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Modified-release Hydrocortisone in Congenital Adrenal Hyperplasia

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Abstract

Background: Standard glucocorticoid therapy in congenital adrenal hyperplasia regularly fails to control androgen excess, causing glucocorticoid over-exposure and poor health outcomes. We investigated whether modified-release hydrocortisone (MR-HC), which mimics physiologic cortisol secretion, could improve disease control.

Methods: 6-month randomized phase III study, MR-HC versus standard glucocorticoid, followed by single-arm MR-HC extension study. Primary outcomes were change in 24-hour standard deviation score (SDS) of androgen precursor 17-hydroxyprogesterone (17OHP) for phase III, and efficacy, safety and tolerability of MR-HC for the extension study.

Results: The phase III study recruited 122 adult CAH patients. While the study failed its primary outcome at 6 months, there was evidence of better biochemical control on MR-HC, with lower 17OHP SDS at 4 (P=0.007) and 12 (P=0.019) weeks, and between 07:00h to 15:00h (P=0.044) at 6 months. The percentage of patients with controlled 09:00h serum 17OHP (<1200 ng/dl) was 52% at baseline, at 6 months 91% for MR-HC and 71% for standard therapy (P=0.002), and 80% for MR-HC at 18 months extension. The median daily hydrocortisone dose was 25mg at baseline, at 6 months 31mg for standard therapy and 30mg for MR-HC, and after 18 months 20mg MR-HC. Three adrenal crises occurred in phase III, none on MR-HC and 4 in extension study. MR-HC resulted in patient-reported benefit including menses restoration in eight patients (one on standard therapy), and 3 patient and 4 partner pregnancies (none on standard therapy).

Conclusion: MR-HC improved biochemical disease control in adults with reduction in steroid dose over time and patient-reported benefit.

Keywords: Congenital adrenal hyperplasia, 21-hydroxylase deficiency, glucocorticoid, hydrocortisone, adrenal insufficiency

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Introduction

Classic congenital adrenal hyperplasia, due to 21-hydroxylase deficiency (21-OHD-CAH), is a genetic disorder of steroidogenesis affecting ~1:15,000 live births (1). Lack of 21-hydroxylase causes cortisol deficiency and a counter-regulatory increase in pituitary adrenocorticotropic hormone (ACTH) secretion, which drives overproduction of adrenal androgens, and adrenal hyperplasia. Patients with 21-OHD-CAH have two major problems: adrenal insufficiency and androgen excess. Adrenal insufficiency causes life threatening adrenal crises (1-3), while androgen excess causes atypical genitalia in 46,XX neonates, promotes abnormal growth, short stature and precocious puberty, and in adulthood, virilization of women and infertility in both sexes (4). Treatment aims to replace cortisol, and, where necessary, aldosterone. Supra-physiologic doses of glucocorticoid are typically needed to suppress ACTH and adrenal androgens. Management involves balancing glucocorticoid doses to avoid both glucocorticoid deficiency, risking adrenal crisis, and iatrogenic glucocorticoid excess, leading to short stature, obesity, hypertension, osteoporosis and an adverse metabolic profile (1-3,5-7). Patients with 21-OHD-CAH have increased mortality (8,9), and poor health outcomes (10,11), as current therapy fails to control adrenal androgen excess resulting in glucocorticoid overtreatment (5,12).

Cortisol has a circadian rhythm with a nadir on going to sleep, increasing during early morning hours, peaking on waking, then decreasing through the day (13). In 21-OHD-CAH, absent cortisol overnight results in excess early morning ACTH which in turn drives excess generation of adrenal androgens. The adrenal androgen precursors, 17-hydroxyprogesterone (17OHP) and androstenedione are used for monitoring. Current glucocorticoids used in the treatment of 21-OHD-CAH are immediate release preparations such as hydrocortisone, prednisolone, prednisone, and dexamethasone, which fail to mimic the early morning cortisol rise (10,11). There is consensus that hydrocortisone should be used in children to avoid risk of growth suppression with long-acting glucocorticoids (14); however, in adults, there is no agreement on which glucocorticoid to use. Patients often take glucocorticoids later in the evening to achieve biochemical control, when cortisol is normally low, resulting in metabolically adverse consequences (15). Despite different treatment regimens, optimal biochemical control, defined as 17OHP below three times the upper limit of normal (<1200 ng/ml, 36 nmol/l) and androstenedione within the reference range, is only achieved in ~40% of patients (10,11).

Hydrocortisone infusions mimicking the cortisol circadian rhythm have demonstrated improved biochemical control of 21-OHD-CAH (16,17). A modified-release formulation of hydrocortisone (MR-HC), with a delayed-release action, given twice daily, simulates the overnight

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rise of cortisol (18,19), and improved 21-OHD-CAH disease control in a phase II study (19). We now report findings from a phase III study of MR-HC versus standard glucocorticoid therapy followed by a single arm efficacy and safety extension study in adults with 21-OHD-CAH.

Methods

Patients

Patients were recruited from 10 centers (7 countries) from February 2016 to January 2018. Patients had classic 21-OHD-CAH diagnosed in childhood, adequate mineralocorticoid replacement with renin less than 2 times the upper limit of normal, and were on stable glucocorticoid therapy over the preceding six months. Exclusion criteria included use of medication interfering with glucocorticoid metabolism, bilateral adrenalectomy and night shift work. The study protocols for the phase III extension study were approved by local Ethics/Institutional Review Boards and the Medicines and Healthcare Products Regulatory Agency (NCT03062280, Eudract 2015-005448-32). The trials were performed in accordance with the principles of the Declaration of Helsinki.

