole blood). All pharmacodynamic parameters assessed as a secondary endpoint (ie, all parameters except UFC) were measured at each visit and were analyzed at one of two central laboratories (Quest Diagnostics or Quotient). Mineralocorticoid and glucocorticoid parameters were assessed using LC-MS/MS (plasma 11-deoxycortisol, plasma and urinary 11-deoxycorticosterone, plasma cortisol, and plasma and salivary aldosterone; CV ≤20% [except estradiol, which had a CV ≤30%]; no known or negligible cross-reactivity), RIA (plasma renin and urinary aldosterone; CV ≤20%; no known or negligible cross-reactivity), or chemiluminescent immunoassay (ACTH; CV ≤10%; reagents formulated to minimize the risk of interference).

Pharmacokinetics

Trough LCI699 concentrations were measured 12 hours after the penultimate evening dose at the end of each 14-day treatment period, up to day 70. Pharmacokinetic calculations were performed using WinNonlin (Pharsight Products).

Safety assessment

Safety was assessed based on the monitoring and recording of all adverse events (AEs), which were defined using terminology in the *Medical Dictionary for Regulatory Activities* (MedDRA version 13.1). Laboratory evaluations (hematology, clinical chemistry, and urinalysis) and vital signs (including BP and weight) were performed at each visit. Sodium and potassium levels were measured at each visit and analyzed at central (urine samples) or local (serum samples) laboratories.

Statistical analyses

A sample size of 12 to 15 patients was required to provide 70% to 84% power to reject the null hypothesis of a 15% response rate when the alternative hypothesis of a 50% response rate was true based on an exact binomial test for a single proportion at a significance level of 0.05. This assumed that response rates of ≤15% were unacceptable and that rates of ≥50% were considered a good indication of a beneficial effect. The proportion of responders among patients with UFC measurements at both baseline and day 70 and the associated 95% confidence intervals were calculated using the exact binomial test. Patients with at least two 24-hour UFC measurements at both baseline and day 70 were included in the primary efficacy population. Summary statistics of UFC levels and pharmacodynamic parameters were evaluated at each visit and a paired *t* test was performed to compare levels at baseline vs day 70; values were log-transformed before analysis. Point estimates and associated 95% confidence intervals for the ratio of geometric means (day 70/baseline) were obtained from the paired *t* test. Missing values were not imputed for the primary analysis but were imputed using last observation carried forward for other analyses. All patients with evaluable pharmacokinetic data were included in the pharmacokinetic population. All patients who received at least one dose of study drug were included in the safety population.

Results

Patient population

Twelve patients, all of whom had received prior pituitary surgery and none of whom had previously received pituitary irradiation, were enrolled and all completed the

Downloaded from https://academic.oup.com/jcem/article/99/4/1375/2537458 by guest on 19 April 2024

