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Arlt, W. orcid.org/0000-0001-5106-9719, Brac de la Perrière, A. orcid.org/0000-0001-6453-8326, Hirschberg, A.L. orcid.org/0000-0001-6481-6277 et al. (10 more authors) (2025) Long-term outcomes in patients with congenital adrenal hyperplasia treated with hydrocortisone modified-release hard capsules. European Journal of Endocrinology, 193 (1). pp. 76-84. ISSN 0804-4643

https://doi.org/10.1093/ejendo/lvaf130

European Journal of Endocrinology, 2025, **193**, 76–84
https://doi.org/10.1093/ejendo/lvaf130
Advance access publication 17 June 2025
Original Research

Long-term outcomes in patients with congenital adrenal hyperplasia treated with hydrocortisone modified-release hard capsules

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Abstract

Background: Hydrocortisone modified-release hard capsules (MRHC, development name Chronocort) replace the physiological overnight cortisol rise and improve the biochemical control of congenital adrenal hyperplasia (CAH).

Aim: This study aims to evaluate long-term safety, tolerability, and efficacy of MRHC.

Methods: This is an open-label follow-on study.

Results: Ninety-one patients with classic CAH, mean age 37 years, 68% female, 32% male, entered the study and 22 discontinued. Median treatment duration was 4 years (range 0.2-5.8). Median hydrocortisone dose at study entry was 30 mg/day and reduced to 20 mg/day after 24 weeks and stayed stable thereafter until 48 months ($P < .0001$). Disease control improved on MRHC for the steroid disease markers serum 17-hydroxyprogesterone (17OHP) ($P < .03$) and androstenedione (A4) ($P < .002$). After 4 years, the majority of patients had a 17OHP < 4-fold upper limit of normal (ULN) (71%) and an A4 <ULN (90%). Measurement of 17OHP and A4 at 09:00 h and 13:00 h gave similar results. Of the 37 women < 50 years of age who were not on contraceptives over the whole study period, 5 became pregnant (13.5%). Of the men, 13.8% (4/29) had a partner pregnancy. Seven patients had an adrenal crisis with 1 patient reporting 8 of these giving an incidence of 3.9 crises per 100 patient years.

Conclusions: Modified-release hard capsule treatment resulted in hydrocortisone dose reduction followed by a stable dose with improved biochemical control associated with fertility. Biochemical control could be reliably monitored by a single blood sample taken between 09:00 and 13:00 h. The incidence of adrenal crises was below that reported previously in patients with CAH.

Keywords: congenital adrenal hyperplasia, 21-hydroxylase deficiency, adrenogenital syndrome adrenal insufficiency, hydrocortisone, glucocorticoid, Chronocort

Significance

Hydrocortisone modified-release hard capsules have been shown in a randomized controlled study to improve the biochemical control of congenital adrenal hyperplasia (CAH). This study provides long-term follow-up data in a prospective open-label monitored study of hydrocortisone modified-release hard capsules in 91 CAH patients. The results show that the improved disease control on hydrocortisone modified-release hard capsules was maintained on lower dose of hydrocortisone over time, that this was associated with fertility, and the incidence of adrenal crises was below that reported previously in patients with CAH.

Received: March 18, 2025. **Revised:** May 16, 2025. **Editorial Decision:** June 10, 2025. **Accepted:** June 13, 2025

Introduction

Classic congenital adrenal hyperplasia (CAH) is a genetic disorder caused by defective adrenal steroidogenesis and cortisol deficiency.[1] The most common underlying pathogenic variants are located in the gene that encodes 21-hydroxylase accounting for approximately 95% of cases. In healthy individuals, cortisol has a distinct circadian rhythm with levels rising in the early morning to peak on waking and then falling during the day to low levels in the evening. Cortisol levels are controlled by the pituitary hormone adrenocorticotropic hormone (ACTH), with regulation by negative feedback from cortisol at the hypothalamus and pituitary. In CAH, conventional, immediate-release hydrocortisone (irHC) treatment replaces cortisol and controls ACTH-driven excess adrenal androgen production during the day. However, irHC fails to do so during the night due to its rapid release and short half-life in the bloodstream. This results in an excessive overnight rise of ACTH and consequently an accumulation of 17-hydroxyprogesterone (17OHP) prior to the enzymatic block in steroidogenesis, which in turn drives excess production of the adrenal androgen precursor androstenedione (A4). Excess adrenal androgens cause virilization of the female infant and precocious puberty, short stature, and reduced fertility in both sexes. Treatment is generally managed clinically for cortisol replacement and by measuring the adrenal steroids 17OHP and A4 to monitor control of adrenal androgens. Congenital adrenal hyperplasia cohort studies in the last 20 years have shown poor health with increased mortality, height below genetic potential, reduced fertility, decreased bone mineral density (BMD), obesity, and increased cardiometabolic risk, all pointing to inadequate and often excessive glucocorticoid (GC) replacement as the main cause of the poor health outcomes.[2,3]

To address the poor health outcomes in patients with CAH, a modified-release hard capsule formulation of hydrocortisone (MRHC) was developed, with the development name Chronocort, and is now licensed in Europe to treat adults and paediatric patients aged 12 years and over with CAH (Efmody®, Neurocrine B.V., NL). MRHC is a multiparticulate formulation with a modified-release coating that allows for the delayed and sustained absorption of hydrocortisone (HC).[4] Taken twice daily in a "toothbrush" regimen, last thing at night and first thing in the morning, MRHC restores the physiological overnight rise and diurnal rhythm of cortisol.[4] MRHC has been shown to improve the biochemical control of CAH in phase 2 and 3 clinical trials.[5,6] Patients from the phase 2 and 3 clinical trials were entered into a phase 3 extension study of the efficacy, safety, and tolerability of MRHC in the treatment of CAH. Here, we report the end-of-study data for the phase 3 extension study, wherein the majority of patients had at least 4 years of treatment with MRHC.

