

25 March 2021 EMA/CHMP/233437/2021 Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

# Efmody

International non-proprietary name: hydrocortisone

Procedure No. EMEA/H/C/005105/0000

# Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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# List of abbreviations

Abbreviation	Definition
17-OHP	17-hydroxyprogesterone
A4	Androstenedione
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AI	Adrenal insufficiency
ANCOVA	Analysis of Covariance
AUC	Area under the plasma concentration versus time curve
AUC0-inf	Area under the plasma concentration versus time curve from the time of dosing
	extrapolated to infinity based on the last observed concentration
AUC0-t	Area under the plasma concentration versus time curve from the time of dosing to the time of the last observed concentration
BA	Bioavailability
BMI	Body mass index
BSA	Body surface area
CAH	Congenital adrenal hyperplasia
CHMP	Committee on Human Medicinal Products
CI	Confidence interval
Cmax	Maximum plasma concentration
CTX	C- terminal telopeptide
CYP21	Cytochrome P450 21-hydroxylase gene
CYP3A4	Cytochrome P450 3A4
DHEA	Dehydroepiandrosterone
ECG	Electrocardiogram
EES	Efficacy evaluable set
EMA	European Medicines Agency
EO-5D	Standardised Health Ouestionnaire (5-level)
ERA	Environmental Risk Assessment
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
Fpen	Market Penetration Factor
GC	Glucocorticoid
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HbA1c	Glycated haemoglobin
НС	Hydrocortisone
Hr	Hour(s)
i.v.	Intravenous
IR	Immediate-release
IRHC	Immediate-release hydrocortisone
ITT	Intent To Treat
IWRS	Interactive Web Response System
L	Least square
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LLN	Lower Limit of Normal
Log Kow	Bioaccumulation Potential
MAA	Marketing Authorisation Application
MAF	Muldimensional Assessment of Fatigue
PBPK	Population Based Pharmacokinetics
PBT	Persistence-Bioaccumulation-Toxicity
PD	Pharmacodynamic
PECsw	Predicted Environmental Concentration in surface water
PTI	Patient Information Leaflet
PK	Pharmacokinetics
PRA	Plasma Renin Activity
PT	Preferred term
	Quality of life

RBC	Red Blood Cell
RMP	Risk Management Plan
SAE	Serious adverse event
SD	Standard deviation
SDS	Standard deviation score
SF-36	36-Item Short Form Heath Survey
SmPC	Summary of Product Characteristics
SoE	Strength of Evidence
StAR	Steroidogenic acute regulatory deficiency
t1/2	Half-life
TEAE	Treatment-emergent adverse event
tmax	Time at which the maximum plasma concentration occurred
UK	United Kingdom
ULN	Upper Limit of Normal
Un	Uncertainty
US	United States

# 1. Background information on the procedure

# 1.1. Submission of the dossier

The applicant Diurnal Europe BV submitted on 12 December 2019, an application for marketing authorisation to the European Medicines Agency (EMA) for Efmody, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 June 2018.

The application concerns an hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant initially applied for the following indication:

Replacement therapy for congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults.

The final applied indication was as follows:

Treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults.

Efmody, was designated as an orphan medicinal product EU/3/05/296 on 27 July 2005. Efmody was designated as an orphan medicinal product in the following indication: Treatment of congenital adrenal hyperplasia.

#### The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is

composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product (Hydrocortone, hydrocortisone 20 mg tablets) and appropriate non-clinical and clinical data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Hydrocortone, hydrocortisone 20 mg tablets
- Marketing authorisation holder: Auden McKenzie
- Date of authorisation: 23 February 1989
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom
    - National procedure
- Marketing authorisation number: PL17507/0098

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Hydrocortone, hydrocortisone 20 mg tablets
- Marketing authorisation holder: Auden McKenzie

- Date of authorisation: 23 February 1989
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom
    - National procedure
- Marketing authorisation number: PL17507/0098

### Information on paediatric requirements

Not applicable

### Information relating to orphan market exclusivity

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 16 April 2021 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website ema.europa.eu/en/medicines/human/EPAR/Efmody.

### Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

### Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference
1 June 2007	EMEA/CHMP/SAWP/155103/2007
24 July 2014	EMA/CHMP/SAWP/430444/2014
28 March 2019	EMA/CHMP/SAWP/185957/2019

The Protocol assistance pertained to the following quality and clinical aspects:

Quality:

•Use of a bracketing strategy for the evaluation of the stability performance

Multidisciplinary Quality-Clinical:

- •In vitro determination of drug release properties
- •Evaluation of the effect of concomitant dosing with gastric pH modifying agents

Clinical:

Pharmacokinetic characteristics

- Design of the pivotal study, in particular the choice of comparator, use of biochemical markers to measure disease control, choice of endpoints, sample size and planned statistical analyses
- Inclusion of a sub-set of patients for pharmacokinetic analysis
- Definition of patient population
- Planned procedures for safety monitoring
- Duration of planned Phase 2 study
- Paediatric development programme
- Overall aims of the development programme
- Design of the proposed single Phase 3 study
- Method of analysis for the primary endpoint
- Design of the food-effect study
- Sufficiency of the clinical data package for MAA

### 1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Kristina Dunder

The application was received by the EMA on	12 December 2019
The procedure started on	26 March 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 June 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	15 June 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 June 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	9 December 2020
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	4 January 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 January 2021

The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	28 January 2021
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	18 February 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 March 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Efmody on	25 March 2021
The CHMP adopted a report on similarity of Efmody with Plenadren on	25 March 2021

# 2. Scientific discussion

# 2.1. Problem statement

# 2.1.1. Disease or condition

The indication applied for is: "Treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults."

CAH is caused by genetic mutations in genes responsible for adrenal steroid hormone synthesis. Approximately 95% of CAH cases are caused by mutations in CYP21A2, the gene encoding adrenal steroid 21-hydroxylase.

# 2.1.2. Epidemiology

The most recent estimates are that the worldwide birth prevalence of classical CAH (CAH due to 21hydroxylase deficiency presenting at birth/during childhood) ranges from 1:11,000 to 1:18,000 births (10,000 to 1:16,000 live births in the European and North American populations). A reasonable estimate is that CAH affects 0.5 to 2:10,000 people within the European Union (EU).

# 2.1.3. Biologic features, aetiology and pathogenesis

CAH is an autosomal recessive condition commonly caused by mutations in the 21 hydroxylase gene (CYP21A2), which plays a role in the cortisol biosynthetic pathway. Patients with CAH have a cortisol deficiency, hyperandrogenism and may also present with impaired production of aldosterone, which regulated the mineral homeostasis.



Figure 1 Adosterone, Cortisol, Testosterone biosynthetic pathways

This enzyme converts 17-OHP to 11-deoxycortisol and progesterone to deoxycorticosterone, with these products being precursors for cortisol and aldosterone. The blockage of cortisol synthesis leads to a rise in Adrenocorticotropic hormone (ACTH) stimulation of the adrenal cortex, resulting in a build-up of steroid precursors such as progesterone, 17-hydroxypregnenolone, and especially 17-hydroxyprogesterone (17-OHP). A substantial fraction of the increased 17-OHP levels is diverted to the synthesis of dehydroepiandrosterone (DHEA), androstenedione (A4) and testosterone. See Figure 1.

