Single-Dose Study of a Corticotropin-Releasing Factor Receptor-1 Antagonist in Women With 21-Hydroxylase Deficiency

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Context: Treatment of 21-hydroxylase deficiency (21OHD) is difficult to optimize. Normalization of excessive ACTH and adrenal steroid production commonly requires supraphysiologic doses of glucocorticoids.

Objectives: We evaluated the safety and tolerability of the selective corticotropin releasing factor type 1 (CRF_1) receptor antagonist NBI-77860 in women with classic 21OHD and tested the hypothesis that CRF_1 receptor blockade decreases early-morning ACTH and 17α-hydroxyprogesterone (17OHP) in these patients.

Participants: The study enrolled eight classic 21OHD females, ages 18–58 years, seen at a single tertiary referral university setting.

Design: This was a phase Ib, single-blind, placebo-controlled, fixed-sequence, single-dose trial. During three treatment periods separated by 3-week washout intervals, patients sequentially received placebo, NBI-77860 300 mg, and NBI-77860 600 mg at 10 PM; glucocorticoid therapy was withheld for 20 hours. We evaluated ACTH, 17OHP, androstenedione, and testosterone as well as NBI-77860 pharmacokinetics over 24 hours.

Results: Dose-dependent reductions of ACTH and/or 17OHP were observed in six of eight subjects. Relative to placebo, NBI-77860 led to an ACTH and 17OHP reduction by a mean of 43% and 0.7% for the 300 mg dose, respectively, and by 41% and 27% for the 600 mg dose, respectively. Both NBI-77860 doses were well tolerated.

Conclusion: The meaningful reductions in ACTH and 17OHP following NBI-77860 dosing in 21OHD patients demonstrate target engagement and proof of principle in this disorder. These promising data provide a rationale for additional investigations of CRF_1 receptor antagonists added to physiologic doses of hydrocortisone and fludrocortisone acetate for the treatment of classic 21OHD. **(*J Clin Endocrinol Metab* 101: 1174–1180, 2016)**

Congenital adrenal hyperplasia comprises a set of enzymatic defects in the cortisol synthetic pathway. The most common form, accountable for more than 90% of cases, is 21-hydroxylase deficiency (21OHD) (1). In response to the impaired cortisol production, the hypothalamus and pituitary augment the secretion of corticotropin-releasing factor (CRF) and ACTH, respectively, leading to adrenal cortex hyperplasia. The elevated ACTH stimulates the steroid biosynthetic pathways; however, in the face of 21-hydroxylase blockage, upstream precur-

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Abbreviations: AUC_{0-24}, area under the concentration curve from 0 to 24 hours; BMI, body mass index; CRF, corticotropin releasing factor; HPA, hypothalamic-pituitary-adrenal; 21OHD, 21-hydroxylase deficiency; 17OHP, 17α-hydroxyprogesterone; TEAE, treatment-emergent adverse event.

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sors, such as 17α-hydroxyprogesterone (17OHP), accumulate and proceed along pathways toward androgens. The enzymatic impairment varies from complete to mild, resulting in a wide range of disease manifestations. The most severe or "classic" disease always features cortisol deficiency with or without concomitant aldosterone deficiency, while patients in whom cortisol production is preserved are classified as "nonclassic." Girls with classic 21OHD are born with variably virilized external genitalia from intrauterine androgen excess, whereas patients with nonclassic 21OHD might present with premature pubarche, hirsutism, and acne (2).

Treatment of classic 21OHD aims to replace the deficient hormones and at the same time to restore the negative feedback on the hypothalamus and pituitary to reduce the excessive adrenal androgen synthesis. This therapeutic balance is often difficult to achieve. Supraphysiologic glucocorticoid doses are frequently required to normalize the androgens, promoting iatrogenic Cushing syndrome and associated health consequences. Adults with 21OHD suffer high rates of obesity, metabolic syndrome, and low bone mass (3, 4). Novel nonglucocorticoid treatments to reduce adrenal androgen production could minimize excess glucocorticoid exposure and its side effects.