Methods

Study protocol

This was a phase 3 open-label extension study. Participants who completed either phase 2 or phase 3 MRHC studies were offered the opportunity to continue open-label MRHC therapy. After screening, all participants underwent a full set of baseline assessments before starting treatment. Participants entering immediately from the phase 3 study, who were previously on MRHC, continued the same dose of MRHC that they were receiving at the end of the feeder study. The other participants who were on standard therapy at the start of the extension study had their initial MRHC dose determined using the identical HC dose or equivalent (5× for prednis(ol)one and 80× for dexamethasone, capped at 30 mg/day). Approximately two-thirds of the daily MRHC dose was given in the evening (~23:00 h), with the remainder given in the morning (~07:00 h). Stress doses to be used when the sick day rules were implemented were supplied by the study site as part of a safety pack, which typically included (according to local practice) the following:

- A supply of 42 × 10 mg oral HC tablets to allow dosage of up to 20 mg 3 times daily for 1 week
- Two vials of HC for injection plus syringes and needles
- The site's standard information guidance regarding sick day rules (routinely given to any patient receiving HC replacement therapy)

Participants returned to the study centre at 4, 12, and 24 weeks after starting the open-label extension study and 6 months thereafter for follow-up assessments. Dose titration was performed by the local study site investigator at these visits. The intention of dose adjustment was to optimize control of CAH according to current standard of care which in previous studies was considered a 17OHP < 36 nmol/L (1200 ng/dL), equivalent to ~4-fold the upper limit of normal (ULN) depending on the assay (for this study 10.4 nmol/L [300 ng/dL]) and A4 <ULN (7.0 nmol/L (200 ng/dL) [♀], 5.2 nmol/L (150 ng/dL) [♂]). Dose adjustments were based on clinical symptoms using an Adrenal Insufficiency Checklist (Table S1) and the results of serum 17OHP and A4 measurements at 2 time points (09:00 and 13:00 h). Steroid concentrations were measured in serum by high-performance liquid chromatography–tandem mass spectrometry (Q2 Solutions, USA). The primary objective was to evaluate the safety and tolerability of MRHC over time, as assessed by signs and symptoms suggestive of either adrenal insufficiency or glucocorticoid overtreatment, adrenal crisis, adverse events (AEs), laboratory measures, BMD measured by dual-energy X-ray absorptiometry scan (DEXA) and clinical observation.

Key inclusion and exclusion criteria

Key inclusion criteria

- Participants with classic CAH due to 21-hydroxylase deficiency who successfully completed the phase 2 or phase 3 clinical studies

Key exclusion criteria

- Co-morbid condition requiring daily administration of a medication (or use of any medications/supplements) that interfere with the metabolism of glucocorticoids.
- Clinical or biochemical evidence of hepatic or renal disease.
- Participants on regular daily inhaled, topical, nasal, or oral steroids for any indication other than CAH.
- A history of bilateral adrenalectomy.
- Routinely night shift working.

- Pregnancy: Women who were pregnant or lactating were not allowed to enter the study. However, no specific contraception requirements were required by the protocol during the study since it was a long-term study, and all participants needed to be on continuous HC treatment for their underlying condition. Therefore, the risks of pregnancy whilst receiving MRHC were perceived to be no greater than the risks of pregnancy on standard HC treatment. If a participant became pregnant during the study, they were to be withdrawn, not due to safety reasons but because pregnancy may interfere with the study endpoints. However, participants who withdrew from the study due to pregnancy could re-enter the study after the pregnancy.

Ethics

All participants gave written informed consent. The study protocols were approved by the East Midlands—Leicester Central Research Ethics Committee (ref: 16/EM/0278), the Medicines and Healthcare Products Regulatory Agency (NCT03062280; EudraCT 2015-005448-32), and local ethics committees. The study complied with the Declaration of Helsinki.

Statistics

The full analysis set was used to summarize the safety and efficacy in this study. The full analysis set comprised all participants who entered the extension study and subsequently received at least 1 dose of MRHC. Clinical outcomes at 4 years are reported with descriptive statistics only. Baseline was defined as the first visit of Study DIUR-006 for all subjects. Dual-energy X-ray absorptiometry scan data were not available for some participants at the 4-year time point, owing to COVID-19 restrictions on study visits; therefore, DEXA 36-month data are imputed in 28/45 participants. To compare MRHC dose between baseline and 4 years, post hoc statistics were calculated using Wilcoxon matched-pairs signed rank test (2-tailed). Quadrant analyses were conducted using individual patient 09:00 h either 17OHP or A4 and HC dose; participants were considered responders when 09:00 h 17OHP $\leq$ 36 nmol/L or A4 $\leq$ 7 nmol/L and HC dose $\leq$ 25 mg/day (ie, the upper dose recommended for the replacement of adrenal insufficiency in adults[7]), respectively. A 2-sided Fisher's exact test was used compare responder rates between baseline and 4 years. All *P* values considered nominal.

Safety

Adverse events were recorded including AEs of special interest such as adrenal crisis. The investigators were given guidance that an adrenal crisis was defined according to the recommendations of Allolio[8] to include (1) major impairment of general health with at least 2 signs/symptoms and (2) parenteral glucocorticoid (hydrocortisone) administration followed by clinical improvement.

Results

Patients

A total of 92 participants gave informed consent. One participant was a screen failure so 91 participants received at least 1 dose of MRHC and were included in the full analysis set (Figure 1). Of these 91 participants, 81 entered directly from the phase 3 study, 6 entered from the phase 3 study after a gap during which they received non-study glucocorticoid (GC) therapy, and 4 entered from the phase 2 study after a gap during which they received non-study GC therapy. A total of 69 participants (75.8%) completed the study, with 22 participants (24.2%) discontinuing from the study: 11 at their own request, 5 due to pregnancy (2 of whom re-entered the study), 2 due to undergoing fertility treatment, 2 due to physician or sponsor request, 1 due to an AE (carpal tunnel syndrome), and 1 due to death (female aged 54 years due to myocardial infarction). Overall mean participant treatment compliance was high at 98.9%. The median total treatment duration in the extension study was 1500 days, ie, approximately 4 years, with a range from 62 to 2118 days (0.2-5.8 years). The total exposure was 357 participant-years.