Disease severity is correlated with genotype. Almost 300 pathogenic mutations in CYP21A2 are known, but genotyping individuals with CAH is difficult due to the complexity of gene duplications, deletions, and rearrangements within chromosome 6p21.3.

A minority of patients have mutations in 11-beta-hydroxylase, 3-beta-hydroxysteroid dehydrogenase, 17-hydroxylase or steroidogenic acute regulatory (StAR) deficiency (approximately 5% of the cases).

# 2.1.4. Clinical presentation, diagnosis

CAH due to 21-hydroxylase deficiency is divided into the classic (severe, early-onset) form and the non-classic (mild, late-onset) form. Classic CAH can be subdivided in salt-wasting CAH (approximately two-thirds of patients) and simple-virilising CAH (one-third of patients), reflecting the degree of aldosterone deficiency.

#### Clinical presentation in females

Females with severe forms of adrenal hyperplasia due to deficiencies of 21-hydroxylase, 11-betahydroxylase or 3-beta-hydroxysteroid dehydrogenase have ambiguous genitalia at birth due to excess adrenal androgen production in utero. Salt-wasting CAH presents in the first weeks of life with failure to thrive, recurrent vomiting, dehydration, hypotension, hyponatremia, hyperkalaemia, and shock.

Simple-virilising adrenal hyperplasia is identified later in childhood because of precocious pubic hair, clitoromegaly, or both, often accompanied by accelerated growth and skeletal maturation due to excess postnatal exposure to adrenal androgens.

Milder deficiencies of 21-hydroxylase or 3-beta-hydroxysteroid dehydrogenase activity (non-classic adrenal hyperplasia) may present in adolescence or adulthood with oligomenorrhea, hirsutism, and/or infertility.

Females with 17-hydroxylase deficiency appear phenotypically female at birth but do not develop breasts or menstruate in adolescence because of inadequate estradiol production. They may present with hypertension.

#### Clinical presentation in males

21-hydroxylase deficiency in males is generally not identified in the neonatal period because the genitalia are normal. If the defect is severe and results in salt wasting, these male neonates present at age 1-4 weeks with failure to thrive, recurrent vomiting, dehydration, hypotension, hyponatremia, hyperkalemia, and shock. Patients with less severe deficiencies of 21-hydroxylase present later in childhood because of the early development of pubic hair, phallic enlargement, or both, accompanied by accelerated linear growth and advancement of skeletal maturation (simple-virilising CAH).

#### Adrenal crisis

Due to the insufficient or absent cortisol production, patients with CAH are at risk of adrenal crisis when experiencing physiological stress. This life-threatening condition requires emergency medical treatment.

#### Diagnosis

CAH is included in many neonatal screening programmes in the EU. Early diagnosis can prevent significant morbidity and mortality. In general, the diagnosis is based on clinical symptoms and the demonstration of inadequate production of cortisol, aldosterone, or both in the presence of accumulation of excess concentrations of precursor hormones such as 17-OHP.

# 2.1.5. Management

The main goal of CAH treatment is glucocorticoid replacement therapy, ie replacing the deficiency in corticosteroids while minimising adrenal sex hormone and glucocorticoid excess, preventing virilisation, optimising growth, and protecting potential fertility. Management of classic CAH is, therefore, a difficult balance between hyperandrogenism and hypercortisolism. Optimal treatment is hampered by the physiological rhythms in hormone production, which is difficult to mimic with oral replacement therapy.

The first drug of choice is oral hydrocortisone (HC). Hydrocortisone was introduced as replacement therapy in patients with CAH in the 1950s. The majority of existing marketed oral formulations of hydrocortisone are provided at doses of 10 mg and 20 mg and are designed to deliver "immediate-release" of the active ingredient. Given the short plasma half-life of hydrocortisone, to achieve efficacious plasma levels of hydrocortisone throughout the day multiple daily dosing is required (typically 3 times a day). This treatment regimen provides supra-physiological levels of hydrocortisone within 1-2 hours of dosing, but this results in high peak-to-trough fluctuations in plasma concentrations. This 3-times daily dosing with immediate-release hydrocortisone (IRHC) also results in abnormally low early morning cortisol levels before the first hydrocortisone dose is taken, which in turn, due to the lack of a negative feedback, causes high ACTH levels leading to high adrenal androgen levels in the morning.

Alternative treatment regimens involve giving a high dose of steroids before bedtime (reverse circadian), but this is unphysiological, and some patients complain that it affects their sleeping pattern. In addition, there is a greater risk of giving excess steroid doses as the patient still needs steroid replacement during the day. It has been suggested that a delayed (modified) release steroid, such as

those used to treat ulcerative colitis, might be useful in the treatment of CAH. One such "modifiedrelease" formulation (Plenadren, Shire Pharmaceuticals Ltd.) has been marketed in Europe for the separate indication of adrenal insufficiency (AI) in adults only. However, Plenadren has an immediate and sustained release profile and is given once daily in the morning to replace daytime cortisol levels i.e. it does not mimic the physiological secretion of cortisol. In particular, it does not release hydrocortisone overnight, and therefore there are still abnormally low morning cortisol levels and unrestrained ACTH secretion overnight, with resultant high adrenal androgens in the morning in patients with CAH.

According to the Endocrine Society Clinical Practice Guideline 1 (2018), hydrocortisone should be administered at a dose of 15 mg to 25 mg for adults and 10 mg/m2/day to 15 mg/m2/day in children, usually as 2 or 3 divided oral doses per day. Insufficient data exist to recommend fractional distribution of doses throughout the day or empiric dosing in the very early morning hours. However, the usual practice is to give the highest dose (50-66%) in the morning at awakening, the next either in the early afternoon (2 hours after lunch and 6-8 hours after the morning dose if using a 2-dose regimen) or at lunch (4-6 hours after the first dose) and evening (4-6 hours after the second dose) for a 3-dose regimen. Decisions on dosing are based on regular assessments of weight (including Body Mass Index, ie BMI), blood pressure, examination for Cushingoid features and, in growing adolescents, growth velocity and bone age estimation, in addition to obtaining biochemical measurements to assess the adequacy of the glucocorticoid replacement. The goal is to achieve the best clinical result with the lowest possible daily dose of steroid.

As an alternative to hydrocortisone, another synthetic longer-acting glucocorticoid, prednisone (which is converted to active prednisolone) at a dose of 4-7.5 mg/day can be used, administered orally once or twice daily. Prednisone/prednisolone/methylprednisolone are 4 to 5 times more potent than hydrocortisone and have a longer duration of action of around 12 hours and so are useful in patients who are not compliant with the 2 or 3 times daily dosing regimen of IRHC; however, they may be up to 15 times more growth-suppressive. In patients with salt-wasting, the requirement for aldosterone may be greater when taking long-acting glucocorticoids, since hydrocortisone has a greater mineralocorticoid action than prednisolone and dexamethasone. This mineralocorticoid deficiency can be treated with fludrocortisone.

Dexamethasone, another long-acting glucocorticoid, is not usually recommended for the treatment of CAH because of its potent growth-suppressive effect and the risk of Cushingoid side effects due to difficulties in dose titration. If used, glucocorticoid replacement should be monitored using clinical assessments such as body weight, postural blood pressure, energy levels, and signs of glucocorticoid excess.