Trial Design

Patients, stratified by baseline glucocorticoid treatment (Table 1), were randomized by an Interactive Web Response System to receive MR-HC (Chronocort® Diurnal Ltd. UK) or to continue on standard therapy and after 6 months were offered MR-HC in the extension study. MR-HC was prescribed as 5, 10 or 20 mg capsules and the initial dose was the hydrocortisone dose equivalent to their baseline therapy with approximately $^{1}/_{3}$ of the daily dose taken at 07:00h and $^{2}/_{3}$ of the daily dose taken at 23:00h. At 4 and 12 weeks, dose titrations were made for both treatment groups, using identical rules, following centralized advice by two independent physicians blinded to all data except 24-hour hormone profiles and an investigator-completed adrenal insufficiency checklist. The blinded titrators considered morning and/or evening dose adjustments of either MR-HC or standard glucocorticoid using 17OHP/androstenedione measurements from the 24-hour profile and adrenal insufficiency symptom questionnaire (Table 2) results using the following algorithm:

- The 5 samples between 01:00 to 09:00hrs were considered to reflect glucocorticoid given in the evening/night time

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- The 5 samples between 11:00 and 19:00hrs to reflect glucocorticoid given in the morning.
- If 3 or more of these 5 samples were out of range, dose adjustments would be made, unless the adrenal insufficiency symptom questionnaire was in conflict with the biochemical findings.
- If 17OHP and androstenedione were inconsistent then the androstenedione results were to take precedence.

Target ranges for titration were the optimal range for 17OHP and reference range for androstenedione as follows:

- 17OHP 40-1200ng/dl (1.2 – 36.4 nmol/l)
- androstenedione (males) 40-150 ng/dl (1.4 - 5.2nmol/L)
- androstenedione (females) 30-200ng/dl (1.0 - 7.0 nmol/L)

Local investigators and patients were aware of the trial-group assignment but were otherwise blinded. After 6 months, patients who had enrolled in the phase III, and the previous phase II studies were invited to enroll in the extension study. The initial dose of MR-HC was the hydrocortisone dose equivalent to their dose at time of enrollment in the extension study. Dose titration was performed by the local investigators according to hormone results and symptoms of over- or under-replacement. Hydrocortisone stress dosing and fludrocortisone dose adjustment occurred as medically indicated (20).

Trial Procedures

In the phase III study, 17OHP and androstenedione were measured at baseline, 4, 12, and 24 weeks every 2 hours from 15:00hrs to 15:00hrs, and in the extension study, blood was drawn at 09:00h and 13:00h. Hormones were measured by HPLC–tandem mass spectrometry (Q^2 Solutions, USA). Additional assessments included; body composition, DEXA scanning, metabolic bloodwork (C-terminal cross-link telopeptide, fasting osteocalcin, highly sensitive C-reactive protein (hsCRP), fasting glucose, fasting insulin, HbA1c, plasma renin activity, total testosterone) and Quality of Life (QoL) assessments (SF-36, Global Fatigue Index, EQ-5D).

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Outcome Measures

The primary outcome in the phase III study was the change from baseline to 24 weeks in the mean of the 24-hour 17OHP standard deviation scores (SDS). Natural log transformation was performed to approximate a normal distribution. For each 2-hourly value of log 17OHP, the number of standard deviations from the midpoint of the natural logarithm of the reference range (males 40-220ng/dl (1.2-6.7 nmol/L), females 40-285 ng/dl (1.2-8.6 nmol/L)) was calculated, unsigned to provide equal weight to values above or below the midpoint. Secondary outcomes included serum androstenedione, safety (specifically stress dosing and adrenal crises)(21), and changes in weight, body mass index (BMI), waist circumference, body composition and blood pressure (BP). Exploratory endpoints included the primary outcome at 4 and 12 weeks. Post hoc analyses included percentage of patients with good disease control defined as 09:00h for 17OHP <1200 ng/dl (<36 nmol/L) and for androstenedione below the reference range upper limit as previously defined (10,11); areas under the curve (AUC) of 17OHP and androstenedione; and 17OHP variability expressed as the ratio of arithmetic range of concentrations over 24-hours at 24 weeks to baseline. In the extension study, the primary endpoint was MR-HC safety assessed longitudinally using signs and symptoms of adrenal insufficiency or over-treatment; use of sick day rules; and adverse events including adrenal crises. The secondary endpoints included MR-HC long-term efficacy measurements such as daily dose of hydrocortisone and disease control assessed via 17OHP and androstenedione. As patients had differing exposure to MR-HC before the study start, assessment was made against a pre-MR-HC baseline.

Statistical Analysis

The trial was designed to have > 95% power, at a 2-sided alpha of 5%, to detect a difference between treatment groups in the primary outcome consistent with the phase II study results. The primary outcome was compared between treatment groups within an analysis of covariance (ANCOVA) linear model with pre-study treatment category and baseline mean SDS as covariates. The same model was used for secondary and exploratory analyses of SDS and the area under the 24-hour profiles curve (AUC). Variability (amplitude) within a 24-hour hormone profile was defined as the maximum value divided by the minimum value. The change in the amplitude between baseline and 24 weeks, expressed as a ratio, was compared between treatment groups using a Wilcoxon test. The proportion of patients with good disease control at 24 weeks (09:00h 17OHP less than 1200 ng/dL) was compared between treatment groups using a logistic model, adjusting for good disease

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control at baseline. All P values are two-tailed and all confidence intervals (CIs) are 95% two-sided. Since all subjects participating in the extension trial received MR-HC there were no formal treatment comparisons, but summaries over time were produced for safety and efficacy parameters.

Safety

Adverse events were recorded including adverse events of special interest such as adrenal crisis. Events of therapeutic benefit such as restoration of menstruation have been recorded using the MedDRA term "Unexpected therapeutic benefit" as recommended by regulators.

RESULTS

Patients

In the phase III study, 138 patients were screened, 122 randomized, 117 completed the study, and 105 met criteria for efficacy analysis (Figure 1). Between 3 and 25 patients were recruited from each European center with 8 from the US center. Overall, the two treatment groups were balanced (Table 1), but the number of patients with good baseline disease control was higher in the standard group. At baseline, 84% of patients were taking standard glucocorticoid after 18:00hrs, and 84% of patients were diagnosed as salt wasting (Table 1). Five patients (3 MR-HC, 2 standard) had experienced an adrenal crisis in the preceding year. In the extension study, 91 patients received at least one dose of MR-HC and 83 were participating at time of this data cut (Figure 1). Safety data are presented up to 2 years and biochemical up to 18 months. Patients who chose not to participate in the extension study did so predominantly from one center because of logistical reasons (n=13). Withdrawals were primarily for practical reasons including desire for pregnancy.