Demographics and baseline characteristics

The median (range) age of participants was 35 (20, 67) years. More women than men were enrolled (68.1% vs 31.9%). All but one of the participants entering this study were white. Median BMI was 28.28 kg/m^2, ranging from 17.96 to 43.72. Five participants (5.5%) had an adrenal crisis in the year prior to enrolment in the study. Prior to MRHC therapy, 79% of participants had received hydrocortisone, 19% prednisolone, 3% prednisone, and 4% dexamethasone; some patients had received a combination therapy. Just under half of the participants in this study (45.1%) were receiving MRHC therapy within the 12 months prior to this study due to their prior randomization in the phase 3 study.

MRHC dose titration during the extension study

Local site investigators titrated the MRHC dose according to recommendations in the protocol using patient feedback from the Adrenal Insufficiency Checklist (Table S1) and aiming at 9:00 and 13:00 h serum 17OHP <4-fold ULN and serum A4 <sex-specific ULN. Most of the dose titrations took place in the first 6 months when signs and symptoms of glucocorticoid over- or under-treatment were most commonly reported (Figure 2). Thereafter, daily doses during this extension study were relatively stable (Figure 3) with only a few patients reporting any symptoms of over- or under-treatment (Figure 2). At baseline, which was defined as the first visit of the phase 3 long-term extension study for all participants, the median daily hydrocortisone dose was 30 mg/day (15.8 mg/m^2/day), and with dose titration, the median dose at 48 months was significantly lower at 20 mg/day (11.6 mg/m^2/day) ($P < .0001$). At the end of the study, 9 patients (8%) had an MRHC dose < 15 mg/day and 1 patient was on only 5 mg MRHC at night. These 9 patients were all female with a spread of weight from 44 to 76 kg, dose by BSA mean (range) 6.0 (3.2-6.9) mg/m^2/day, all had classic CAH and an elevated 17OHP at some point in the study, and there were no adrenal crises ascribed to dose titration.

Biochemical monitoring

Serum 17OHP and A4 concentrations were at their lowest at month 1 when patients who entered directly from the phase 3 study were already on MRHC and patients who had previously been on standard glucocorticoids had been switched from their daily dose on standard treatment to an equivalent daily hydrocortisone dose of MRHC (Figure 4). The 17OHP

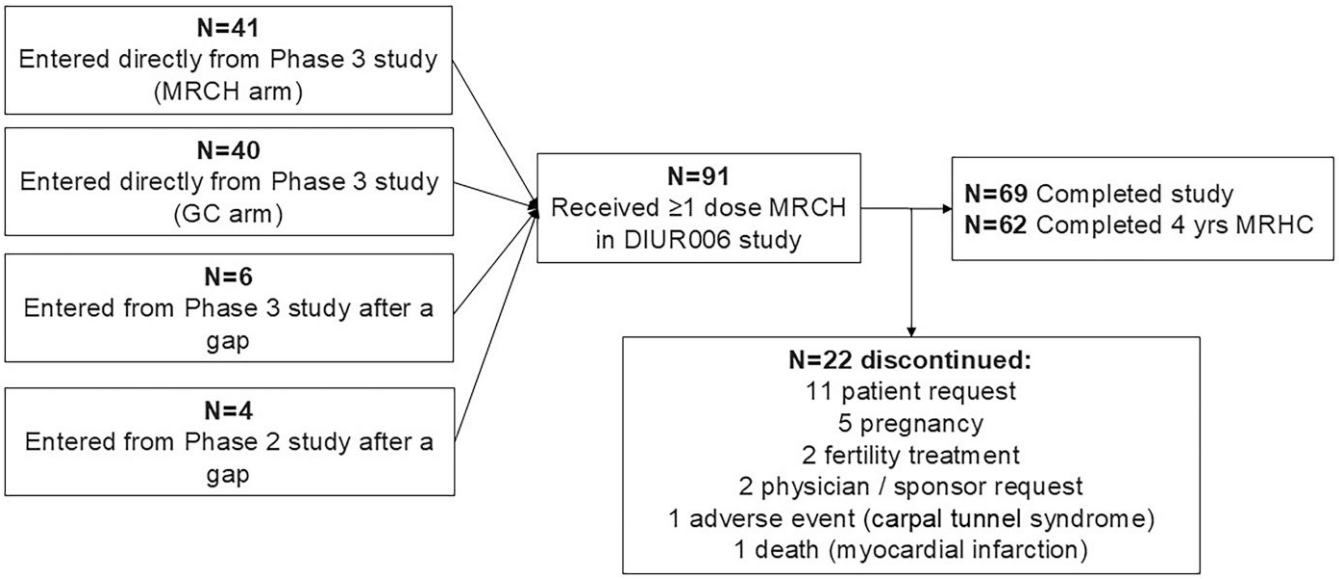

Figure 1. Consort diagram showing disposition of patients.