However, the longer-acting glucocorticoids have also been reported to have greater catabolic activity on bone. Although there is no direct evidence that longer-acting glucocorticoids behave differently to cortisol, the effects on bone are probably because these glucocorticoids are being used at inappropriately high doses. The longer biological half-life of prednisone/prednisolone is also likely to result in unfavourably high night-time glucocorticoid activity, with potentially detrimental effects on insulin sensitivity and bone mineral density, as well as disturbed sleep.

In the only published survey to date, it was seen that physicians used the different IRHC and long-acting glucocorticoids in equal proportions, confirming that there is no consensus for treating adults. It remains to be seen whether the 2018 guidelines are taken up widely and help to rationalise the approach to therapy.

Thus, there is an unmet medical need for more physiological hydrocortisone replacement options that

<sup>&</sup>lt;sup>1</sup> Endocrine society Clinical practice guideline, Speiser er al, J Clin Endocrinol Metab, November 2018, 103(11):4043-4088

allow for control of cortisol and androgen levels, without exposing patients to unnecessarily high steroid doses.

#### Mineralocorticoid use.

All classic CAH patients should be treated with fludrocortisone at diagnosis in the new-born period. Dosage requirements in early infancy range from 0.05–0.30 mg/d, whereas typical maintenance doses are 0.05–0.2 mg/d, depending on the sodium intake. Such therapy will reduce vasopressin and ACTH levels and lower the dosage of glucocorticoid required. The need for continuing mineralocorticoids should be assessed based on plasma renin activity (PRA) and BP. Sodium chloride supplements are often needed in infancy.

The non-classic form of CAH is not usually treated with complete replacement therapy (only supplementation in stress situations).

### About the product

The active compound in Efmody is hydrocortisone (HC). HC is the synthetic form of cortisol. HC is used to treat immune, inflammatory, and neoplastic conditions. It was discovered in the 1930s by Edward Kendall and named Compound F, or 17-hydroxycorticosterone. It is on the World Health Organization's List of Essential Medicines and was granted FDA approval on 5 August 1952.

Corticosteroids influence the functioning of most of the body's systems (heart, immune, muscles and bones, endocrine and nervous system). They exert a wide array of effects including effects on the metabolism of carbohydrates, protein and fats. They help to maintain the balance of fluids and electrolytes.

Hydrocortisone is classified as a glucocorticosteroid (ATC code H02AB09; Glucocorticoids, hydrocortisone).

Efmody is a modified-release formulation of hydrocortisone that was designed to treat CAH more effectively.

Efmody is claimed to present an optimal delivery of hydrocortisone with a dosage form that has a delayed-release and sustained absorption. With this drug delivery modality, dosing the formulation at night (and early in the morning) would lead to a profile of hydrocortisone levels more similar to endogenous daily cortisol rhythm (without the necessary spikes in stress situations).

The applicant initially developed Efmody using the name Chronocort. This name may appear in figures and tables and is the previous name used for Efmody.

### 2.2. Quality aspects

### 2.2.1. Introduction

The product is available in high-density polyethylene bottles with child resistant, tamper-evident polypropylene screw cap with integrated desiccant, as described in section 6.5 of the SmPC.

The finished product is presented as hard gelatine capsules filled with modified release granules containing 5 mg, 10 mg or 20 mg of hydrocortisone as active substance.

Other ingredients are:

<u>Granules</u> Microcrystalline cellulose Povidone (E1201) Methacrylic acid-methyl methacrylate copolymer (1:2) Methacrylic acid-methyl methacrylate copolymer (1:1) Talc Dibutyl sebacate

<u>Capsule shell</u> Gelatin

Efmody 5 mg modified release hard capsules (white/blue)

Titanium dioxide (E171) Indigotine (E132)

Efmody 10 mg modified release hard capsules (white/green)

Titanium dioxide (E171) Indigotine (E132) Yellow iron oxide (E172)

Efmody 20 mg modified release hard capsules (white/orange)

Titanium dioxide (E171) Yellow iron oxide (E172) Red iron oxide (E172)

<u>Printing ink</u> Shellac Black iron oxide (E172) Propylene glycol Potassium hydroxide

The product is available in high-density polyethylene bottles with child resistant, tamper-evident polypropylene screw cap with integrated desiccant, as described in section 6.5 of the SmPC.

# 2.2.2. Active substance

#### General information

The chemical name of hydrocortisone is (8*S*,9*S*,10*R*,11*S*,13*S*,14*S*,17*R*)-11,17-Dihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-2,6,7,8,9,11,12,14,15,16-decahydro-1*H*-cyclopenta[a]phenanthren-3-one corresponding to the molecular formula C<sub>21</sub>H<sub>30</sub>O<sub>5</sub>. The structure of this active substance is described in Figure 1. It has a relative molecular mass of 362.5 g/mol. It appears as white to almost white, non-hygroscopic crystalline powder. It is practically insoluble in water, sparingly soluble in acetone and in alcohol and slightly soluble in methylene chloride. Only one polymorphic form is consistently formed during the active substance production and used in the manufacture of the finished product. This active substance is described in the Ph. Eur.



Figure 2: hydrocortisone structure

Hydrocortisone exhibits stereoisomerism due to the presence of 6 chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation.

Information on the chemistry, manufacturing and control on hydrocortisone has been evaluated by the EDQM and a European Certificate of Suitability of the Monograph of the European Pharmacopoeia (CEP) has been issued. It was noticed that two additional supplementary tests (Other impurities, particle size and residual solvents) were included in the CEP.

#### Manufacture, characterisation and process controls

The manufacturing process, process controls and active substance characterisation are covered by the EDQM Certificate of Suitability. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

A valid QP declaration was provided by the QP of the proposed batch release site , on the basis of an on-site audit of the manufacturing site carried out by a third party. The operations include the manufacture and micronisation of the active substance.

The active substance is packed as stated on the EDQM Certificate of suitability.

The primary packaging used for hydrocortisone complies with the current regulations contained in Ph.Eur. Monograph 3.1.3 (Polyolefins), -Ph.Eur. Monograph 3.2.2 (Plastic Containers and Closures for Pharmaceutical Use).

#### Specification

The active substance specification, , includes tests for appearance, identity (IR, HPLC), assay (HPLC), optical rotation (Ph.Eur.), loss on drying (Ph.Eur.), impurities (HPLC), residual solvents (GC), residual catalyst – chromium- (AAS) and particle size (light diffraction).

The specification of the active substance manufacturer has been assessed by the EDQM for the grant of the CEP. The active substance is compliant with the Ph.Eur. monograph on hydrocortisone with additional tests for related substances residual solvents, residual catalyst) and particle size distribution. The specifications also comply with ICH Q3A.

The active substance manufacturer conducts testing, according to Ph. Eur. and therefore, no validation of the analytical methods has been provided. Full method validation data was provided for the in-house analytical methods and are in accordance with the relevant ICH Guidelines.

Batch analysis data of the active substance were provided. The results are within the specifications and consistent from batch to batch. The results of parallel testing of three active substance batches conducted by the finished product manufacturer are comparable.

#### Stability

Long-term stability data at 25°C/60% RH were presented for twenty-three batches covering up to 60 months packaged in the proposed packaging. Stability data at 30°C/65% RH were presented for 2 batches covering up to 24 months. The following parameters were tested: hydrocortisone assay dried basis, loss on drying and related substances. The active substance is stable, and no negative trends can be observed. The stability studies were performed according to ICH guidelines.