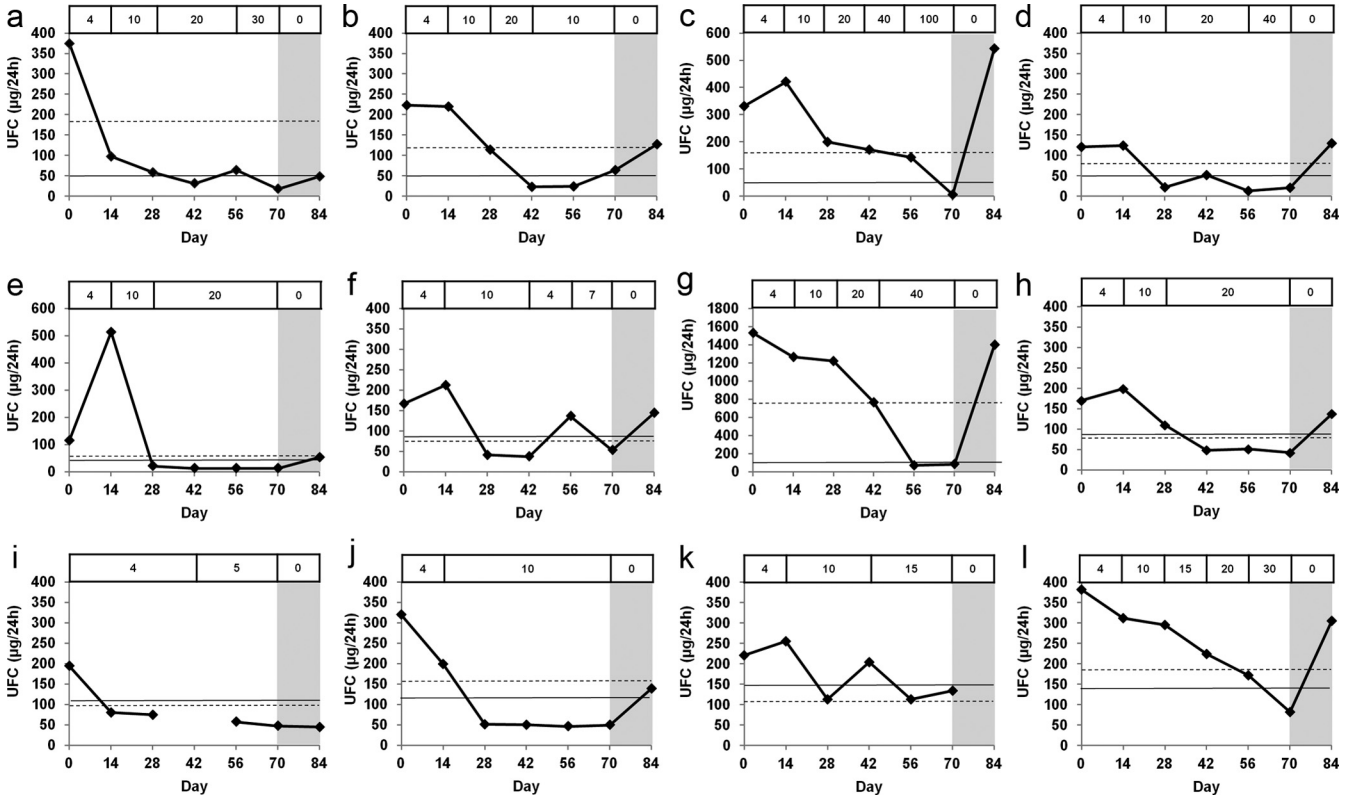

Figure 2. UFC levels over time in individual patients (a–l). On each individual plot, the values in the bar at the top represent the total daily doses of LCI699 in milligrams per day; the dotted line represents 50% of the baseline value; the solid line represents the ULN for the assay used for that particular patient; and the shaded area represents the 14-day washout period post-LCI699 dosing.

study. The mean age of patients was 39 years (SD 10.3; range 25–55), with a female-to-male ratio of 8:4; all patients were Caucasian and had a mean body mass index of 33.8 kg/m^2 (SD 8.5; range 23.8–48.7). Most patients (83%) had microadenomas and all had undergone prior pituitary surgery. At the time of study entry, the mean UFC was 4.7-fold above the ULN (SEM 1.3; range 1.6–17.0). Only one patient had received medical therapy for Cushing's disease (cabergoline) before enrollment; the patient stopped cabergoline treatment >8 weeks before dosing with LCI699. All 12 patients had three UFC collections at baseline; at day 70, nine patients had at least two UFC collections and three patients had one collection.

Efficacy of LCI699: UFC

By day 70, all 12 patients (95% confidence interval: 74%, 100%) normalized UFC levels or achieved a >50% reduction in UFC; the mean ± SD time to achieving this response was 34.3 ± 14.1 days. UFC levels normalized at least once during treatment in all 12 patients, and 11 of 12 patients (91.7%) had UFC levels within the normal range on day 70. Individual patient responses and doses are shown in Figure 2. A notable decrease in mean UFC level was seen after 28 days when most patients had completed the 10 mg/d dose, and UFC levels continued to decline to day 70 (Figure 3). Overall, 75% of patients (n = 9) achieved normalized UFC with an LCI699 dose of ≤20 mg/d; most of these patients required 10–20 mg/d. The remaining three patients required LCI699 doses of 30, 40, and 100 mg/d, respectively. The mean ± SEM UFC level was 0.6 ± 0.1 ULN on day 70 (range 0.1–1.4). The geometric mean ratio of 0.139 indicates a significant mean UFC reduction of 86% from baseline ($P < .0001$).