Biochemical Disease Control

In phase III, both groups achieved better hormonal control at 24 weeks compared to baseline reflected by a negative change in the 17OHP SDS 24-hour profile, therefore the trial failed its primary outcome (P=0.55) (Table 3). There was no statistical difference between any of the groups and removing any of the groups from the analysis did not change the primary outcome. The change from baseline was greater in MR-HC group at 4 (P = 0.007) and 12 (P = 0.019) weeks. At 24 weeks, a greater reduction in the 17OHP SDS profile was observed in the MR-HC group compared to the standard group between 07:00h and 15:00h (P = 0.044), and a reduction in the 17OHP AUC occurred

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in both groups, with greater reduction in the MR-HC group (P = 0.025). At 24 weeks, compared to standard group, good disease control (17OHP <1200ng/dl at 09:00h) was achieved more often in the MR-HC group (90.6% *vs.* 71.2%, P = 0.002) and 17OHP variability (amplitude) over 24 hours was reduced in the MR-HC group (P < 0.001). At baseline the group randomised to continue on standard treatment were better controlled than the MR-HC group 32/52 (62%) vs 20/53 (38%) and after 24 weeks 28/33 (85%) of those not in control at baseline were controlled in the MR-HC group and 10/20 (50%) in the standard treatment group. The androstenedione SDS profile and change in AUC was similar to that for 17OHP. The pattern of biochemical control displayed in the 24-hour profiles differed between the two groups (Figure 2). At 24 weeks, the MR-HC group 24 hour profile flattened and normalized for both 17OHP (Figure 2A) and androstenedione (Figure 2B), while the pathological morning rise in adrenal androgen precursors persisted in the standard group (Figure 2C, 2D). Thus, a difference between the two groups at week 24 was observed during the morning hours, but not throughout the day (Figure 2E, 2F). In the extension study, the number of patients in good disease control for 17OHP at 09:00h was 80% at 18 months versus 52% at baseline (Figure 2G, Table 1&3) and for androstenedione 96% versus 45% at baseline. In the phase III study it didn't make a difference to the analysis whether good control was measured at either 0700h or 0900h so we used 0900h in the extension study as this is when many clinics measure hormones.

Daily glucocorticoid and mineralocorticoid dose

At 24 weeks, the MR-HC group increased from a median dose of 25mg to 30mg and standard glucocorticoid from 25mg to 31mg hydrocortisone dose equivalent (Table 4). Overall and by type of glucocorticoid at baseline, the MR-HC and standard groups were receiving similar glucocorticoid doses, but more patients required up-titrations in the standard group (31 vs. 28) and more required down-titrations in MR-HC group (13 vs. 3). The dose of fludrocortisone was changed in 3 patients (2 MR-HC and one Standard). In the extension study, patients were down-titrated and the median dose at 18 months was 20mg (Table 4).

There was no statistical difference between subjects on the different standard treatment regimens at baseline and removing any of the groups from the analysis did not change the primary outcome. In the prednisolone / prednisone at baseline patient group, the hydrocortisone dose on MR-HC fell from a median of 30mg at baseline to 27.5mg at 24 weeks and for those that continued on prednisolone, the hydrocortisone dose equivalent increased from 26.6 to 32.8mg,. There were

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relatively few patients on dexamethasone at baseline (n=10) and they were split into those continuing dexamethasone (n=5) and those who transferred to MR-HC (n=5). For the patients who were on dexamethasone at baseline the median dose in hydrocortisone equivalents of dexamethasone and MR-HC did not change from baseline to 24 weeks.

Secondary outcomes of interest

No differences between the two treatment groups were seen for fat mass, lean mass or bone mineral density by DEXA; bone markers (serum C-terminal telopeptide and fasting osteocalcin); laboratory assessments of interest including high-sensitivity C-reactive protein, fasting glucose, fasting insulin, homeostatic model assessment of insulin resistance, glycated hemoglobin, total testosterone, and plasma renin activity (Table 5). No significant changes in QoL were seen although responses for the majority of domains improved (Table 6).

Safety

In phase III study, no patients experienced adrenal crises in the MR-HC group compared with three (4.9%) in the standard group. A total of 299 adverse events (15 of therapeutic benefit) were reported by 96.7% of patients in the MR-HC group and 224 adverse events (1 of therapeutic benefit) were reported by 78.7% of patients in the standard group. No serious adverse event was considered causally related to study intervention. Glucocorticoid stress dosing was reported by 26 patients (42.6%) in the MR-HC group and 36 patients (59.0%) in the standard group. Unexpected events considered to be of therapeutic benefit included resumption of regular menses in 5 patients (4 MR-HC, 1 standard), partner pregnancies of two patients in the MR-HC group with full-term deliveries; one of these patients had a history of testicular adrenal rest tissue with documented sperm count improvement (<0.1 million/ml prior to MR-HC and 10.3 million/ml during MR-HC treatment).

In the extension study there were 4 patients with adrenal crisis. A total of 780 AEs (29 of therapeutic benefit) were reported by 87 participants (95.6%). SAEs were reported for 14 participants (15.4%), of which one was considered related to MR-HC (hypokalemia). Glucocorticoid stress dosing was reported for 72 participants (79.1%). The most common 18 patients (19.8%) reported events considered to be of therapeutic benefit were feeling more alert (11 patients), and improved menstrual cycle (4 patients). The partner of two patients on MR-HC became pregnant

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during the study and successfully delivered. Three patients became pregnant on MR-HC, one suffered an early miscarriage after transitioning to standard therapy.

DISCUSSION

This is the first randomized controlled trial of glucocorticoid treatment in patients with 21-OHD-CAH. Patients who received MR-HC had superior hormonal control during the morning and early afternoon compared to those receiving standard therapy and this was sustained over 18 months follow up. Morning hormonal control is important in 21-OHD-CAH as failure to control the overnight rise in adrenal androgens results in excess glucocorticoid exposure and poor health outcomes (5). The trial failed its primary endpoint because the difference between the two groups in the morning did not translate into a difference over 24 hours at 24 weeks. The primary outcome was based on a phase II trial (19), however the analysis was unhelpful in the phase III randomized trial as the SDS analysis overemphasized scores below the midpoint of the reference range and the logarithmic transformation and use of a mean score over 24 hours obscured the impact of MR-HC in the morning and early afternoon. The raw data showed significant improvement of the clinically relevant endpoint of morning biochemical control, with reduced AUC and 17OHP amplitude in patients receiving MR-HC. The improvement in biochemical control was maintained at 18 months, with 80% displaying good control for 17OHP and 96% for androstenedione versus 52 and 45% at baseline despite reduction of the hydrocortisone dose by 33%, to doses regularly used for adrenal replacement therapy.