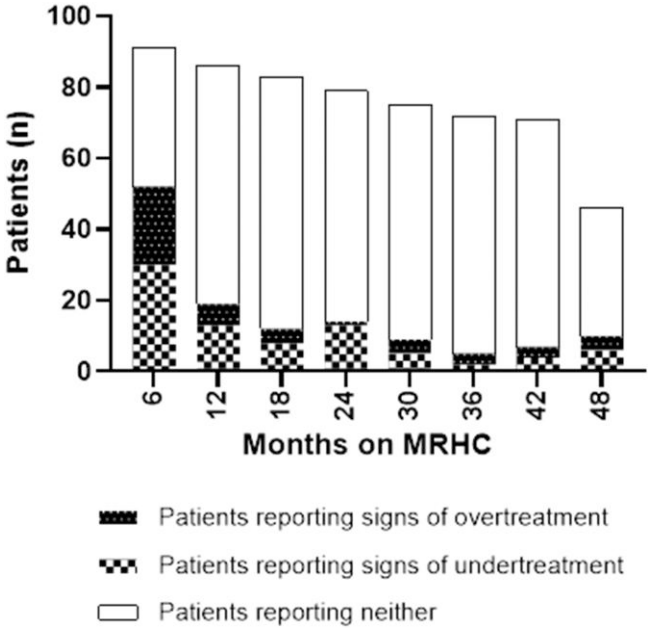

Figure 2. Reports of signs and symptoms of over- or under-treatment. MRHC, modified-release hydrocortisone.

and A4 levels rose a little over the next 6 months but were stable from month 12 to 48, and this reflected the dose titration with a decrease in hydrocortisone dose over the first 6 months. Measurement of 17OHP and A4 at 09:00 and 13:00 h showed very similar results (Figure 4). At 4 years, 71% of patients had a 17OHP <4-fold ULN (36 nmol/L) and 90% of patients had an A4 <ULN (7 nmol/L) (Figure 5). When a higher proportion of the MRHC dose was given at bedtime (with consequently a lower proportion of the dose taken in the morning), a higher percentage of responders was seen at the 13:00 h time point for both 17OHP and A4. Quadrant analysis (Figure 5) showed that more patients had a 17OHP <4-fold ULN ($P < .03$) and A4 <ULN ($P < .002$) on a hydrocortisone daily dose of ≤25 mg on MRHC vs their baseline treatment at the start of the extension study.

Body composition and metabolic parameters

Weight and BMI showed a minor increase over 4 years, median change from baseline (Q1, Q3: 2.55 [−1.03, 6.05] kg and 0.941 [−0.387, 2.39] kg/m^2, respectively) (Table 1). Similar results were seen for body composition analysis by DEXA with a small increase in fat mass but no clinically significant change in bone mineral density (Table 1). Dual-energy X-ray absorptiometry scan was only performed in 45 patients as measurement was not permitted in some countries such as Germany. Other measures including blood pressure, insulin, blood glucose, HbA1c, and bone markers showed no clinically significant change over time (Table 1).

Fertility

Nine of the 91 patients (9.9%) had an associated pregnancy in the 4 years. Five of the 37 women <50 years of age who were not on contraceptives over the whole study period became pregnant (13.5%) on MRHC. Of those, 4 had a normal course of pregnancy followed by live birth. The fifth patient had a spontaneous abortion and thereafter re-entered the study and had a second spontaneous abortion. All the women who fell pregnant were <35 years at baseline so that the number of pregnancies in women <35 years not on contraception was 6 out of 26 women. Four partners of 4 male study participants (13.8%) became pregnant during the study, with 1 partner having 3 pregnancies whilst her partner was on MRHC.

Safety

Compliance was high at 98.9% based on study pharmacist's assessment of packs returned. A total of 18 AEs in 7 participants (7.7%) were reported as AEs considered indicative of adrenal crisis, with none of them considered causally related to MRHC therapy. The number of adrenal crises per 100 patient years based on 357 participant-years was calculated as an incidence rate of 5.0 adrenal crises per 100 patient years.

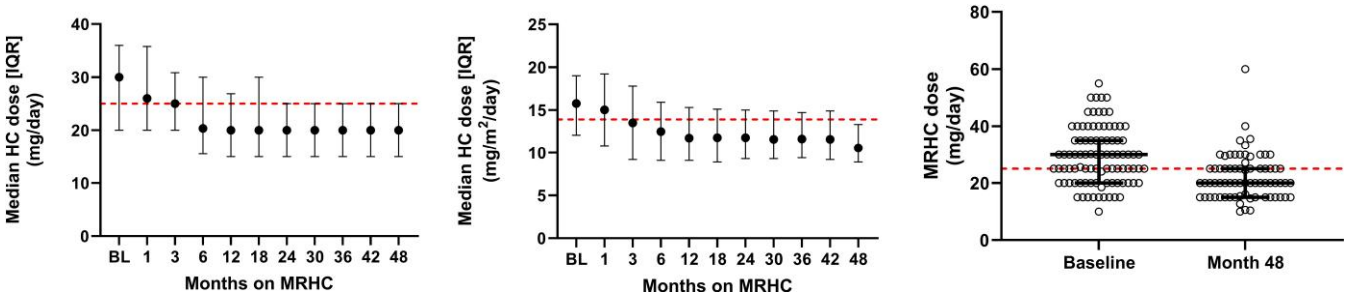

Figure 3. Hydrocortisone (HC) dose on modified-release hydrocortisone (MRHC) during the extension study in mg/day and mg/m^2/day. The HC dose was significantly lower at 48 months compared to baseline (Wilcoxon matched pairs signed test [2-tailed], $P < .0001$). In calculating dose in mg/m^2, the BSA from baseline was used. The red line represents the upper dose recommended for the replacement of adrenal insufficiency in adults.