In the nine patients who had at least two UFC measurements at both baseline and day 70 and therefore met the predetermined criterion for

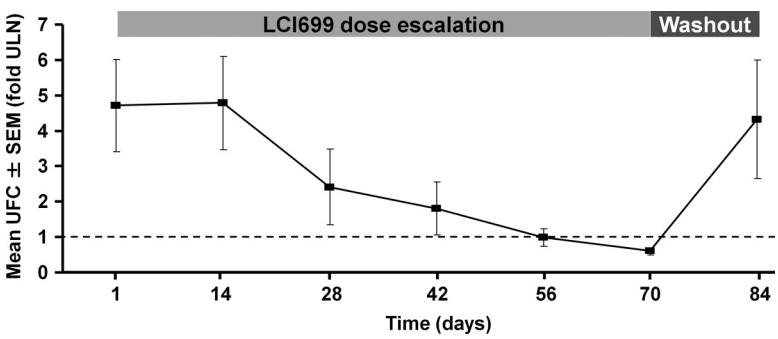

Figure 3. UFC (fold ULN) over time in all patients. Data are mean ± SEM.

Downloaded from https://academic.oup.com/jcem/article/99/4/1375/2537458 by guest on 19 April 2024

the primary efficacy endpoint, all had normal UFC levels at the end of the treatment period. The geometric mean ratio of 0.103 indicates a significant mean UFC reduction of 90% from baseline ($P < .001$) in these patients.

After treatment discontinuation (day 84), mean UFC returned to levels above ULN in the 10 patients with available samples.

Other pharmacodynamic markers

Morning plasma levels of cortisol and aldosterone decreased significantly from baseline to day 70 (geometric mean: 24.9 to 10.2 μg/dL, $P < .001$, and 4.2 to 1.3 ng/dL, $P = .03$, respectively). A significant increase in plasma levels of the precursors 11-deoxycortisol (geometric mean: 84 to 1098 ng/dL, $P < .0001$) and 11-deoxycorticosterone (geometric mean: 3.5 to 147.5 ng/dL, $P < .0001$) was observed from baseline to day 70 (Figure 4). Plasma levels of all four parameters recovered toward baseline after 14 days' washout (day 84). Salivary aldosterone levels showed a similar pattern of response to plasma levels, while most urinary aldosterone results were below the level of quantification of the assay and data were therefore not measurable. Plasma renin levels decreased during LCI699 treatment (geometric mean: 13 to 8 ng/L) and remained suppressed on day 84 (Figure 4), although these changes were not statistically significant ($P = .19$). A number of patients received drugs during the study that could potentially interfere with the renin–angiotensin–aldosterone system (eg, lisinopril, n = 3; ibuprofen, n = 2; atenolol, n = 1; spironolactone, n = 1). However, because of the small patient population, we are unable to perform a proper statistical evaluation of the effect of LCI699 treatment on the renin–angiotensin–aldosterone system. Urinary levels of 11-deoxycorticosterone increased 18-fold from baseline to day 70. The decrease in UFC resulted in a compensatory increase in plasma ACTH levels from baseline to day 70 (geometric mean: 71.2 to 173.8 pg/mL, $P = .012$).

No important change in insulin levels was observed, although a small but notable decrease in HbA_{1c} was noted (0.3%, $P = .056$). Three patients had baseline HbA_{1c} levels >6.5% (8.2%, 8.8%, and 6.6%, respectively) and showed a 0.3%, 0.5%, and 0.8% decrease in HbA_{1c}, respectively. The patient with baseline HbA_{1c} levels of 8.8%, as well as two additional patients (who had baseline/day 70 HbA_{1c} values of 5.7/5.7% and 6.1/6.2%), received antidiabetic medication during the study.

In the eight female patients, geometric mean serum testosterone levels increased significantly at day 56 (the last day that testosterone was measured during LCI699 treatment) from 27.8 to 60.7 ng/dL ($P = .034$) and then de-