MR-HC replicates the physiological overnight rise in cortisol thereby preventing ACTH driven excess production of adrenal androgens (19). MR-HC given twice daily replicates both the early morning rise in cortisol as well as daytime cortisol levels (22). There is some evidence that cortisol clearance may vary over 24 hours, possibly related to a circadian rhythm in cortisol-binding protein; however, the amplitude of this variation is small and does not appear clinically significant (23). Biochemical control was better on MR-HC compared to standard glucocorticoid at 4 weeks (i.e. prior to dose titration) when patients were receiving MR-HC at an equivalent daily dose to baseline treatment. At 24 weeks, following dose titration, morning control was better on MR-HC than standard glucocorticoid, 91% in control versus 71%, respectively, with little fluctuation in 17OHP and no morning rise in the MR-HC treated patients, similar to the profile of 17OHP in normal physiology.

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These findings are important as it is the high excursions in 17OHP that drive production of androstenedione and androgens that impact growth, puberty and fertility.

Immediate-release hydrocortisone is the recommended first line therapy in 21-OHD-CAH; prednisolone and dexamethasone are introduced when biochemical control cannot be achieved, but are associated with higher rates of adverse outcomes (15,24,25). Higher bedtime doses (reverse circadian regimen) are commonly used in an attempt to improve androgen control (11,26,27), 84% at baseline in this study; however, evening glucocorticoid administration has potential for adverse metabolic actions (28), and insomnia. The median hydrocortisone dose at 24 weeks was 15.8 and 17.0 mg/m^2/day for MR-HC and standard group, respectively, similar doses to those reported in cohort studies (15-18 mg/m^2/day) where biochemical control was worse than in this trial (10,11,29,30). In the extension study, with local clinicians performing dose titrations, biochemical control was maintained at a reduced daily dose of 20mg consistent with that recommended for replacement in adrenal insufficiency; 15-25mg daily (31). Upon study entry the patients had their therapy optimized for 6 months, and yet were able to have a sustained dose reduction in the extension study. Optimal control of adrenal androgens is required for fertility in men and women with 21-OHD-CAH (32-34). Our findings demonstrate clinical value for improved morning hormonal control, with women restarting menstruation, improved sperm quality in a patient with testicular adrenal rest tissue, and four partner and three patient pregnancies on MR-HC.

There are few published data on the circadian variation of 17OHP in healthy individuals but, what there is, demonstrates that in the normal individual 17OHP displays minor circadian variability within the reference range and varies by the phase of the menstrual cycle in females (35,36). The reference range for 17OHP at the Mayo is <285 ng/dL during the luteal phase which is the highest level seen in healthy subjects. Clinicians have recognised that in patients with CAH receiving standard therapy it is not possible to control 17OHP in the morning even when raising the dose of glucocorticoid. This is shown in the current study in patients on standard treatment where their glucocorticoid dose was increased. To avoid over treatment, guidelines have suggested to not suppress the 17OHP in to the reference range and two observational cohort studies of CAH defined an optimal range of 17OHP to be < 1200ng/dl which approximates to three times the upper limit of the normal range (11,37). Our phase III study shows that by treating with MR-HC, which provides a physiological rise in cortisol levels overnight, it is now possible to control the overnight rise in 17OHP such that a relatively flat 17OHP profile over 24 hours is achieved, similar to that seen in healthy subjects. In the phase III study, we found that MR-HC at 30mg a day controls many patients in to the reference range and this dose is similar to that reported in all four CAH cohort studies where dose is

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provided and where control is generally < 50% (10,11,29,30). When the dose of MR-HC was reduced in the extension study to adrenal replacement levels, median dose 20mg, the 17OHP remained in the optimal range in 80% of patients. This median dose is 20 to 40% less (5 to 10mg a day less) than that reported in the cohort studies (10,11,29,30). The "optimal" 17OHP level could be debated and practices vary among clinicians; however, there is agreement that lower glucocorticoid doses are beneficial and this was achieved in the extension study with female patients reporting improvements in menstrual regularity and improvement in fertility in both sexes.

The evidence that an adrenal replacement dose of hydrocortisone has better health outcomes than the higher doses more commonly used in CAH, comes from the literature examining hydrocortisone replacement therapy in adrenal insufficiency. In a large retrospective studies of patients on glucocorticoids a hydrocortisone equivalent dose > 20mg / day was associated with an unfavourable metabolic profile (38), and a daily dose of HC greater that 25mg / day was associated with increased mortality (39). Similarly higher replacement doses of hydrocortisone have been associated with lower quality of life (QoL) in patients with adrenal insufficiency (40), and lower psychological wellbeing (41). In a large longitudinal historical cohort study in paediatric patients the dose of hydrocortisone in patients with CAH was negatively associated with final height with each 1mg/m^2/day of hydrocortisone equating to a loss of 0.37cm height (42).