Because elevated ACTH is the primary driver for adrenal steroid production in 21OHD, a successful treatment strategy might be to develop nonsteroidal agents that can directly block ACTH synthesis. CRF is the primary regulator of the hypothalamic-pituitary-adrenal (HPA) axis and is released from the hypothalamus into the hypophyseal portal system, acting directly on specific receptors on pituitary corticotropes. Two different types of CRF receptors exist: CRF type 1 (CRF_1) receptor, abundant in the pituitary and in the neocortex, and CRF type 2 receptor, predominantly found in the periphery, but also in some brain areas such as the septum, ventromedial hypothalamus, and dorsal raphe nucleus (5, 6). CRF receptor antagonists have been shown to reduce ACTH release both in vitro and in vivo (7–10). By acting directly on the pituitary to decrease ACTH, CRF_1 receptor antagonists could effectively reduce adrenal steroid production, while obviating the need for supraphysiologic doses of glucocorticoids. The present study was designed to evaluate the safety and tolerability of the selective small-molecule CRF_1 receptor antagonist NBI-77860 in women with classic 21OHD. We specifically tested the hypothesis that CRF_1 receptor blockade can effectively decrease the early-morning rise of ACTH from the pituitary and subsequently 17OHP rise from the adrenal. This result would provide proof of concept and justify multiple-dose studies to determine downstream effects to lower androgens in patients with 21OHD.