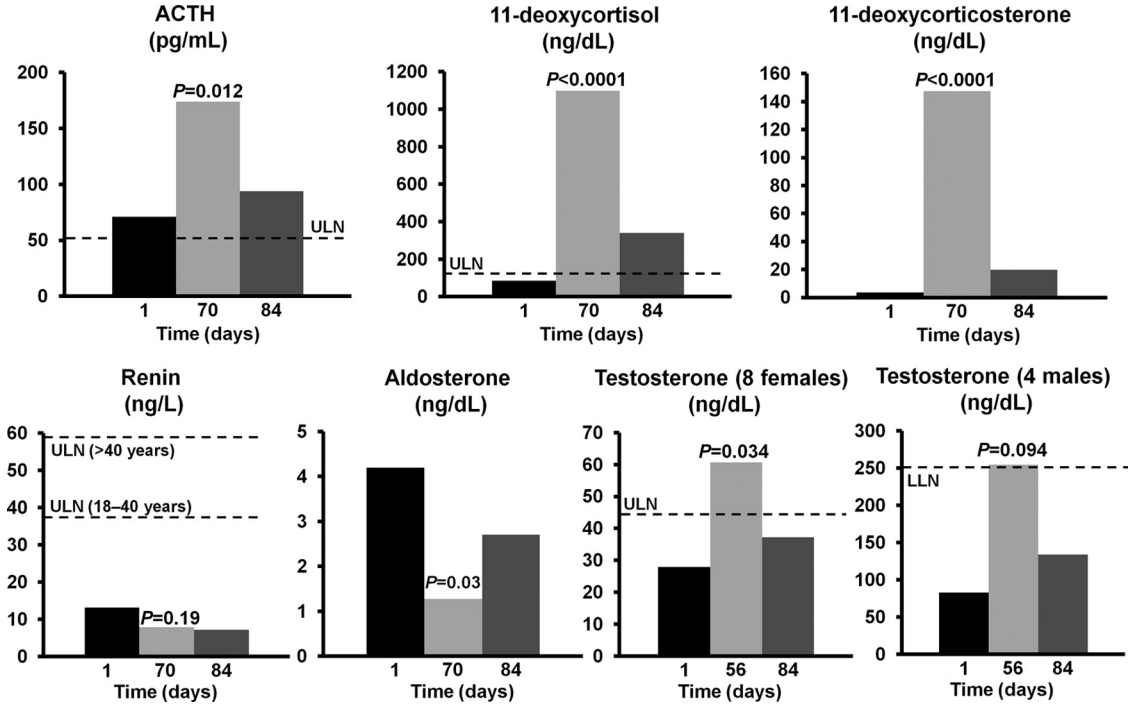

Figure 4. Levels of pharmacodynamic markers before, during, and after treatment with LCI699. All data are geometric means. All *P* values are day 70 (day 56 for testosterone) vs baseline. ULN for each parameter is as follows: ACTH, 50.5 pg/mL; 11-deoxycortisol, 119 ng/dL; renin, 38.7 ng/L in patients aged 18–40 years and 59.4 ng/L in patients aged >40 years; testosterone, 45.0 ng/dL (females). LLN for testosterone in males is 250.1 ng/dL. No ULN is available for 11-deoxycorticosterone or aldosterone (which is affected by diet and body posture) as the LC-MS/MS assay was specifically designed for this study and no normal ranges have been established. Day 84 represents the 14-day washout period post-LCI699 dosing. LLN, lower limit of normal.

Downloaded from https://academic.oup.com/jcem/article/99/4/1375/2537458 by guest on 19 April 2024

clined toward baseline values at day 84 (Figure 4). Six of these patients had testosterone levels within the normal range at baseline and levels above ULN on day 56. One patient had high levels of testosterone before dosing that remained at a similar level throughout treatment, whereas the remaining patient had levels above ULN at screening but not at baseline, with levels that continued to fluctuate throughout the study. No significant changes in estradiol, LH, or FSH were observed in the female patients. Of note, no female patients enrolled in the study were postmenopausal. In the four male patients, geometric mean serum testosterone levels increased nonsignificantly from 82.8 ng/dL at baseline to 254.6 ng/dL at day 56. A 7.5-fold decrease in LH was noted, with samples from all males being below the level of quantitation (<0.2 U/L) on day 70 (data not shown).

Pharmacokinetic analysis

Two patients were excluded from the pharmacokinetic analysis (because their blood samples were received thawed and could not be used). The trough LCI699 plasma concentrations from the remaining 10 patients ranged from 0.34 ng/mL (after the 4 mg/d dose) to 204 ng/mL (after the 100 mg/d dose).