Hydrocortisone micronised was found to be photostable, there was no significant change in visual appearance, colour in solution and potency. There were no impurities at 0.10% or greater in the material exposed to light. The photostability study performed complies with ICH Q1B. The active substance is proved to be photostable.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period and storage conditions in the proposed container.

## 2.2.3. Finished medicinal product

#### Description of the product and Pharmaceutical development

Efmody is presented as modified release hard capsules filled with a multiparticulate granule formulation of hydrocortisone.

The dosage form is a hard gelatine capsule filled with white to off-white granules with a modified release coating. They are filled into capsules at different fill weights to produce three strengths of the finished product 5 mg, 10 mg and 20 mg. The different strengths are sufficiently distinguished.

The physical descriptions of the finished product are:

- for 5mg strength - Size 1 capsule with opaque white body and opaque blue cap printed with "CHC 5mg" on the body

- for 10mg strength - Size 1 capsule with opaque white body and opaque green cap printed with "CHC 10mg" on the body

- for 20mg strength - Size 0 capsule with opaque white body and opaque orange cap printed with "CHC20mg" on the body.

The composition of hydrocortisone granules and the composition of modified release coating of granules per capsule is presented.

No overage is included in the final product.

This is a hybrid product to Hydrocortone. Due to changes in pharmaceutical form and changes in strength bioequivalence cannot be demonstrated through bioavailability studies.

The dosage form has been developed to imitate the hydrocortisone circadian profile. A pharmaceutical form was developed to achieve the following target product profile:

- An initial absence of release to allow transit through the stomach
- pH-triggered dissolution when the dosage form reaches the mid-distal region of the small intestine.
- A sustained release phase (after the initial delayed release period)
- Oral route of administration
- Accurate dosing at various dose strengths

Micronised hydrocortisone crystal form is used in the finished product manufacture. The particle size and polymorphic form are controlled by the active substance manufacturer.

All excipients are commonly used in pharmaceutical preparations. The compatibility of the active substance with excipients was demonstrated by stability data. No novel excipients have been used. The excipients used within the finished product were selected in order to provide a multi-particulate dosage form that would yield a lag and then release the active substance at a specific pH.

The suitability of chosen excipients and capsule sizes for the target age group of adolescents aged 12 to 18 years have been adequately discussed. The capsules should be swallowed whole and are not to be opened or chewed. The accuracy of dosing in the target age group 12 to 18 years is ensured.

Excipients were chosen as both exhibit pH dependent dissolution, with the pH solubility threshold . The plasticizer and glidant chosen was DiButyl Sebacate (DBS) in combination with Talc. The choice of excipients and levels therein was as suggested by the enteric polymer manufacturer to enable the production of robust and dense film coats.

The most optimal ratio of excipients was selected to yield a dissolution at a specific pH . A total weight gain in relation to the Hydrocortisone coated microcrystalline spheres was selected on the basis that it had provided good reproducibility in dissolution performance.

The lead formulation was chosen based on the selection of desired *in vitro* dissolution profiles of prototype formulations which were then used in pilot clinical evaluations in human volunteers. The granule formulation utilised in all late stage clinical studies and stability programs, and intended for commercial production, has remained unchanged.

Comparison of dissolution profiles of each dose strength of hydrocortisone modified release capsules in pH media and under the QC test method conditions demonstrated their similarity.

The QC dissolution test complies with Ph. Eur. 2.9.3 (apparatus 1, basket, rotation speed 100 rpm). The specification of the dissolution test includes points: to demonstrate resistance of the modified release coating to release in the fed stomach; and to ensure that majority of active substance has been released.

The QC dissolution test method was proved to be robust to changes in dissolution media volume and stirring rate. The test method is able to discriminate between batches with different coating levels.

The impact of gastric conditions has been evaluated *in vitro* in two studies. Pharmacokinetic data indicate that absorption of hydrocortisone is delayed when given shortly after food; however, this is not considered to be clinically significant.

The impact of alcohol consumption on the modified release characteristics and the probability of dose dumping was also investigated in an *in vitro* study. No significant drug release was observed prior to the final pH change media at various alcohol concentrations. It was concluded that the delayed release coating provides robust enteric performance without resulting in premature coat dissolution or affecting the downstream release of hydrocortisone in the presence of typical alcohol consumption levels.

To achieve modified release of hydrocortisone to produce a common multiparticulate granule formulation. The process involves layering steps. The granules are filled into the individual hard capsules at different fill weights to produce the different dose strengths.

The first batches for clinical studies were manufactured at small scale and then transferred to a new manufacturing site where the process was scaled up and optimized . An evaluation of the manufacturing process parameters that may affect the finished product quality attributes, the potential failure mechanism and the actions taken to address the risk for each step of manufacturing process were discussed. The CQA were identified. A 'side by side' comparison of the small-scale manufacturing process parameters and of commercial scale process parameters for the production stages have been presented.

The proposed primary packaging for all strengths of the finished product is an opaque HDPE (High Density Polyethylene) bottle, closed with a child-resistant, tamper-evident PP screw cap with integrated desiccant. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The HDPE bottle and PP screw cap were well characterised and compliance with Commission Regulation (EU) No 10/2011 has been declared. The resins used in bottle and closure meet the Ph. Eur. monographs requirements. The desiccant is declared to be in compliance with Regulation (EC) 1935/2004 and EU regulation 10/2011. The PP closure is certified child resistant, according to ISO 8317 (2015).

#### Manufacture of the product and process controls

The manufacturing process consists of four main steps: preparation of hydrocortisone coated granules, preparation of modified release coated granules, encapsulation and bulk packaging and primary packaging. The process is considered to be a non-standard manufacturing process.

The final theoretical batch size for hydrocortisone modified release bulk granules is presented.

The stability study to support the proposed holding times for intermediates was carried out under  $20^{\circ}C \pm 5^{\circ}C/<85\%$  RH. Very little change was observed in all testing parameters across all intermediates and the bulk product. Holding times for hydrocortisone coated granules, hydrocortisone modified release granules and bulk hydrocortisone modified release capsules have been declared and accepted. The shelf life is calculated according to the Note for guidance on the manufacture of the finished dosage form.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

A comprehensive process validation conducted on three batches of a common blend of the finished product has been performed at the proposed commercial manufacturing scale. In terms of the Guideline on process validation for finished products – a manufacture of modified release preparations is a non-standard process. However, the Applicant designated the manufacture of the proposed product as a standard process, and this was appropriately justified based on previous experience with the same manufacturing principle, and therefore this was accepted.

#### Product specification

The finished product release specifications include appropriate tests for this kind of dosage form appearance, identity (HPLC/UV), assay (HPLC), uniformity (HPLC), dissolution (HPLC), purity (GC) and microbiology.

The proposed specification parameters and limits are adequately set in line with ICH Q6A and are generally acceptable for this type of dosage form.

Risk assessment for elemental impurities according to ICH Q3D is acceptable as presented in the dossier. The risk assessment involved following potential sources of elemental impurities, excipients, capsule shells, container closure system, and manufacturing process and equipment. The calculated potential total daily exposure from the Class 1 and 2A elemental impurities in the finished product at a maximal dose of 40 mg/day are all well below the alert threshold of 30% of the oral PDE. There is no risk of elemental impurity contamination from either the container closure system or the manufacturing process. No additional controls are required to be applied for the finished product.