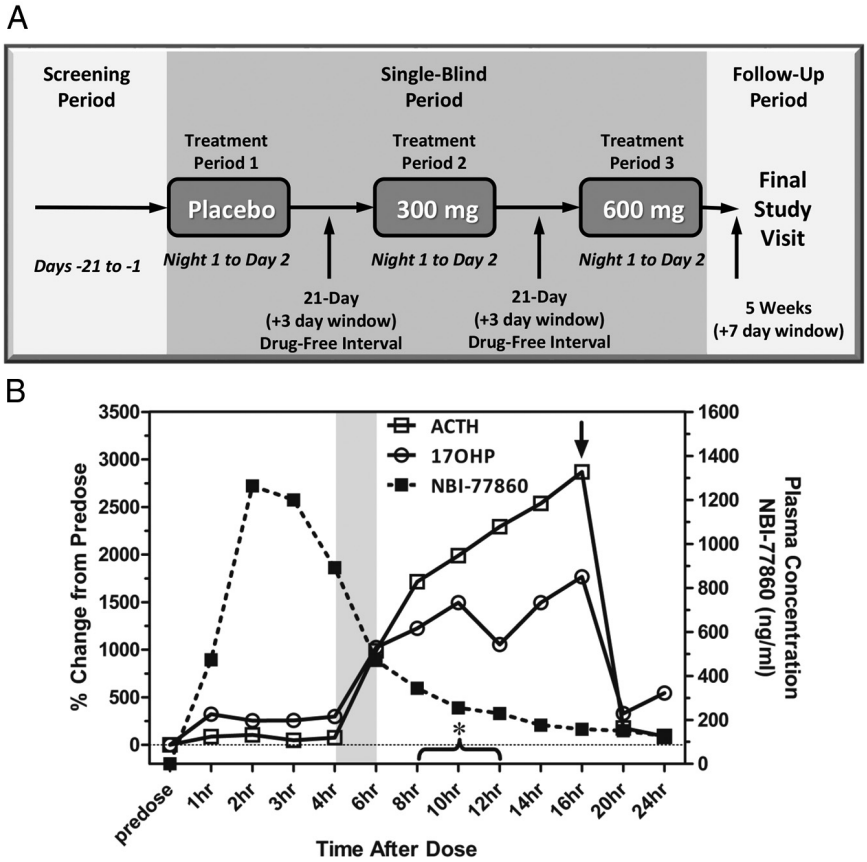

Figure 1. Design of NBI-77860 phase I study (A). Participants (n = 8) received a fixed sequence of three single-dose treatments, administered at approximately 10 PM. For each treatment, subjects were admitted for 24 hours, and blood samples were obtained predose, hourly for the first 4 hours, every 2 hours between 4 and 16 hours postdose, and every 4 hours between 16 and 24 hours after each treatment. Plasma drug concentrations and the hypothalamic-pituitary-adrenal axis biomarkers ACTH, 17OHP, androstenedione, testosterone, and cortisol were measured in all samples. Plasma ACTH rises during the placebo period (B). The concentration × time profile of 600 mg NBI-77860 (dotted line) is shown in relation to the early morning rise of both ACTH (open squares) and 17OHP (open circles) at 2–4 AM (shaded bar at 4–6 hours postdose) and the prespecified morning window of 6–10 AM (bracket with asterisk at 8–12 hours postdose). Arrow marks PM, when hydrocortisone was administered.

Participants and Methods

Study design

We conducted a phase Ib, single-blind, placebo-controlled, fixed-sequence, single-dose study at the University of Michigan, Ann Arbor. Participants were eight adult females with classic 21OHD, confirmed by ge-

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notype, aged 18–58 years, and body mass index (BMI) 18–35 kg/m^2. Inclusion criteria included a morning serum 17OHP higher than 1000 ng/dL (30 nmol/L), serum cortisol of lower than 5 μg/dL (138 nmol/L), and ACTH of at least 20 pg/mL (4.4 pmol/L). All participants received a stable glucocorticoid replacement regimen for a minimum of 30 days before study enrollment (as detailed in Supplemental Table 1) and throughout the duration of study, with the exception of intercurrent illnesses. Contraception was required throughout the study duration for premenopausal women with a uterus. Patients with evidence of substance abuse, hepatitis B or C, HIV infection, or dexamethasone therapy were excluded. Concurrent use of other investigational drugs, strong or moderate CYP3A4 inhibitors, or inducers was not permitted throughout the study duration. The study was conducted following institutional review board approval (HUM00077960) under written informed consent from all participants. All participants completed the entire study dosing and pharmacokinetic sampling protocol.

Participants received a fixed sequence of three single-dose treatments administered at approximately 10 PM: placebo or NBI-77860, 300 mg and 600 mg, separated by 3-week drug-free intervals (Figure 1). To facilitate an unimpeded rise of ACTH, glucocorticoid therapy was withheld for 20 hours from 6 PM the day of treatment until 2 PM the following day. For each treatment period, blood samples were obtained predose, hourly for the first 4 hours, every 2 hours between 4 and 16 hours postdose, and every 4 hours between 16 and 24 hours after each treatment. In addition, samples were obtained weekly during the 21-day drug-free interval and approximately 5 weeks after the last dose of NBI-77860. Pharmacokinetic assessments for NBI-77860 included the area under the concentration curve from 0 to 24 hours (AUC_{0-24}), maximum plasma concentration (C_{max}), and time to achieve maximum plasma concentration. The HPA axis biomarkers ACTH, 17OHP, androstenedione, testosterone, and cortisol, as well as tests of safety, were measured at the same sampling time points. ACTH and 17OHP measurements during a prespecified period of 6–10 AM (8–12 hours postdose) were chosen as the primary pharmacodynamic measure, corresponding to the time when control of adrenal steroid synthesis is most difficult to achieve in this population with physiologic glucocorticoid dosing. ACTH was assayed by immunochemiluminescence, and steroid assays were performed with liquid chromatography-tandem mass spectrometry at Quest Diagnostics; comprehensive steroid panel 90392. Quest also performed *CYP21A1P*/*CYP21A2* genotyping to confirm the classic 21OHD diagnosis.