Safety and tolerability

AEs

All patients experienced at least one AE during LCI699 treatment. The most common AEs were gastrointestinal events, including nausea and diarrhea (Table 1). Most AEs were mild or moderate in nature and none led to treatment discontinuation. There were no reports of changes in liver enzyme levels during LCI699 treatment. Four patients had AEs that were managed with dose reduction (from 20 to 10 mg/d in three patients and from 10 to 4 mg/d in one patient, which lasted from 4 to 34 days) or temporary interruption (maximum of two consecutive doses were withheld); these AEs were consistent with adrenal insufficiency and/or steroid withdrawal (moderate fatigue in three patients, mild nausea in two patients, and mild dizziness, mild muscle spasms, and moderate hypotension [systolic/diastolic BP 90/60 mmHg] in one patient each). This is supported by the fact that UFC levels before the AE were below ULN in three of the four patients, whereas the other patient had a plasma aldosterone level below the lower limit of detection (28 pmol/L). One of the patients who experienced fatigue received a single dose of hydrocortisone. One patient, who experienced edema during the study, had a weight increase of 19 kg; during treatment, the patient's 11-deoxycorticosterone levels increased 140-fold and ACTH levels increased 17-fold. The patient had a large pituitary macroadenoma and, notably, experienced a 7-kg weight gain within the month before the start of the study. One male patient experienced mild acne on day 71, which was ongoing at day 84 but required no treatment. During the treatment period, the patient's 11-deoxycortisol levels increased ~10-fold; his 11-deoxycorticosterone levels increased ~22-fold, and his testosterone levels increased ~2.5-fold (although they were still within the normal range). There were no reported AEs of hirsutism in the female patients. One serious AE (SAE) was reported but was not suspected to be related to study drug. The patient experienced anemia (hemoglobin level rapidly decreased from 7.5 to 4.1 g/dL), with palpitations and chest pain secondary to reactivation of previous Takayasu arteritis. This event resolved with transfusion and may have been related to resolution of hypercortisolemia.

Table 1. Most Common AEs[a] During Treatment With LCI699 (n = 12), as Reported by the Investigator (occurring in at least two patients)

AE	n (%)
Fatigue	7 (58.3)
Nausea	5 (41.7)
Diarrhea	3 (25.0)
Headache	3 (25.0)
Hypokalemia	3 (25.0)
Muscle spasms	3 (25.0)
Vomiting	3 (25.0)
Abdominal discomfort	2 (16.7)
Abdominal pain	2 (16.7)
Arthralgia	2 (16.7)
Arthropod bite	2 (16.7)
Dizziness	2 (16.7)
Lipase increased	2 (16.7)
Pruritus	2 (16.7)

[a] Assessed based on MedDRA preferred terms.

Changes in clinical and laboratory features

There were no clinically relevant changes in mean vital signs or electrocardiogram measurements over the study period. Mean ± SEM body weight increased from baseline to day 70 by 3.5 ± 1.4 kg; excluding the patient with edema, who had a weight increase of 19 kg, overall mean body weight increased by 2.4 kg. On day 70, mean ± SEM systolic and diastolic BP had decreased from baseline by 10.0 ± 4.3 (range −36 to 8) and 6.0 ± 4.3 (range −34 to 10) mmHg, respectively (Table 2). Of three patients who were clearly hypertensive at baseline (systolic BP >140 mmHg and diastolic BP >90 mmHg), two were normotensive at day 70 and one remained hypertensive.

There was a small initial increase in mean serum potassium (<0.2 mEq/L) from baseline to day 14, followed by a slow decrease to below baseline by day 70; levels returned to baseline after treatment discontinuation (day 84). The overall mean ± SEM decrease in potassium levels

Downloaded from https://academic.oup.com/jcem/article/99/4/1375/2537458 by guest on 19 April 2024

Table 2. Clinical and Laboratory Features During LCI699 Treatment

	Baseline (n = 12)	Day 70 (n = 12)	Change From Baseline (n = 12)
Systolic BP, mmHg	139.3 ± 4.4	129.3 ± 5.5	−10.0 ± 4.3
Diastolic BP, mmHg	88.8 ± 3.8	82.8 ± 3.0	−6.0 ± 4.3
Weight, kg	96.8 ± 8.8	100.3 ± 9.5	3.5 ± 1.4
Glucose, mmol/L	5.4 ± 0.5	5.7 ± 0.4	0.3 ± 0.3
Potassium, mEq/L	4.1 ± 0.1	3.8 ± 0.2	−0.3 ± 0.2
Sodium, mEq/L	140.3 ± 1.1	140.8 ± 1.0	0.5 ± 1.1

Data are mean ± SEM.

from baseline during LCI699 treatment was −0.3 ± 0.2 mEq/L (range −1.3 to 0.5, $P = .083$), representing an 8% decrease. No patients had hypokalemia at baseline. Four patients experienced study-drug–related hypokalemia during treatment, defined as potassium levels <3.5 mEq/L (minimum recorded value was 3.1 mEq/L). This was reported as an AE in only three patients (see Table 1), as the minimum recorded value in one patient was below 3.5 mEq/L but not below the lower limit of normal at the reporting center. All three patients received oral potassium supplementation and had subsequent potassium values >3.5 mEq/L. No LCI699 dose reductions were required due to hypokalemia. There were no notable changes in serum sodium levels (mean change of 0.5 ± 1.1 mEq/L from baseline to day 70; range −8 to 5). Treatment with LCI699 had no notable effects on urinary potassium or sodium levels.