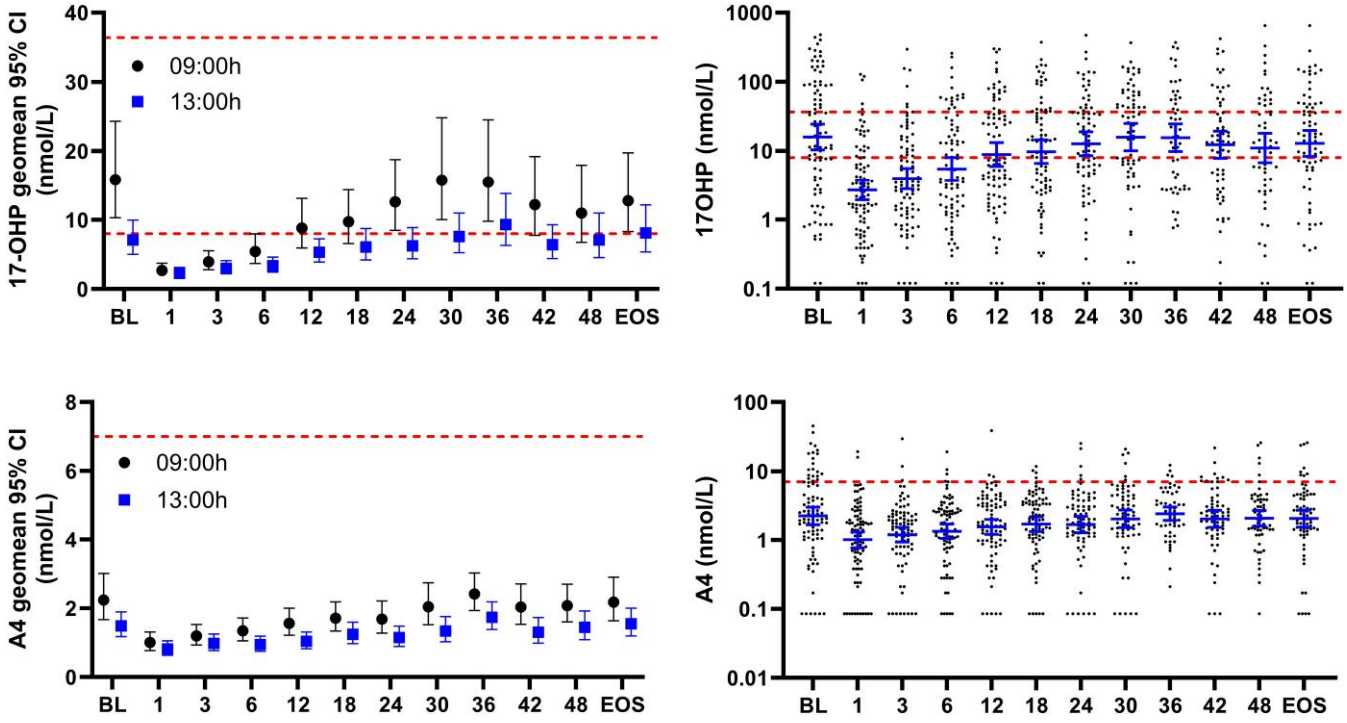

Figure 4. 17-Hydroxyprogesterone (17OHP) and androstenedione (A4) levels across the duration of the study; both geometric mean and raw data shown. Panel (A) shows 17OHP geometric mean and 95% CI for measurements taken at 09:00 and 13:00 h and panel (B) the same for A4. Panels (C) (17OHP) and (D) (A4) show the individual patient data with logarithmic *y*-axis at 09:00 h during the study. Blue bars depict geomean and 95% CI. The red dashed line represents upper limit of normal (ULN) and 4× ULN for 17OHP (36 nmol/L) and ULN A4 (7 nmol/L). EOS, end of study; BL, baseline (prior to the first dose of MRHC).

However, some investigators had recorded more than 1 AE indicative of an adrenal crisis on the same day in the same participant as they had multiple symptoms indicative of an adrenal crisis. If the multiple coded adrenal crises on 1 day in the same participant were counted as just 1 adrenal crisis then, there were a total of 14 adrenal crises in 7 participants with 1 participant reporting 8 of these crises due to gastroenteritis and respiratory tract infection. Based on the 14 adrenal crises, this gave a rate of 3.9 adrenal crises per 100 patient years. On-treatment serious AEs (SAEs) were reported for 28 participants (30.8%), with 2 SAEs being considered by the investigator to be related to MRHC and hypokalaemia in both participants, and in both, the Florinef dose was reduced and hypokalaemia did not recur. One participant died due to an SAE (myocardial infarction) not considered related to MRHC. A total of 700 AEs in 80 participants (87.9%) led to use of sick day rules. The most common AEs leading to use of sick day rules were pyrexia (35.2%), vomiting (30.8%), fatigue (28.6%), and nasopharyngitis (26.4%). One AE (mild fatigue) that led to the use of sick day rules was considered causally related to MRHC. A total of 33 events considered to be of unexpected therapeutic benefit were reported for 21 participants (23.1%). The most common of these were feeling more alert/less tired/better sleep (14 participants), improved menstrual cyclicity (5 participants), and increased bone density (3 participants).

Discussion

Switching patients to MRHC given twice daily at the equivalent dose of their prior glucocorticoid therapy resulted in a reduction of 17OHP and A4, the steroid markers of disease