During the assessment a major objection was raised on the nitrosamines; the company provided a risk assessment regarding the presence of nitrosamine that was incomplete. A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report-Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

With regards to primary packaging (a HDPE bottle with PP cap with desiccant), only absence of nitrosamines in the manufacture of PP cap is confirmed by its supplier. It is acknowledged that an updated documentation for HDPE bottle by its supplier to confirm the absence of nitrosamines is awaited by company and the finished product risk assessment will be provided following the receipt of the updated conformance documentation by the bottle supplier. No risk is expected as the bottling process is not a heat-based process and formation of nitrosamines is likely during printing of the blister's lidding foils, not HDPE bottles.

However, as the risk evaluation report remains incomplete, this was raised as a recommendation. The information about packaging process and container closure system (HDPE bottle with PP screw cap) should be included in the evaluation report for nitrosamines (Recommendation(s) for future quality development).

The test methods and the specification limits for the following tests are referenced to the Ph.Eur. monographs: uniformity of dosage units (limit based on Ph.Eur. 2.9.40) and microbiological testing (2.6.12, 2.6.13). The proposed limits for residual solvents are in line with ICH Q3C and the limits for impurities are set in line with ICH Q3B (R2) and Ph. Eur. Monograph for Hydrocortisone 0335.

All analytical methods were described in detail. In-house methods were developed for identification, uniformity of dosage units, assay, impurities, residual solvents and dissolution.

Results from method validation were presented in tabulated form for in-house methods. Validation of in-house analytical methods is in line with ICH guideline Q2 (R1). Representative chromatograms have been included.

Forced degradation study for this HPLC method was performed, and the assay results were presented, including the results of individual impurities and mass balance data. Assay and related substances were shown to be stability indicating.

The Primary Reference Standard used by the finished product manufacturer for quantitative analysis (as described for assay, content uniformity and dissolution testing of the capsules) is the Ph. Eur. Hydrocortisone Certified Reference Standard (CRS) or an active substance batch which has been certified as a working reference standard against the Ph. Eur. Hydrocortisone CRS reference standard. Analytical results of commercial-scale batches are in compliance with specification proposed and confirm consistency and uniformity of finished product.

#### Stability of the product

The stability studies were conducted with a bracketing approach on three production scale batches of 5 mg and 20 mg strengths and one production scale batch of 10 mg of the finished product under long-term conditions of 30°C/75% RH and accelerated conditions of 40°C/75% RH. The bracketing approach is justified since the different dose strengths are manufactured from a common granulate filled at different weights to produce the required strength. The deviation in the long-term storage conditions (30°C/75% RH instead of standard 30°C/65% RH) is in line with the Explanatory Note on the Withdrawal of ICH Q1F (CPMP/ICH/421/02). The testing frequency in stability studies is in line with ICH Q1A. Stability batches were tested for appearance, assay, purity, dissolution and microbiology (annually). The analytical procedures used are stability indicating.

Real-time data for the finished product stored 30°C/75% RH covering 24 months are available. The proposed product was shown to be stable when stored in the proposed container. At accelerated storage conditions 40°C/75% RH, all three strengths were shown to be stable for up to 6 months when stored in the proposed container. No out of specification results were reported, and extrapolation of up to 12 months is accepted.

Photostability testing was conducted under ICH Q1B conditions on one batch of each strength. The results of the samples packed in the HDPE bottle remained largely unchanged. It is concluded that the product is photostable.

An in-use stability study has been performed on one batch of 5 mg and one batch of 20 mg dose strength capsules stored in the proposed packaging and stored at 25°C/60% RH. The study was designed to simulate routine use and samples were tested for appearance, assay, purity, dissolution and microbiology. The data after storage for 30 and 60 days show that all results are within specification and no trends in data were observed. As no relevant deterioration was observed in long-term, accelerated and in-use stability studies, there is no need to claim in-use shelf life as outlined in the Quality of medicines Q&A Part 2.

Based on available stability data, the proposed shelf-life of 3 years and storage conditions "Store in the original package. Keep the bottle tightly closed in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.", as stated in the SmPC (section 6.3) are acceptable.

#### Adventitious agents

TSE/BSE certificates for the active substance and all the excipients are provided. This is considered to be adequate. The gelatine used in the hard capsules is of animal origin and is obtained from suppliers who are holders of valid TSE CEP certificates.

### 2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. A Major Objection on the risk of nitrosamines was raised during the assessment that has been practically resolved. At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to nitrosamines. This point is put forward and agreed as a recommendation for future quality development.

# 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

The CHMP has identified the following measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product:

- An incomplete risk evaluation report was submitted. The information about packaging process and container closure system (HDPE bottle with PP screw cap) should be included in the risk evaluation report for nitrosamines. No risk is expected as the bottling process is not a heat-based process and formation of nitrosamines is likely during printing of the blister's lidding foils, not HDPE bottles.

# 2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

• The applicant is requested to provide missing parts of a risk evaluation for potential formation of nitrosamines, i.e. an evaluation of the packaging process together with the container closure system (HDPE bottle with PP screw cap with desiccant).

# 2.3. Non-clinical aspects

# 2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology and toxicology data. The non-clinical aspects of the Summary of Product Characteristics (SmPC) are in line with the SmPC of the reference product.

Therefore, the CHMP agreed that no further non-clinical pharmacology and toxicology studies are required. The applicant submitted new non-clinical pharmacokinetics data to support the modified-release formulation of the product, intended to treat CAH more effectively.

# 2.3.2. Pharmacokinetics

Two non-clinical pharmacokinetic studies in dexamethasone-suppressed beagle dogs have been performed in which five early development formulations of Efmody were evaluated and (in one study) compared with an immediate release product. Exposure following administration of 30 mg is shown in Figure 2.



**Figure 3 Comparison of exposure following oral administration of 30 mg of 5 different early development formulations of Efmody (DIURF-000-006) and an immediate release product (IR).** *Note: Results of study S34516 (IR, DIURF-000 and DIURF-002) and study S35326 (DIURF-004, DIURF-005 and DIURF-006) are plotted in a single graph. In both studies, the same dogs were used.* 

According to the clinical overview, in healthy volunteer studies in which the subjects received dexamethasone to suppress endogenous cortisol production, formulation DIURF-006 provided the highest cortisol levels and increased exposure compared to the other formulations and showed the closest match to the cortisol profile in healthy humans. Therefore, this formulation was selected as the final Efmody formulation.

# 2.3.3. Ecotoxicity/environmental risk assessment

The applicant conducted a Persistence-Bioaccumulation-Toxicity (PBT) screening/assessment and a Phase I ERA calculation on the basis of a refined market penetration factor (Fpen) value based on the prevalence of CAH.

According to the applicant, the bioaccumulation potential (log Kow) is below 4.5. The Predicted Environmental Concentration in surface water (PECsw) is below the trigger value of 0.01. In addition, literature data indicate that hydrocortisone is readily biodegradable. The applicant concluded that the absence of tailored Phase II ERA with further studies could be justified. However the CHMP could not accept the published reference to support the ERA.

Therefore the CHMP, in the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed post-authorisation:

- To provide a test on ready biodegradability. In case that hydrocortisone is readily biodegradable the tailored ERA can stop;

- To provide the study protocol or literature of the log Kow data.