Currently there is no consensus on monitoring glucocorticoid therapy in CAH (10). Clinicians measure biomarkers both before and after dosing (43), and aim for 17OHP levels above the reference range and androstenedione within the reference range for good control, with normal 17OHP indicating over-treatment and high androstenedione indicating under-treatment (14,24). In 21-OHD-CAH, the physiological pathway to androstenedione biosynthesis from 17-hydroxypregenolone via DHEA is downregulated (43,44), and androstenedione biosynthesis primarily occurs through conversion of excess 17OHP. With MR-HC treatment, we observed near normalization of 17OHP and concurrently low androstenedione, despite a median daily MR-HC dose of 20mg, suggesting that the low androstenedione is not explained by glucocorticoid-mediated suppression. Thus, you can't keep down titrating the glucocorticoid dose based on a low A4 as you will go below adrenal replacement doses and risk adrenal insufficiency. The mode of action of MR-HC flattens the 24 hour 17OHP profile, similar to that seen in healthy subjects, and provides the rationale for a monitoring and titration scheme whereby the morning 17OHP reflects the evening dose and the afternoon 17OHP the morning dose of MR-HC. Thus, in the extension study, patients have been titrated using a sample measured at 0900h and 1300h which are times suitable for the clinic. Two samples are required and could potentially be provided remotely if suitable validated

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assays for saliva and blood spot are available. MR-HC provides a potential simplified paradigm for the treatment and monitoring of CAH with dosing at bedtime and waking, and hormonal measurements at 0900h to judge the nighttime dose and around midday to judge the morning dose.

The lack of significant differences in clinical and patient reported outcomes between the two groups in the phase III study reflects the short duration of the study and similar daily glucocorticoid doses. QoL has been shown to improve when using a pump to deliver subcutaneous diurnal hydrocortisone infusion to 21-OHD-CAH patients with poor control and QoL at baseline (17); however, QoL in 21-OHD-CAH has variably been reported as either impaired or normal (45). Our patients were a diverse population at baseline with similar QoL to the general population, which would make demonstrating improvement difficult.

Over a third of patients had an infection during the study consistent with the observation that patients with adrenal insufficiency have higher infection rates (46), and emphasizes the importance of teaching patients sick day rules. Mortality in patients with 21-OHD-CAH is increased and adrenal crisis is responsible for up to 42% of excess deaths (8,9). The incidence of adrenal crisis in patients with adrenal insufficiency is estimated to be 5–10 adrenal crises/100 patient years with a mortality rate of 0.5/100 patient years (20,21,47-49). Five of 122 patients had an adrenal crisis in the year before the study (3 randomized to MR-HC), and during the randomized study, 3 patients in the standard group had an adrenal crisis but none in the MR-HC group. In the extension study, 4 patients had an adrenal crisis with a frequency of 6.2 crises per 100 treatment years, similar to population estimates (20,49,50), and providing confidence that the safety profile of MR-HC does not differ from that of immediate-release hydrocortisone.

A strength of our phase III study was the international multicenter randomized design enabling us to study a large cohort in a rare disease; the extension study provided data on up to 2 years of treatment with MR-HC, a sound basis for efficacy and safety assessment. The limitations of the phase III study include; the open label design (mitigated by the blinded dose titration), and the complexity of the protocol and statistical analysis. Blinding was considered impractical due to multiple dosing regimens and the difficulties replicating the bitterness of hydrocortisone in a placebo. It was challenging to admit patients for a 24-hour profile, which may have restricted recruitment and created a selection bias for better controlled patients. The intensive monitoring and more aggressive dose up-titration than usually performed in clinical practice may explain the improved control in the standard group compared to previous observational studies of 21-OHD-CAH,(10,11) and the extension study demonstrated that MR-HC dose reduction could be achieved with more simplified monitoring.

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In conclusion, we found that MR-HC improved morning and early afternoon biochemical control of 21-OHD-CAH over standard glucocorticoid therapy. This control was sustained for 18 months on hydrocortisone doses recommended for adrenal replacement therapy and lower than doses normally used in 21-OHD-CAH. MR-HC provides a well-tolerated and practical twice-daily treatment regimen for 21-OHD-CAH.

Author contribution statement:

The first and last authors vouch for the accuracy, completeness of the data and analyses. All authors critically reviewed the manuscript, participated in the design and analysis of the trial.

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Figure Legends

Figure 1: Screening, Randomization Treatment and Follow-up of the Patients.

The safety population included all randomly assigned patients who received at least one dose of trial treatment. *Patients could have more than one reason for study exclusion and withdrawn patients are included in patients excluded.

Figure 2: 24 Hour Endocrine Profiles for 17-Hydroxyprogesterone (17OHP) and Androstenedione at Week 24 versus Baseline (geometric mean ± 95% CIs, patients meeting the criteria for the efficacy analysis) and 09:00hrs 17OHP during the extension study.

At week 24, the 17OHP 24-hour profile for patients receiving MR-HC was flat, and the morning rise in 17OHP observed at baseline was no longer present (Panel A). Similar results were observed for androstenedione (Panel B). Patients in the standard glucocorticoid group had improvement in hormonal control with glucocorticoid dose adjustments according to the protocol, but the pattern of hormone secretion did not change: the 17OHP (Panel C) and androstenedione (Panel D) profiles continued to display a morning increase. At week 24, the MR-HC vs. standard groups differed during the morning hours but not throughout the 24 hours for 17OHP (Panel E) and androstenedione (Panel F). During the extension study, the geometric mean 09:00h 17OHP fell from baseline into the optimal range and remained there despite a reduction in MR-HC daily dose (Panel G).

Data Availability: Datasets generated during and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Table 1. Baseline Characteristics of Patients

Characteristic	Modified-release Hydrocortisone Group	Standard Glucocorticoid Group	Safety Extension Study
Number	61	61	91
Age yrs - median (range)	35 (19-61)	40 (19-68)	35 (20- 67)
Female sex - no. (%)	42 (68.9)	36 (59)	62 (68.1)
Salt-wasting – no. (%)	49 (80)	51 (84)	77(85)
BMI (kg/m^2) median (range)	27.8 (18.0-43.7)	27.0 (19.7-36.8)	28.3 (18.0, 43.7)
Fludrocortisone use - no. (%)	52 (85)	52 (85)	77 (85)
Fludrocortisone mcg/day, median (range)	100 (25-400)	100 (25-400)	100 (25-500)
Good disease control ¥ * no. (%)	20 (37.7)	32 (61.5)	52 (50.0)
Pre-study Glucocorticoid treatment			
Hydrocortisone - no. (%)	36 (59.0)	39 (63.9)	-
Prednisolone - no. (%)	21 (34.4)	22 (36.1)	-
Dexamethasone - no. (%)	5 (8.2)	5 (8.2)	-
Prednisone - no. (%)	3 (4.9)	2 (3.3)	-

¥Good disease control defined as 09:00h 17OHP <1200 ng/dl.