Statistical analyses and safety

All pharmacodynamic, pharmacokinetic, and safety analyses included all participants who received at least one dose of study drug in any treatment period. Descriptive statistical methods were used to summarize data from this study. The statistical output was generated using SAS software (version 9.3), and participant medical history and adverse event data were coded using the Medical Dictionary for Regulatory Activities (version 16.0).

Pharmacodynamic data. Serum 17OHP, plasma ACTH, serum androstenedione, and serum testosterone levels were summarized for each treatment period (placebo, NBI-77860 300 mg, and NBI-77860 600 mg) using the observed (raw) concentrations as well as the absolute and percent change from predose levels. A timepoint aggregate was added to this analysis to define the "morning window," ie, the data recorded at 8, 10, and 12 hours postdose (between 6 and 10 AM).

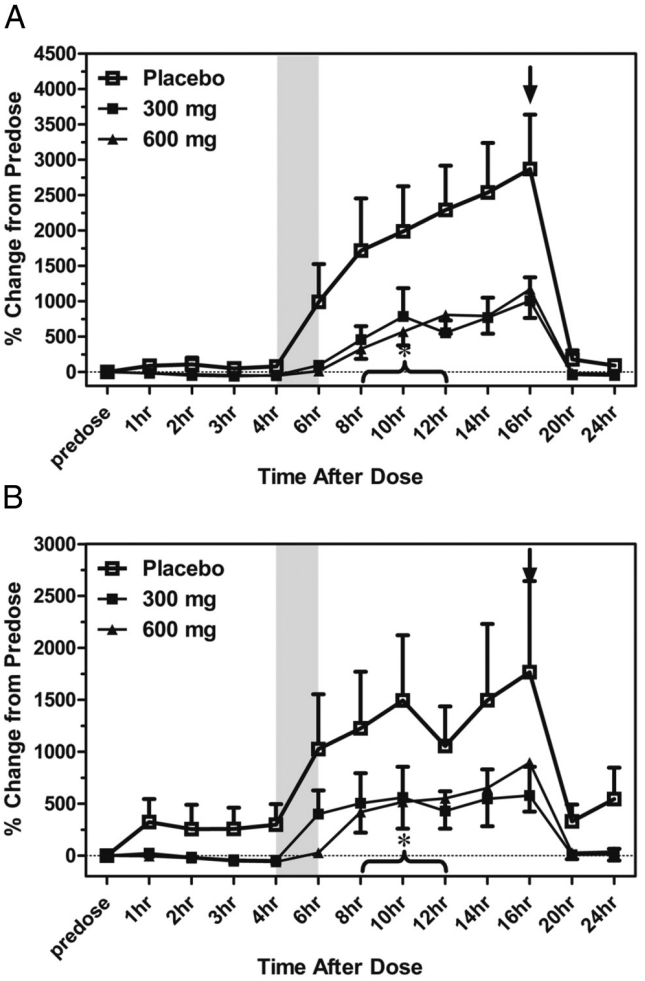

Figure 2. Primary endpoint results. Mean percent changes from predose concentrations of ACTH (A) and 17OHP (B) are shown for placebo (open squares) and NBI-77860 300-mg (open circles) and 600-mg (closed circles) treatment periods. The shaded area represents the time of the early-morning rise observed in both ACTH and 17OHP. This period was used as an indicator to assess the pharmacologic effect of NBI-77860 comparing exposure of the compound on the direct (ACTH) and indirect (17OHP) measures. The bracket with asterisk indicates the prespecified 8–10 AM window used for the primary endpoint. Arrow marks 2 PM, when hydrocortisone was administered.

Pharmacokinetic data. Plasma concentrations of NBI-77860 were summarized by nominal (scheduled) timepoint and NBI-77860 dose (300 or 600 mg). Pharmacokinetic parameters, including AUC_{0-24} and C_{max}, were calculated for NBI-77860 using noncompartmental methods.