# 2.3.4. Discussion on non-clinical aspects

Hydrocortisone is a well-known and widely used substance. Therefore no non-clinical studies are submitted, except for two non-clinical pharmacokinetic studies in dexamethasone-suppressed beagle dogs; instead reference is made to published literature to demonstrate adequate non-clinical safety. This is considered sufficient by the CHMP. The conducted pharmacokinetic studies in beagle dogs in which five early development formulations of Efmody were evaluated and compared with an immediate release product, support (together with the results of the clinical studies) the choice for formulation

DIURF-006.

# 2.3.5. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of Efmody have been adequately documented and meet the requirements to support this application.

In order to conclude on the environmental risk of Efmody, the CHMP recommended the applicant to address the remaining issues in the context of their obligation to take due account of technical and scientific progress.

### 2.4. Clinical aspects

# 2.4.1. Introduction

#### GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1	Tabular	overview	of clinical studies

Study ID	No. of	Design/ Study	Study Posology	Subjs by arm	Duration	Gender	Diagnosis	Primary Endpoint
	centres /	objective		compl.		M/F	Incl. criteria	
	locations					Median Age		
DIUR- 002	Single centre	Phase I, open-label, randomised, single dose, crossover study Part A:To compare the PK of 6 formulations of Efmody over an 18-hour period. Part B (4-period crossover): To determine dose proportionality of the Efmody formulation selected from Part A at 3 doses within the dose range of 5 mg to 40 mg dosed at night and when dosed on 2 occasions over a 24-hour period (at night and morning), at a total combined dose not exceeding 60 mg.	Part A1 (all 3 treatments in random order): 30 mg of formulations DIURF-001, DIURF-002 and DIURF-003 at night Part A2 (all 3 treatments in random order): 30 mg of formulations DIURF-004, DIURF-005 and DIURF-006 at night Part B (all 4 treatments of DIURF-006 in random order): 5 mg, 10 mg, 20 mg at night and 10 mg in morning	N=28 planned/ n=28 treated. A1: n=6 A2: n=6 B: n=16	Single dose	M: n=28	Healthy volunteers between 18 and 60 years who did not work shifts	Part A1 and A2: Cmax, Tmax, AUCO-t, AUCO-∞, AUCO-8, AUC8-18, t1/2 and CL • Part B: Cmax, Tmax, AUCO- t, AUCO-∞, AUCO-8, AUC8-18, AUC18-24, t1/2 and CL

DIUR- 003	Single centre	Phase II, 2-part, single cohort, open-label, multiple dose study No control PK study To characterise the PK profile of short-term treatment with Efmody in adult subjects with CAH	Efmody oral capsules given twice daily up to a maximum dose of 50 mg/day Part A: Efmody 30 mg/day for 6 days Part B: Efmody 30 mg/day starting dose for 6 months, with dose adjustment allowed at 2 weeks and at 2 and 4 months if needed	16	6 months	M: n=8, median age = 26 F: n=8, median age = 22	Male or female adults > 18 years with classic CAH, due to 21- hydroxylase deficiency	РК
DIUR- 004	Single centre	Single centre, open-label, randomised, single dose, 3-period, crossover study IRHC tablet Primary: To compare the PK of Efmody under fed and fasted conditions at a single dose of 20 mg and to evaluate the relative BA of Efmody and IRHC at a single dose of 20 mg in the fasted state	Efmody oral capsules given at a dose of 20 mg 20 mg IRHC oral tablets All 3 treatments in random order: Efmody 20 mg in fed state; Efmody 20 mg in fasted state; IRHC 20 mg in fasted state	18	Single dose	M: n=18, median age = 34	Healthy male volunteers between 18 and 60 years of age	PK: Serum Cortisol and Derived Free Cortisol (Baseline Adjusted): Maximum concentration (Cmax), time to Cmax (tmax), elimination rate constant ( $\lambda$ z), terminal elimination half-life (t1/2), area under the concentration- time curve (AUC) from time of dosing to last measurable concentration (AUC0-t) and extrapolated to infinity (AUC0- inf) and clearance (CL/F).
DIUR- 005	11 study sites in 7 countries.	Phase III, Parallel arm, randomised, open-label comparing Efmody with	Efmody oral capsules provided as 5 mg, 10 mg and 20 mg and given at a starting	122 enrolled and treated	6 months	M: n=44, F: n=78	Known CAH due to 21- hydroxylase deficiency (classic CAH)	the change from baseline to 24 weeks of the mean of the 24-hour standard deviation score (SDS) profile for 17-OHP.

		Standard glucocorticoid replacement therapy (superiority study) Efficacy and Safety	dose based on the subject's previous glucocorticoid therapy dose and titrated to effect if necessary at 4 and 12 weeks Standard glucocorticoid replacement therapy as per the subject's usual routine and titrated as necessary at 4 and 12 weeks				diagnosed in childhood with documented(a t any time) elevated 17- OHP and/or A4	
DIUR- 006	8 study sites in 5 countries.	Open-label extension study for subjects entered into studies DIUR-003 and DIUR-005 No control Primary: Safety and tolerability of Efmody over time	Efmody oral capsules provided as 5 mg, 10 mg and 20 mg and given at a starting dose based either on the subject's current Efmody dose (if entering from the Efmody arm of DIUR-005) or based on the subject's previous glucocorticoid therapy dose if entering from standard therapy arm of DIUR-005 or from study DIUR-003. Doses titrated to effect if necessary at 4, 12 and 24 weeks and then 6 monthly if needed	91	3.5 years ongoing	M: n=29, F: n=62	Participants with CAH who successfully completed the DIUR-003 or DIUR-005 clinical studies with the current formulation of Efmody.	The primary endpoint was the safety of Efmody over time

DIUR- 008	Single centre	Single centre, open-label, randomised, single dose, 2-period, crossover study Cortef tablet Primary: To evaluate the relative BA of Efmody and Cortef at a single dose of 20 mg in the fasted state based on serum cortisol	Efmody oral capsules given at a dose of 20 mg Cortef oral tablets given at a dose of 20 mg	25	Single dose		Healthy male volunteers between 18 and 45 years of age	<i>PK:</i> Serum cortisol: Area under the concentration-time curve (AUC) extrapolated to infinity (AUC0-inf) of Efmody to Cortef.
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# 2.4.2. Pharmacokinetics

Pharmacokinetic data were obtained in studies DIUR-002, DIUR-004 and DIUR-008, including healthy adult volunteers and in study DIUR-003, including adult patients with CAH. For the analysis of cortisol in human serum, a LC-MS/MS assay was applied. The method proved to be sensitive and robust for analysis of cortisol in serum. Cortisol stability in serum during sample handling was shown. Validation results showed acceptable performance within the normal standard criteria. Incurred sample reanalysis also showed good reproducibility.

The applicant used pharmacokinetics for bridging to the marketed immediate-release tablet. Efmody needed to show a similar total exposure (AUC) of the active substance hydrocortisone as for the immediate release hydrocortisone formulation, without requirement for bioequivalence.

A population based pharmacokinetics (PBPK) model for Efmody was developed in adults and then verified using data from studies in adults (single-dose studies DIUR-004 and DIUR-008 and the multiple-dose study DIUR-003). Studies DIUR-003 and DIUR-004 were used for model development and verification in this study, and the model was further verified using data from DIUR-008. The adult PBPK model was applied to predict the paediatric pharmacokinetics of Efmody. The adult healthy volunteer population and the paediatric population were used for the adult and paediatric simulations. The PBPK model was developed from a previous PBPK model for Infacort (Alkindi immediate release granules) from the same Applicant (EMEA/H/C/004416/0000).