* patients meeting the criteria for the efficacy analysis

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Table 2: Adrenal Insufficiency Checklist

*This questionnaire should be used to determine if symptoms of **under- or over-replacement of glucocorticoids** have occurred in the preceding 4 weeks.*

Date of assessment (mm/dd/yyyy):

Please ask subject: Have you experienced any of the following symptoms more than once per week in the last 4 weeks?

Symptoms	Yes	If Yes, do you believe this to be related to under or over replacement of glucocorticoid? Please state over/under	No	Any clinically significant findings? Y/N
Sudden weight loss				
Sudden weight gain				
Lack of appetite				
Nausea				
Vomiting				
Headache				
Blurred vision				
Fatigue				
Weakness				
Dizziness				
Lightheadedness				
Syncope (sudden loss of consciousness)				
Sleeping difficulties				
Increased acne				
Other				
If yes to other please specify:				

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Table 3. Study Outcomes and Disease Relevant Clinical Events *

	MR-HC Group	Standard Group	Comparison between groups
Biochemical Outcomes from Phase III	**(N=53)**	**(N=52)**	**Treatment Effect[#] [95% CI], *P*-value[$]**
Baseline natural log 17OHP SDS profile	1.25 ± 0.73	1.03 ± 0.82	
Change from baseline in natural log 17OHP SDS profile			
24 hour profile at 4 weeks	-0.37 ± 0.63	-0.07 ± 0.42	-0.26 [-0.46, -0.07], P=0.007
24 hour profile at 12 weeks	-0.52 ± 0.85	-0.10 ± 0.67	-0.30 [-0.54, -0.05], P=0.019
Primary endpoint: 24 hour profile at 24 weeks	-0.40 ± 0.85	-0.17 ± 0.78	-0.07 [-0.30, 0.16], P=0.55
07:00h – 15:00h profile at 24 weeks	-0.69 ± 0.96	-0.21 ±0.79	-0.29 [-0.56, -0.01], P=0.044
Baseline natural log 17OHP 24-hour AUC	65.2 ± 38.5	54.0 ± 39.2	
Change from baseline in natural log 17OHP 24-hour AUC			
24 hour profile at 4 weeks	-23.9 ± 27.7	-6.1 ± 19.3	-16.6 [-25.5, -7.8], P<0.001
24 hour profile at 12 weeks	-35.5 ± 35.3	-13.5 ± 28.5	-17.8 [-29.0, -6.6], P=0.002
24 hour profile at 24 weeks	-37.7 ± 42.6	-17.8 ± 29.0	-13.8 [-25.8,-1.8], P=0.025
Amplitude ratio of 17OHP[¶] : median [95% non-parametric CI]	0.36 [0.24, 0.65]	0.92 [0.77, 1.37]	0.38 [0.24, 0.61], P<0.001
Baseline natural log Androstenedione 24-hour AUC	21.4 ± 30.4	13.9 ± 32.2	
Change from baseline in natural log Androstenedione 24-hour AUC			
24 hour profile at 4 weeks	-12.5 ± 22.2	-3.1 ± 11.3	-8.9 [-15.6, -2.1], P=0.011
24 hour profile at 12 weeks	-20.6 ± 23.8	-8.0 ± 15.1	-10.9 [-18.3, -3.5], P=0.004
24 hour profile at 24 weeks	-22.9 ± 26.9	-9.3 ± 20.4	-10.5 [-18.7, -2.3], P=0.013
Disease Relevant Clinical Events Phase III Study	**(N=61)**	**(N=61)**	
Adrenal Crises, n of patients(%)	0 (0)	3 (5.8)	N/A
Stress dosing, n of patients (%)	26 (49.1)	36 (69.2)	N/A
Restoration of menses, n of patients (%)	4 (7.5)	1 (1.9)	N/A
Partner pregnancy (%)	2 (3.8)	0 (0)	N/A
Biochemical Outcomes from Extension Study	**(N=50)**		
Good Disease control (17OHP) at 18 months, n of patients (%)	40 (80.0)	-	N/A
17OHP suppressed, n of patients (%)↓	2 (4.0)	-	N/A

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Disease Relevant Clinical Events Phase III Study	**(N=91)**		
Adrenal Crises, n of patients (%)	4 (4.4)	-	N/A
Stress dosing, n of patients (%)	72 (79.1)	-	N/A
Restoration of menses, n of patients	4 (4.4)	-	N/A
Patient pregnancy	2 (2.2)	-	N/A
Partner pregnancy	1 (1.1)	-	N/A

*Plus-minus values are means ± SD. CI denotes confidence interval.

[#]Treatment effect is defined as least-squares mean difference (MR-HC minus Standard GC) for SDS profiles and 24-hour AUC adjusted for baseline value and pre-baseline therapy; as the ratio MR-HC to Standard GC for amplitude ratio; and as the odds ratio MR-HC versus Standard GC for good disease control adjusted for baseline disease control status.

[$]Confidence intervals and P-values are obtained from an ANCOVA model for SDS profiles and 24-hour AUC, by the Hodges-Lehmann and Wilcoxon methods respectively for amplitude ratio, and from a logistic model for good disease control.

[¶] Amplitude is defined as the maximum divided by the minimum over the 24-hour assessment period. The ratio is the amplitude at 24 weeks divided by the amplitude at baseline.