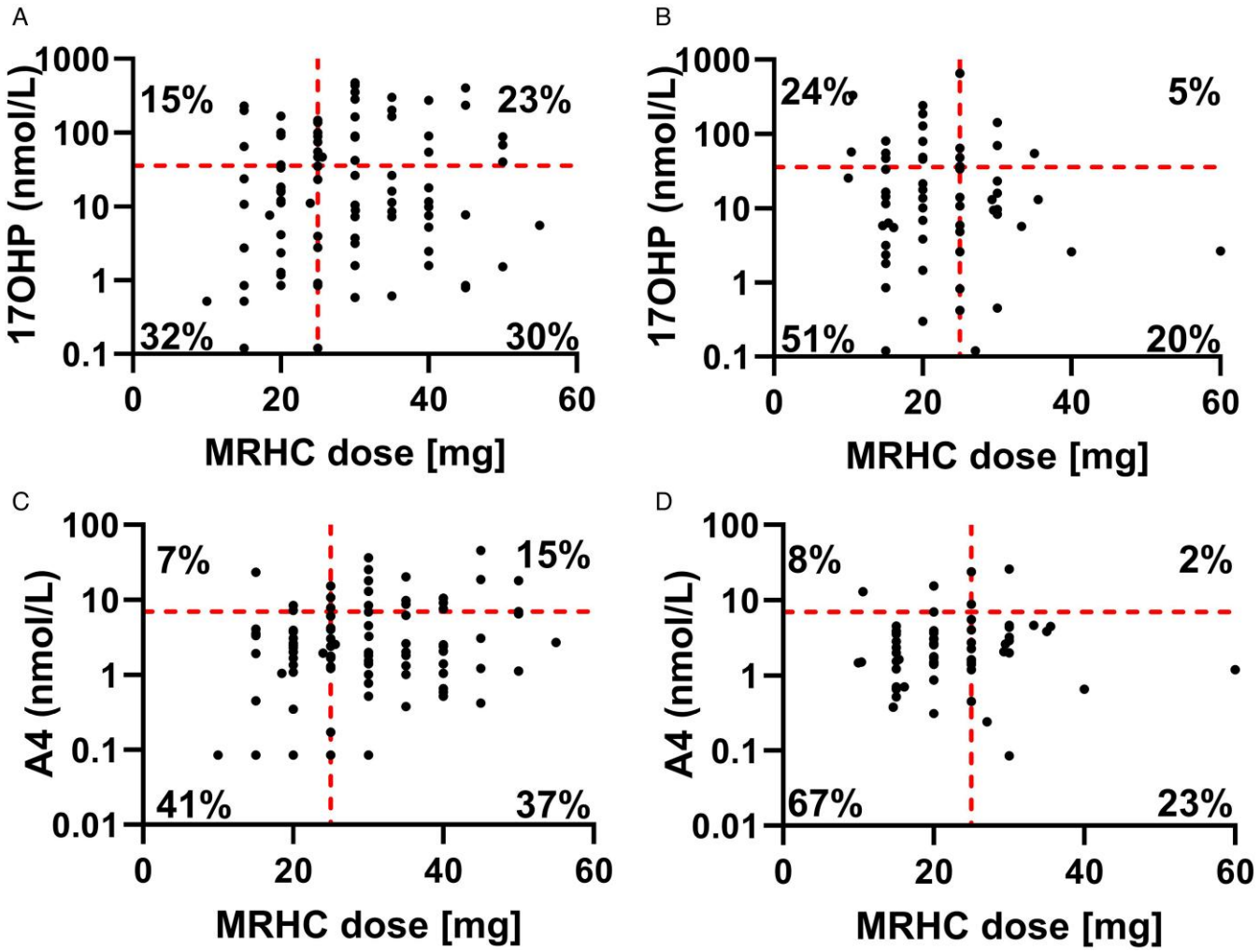

Figure 5. Quadrant analysis of 17-hydroxyprogesterone (17OHP) and androstenedione (A4) at baseline (A and C) and 48 months (B and D) showing the number of patients with either 17OHP < 4× upper limit of normal (ULN) or A4 <ULN (dashed horizontal red line ULN for women and men lower at 5.2 nmol/L) and daily hydrocortisone dose ≤ 25 mg/day (dashed vertical red line). On treatment with modified-release hydrocortisone (MRHC), patients who moved to the bottom left-hand quadrant were defined as responders, with significantly improved biochemical control on a lower dose of hydrocortisone for 17OHP and A4; $P < .03$ and $P < .002$, respectively.

control. Individual clinicians titrated the MRHC dose according to current guidelines, and in the majority of patients, the dose of MRHC was down-titrated over the first 6 months of treatment. Thereafter, the dose and disease control remained stable over the entire duration of the study. The improved disease control on MRHC was associated with fertility in 9/91 (9.9%) of patients who had an associated pregnancy. There were no new safety signals, and the adrenal crisis rate was below that reported in previously published cohort studies.[9-12]

The modified-release formulation works through a pH-triggered delayed release coating such that a dose taken last thing at night only starts to release in the last third of the small bowel where the pH rises above 6.8.[13] This results in a release during the early morning hours and provides a physiological overnight rise in cortisol, with levels peaking in the morning, with a second, lower dose taken in the morning providing cortisol cover during the afternoon.[4] This study confirms that MRHC can improve the biochemical control of CAH by preventing the excessive rise in ACTH overnight that drives excess adrenal androgen production. In this study, patients taking a greater dose of MRHC at night than in the morning had better control of their 17OHP and A4 at 13:00 h, suggesting that controlling the overnight rise in biochemical markers also means better control throughout the day.

There has been no consensus on when to measure biomarkers of disease control in CAH and current guidelines recommend "monitoring treatment through consistently timed hormone measurements relative to medication schedule and time of day".[14] Serum 17OHP and A4 are the traditional indicators of the adequacy of GC treatment in CAH.[14] In this study, clinicians took a morning sample ~09:00 h with the aim to adjust night-time dose and a sample at ~13:00 h to adjust the morning dose of MRHC. The blood samples were taken independent of the time of dosing, and samples taken in the morning (09:00 h) and early afternoon (13:00 h) showed very similar results. If the patient was controlled in the morning, they were likely to be controlled on the afternoon sample suggesting that only 1 sample during the day is generally needed to assess control. MRHC, therefore, provides an easier and more rational regimen for monitoring CAH disease control as a single sample taken in a morning or afternoon clinic can provide a good indication of disease control.

Table 1. Body composition and metabolic parameters at 4 years of MRCH treatment.