There were no marked changes in hematology values at day 70. A slight reduction (1 g/dL) in mean hemoglobin was observed between days 28 and 70, but this was not considered to be treatment related and was driven by the patient with an SAE of anemia.

Discussion

This 10-week, multicenter, proof-of-concept study demonstrated that LCI699, a potent inhibitor of 11β-hydroxylase, rapidly and effectively decreased UFC levels in patients with moderate-to-severe Cushing's disease. UFC levels were normalized at least once in all 12 patients, and 11 patients had normalized UFC at the end of treatment with LCI699.

Oral doses of LCI699 10–20 mg/d were most frequently associated with UFC normalization, which suggests that this dose range may be appropriate for use in future investigations. In the current study, the interval between dose escalations was dependent on UFC assessments, which were performed every 14 days.

Data from previous studies showed that lower doses of LCI699 (0.25–2 mg/d) decreased aldosterone, inhibited ACTH-induced cortisol stimulation, and increased 11-deoxycorticosterone levels in patients with essential hypertension and primary aldosteronism (17, 18). The present study demonstrated that LCI699 has similar effects in patients with Cushing's disease. These changes, particularly the substantial increase in plasma 11-deoxycorticosterone levels, suggest that hypermineralocorticism may have resulted in weight gain and decreases in potassium and renin levels. Three patients experienced hypokalemia that was considered by the investigator to be related to treatment; levels returned to normal with modest potassium supplementation, and no LCI699 dose reductions for hypokalemia were needed. There was a trend toward a decrease in BP, which is a potentially important benefit in this patient population. It could be hypothesized that the decreased BP, despite a state of hypermineralocorticism, is a beneficial effect of LCI699 treatment in decreasing excess cortisol levels; other mechanisms, including a direct effect of cortisol lowering on the blood vessel wall, are also possible (21). Because changes in antihypertensive medications were not restricted during the study, a number of patients started/stopped medication or changed to a different medication. Thus, it is not possible to interpret the effects of antihypertensive medication on changes in BP. In addition, no statistical analysis of the changes in BP was possible because of the small patient population; larger studies that also take into account the possible use and doses of concomitant antihypertensive medications are required to investigate this further.

Despite the similarities in the mechanism of action between LCI699 and metyrapone, LCI699 is a more potent drug and appears to be effective at doses around 100 times lower. Although metyrapone has been used to treat patients with Cushing's syndrome, most published studies were not based on well-defined efficacy endpoints and were often conducted in patients who received metyrapone after, or in parallel with, pituitary radiotherapy (10, 19, 22, 23). One of the most significant adverse effects of long-term treatment with metyrapone is hirsutism in women due to increases in testosterone levels (10, 19). In

Downloaded from https://academic.oup.com/jcem/article/99/4/1375/2537458 by guest on 19 April 2024

one study, testosterone levels increased from a baseline median of 63.4 ng/dL (range 23.1–126.8) to a peak median of 193.1 ng/dL (range 77.8–495.7) (10). In the present study, testosterone levels increased significantly in the female patients who received LCI699, from a baseline mean of 28.8 to 60.5 ng/dL by day 56. However, as could be expected in this short 10-week study, no cases of hirsutism were reported. Increases in testosterone levels were also observed in male patients; however, the small male population (n = 4) did not allow for a valid statistical analysis. Although it is interesting that testosterone levels increased in men (potentially due to reproductive system recovery as cortisol levels decreased), the data are not sufficient to draw any definitive conclusions. Further studies will evaluate the respective roles of the adrenals and/or the gonadotropins in hormonal changes during LCI699 treatment.