[¥]Good disease control defined as 09:00h 17OHP <1200 ng/dL

↓Suppressed 17OHP defined as undetectable

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Table 4. Glucocorticoid Doses at Baseline, 24 Weeks and During the Extension Study

Dose	Modified-release Hydrocortisone Group		Standard Glucocorticoid Group*	
	Baseline	24 weeks	Baseline	24 weeks
All (hydrocortisone dose equivalents)**				
Median daily dose (mg)	25.0	30.0	25.0	31.3
Range	15-50	10-65	12.5-80	12.5-80
Median dose/BSA (mg/m^2/day)	13.6	15.8	14.4	17.0
On hydrocortisone at baseline				
Median daily dose (mg)	20.0	25.0	23.75	25.0
Range	12.5-40	10-65	12.5-35	15-55
Median dose/BSA (mg/m^2/day)	12.0	15.1	12.3	14.5
On prednis(ol)one at baseline				
Median daily dose (mg)	30	27.5	26.6	32.8
Median dose/BSA (mg/m^2/day)	16.7	16.5	15.7	18.5
Range	12.5-50	15-50	12.5-50	12.5-50
On dexamethasone at baseline				
Median daily dose (mg)	30	30	40	40
Range	29.6-38	30-45	20-80	33.5-80
Median dose/BSA (mg/m^2/day)	17.3	17.3	17.5	20.6

MR-HC Safety Extension Study						
Time from Study Start	0-4 Weeks **MR-HC**	4-12 Weeks **MR-HC**	12-24 weeks **MR-HC**	6-12 months **MR-HC**	12-18 months **MR-HC**	18-24 months **MR-HC**
Median Daily Dose (mg) MR-HC	30	26.0	25.0	20.3	20.1	20.0
Range	10-55	10-55	10-55	10-50.3	10-50.3	7.3-55
Median Dose (mg/m^2/day) MR-HC	15.8	15.0	13.5	12.5	11.7	11.1
Number of patients with data available	91	91	88	87	74	50

BSA, body surface area

* Standard Glucocorticoid Group are patients who continued on their conventional pre-study glucocorticoid treatment

** Conversion factors established in endocrinology were used; prednisone/prednisolone dose was multiplied by 5, and dexamethasone dose was multiplied by 80.[10] This dexamethasone conversion was used up to a maximum starting dose of MR-HC 30mg, split as 20mg at night and 10mg in the morning.

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Table 5. Secondary outcomes and vital signs at baseline and change at 24 weeks and then at 2 years in extension study. Mean (SD)

Outcome	MR-HC Group Baseline & change at 24 weeks		Standard Glucocorticoid Group Baseline & change at 24 weeks		Extension Study MR-HC Baseline & change at 18-24 months	
	N=61		N=61		N=50	
Safety set	**Baseline**	**Change**	**Baseline**	**Change**	**Baseline†**	**Change**
Weight (kg)	75.5 (18.5)	0.87 (3.7)	74.6 (13.2)	1.0 (2.7)	75.6 (16.1)	-0.28 (4.8)
Body mass index (kg/m^2)	28.5 (6.4)	0.3 (1.5)	27.7 (4.3)	0.4 (1.0)	28.8 (5.7)	-0.08 (2.0)
Waist circumference (cm)	90.9 (16.3)	0.2 (5.4)	90.5 (11.8)	1.0 (5.6)	91.5 (14.8)	0.69(5.7)
Systolic blood pressure (mmHg)	120.9 (13.6)	-1.8 (11.4)	120.2 (14.4)	0.5 (11.2)	120.4 (13.9)	-3.1 (10.4)
Diastolic blood pressure (mmHg)	71.1 (10.6)	-0.5 (9.2)	70.6 (11.0)	0.2 (9.2)	70.6 (10.8)	-0.4 (9.4)
Efficacy Evaluable Set	**N=53**		**N=52**		**N=50**	
Fat mass (kg)	29.535 (11.7)	-0.575 (3.3)	26.163 (10.3)	0.445 (2.5)	27.943 (11.5)	-0.718 (4.8)
Lean mass (kg)	46.975 (9.3)	0.640 (2.3)	45.468 (9.1)	0.234 (1.4)	45.819 (9.3)	-0.079 (3.4)
Bone mineral density (g/cm2)	1.126 (0.1)	-0.001 (0.0)	1.111 (0.1)	-0.008 (0.0)	1.094 (0.092)	0.001 (0.04)
C-terminal cross-linked telopeptide (ng/L)	570 (257)	9.3 (161)	590 (260)	-23.3 (120)	540.1 (252)	-52.3(176)
Fasting osteocalcin ug/L	19.93 (8.4)	-0.6 (8.1)	21.51 (10.0)	-2.1 (6.3)	19.49 (7.9)	4.4 (8.2)
hsCRP (mg/L)	1.38 (1.3)	0.54 (2.6)	2.04 (4.4)	0.20 (7.5)	1.78 (5.0)	2.3 (6.2)

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Fasting glucose (mg/dl)	92.1 (8.5)	9.9 (10.2)	90.1 (9.9)	1.8 (8.8)	91.7 (7.8)	2.6 (9.8)
Fasting insulin mIU/L	12.6 (6.3)	1.9 (6.8)	11.7 (5.6)	3.0 (7.4)	13.0 (5.9)	-2.1 (6.3)
HOMA-IR	2.894 (1.6)	0.914 (2.1)	2.59 (1.3)	0.77 (1.8)	-	-
HbA1c (%)	5.16 (0.28)	0.02 (0.26)	5.18 (0.43)	-0.02 (0.28)	5.17 (0.31)	0.12 (0.23)
Plasma Renin Activity (ng/ml/hour)	3.5 (2.5)	-1.0 (2.4)	2.9 (2.4)	0.4 (2.5)	3.2 (3.5)	-0.2 (0.9)
Total Testosterone women (ng/dl)	33 (33.4)	-21 (127.8)	32 (52.9)	-9 (30.4)	147 (263.8)	-13 (63.4)
Total Testosterone men (ng/dl)	453 (320.9)	-26 (284.1)	481 (142.6)	-36 (135.8)	271 (305.9)	77 (177.1)

† Baseline in extension study is pre-MR-HC

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Table 6. Quality of life assessments at 24 weeks (phase III study) and then at 12 and 18 months (extension study). Values are mean (SD).