		Baseline		4 years		CFB	
	N	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3
Weight—all (kg)	58	74.4	66.9, 85.2	77.1	68, 88.5	2.55	−1.03, 6.05
Weight—female (kg)	34	71.8	67.4, 81.1	76.6	64.3, 86.8	2.35	−1.13, 6.53
Weight—male (kg)	24	79.1	66.6, 94.9	80.9	70.1, 98.3	2.55	−0.8, 4.53
BMI—all (kg/m^2)	58	29.2	25.7, 32.5	30.1	25.3, 33.4	0.941	−0.387, 2.39
Waist circumference—all (cm)	56	89.8	83.4, 101	95.6	88, 103	2	−0.375, 7.75
Waist circumference—female (cm)	34	89.8	83.0, 98.4	94.00	85.8, 99.8	1.00	−0.9, 5.8
Waist circumference—male (cm)	22	89.5	86.0, 104.8	99.50	89.0, 103.8	3.5	1.6, 8.6
Diastolic blood pressure (mmHg)	60	68.5	60, 78.8	74.5	68, 81	7	−0.5, 11.8
Systolic blood pressure (mmHg)	60	120	110, 130	120	115, 129	3.5	−8, 11
C-terminal cross-linked telopeptide (ng/L)	62	467	372, 633	413	336, 551	−59.5	−195, 76.8
Osteocalcin (UG/L)	62	17.4	13.4, 22.9	21	17, 26.3	2.9	−2.93, 8.65
Fasting glucose (mmol/L)	61	4.9	4.8, 5.4	4.9	4.6, 5.1	−0.2	−0.4, 0.2
Fasting insulin (pmol/L)	62	72	52.5, 91.5	72	60, 102	6	−12, −19.5
HbA1c	61	5.2	4.9, 5.4	5.3	5.1, 5.4	0.1	0, 0.25
High-density lipoprotein cholesterol (mmol/L)	61	1.5	1.3, 1.7	1.7	1.4, 1.9	0.1	−0.1, 0.3
Triglycerides (mmol/L)	61	1.0	0.8, 1.3	1.0	0.8, 1.4	0.0	−0.2, 0.2
PRA	62	0.515	0.308, 0.93	0.595	0.31, 0.97	0.035	−0.335, 0.233
BMD z score—all (g/cm^2)	45	−0.35	−0.9, 0.15	−0.5	−0.875, 0.493	0.1	−0.1, 0.5
BMD z score—female (g/cm^2)	45	−0.3	−0.5, 0.2	−0.45	−0.675, 0.55	0.05	−0.2, 0.3
BMD z score—male (g/cm^2)	45	−0.85	−1.48, −0.15	−0.7	−0.9, 0.368	0.25	0, 0.581
Lean mass female (kg)	45	41.3	37.4, 47.1	41.6	38.7, 47.7	−0.07	−1.97, 2.02
Lean mass male (kg)	45	54.6	49.2, 62.9	55	49.2, 64.2	0.185	−2.28, 4.33
Fat mass female (kg)	45	27.8	24.9, 34.3	27.8	22.7, 33.3	1.99	−1.92, 4.28
Fat mass male (kg)	45	20.2	14.8, 35.3	22.4	17.6, 34	2.16	−5.28, 3.85

Body composition data from 45 patients only as dual-energy X-ray absorptiometry (DEXA) scans not permitted in Germany and COVID-19 impacted measurements for some patients. In subjects missing 48-month DEXA data, 36-month data are imputed (28/45 patients).
BMD, bone mineral density; CFB, change from baseline; PRA, plasma renin activity; Q1, first quartile; Q3: third quartile.

Titrating glucocorticoid replacement is challenging in CAH as the majority of patients require a supraphysiological dose of glucocorticoid to normalize the biomarkers, putting them at risk of excess glucocorticoid therapy.[15] The Endocrine Society guidelines recommend "complete suppression of serum 17OHP level is not a treatment goal but instead indicates overtreatment. A4 levels should be referenced to age- and sex-specific norms".[14] In this study, investigators were asked to aim for a 17OHP <4-fold ULN and A4 <ULN for sex reflecting the guidelines. Using these recommendations, the majority of patients had improved biochemical control on MRHC compared to baseline. In our previous phase 3 study, when blinded titrators were using these criteria, it appears that in the first 6 months of the study, patients were frequently over-treated with 17OHP in the reference range and the associated A4 levels were very low.[6] In this extension study, when unblinded local site investigators were titrating the glucocorticoid replacement, the MRHC dose was reduced and levels of 17OHP rose a little although in the majority of patients the A4 remained below the ULN and was still suppressed in some patients. A consistent observation was that when 17OHP was well controlled, A4 was usually in the lower part of the reference range reflecting the fact that in CAH, A4 biosynthesis is dependent on higher 17OHP levels and direct conversion from 17OHP to A4 rather than physiological generation of A4 from DHEA in the classic androgen pathway.

The dose of glucocorticoid used to treat patients with CAH is generally higher than that recommended for adrenal replacement. For example, in children, the recommended dose of hydrocortisone is 10-15 mg/m^2/day in CAH[14] and 8 mg/m^2/day in non-CAH primary adrenal insufficiency.[7] This was reflected in our adult study where the median baseline hydrocortisone dose equivalent was 30 mg/day, above the 15-25 mg daily dose that is recommended for adrenal replacement in adults with primary adrenal insufficiency.[7] On MRHC, the daily hydrocortisone dose came down to a median dose of 20 mg (which equates to ~ 11.6 mg/m^2/day) in this CAH cohort; however, the spectrum of daily doses ranged from a single 5 mg dose at night to a daily dose of 60 mg MRHC. Cortisol levels vary in normal individuals, and it is likely that the MRHC dose required for adrenal replacement will vary in patients with CAH. On MRHC, only 67% of patients had an A4 <ULN with a MRHC dose ≤25 mg/day suggesting that in the remaining CAH patients, there are factors other than physiological glucocorticoid replacement that would require a higher MRHC dose. Eight per cent of patients had a MRHC dose < 15 mg/day, and this did not appear to relate to weight which suggests that some patients only require a relatively low dose for adrenal replacement. There were no adrenal crises in this low dose group. Compliance is often blamed for poor biochemical control in CAH; however, compliance based on study pharmacist's assessment of packs returned was good in this study, which may relate to the twice daily "toothbrush" regimen taken last thing at night and first thing in the morning, with no need to take doses at other time points during the day.