Treatment with LCI699 was well tolerated. Most AEs were mild or moderate and none led to treatment discontinuation. Only one patient experienced an SAE, which was not suspected to be related to LCI699 and resolved with additional treatment. As could be anticipated with such a potent drug, some patients had clinical effects that were consistent with adrenal insufficiency and/or steroid withdrawal based on clinical evidence (UFC levels were <ULN). It is worth noting that the unequivocal demonstration of hypoadrenalism would have required the use of a dynamic test such as ACTH stimulation or the assessment of early-morning baseline plasma cortisol, which, although having lower sensitivity than ACTH stimulation, can be diagnostic for adrenal insufficiency. In most cases, these clinical effects resolved with temporary decreases in LCI699 dose (hydrocortisone was given to one patient). Overall, these initial efficacy and safety data for LCI699 are promising.

The limitations of the current study are that it was a short-term study in a small patient population and it was mainly designed as a proof-of-concept trial for future LCI699 therapy. It was not designed to allow correlation between the LCI699 dose required to normalize UFC and the baseline hormonal data, or between the increase in ACTH and the secondary increases in steroid precursors, androgens, and mineralocorticoids. Although UFC levels were measured using different assays at local laboratories, ULN values were used to normalize the data; nevertheless, the use of different assays with different ULN values is a limitation of the study. In addition, dose escalation during the study period was based on a single UFC measurement; this is also a limitation considering the natural day-to-day variation in cortisol levels (24). It should also be noted that adrenal insufficiency was assessed based on clinical judgment; one of the limitations of treating Cushing's disease is that there are no biomarkers that can reliably detect hypoadrenalism.

In conclusion, LCI699 demonstrated efficacy with a satisfactory safety and tolerability profile in this proof-of-concept study in Cushing's disease. A larger study of longer duration is ongoing to further evaluate the efficacy and safety of LCI699 in patients with Cushing's disease (LINC 2 study; clinicaltrials.gov identifier NCT01331239).

Acknowledgments

We thank Andrew Jones, PhD for medical editorial assistance with this manuscript. This study was funded by Novartis Pharma AG. Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation.

Address all correspondence and requests for reprints to: Xavier Bertagna, Department of Endocrinology, Hôpital Cochin, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France. E-mail: xavier.bertagna@cch.aphp.fr.

Clinical trials registration: Clinicaltrials.gov identifier: NCT01331239.

Disclosure Summary: In the past 2 years, X.B. has been an occasional consultant for Novartis, Ipsen, and HRA Pharma. R.P. has served as principal investigator on research grants from Novartis and has received research grants from Viropharma and Institut Biochimique SA, has been an occasional consultant for Novartis, Ipsen, Italfarmaco, Pfizer, Ferring, and Viropharma and has received lecture fees from Novartis. M.F. is a principal investigator in clinical trials sponsored by Novartis Pharmaceuticals and Corcept Therapeutics, with research support to Oregon Health and Science University. M.F. has received payments for consulting for Novartis. This potential conflict of interest has been reviewed and managed by Oregon Health and Science University. A.H.H. has received lecture fees from Novartis, Ipsen, and Pfizer and has served as a consultant to Ipsen and Pfizer. In the past 2 years, B.M.K.B. has served as the principal investigator on research grants from Novartis and Corcept to the Massachusetts General Hospital Neuroendocrine Unit and as a consultant to Novartis and HRA Pharma. Y.Z., P.R., A.T., and C.E.W. are all employees of Novartis. M.M. is a former employee of Novartis. M.B. has no conflicts of interest to declare.

References

1. **Pivonello R, De Martino MC, De Leo M, Lombardi G, Colao A.** Cushing's syndrome. *Endocrinol Metab Clin North Am*. 2008;37:135–149.
2. **Newell-Price J, Bertagna X, Grossman AB, Nieman LK.** Cushing's syndrome. *Lancet*. 2006;367:1605–1617.
3. **Biller BMK, Grossman AB, Stewart PM, et al.** Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab*. 2008;93:2454–2462.
4. **Tritos NA, Biller BM, Swearingen B.** Management of Cushing disease. *Nat Rev Endocrinol*. 2011;7:279–289.
5. **Novartis Pharma AG. Signifor Summary of Product Characteristics.** 2012. Available at: http://www.signifor.com/european-product-characteristics.jsp. Accessed February 5, 2014.