Safety data. Treatment-emergent adverse events (TEAEs) were defined as events with an onset that occurred any time after the first dose of study drug through the final study visit. The TEAEs were categorized by the Medical Dictionary for Regulatory Activities system organ class and preferred term, and then summarized in frequency tables by treatment. Because of the low incidence of TEAEs during the study period, the two NBI-77860 doses were combined for the purposes of these summaries.

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Table 1. Plasma ACTH and 17OHP After Single Doses of NBI-77860

Participant	Age (y)	BMI (kg/m²)	BSA (m²)	Dose (mg)	ACTH % Change From Placebo (Mean of AM Timepoints)	17OHP % Change From Placebo			Responder/ Nonresponder[a]
						6 AM	8 AM	10 AM	
1011001	58	29.4	1.62	300	−29.7	1.2	16.6	2.3	Nonresponder
				600	−32.9	−4.3	18.1	−52.4	
1011002	22	19.2	1.48	300	−42.8	−19.2	11.4	6.1	Responder
				600	−86.1	−60.7	−65.9	−73.0	
1011003	22	20.1	1.46	300	−51.3	−22.8	−16.0	58.4	Responder
				600	−67.1	−54.4	−49.6	13.6	
1011004	47	33.9	1.83	300	−13.0	29.3	−61.5	167.5	Nonresponder
				600	220	189.3	18.9	−29.0	
1011005	33	23.1	1.47	300	−43.2	−4.8	10.6	7.7	Nonresponder
				600	−54.9	−9.7	−17.1	84.0	
1011006	21	24.6	1.53	300	−89.1	−89.4	−97.1	−96.4	Responder
				600	−61.2	−94.3	−93.7	−49.0	
1011007	25	36.0	1.64	300	−64.9	139.3	63.6	49.8	Nonresponder
				600	−51.7	−11.9	9.8	23.3	
1011008	19	25.3	1.80	300	91.1	31.8	−9.4	−40.3	Responder
				600	11.5	−8.2	−40.3	−90.6	

[a] Patients were classified as "responders" if they had at least a 50% reduction of 17OHP from placebo levels at one or more time points within the 6–10 AM window. BSA, body surface area.

Changes in psychiatric symptoms were also measured using the Brief Psychiatric Rating Scale, version 4.0.

Results

ACTH and steroid dynamics

During the placebo period, the early-morning rise of plasma ACTH began on average at 2–4 AM (4–6 hours postdosing; shaded area in Figure 1B), and ACTH remained high through the predefined morning window (6–10 AM; 8–12 hours postdosing designated by the asterisk in Figure 1B) until the administration of hydrocortisone at 2 PM. During the placebo phase, plasma ACTH and serum 17OHP rose overnight and achieved mean values of 533 pg/mL (117 pmol/L) and 5390 ng/dL (163 nmol/L), respectively (Figures 1B and 2). Administration of NBI-77860 attenuated and delayed the rise in ACTH and 17OHP at both doses (Figure 2). Relative to placebo, NBI-77860 reduced the 6–10 AM ACTH rise by a mean of 43% for 300 mg and by 41% for 600 mg (Table 2 and Figure 2A, 6–10 AM indicated by bracket with asterisk). Both 300 mg and 600 mg NBI-77860 doses also decreased serum 17OHP in the morning window by 0.7% and by 27%, respectively, compared to placebo (Table 2 and Figure 2B, 6–10 AM indicated by bracket with asterisk).

Individually, participants were classified as "responders" if serum 17OHP declined at least 50% from placebo values at one or more time points within the 6–10 AM window. Of the eight participants, four fulfilled this criterion (Table 1). All responders were younger than 25 years of age and all had a BMI lower than 26 kg/m². Conversely, the BMI was more than 26 kg/m² for all but one nonresponder. A direct correlation was observed overall between fractional reductions from predose values in ACTH and in 17OHP (Figure 3A; $N = 193$, $r = 0.814$, $P < .05$). Reductions in serum testosterone and androstenedione were observed in some participants during one or both treatment periods (Table 3).