Fertility is impaired in both women and men with CAH.[1] In this study, overall 9.9% of patients had an associated pregnancy. Patients were not selected for seeking fertility and were excluded from the study if they were pregnant or became pregnant on study so we cannot calculate fertility according to those trying to conceive. So, this was an unexpected fertility rate considering that only 37/62 women were <50 years of age and not on contraceptives over the whole study period.

This suggests that treatment with MRHC may improve fertility. It is likely that this was due to the improved control of adrenal androgens throughout the 24 h, with 5 patients reporting improved menstrual cyclicity as an unexpected therapeutic effect of MRHC treatment. These results, along with similar post-marketing findings were reported to the European Medicines Agency and have resulted in the following wording in the Efmody label: "In both men and women who have lower fertility due to CAH, fertility may be restored shortly after beginning treatment with Efmody, which can lead to unexpected pregnancies".

Weight and BMI showed minor increases over the 4 years similar to what would be expected in both CAH[16] and the healthy population.[17] It might have been expected that weight and BMI would fall with the reduced dose of hydrocortisone; however, this was countered by time, as weight increases over time in CAH[16] and the general population,[17] and the study took place during the COVID-19 pandemic when the general population was taking less exercise.[18] However, the reduction in hydrocortisone dose over time would be expected to reduce cardiovascular risk which has been reported as increased in CAH patients.[19] More longitudinal data will be required to confirm such a beneficial effect.

All-cause mortality is 5-fold increased in CAH,[20] and adrenal crisis is the leading cause of death in CAH patients.[21] The risk of adrenal crisis in this study was 3.9 crises per 100 patient years, which is lower than that reported in previous cohort studies of patients with CAH and adrenal insufficiency.[11] In the only prospective study of adrenal crisis in CAH, the incidence was 8.4 in adults and 5.1 in children per 100 patient years.[11] Adrenal crisis is reported to occur in 6%-8% of patients with adrenal insufficiency each year.[22] The MRHC extension study was carefully monitored so it would be expected to report more AEs than retrospective cohort studies. The definition of adrenal crisis is challenging, and clinicians in this study were recommended to use the "Allolio" definition, which includes the use of parenteral glucocorticoid but does not require a hospital admission unlike definitions used in some of the cohort studies.[8] However, some investigators used a less strict definition, so it is unlikely that incidence of adrenal crisis was under-estimated in this study. The low incidence of adrenal crisis compared to historical data may relate to a number of factors. This was a carefully monitored study, and patients had good compliance and were instructed on sick day rules if unwell which may protect against adrenal crisis. However, in our previous phase 3 study, higher use of sick day rules in the patients on standard treatment compared to MRHC was associated with 3 adrenal crises on standard treatment compared to none for patients on MRHC.[6] Patients with adrenal insufficiency may be relatively immunocompromised compared to the normal population,[23] so adrenal crisis precipitated by an acute illness is common in CAH and adrenal insufficiency.[24] Down titration of MRHC in this study did not lead to an increased risk of adrenal crisis. It may be that along with good compliance and simple stress dosing rules for patients, more physiological cortisol replacement itself reduces the risk of adrenal crisis. A limitation of this study was a lack of data on adolescent patients. MRHC has been approved to treat patients over 12 years of age based on pharmacokinetic modelling of dose for younger patients.[25] A recent study presented data from 13 adolescent CAH patients, mean age 16.2 years (range 12.1-20.7 years), in whom biochemical control improved in most and 12 out of the 13 chose to continue MRHC with the twice daily treatment regimen perceived as an advantage with no need to dose at school.[26]

In conclusion, MRHC improves the biochemical control of CAH allowing reduction in the overall dose of hydrocortisone, which is associated with fertility in women and men. Dose titration can be performed with a simplified monitoring regimen only requiring a single sample of 17OHP and A4 during the day and total daily dose given as approximately two-thirds at night and one-third in the morning. Dose reduction on MRHC is not associated with any new safety signals, and over the 4 years of this study, the incidence of adrenal crisis was lower than in previously reported cohort studies.

Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

Funding

This work was initiated and supported by Diurnal Ltd. UK (now Neurocrine UK Ltd.), with further support from the Intramural Research Program of the National Institutes of Health (NIH). A.P. delivered this study through the National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre (BRC). The views expressed are those of the authors and not necessarily those of the funders, the NIHR, or the Department of Health and Social Care.

Authors' contributions

Wiebke Arlt (Conceptualization [equal], Formal analysis [equal], Writing—review & editing [equal]), Aude Brac de la Perrière (Investigation [equal], Writing—review & editing [equal]), Angelica L. Hirschberg (Investigation [equal], Writing—review & editing [equal]), Deborah P. Merke (Investigation [equal], Writing—review & editing [equal]), John D.C. Newell-Price (Investigation [equal], Writing—review & editing [equal]), Alessandro Prete (Investigation [equal], Writing—review & editing [equal]), D. Aled Rees (Investigation [equal], Writing—review & editing [equal]), Nicole Reisch (Investigation [equal], Writing—review & editing [equal]), Philippe A. Touraine (Investigation [equal], Writing—review & editing [equal]), Hanna Bendfeldt (Formal analysis [supporting], Writing—review & editing [supporting]), John Porter (Conceptualization [equal], Investigation [equal], Project administration [equal], Writing—original draft [equal]), Helen Coope (Project administration [equal], Writing—review & editing [equal]), and Richard J.M. Ross (Conceptualization [lead], Formal analysis [lead], Writing—original draft [lead])

Conflict of interest: The authors have the following conflicts of interest to declare in relation to this work: W.A., A.B.d.l.P., A.L.H., D.P.M, J.D.C.N.-P., A.P., D.A.R., and N.R. were study investigators. D.P.M has received research funds from Diurnal Ltd. (now Neurocrine UK Ltd.) through an NIH Cooperative Research and Development Agreement. R.J.M.R. and J.P. are consultants to, H.B. a contractor to, and H.C. an employee of Neurocrine UK Ltd. N.R. is on the editorial board of EJE. She was not involved in the review or editorial process for this paper, on which she is listed as an author.

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