Downloaded from https://academic.oup.com/jcem/article/99/4/1375/2537458 by guest on 19 April 2024

6. **Novartis Pharmaceuticals. Signifor Prescribing Information.** 2012. Available at: http://www.pharma.us.novartis.com/cs/www.pharma.us.novartis.com/product/pi/pdf/signifor.pdf. Accessed February 5, 2014.
7. **Corcept Therapeutics. Mifepristone (Korlym) Prescribing Information.** 2012. Available at: http://www.korlym.com/docs/KorlymPrescribingInformation.pdf. Accessed February 5, 2014.
8. **Godbout A, Manavela M, Danilowicz K, Beauregard H, Bruno OD, Lacroix A.** Cabergoline monotherapy in the long-term treatment of Cushing's disease. *Eur J Endocrinol*. 2010;163:709–716.
9. **Pivonello R, De Martino MC, Cappabianca P, et al.** The medical treatment of Cushing's disease: effectiveness of chronic treatment with the dopamine agonist cabergoline in patients unsuccessfully treated by surgery. *J Clin Endocrinol Metab*. 2009;94:223–230.
10. **Verhelst JA, Trainer PJ, Howlett TA, et al.** Short and long-term responses to metyrapone in the medical management of 91 patients with Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1991;35:169–178.
11. **Castinetti F, Morange I, Jaquet P, Conte-Devolx B, Brue T.** Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease. *Eur J Endocrinol*. 2008;158:91–99.
12. **Chou SC, Lin JD.** Long-term effects of ketoconazole in the treatment of residual or recurrent Cushing's disease. *Endocr J*. 2000;47:401–406.
13. **Baudry C, Coste J, Bou Khalil R, et al.** Efficiency and tolerance of mitotane in Cushing's disease in 76 patients from a single center. *Eur J Endocrinol*. 2012;167:473–481.
14. **Luton JP, Mahoudeau JA, Bouchard P, et al.** Treatment of Cushing's disease by O,p'DDD. Survey of 62 cases. *N Engl J Med*. 1979;300:459–464.
15. **Schteingart DE, Tsao HS, Taylor CI, McKenzie A, Victoria R, Therrien BA.** Sustained remission of Cushing's disease with mitotane and pituitary irradiation. *Ann Intern Med*. 1980;92:613–619.
16. **Menard J, Watson C, Rebello S, Zhang YM, Dole WP.** Hormonal and electrolyte responses to the aldosterone synthase inhibitor LCI699 in sodium depleted healthy subjects. *J Am Coll Cardiol*. 2010;55:A61.E583.
17. **Amar L, Azizi M, Menard J, Peyrard S, Watson C, Plouin PF.** Aldosterone synthase inhibition with LCI699: a proof-of-concept study in patients with primary aldosteronism. *Hypertension*. 2010;56:831–838.
18. **Calhoun DA, White WB, Krum H, et al.** Effects of a novel aldosterone synthase inhibitor for treatment of primary hypertension: results of a randomized, double-blind, placebo- and active-controlled phase 2 trial. *Circulation*. 2011;124:1945–1955.
19. **Jeffcoate WJ, Rees LH, Tomlin S, Jones AE, Edwards CR, Besser GM.** Metyrapone in long-term management of Cushing's disease. *Br Med J*. 1977;2:215–217.
20. **Novartis Pharma AG. Metopirone (metyrapone) Prescribing Information.** 2004. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/012911s026lbl.pdf. Accessed February 5, 2014.
21. **Singh Y, Kotwal N, Menon AS.** Endocrine hypertension—Cushing's syndrome. *Indian J Endocrinol Metab*. 2011;15(Suppl 4):S313–S316.
22. **Orth DN.** Metyrapone is useful only as adjunctive therapy in Cushing's disease. *Ann Intern Med*. 1978;89:128–130.
23. **Ross WM, Evered DC, Hunter P, Benaim M, Cook D, Hall R.** Treatment of Cushing's disease with adrenal blocking drugs and megavoltage therapy to the pituitary. *Clin Radiol*. 1979;30:149–153.
24. **Petersenn S, Newell-Price J, Findling J, et al.** High variability in baseline urinary free cortisol values in patients with Cushing's disease. *Clin Endocrinol (Oxf)*. 2014;80:261–269.

Downloaded from https://academic.oup.com/jcem/article/99/4/1375/2537458 by guest on 19 April 2024

ENDOCRINE SOCIETY

Download the **Endocrine Society's multi-journal, full-text app** to say up to date on your iPhone, iPad, iTouch, and Android. Available at Apple App Store and Android Market