Pharmacokinetic and safety analysis of NBI-77860

Mean AUC_{0-24} values were 3450 ± 2010 hours/ng/mL for 300 mg and 8300 ± 2750 hours/ng/mL for 600 mg NBI-77860. Mean C_{max} values were 551 ± 343 ng/mL

Table 2. Plasma ACTH and 17OHP During the Morning Window (6–10 AM): Mean ± SD and Percent Reduction From Placebo Period by NBI-77860 Dose

Treatment	ACTH (pg/mL)		17OHP (ng/dL)	
	Mean ± SD	% Reduction from Placebo	Mean ± SD	% Reduction From Placebo
Placebo	533 ± 506	0	5390 ± 3345	0
NBI-77860 300 mg	306 ± 298	43	5428 ± 4160	0.7
NBI-77860 600 mg	316 ± 310	41	3919 ± 2991	27.3

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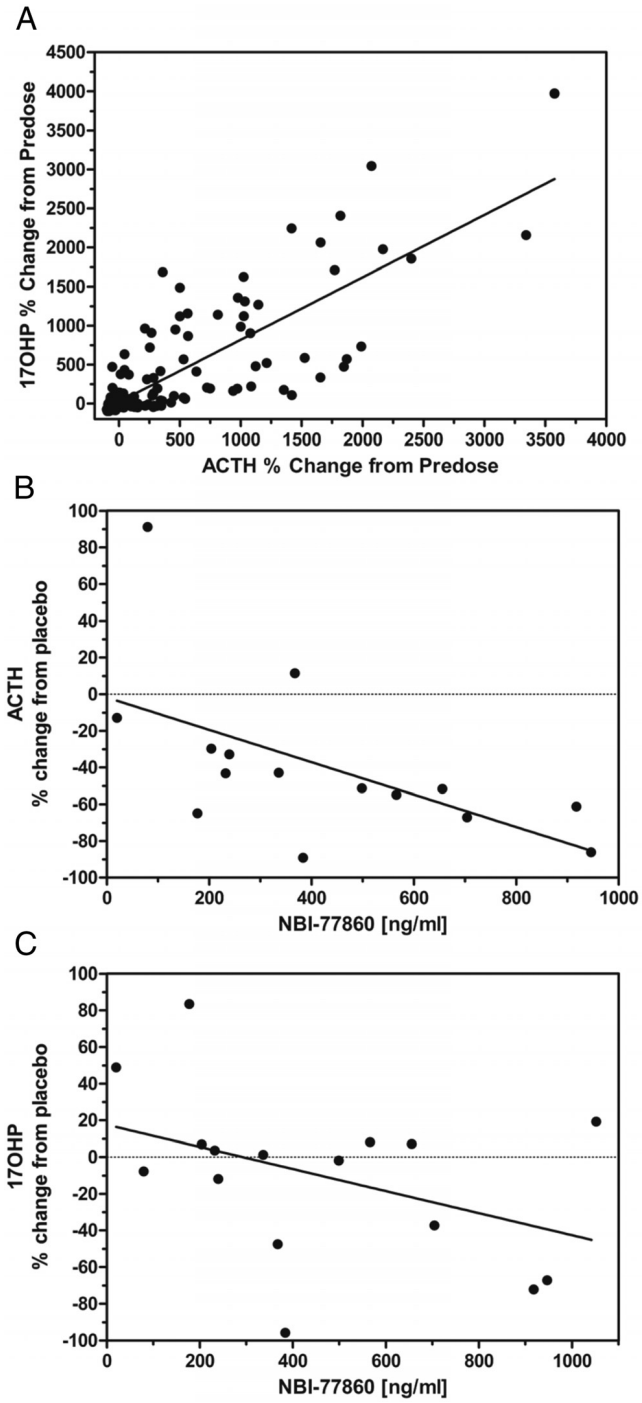