Parameter	Phase III Study		Safety Extension Study	
	MR-HC Group N=53	Standard Group N=52	12 months N=73	18 months N=51
SF-36 Absolute Change from Baseline by domain[+]				
T-score: bodily pain*	N/A	N/A	N/A	N/A
T-score: general health perceptions	0.79 (7.54)	-1.88 (5.97)	1.43 (8.76)	2.11 (5.66)
T-score: mental health	0.86 (7.32)	0.35 (7.81)	1.49 (9.44)	1.33 (6.89)
T-score: physical functioning	1.16 (6.43)	-0.52 (4.27)	0.41 (4.38)	0.28 (4.25)
T-score: role emotional	0.99 (9.95)	-0.34 (9.21)	1.38 (11.65)	0.48 (8.50)
T-score: role physical	1.91 (8.33)	0.50 (6.68)	1.42 (7.53)	0.81 (9.24)
T-score: social functioning	2.18 (9.25)	0.87 (6.86)	2.54 (9.00)	0.89 (8.95)
T-score: vitality	0.79 (9.45)	0.92 (6.10)	2.15 (8.44)	2.56 (6.80)
Global Fatigue Index absolute change in score from baseline				
GFI score derived from MAF	-0.74 (11.1)	-0.26 (7.8)	-1.93 (10.1)	-2.31 (10.6)
EQ-5D Summary changes from baseline				
EQ-5D VAS Score	-1.3 (13.67)	-1.2 (12.62)	2.7 (17.74)	2.3 (12.33)
EQ-5D-5L Index Score	0.02 (0.12)	0.02 (0.14)	-0.01 (0.17)	-0.01 (0.14)

N=number of evaluable participants; SD=standard deviation; SF-36=Medical Outcome Short Form Health Survey Form 36 (Subject Questionnaire). GFI=Global Fatigue Index; MAF=multidimensional assessment of fatigue; EQ-5D = Standardised Health Questionnaire (5L = 5-Level); VAS = Visual Analogue Scale; GFI scores from 1 (no fatigue) to 50 (severe fatigue).

[+]Baseline is defined as start of study in phase III study and pre-MR-HC initiation baseline in safety extension study.

*A technical issue with the scoring of the bodily pain domain meant that these data are not available.

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Figure 1

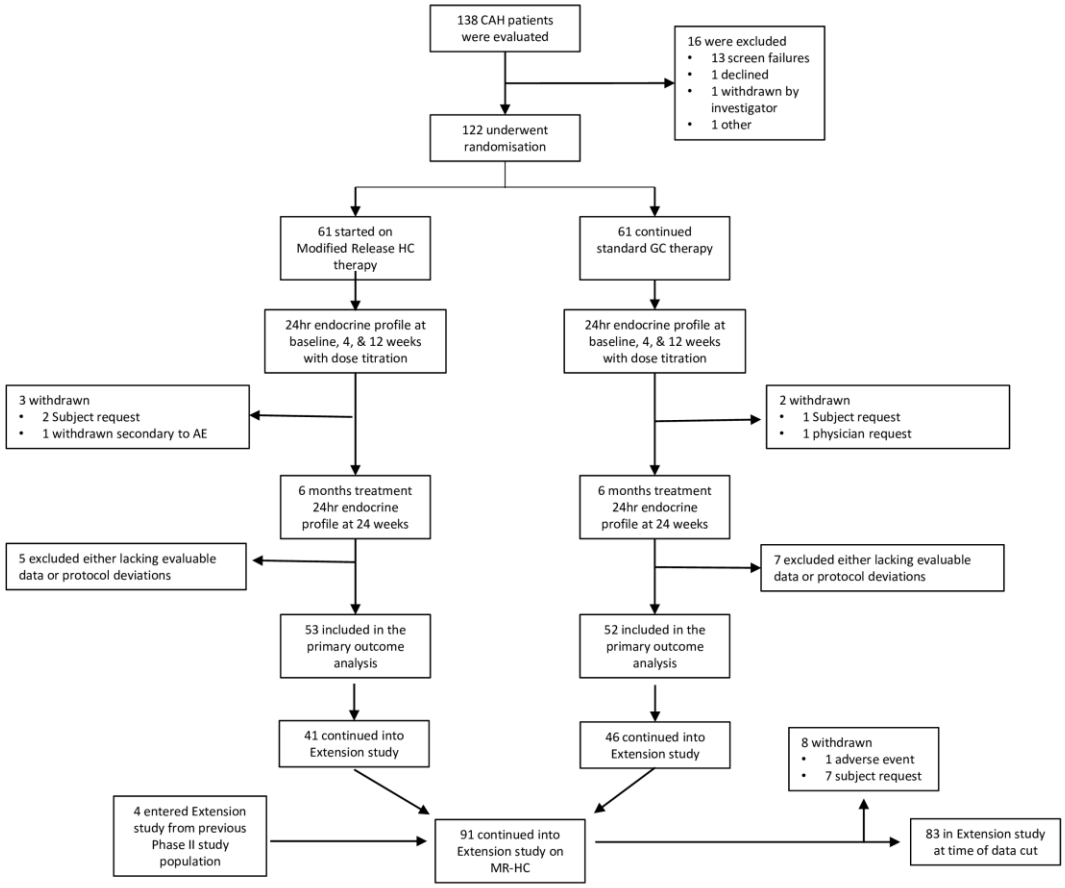

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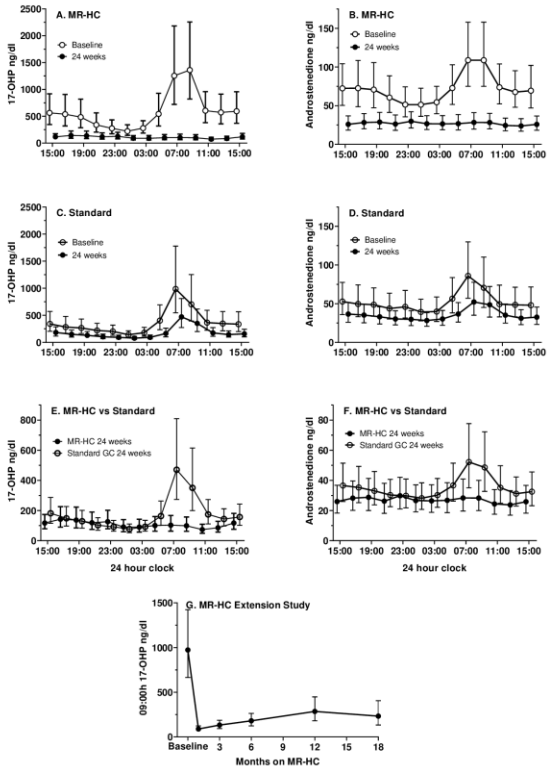
Figure 2



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