# Absorption

The aim of the modified release formulation with dosing at night or at night and early in the morning is to obtain a timely delay and elevation of the hydrocortisone levels following the endogenous profile for cortisol. The formulation that provided the best-fit to the reference endogenous cortisol profile and the projected doses required to provide an optimal 24-hour cortisol coverage based on cortisol normative data (published dataset of endogenous serum cortisol profile over a 24 hr period) appeared to be formulation Efmody 30 mg DIURF-006. This formulation was selected as the clinical trial formulation.

After administration of Efmody, serum cortisol tmax was observed later (0.88h vs 4.5h), Cmax was 17% lower and AUC 19% was higher compared to a 20 mg immediate-release formulation (Auden McKenzie), the reference product, showing the delayed-release properties of Efmody (study DIUR-004).

The inter-subject variability in Cmax and AUC was about 20 - 30%, and the intra-subject variability has not been evaluated.

30 mg Efmody administered as one 20 mg capsule in the evening (23.00 hr) and one 10 mg capsule in the morning (7.00 hr) resulted in about 25% higher exposure compared with a single 30 mg dose (study DIUR-002). When indirectly compared to immediate release hydrocortisone (30 mg, study DIUR-001) data, the 20 mg and 10 mg Efmody administration showed a greater bioavailability than IR 30 mg (AUC 16% higher) and a lower Cmax (42% lower). The 20 mg and 10 mg Efmody administration resulted in a more physiological serum cortisol peak in the morning and sustained cortisol exposure over the day.

In patients, administration of Efmody 20 mg at 23.00 hr and 10 mg at 7.00 hr, resulted in a tmax around 5.00 hr in the morning and a second tmax at 10.00hr – 11.00 hr in the morning. In between a trough is reached at about 8.00 hr. The cortisol profiles after dose titration according to androgen levels indicate that the cortisol profiles at month 2, 4 and 6 were comparable to the pharmacokinetic profile after 2 days. Furthermore, a comparable serum cortisol exposure profile is observed compared

to the physiological circadian rhythm of cortisol observed in healthy dexamethasone-suppressed volunteers and a healthy reference population.

## Dose proportionality and time dependencies

A less than dose-proportional increase in AUC and Cmax is observed over the dose range of 5 – 30 mg as Efmody capsules. It should be noted that the 30 mg dose was not administered as one dose but as a divided dose of 20 and 10 mg with an 8 h interval. Still, over the 5 – 20 mg dose range, a less than dose-proportional increase in AUC and Cmax is observed. However the increase in serum cortisol concentration was linear over the dose-range 5 mg to 30 mg, but the proportionality constant as reflected by a slope for Cmax of 0.486 (95% CI:0.418, 0.555), AUC0-t of 0.692 (95% CI: 0.651, 0.733) and AUC0-inf of 0.668 (95% CI: 0.625,0.711), was not unity.

No unexpected accumulation is observed after applying the SmPC recommended dose scheme. Steadystate was estimated to be reached after 1 - 2 doses, with a low accumulation ratio (Cmin levels at the end of the dosing interval (i.e. at 23.00 hr) were less than about 2% of the Cmax levels).

# Special populations

The model predicted the AUC after a single 20 mg dose under fasting and fed conditions well, with simulated values within 12% of observed values. However, Cmax values were under-predicted, with 31 and 25% lower simulated value vs. observed values after fasting and fed conditions, respectively.

A comparable simulated vs. observed food effect was observed, although the simulated food effect on tmax was considered less pronounced that the observed effect (1.08 fold vs. 1.51-fold).

Model verification with study DIUR-008 (single 20 mg dose, fast) showed a similar pattern, i.e. underpredication of Cmax (-22%), a comparable AUC and an earlier tmax (0.77-fold).

Although after a single-dose the Cmax was under-predicted, after multiple dosing (study DIUR-003) in which 20 mg was given at 23.00h, and 10 mg at 7.00h, simulated mean AUC and Cmax values were within 1.1-fold of the observed values.

Of note, data were used from study DIUR-003, which included CAH patients, while the simulation included a healthy population group. Although the included CAH patients were in general good health conditions, they were on glucocorticoid replacement therapy prior to the start of the study, including dexamethasone which is known to be a CYP3A4 inducer, which could had an effect on CYP3A4 cortisol metabolism. Doses used in the model application simulations were calculated using the body weights and body surface areas of the adult subjects in study DIUR-003. For the body weight-based simulations, the administered doses of 20 mg and 10 mg were divided by the individual body weights of study subjects, resulting in mean body weight-based doses of 0.3 and 0.15 mg/kg, respectively. Similarly, the doses of 20 mg and 10 mg were divided by each individual's body surface area (BSA calculated using the DuBois formula) to obtain BSA-based doses 11.6 and 5.8 mg/m2, respectively.

For single-dose, following body weight-based dosing of 0.3 mg/kg, mean Cmax, tmax, and AUC in paediatrics were within 5% of adult values. Following a body surface area-based dosing of 11.6 mg/m2, mean Cmax, tmax, and AUC in paediatrics were within 15% of adult values.

For the divided dose, i.e. 0.3 mg/kg in the evening (23.00h) and 0.15 mg/kg the following morning (7.00h), mean Cmax and AUC at day 3 in paediatrics were within 8% of adult values. Following a body surface area-based dosing of 11.6 mg/m2 and 5.8 mg/m<sup>2</sup>, respectively, mean Cmax, tmax, and AUC at day 3 in paediatrics were within 5% of adult values.

It should be noted that the quality of the simulations is not considered adequate for making claims on the exposure in the adolescent population. However, the impact of the PBPK model results is low due to the titration guided dosing.

## Pharmacokinetic interaction studies

A high-fat breakfast delayed tmax of serum cortisol levels with about 2 h (from 4.5h to 6.75h), resulting in a 22% lower Cmax and no statistically significant effect on AUCinf (+10%). A comparable pattern was observed for free cortisol levels, with a 33% lower Cmax and 3% lower AUCinf. The lower free cortisol levels reflect the plasma protein binding of cortisol.

To minimise the food effect, and in line with the applied phase 3 dosing recommendations, the morning dose should be taken on an empty stomach at least 1 hour before a meal and the evening dose taken at bedtime at least 2 hours after the last meal of the day.

# 2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

Study DIUR-003 was designed to examine the disease biomarker response to treatment both in the short-term (after 2 days dosing), and after 6 months of treatment in order to inform on the dose and study design for the subsequent phase 3 study inform on the study design and dosing regimen of the phase III studies. The methodology and results of this study are presented at the beginning of section 2.4.4.

# 2.4.4. Clinical efficacy

No formal dose-finding study was performed for Efmody. The starting dose, titration regimen and dosing regimen tested in the phase III studies was based on phase 1 pharmacokinetic (PK) studies and a phase 2 PK/PD study (DIUR-003).

Study DIUR-003 was a Phase 2 pilot, single cohort, multiple-dose, open-label study in 16 patients aged ≥18 years with CAH due to 21-hydroxylase deficiency (classic CAH) based on hormonal and genetic testing currently treated with hydrocortisone, prednisone, prednisolone or dexamethasone on a stable dosage for a minimum of 3 months.