Figure 3. Correlations for study measures. (A) Correlations are shown between percentage reductions from predose concentrations in plasma ACTH and serum 17OHP (N = 193, r = 0.814, $P < .05$). Correlation between plasma concentration (exposure) of NBI-77860 and plasma or serum concentrations of ACTH (B; r = −0.569, $P < .05$) and 17OHP (C; r = −0.422, $P < .05$). All measurements were taken during the early-morning rise of ACTH defined by the increase in all eight subjects and corresponded to the 4- and 6-hour timepoints postdosing (2–4 AM) illustrated in Figure 1B.

and 1420 ± 541 ng/mL for 300 mg and 600 mg NBI-77860, respectively. The peak plasma concentration of NBI-77860 preceded the early-morning rise in ACTH and 17OHP by 2 hours (time to achieve maximum plasma concentration 12:00 AM; early morning rise, 2–4 AM, Figure 1B). Plasma concentration of NBI-77860, measured during that early-morning rise of plasma ACTH or 17OHP, was inversely correlated with both plasma ACTH (Figure 3B; r = −0.569, $P < .05$) and serum 17OHP (Figure 3C; r = −0.422, $P < .05$), demonstrating a pharmacologic concentration-response relationship.

Both NBI-77860 doses were well tolerated. TEAEs are summarized in Supplemental Table 2. No adverse events were consistently observed or confidently attributed to NBI-77680. Three participants experienced six headache events during the study, and two of three experienced headaches after placebo as well. All headaches occurred in the afternoon following the evening dosing and were graded as mild. All headaches lasted less than 2 hours, and acetaminophen 650 mg was administered for relief during one event. No changes in psychiatric symptoms as measured using the Brief Psychiatric Rating Scale, version 4.0, were observed.

Discussion

A central goal of 21OHD treatment is to attenuate the excessive adrenal androgen production. Current therapeutic strategies are limited to glucocorticoids given at supraphysiologic doses and nonphysiologic administration schemes to lower ACTH, which is the main driver of adrenal androgen synthesis. Although effective, these regimens promote iatrogenic Cushing syndrome and discourage adherence (3, 4). Continuous subcutaneous hydrocortisone infusion has been used experimentally in young patients with increased cortisol clearance; this approach achieved lower 17OHP and adrenal androgen production despite a lower total daily dose (11, 12). Although conceptually appealing, this approach is expensive, labor-intensive, and impractical for most patients and physicians. Modified-release hydrocortisone preparations that attempt to mimic the cortisol circadian rhythm and to suppress the ACTH rise in the early morning have recently emerged (13, 14). Compared with conventional therapy, one modified-release hydrocortisone system decreased androstenedione and 17OHP with lower hydrocortisone dose equivalent (13). Although promising, these approaches still rely exclusively on glucocorticoid-mediated negative feedback suppression of ACTH, and long-term superiority vs conventional therapy remains to be shown.

Our study is the first to explore an alternative strategy to lower ACTH in patients with 21OHD, employing a small-molecule antagonist for the CRF_1 receptor. The first CRF_1 receptor antagonists developed were tested for their antidepressant and anxiolytic effects in large well-con-

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Table 3. Serum Androstenedione and Testosterone After Single Doses of NBI-77860, Mean, and Percent Change From Placebo During the Morning Window (6–10 AM)

		Androstenedione		Testosterone	
Participant	Dose	Mean (ng/dl)	% Change From Placebo	Mean (ng/dl)	% Change From Placebo
1011001	Placebo	303.0	0	105.3	0
	300	295.3	−2.5	131.7	25.0
	600	265.7	−12.3	122.7	16.5
1011002	Placebo	185.3	0	49.7	0
	300	190.7	2.9	42.7	−14.1
	600	78.0	−57.9	23.0	−53.7
1011003	Placebo	146.0	0	35.0	0
	300	132.7	−9.1	32.3	−7.6
	600	147.7	1.1	34.0	−2.9
1011004	Placebo	820.0	0	169.3	0
	300	747.7	−8.8	158.7	−6.3
	600	934.0	13.9	164.0	−3.1
1011005	Placebo	308.0	0	76.3	0
	300	377.0	22.4	107.3	40.6
	600	420.3	36.5	83.0	8.7
1011006	Placebo	195.7	0	59.7	0
	300	141.0	−27.9	36.7	−38.5
	600	173.3	−11.4	50.7	−15.1
1011007	Placebo	145.3	0	47.3	0
	300	135.3	−6.9	32.3	−31.7
	600	84.7	−41.7	19.0	−59.9
1011008	Placebo	914.0	0	127.0	0
	300	973.3	6.5	147.3	16.0
	600	1366.3	49.5	194.3	53.0

trolled clinical trials (15, 16), but none has yet progressed beyond the phase 2 proof-of-concept stage. NBI-77860 emerged as a high-affinity CRF_1 receptor antagonist in 2010 (17), and its use has been explored in patients with major depressive disorder (unpublished data referenced in www.ClinicalTrials.gov NCT00733980) and posttraumatic stress disorder (18). In the current study, we tested the ability of NBI-77860 to lower ACTH in patients with classic 21OHD, for whom HPA axis activation is central to the pathophysiology of the disease.

In this initial study, we found that a single bedtime dose of NBI-77860 in women with 21OHD decreased ACTH and/or 17OHP in six of eight study participants. Although the effect was more robust in subjects younger than age 25 years, these women were also leaner than the others. The reduction in ACTH and 17OHP appeared to be dependent on dose and drug exposure. Thus, it is possible that higher doses than 600 mg might be necessary to lower ACTH in some patients, particularly those with BMI higher than 29 kg/m^2. Interestingly, among responders, decreases in serum androstenedione and testosterone following single doses of NBI-77860 were not consistently observed, possibly because suppression of these downstream steroids requires a more sustained ACTH reduction. Chronic dosing of a CRF_1 receptor antagonist would help determine the effectiveness of this potential therapy.

In this study, a single dose of NBI-77860 up to 600 mg was well tolerated. As in prior studies of NBI-77860 in healthy controls and depressed subjects (18), the most common adverse event was headache. All headaches occurred in the afternoon following either placebo or study drug while glucocorticoids were withheld. Because the usual glucocorticoid dose was held the following morning, we speculate that the headache might have been caused by the glucocorticoid withdrawal. The highest doses previously used in clinical trials were 600 mg administered as a single dose and 350 mg administered for 6 weeks (18). Because of the exaggerated ACTH elevation in patients with classic 21OHD, we assessed the safety and tolerability of 300 and 600 mg, and no additional or dose-dependent adverse events were observed in this small trial.

This exploratory proof-of-principle study has limitations typical of phase I clinical trials: a small number of participants, a single and fixed dose of the administered compound, and suspended glucocorticoid therapy during the window of time used for the primary endpoint. For these reasons, our data do not allow a comprehensive assessment of the efficacy and safety of NBI-77860 as it might be used in clinical practice. Nonetheless, the single-dose administration of this CRF_1 receptor antagonist demonstrated positive evidence of target engagement with

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meaningful reductions in the target hormonal biomarkers, ACTH and 17OHP, in most of the patients tested.

In conclusion, in this phase Ib, single-blind, placebo-controlled trial, we showed that one dose of the CRF_1 receptor antagonist NBI-77860 produces clinically significant reductions in morning ACTH and 17OHP in females with classic 21OHD. Our data support the use of CRF_1 receptor antagonists as promising agents for the treatment of patients with 21OHD as a strategy to reduce ACTH production without raising glucocorticoid therapy above physiologic replacement doses. Advancing CRF_1 receptor antagonists into larger, longer term multidose trials will allow better assessment of the efficacy in mitigating adrenal androgen overproduction and improving outcomes in patients with 21OHD.

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