In Part A, the baseline disease control status of patients on standard therapy was assessed by biochemical measurement of androgenic precursor levels. Patients started on Efmody therapy at a 30 mg fixed daily dose (administered as 20 mg at 23:00 hours and 10 mg at 07:00 hours) and, after 2 days, cortisol PK parameters were measured, and disease control (androgenic precursor levels) were compared with baseline levels.

In Part B, patients entered a 6-month dose-titration period to assess the efficacy of Efmody treatment through measurement of biochemical markers, body composition, insulin resistance and bone turnover. Formal dose titration occurred at the start of Part B, and was adjusted as necessary at the 2-month and 4-month CRC visits. Dose adjustments were considered to a maximum daily dose of 50mg if 3 or more of the 5 sample times showed out of range values for 17-OHP and androstenedione.

The main secondary efficacy pharmacodynamic endpoint was to examine the proportion of subjects with (17-OHP) and A4 levels within proposed optimal ranges whilst on Efmody and whilst on standard therapy at baseline. For 17-OHP the normal range was defined as 30-300 ng/dl (1-9 nmol/l), and the

optimal range was defined as the upper limit of normal to 4 times the upper limit of normal 300-1200 ng/dl (9-36 nmol/). For androstenedione the optimal range was defined as the same as the normal range 40-150 ng/dl (1.4-5.2 nmol/l) for males and 30-200 ng/dl (1.0-7.0 nmol/l) for females.



#### Figure 4 Study design DIUR-003 . Note: Efmody was previously known as Chronocort

In study DIUR-003, 8 males and 8 females were enrolled. In the males, the mean age was 33.3 (range of 18-60) years, the mean weight was 67.24 (range of 50.6-88.4) kg, and the mean BMI was 24.44 (range of 19.5-29.5) kg/m2. In the females, the mean age was 24.1 (range of 18-40) years, the mean weight was 72.35 (range of 46.4-115) kg, and the mean BMI was 27.26 (range of 20.5-41.1) kg/m2. The proportion of subjects in DIUR-003 on the different glucocorticoid medications were similar to those reported in large cohort studies from the UK and USA, where in approximately a third of subjects are treated with either dexamethasone, or prednisolone/prednisone, or hydrocortisone.

Results from part B (dose titration, ACTH profiles, androgen control) are presented below in Table 5 and Figure 6, Figure 7,and Figure 8.

 Table 2 Dose titration - Hydrocortisone dose equivalent on standard treatment in Part A visit

 1 and on Efmody (formerly known as Chronocort) at visits 1, 2, 3, and 4 during dose titration.

Standard Treatment*	HC dose equivalent standard treatment** (mg)	Chronocort dose (hydrocortisone mg / 24h)			
		Visit 1	Visit 2	Visit 3	Visit 4
Dex 0.5mg	40	30	40	40	40
Dex 0.2mg	16	30	30	30	30
Dex 0.375mg	30	30	20	20	25
Pred 5mg	25	30	30	30	30
HC 15mg Pred 1mg	20	30	30	30	30
Pred 4mg	20	30	30	20	20
Pred 5.5mg	27.5	30	20	20	15
Pred 6.5mg	32.5	30	30	25	25
Pred 5mg	25	30	25	20	20
Dex 0.25mg	20	30	25	20	15
Pred 7.5mg	37.5	30	30	30	30
HC 30mg	30	30	25	20	20
HC 17.5mg	17.5	30	30	25	20
HC 15mg	15	30	30	30	30
Pred 12.5mg	62.5	30	35	35	35
Dex 0.375mg	30	30	30	30	30
Mean (SD)	28 (11.8)	30 (0.0)	28.8 (5.0)	26.6 (6.3)	25.9 (7.1)

\*Dex= Dexamethasone, Pred = Prednisone, HC= Hydrocortisone, \*\* HC Dose equivalent calculated as Pred dose multiplied by 5 and Dex dose by 80.

On standard treatment, ACTH levels were observed to rise from 0300h, reaching a plateau from 0700h to 1300h, before declining after 1700h. On Efmody, ACTH levels did not rise at 0300h and were stable and notably lower than those on standard treatment through the day. See Figure 6.



# Figure 5 Mean ACTH during standard treatment and during the first day of Efmody (formerly known as Chronocort) administration.

On standard therapy, the mean 17-OHP level was above the optimal range (36 nmol/l) for most of the day and only dipped down when the subjects were given a dose of steroid last thing at night, but then rose from 03: 00h as the pituitary-adrenal axis became active. On Efmody at 6 months, all but one of the mean 17-OHP levels were within the optimal range (9-36 nmol/l). See Figure 7.



Figure 6 Mean 17-OHP levels during standard therapy at baseline, after the first administration of Efmody (Day 1) and following 6 months of continued Efmody treatment (mean  $\pm$  SEM). Note: Efmody was previously known as Chronocort



Figure 7 Mean and SEM A4 level on standard treatment at baseline and after 6 months of treatment with Efmody (formerly known as Chronocort).

After 6 months of treatment, 15 of 16 patients had a 17-OHP (09.00hr) level within the optimal range. For the standard therapy group this was 5 of 16 patients. See Figure 8.

# Study DIUR-005

The pivotal phase III study was a multicentre, open-label, randomized, controlled trial to assess the efficacy and safety of Efmody in patients with CAH.

### Methods

As part of the baseline assessment, participants were admitted overnight for a 24-hour endocrine profile while remaining on their standard glucocorticoid (GC) therapy, with 17-OHP and A4 samples being taken at 15:00, 17:00, 19:00, 21:00, 23:00, 01:00, 03:00, 05:00, 07:00, 09:00, 11:00, 13:00 and 15:00.

24-hour hormone profiles were determined after 4 and 12 weeks of intervention after which dose titration was possible guided by an independent physician.

After 6 months of treatment, all the baseline tests were repeated (including the 24-hour androgen profile). Participants could then either return to their standard GC therapy or enter an open-label extension study (DIUR-006) and receive Efmody on an ongoing basis.



#### Figure 8 Study design DIUR-005. Note: Efmody is formely known as Chronocort.

Patients were recruited in 11 study sites in 7 countries: Denmark (n=1), France (n=2), Germany (n=1), the Netherlands (n=1), Sweden (n=1), the UK (n=4), and the US (n=1).

Main inclusion criteria were: known CAH due to 21-hydroxylase deficiency (classic CAH) diagnosed in childhood with documented (at any time) elevated 17-OHP and/or A4 and treated at entry into the study with hydrocortisone, prednisone, prednisolone or dexamethasone (or a combination of the aforementioned GCs) on a stable GC therapy for a minimum of 6 months; Male or female participants aged 18 and above.

Main exclusion criteria were: co-morbid condition requiring daily administration of a medication (or consumption of any material) that interfered with the metabolism of GCs; 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; participants with a history of bilateral adrenalectomy; participants having previously been exposed to Efmody; participants who routinely worked night shifts and so do not sleep during the usual night-time hours.

# Treatments

Investigational medicinal products:

- Efmody (hydrocortisone modified release capsule) supplied in 3 unit dose strengths of 5 mg, 10 mg and 20 mg per capsule. Oral administration. The starting dose for each participant was the hydrocortisone equivalent of their previous GC therapy dose with the hydrocortisone dose calculated as prednisone dose multiplied by 5 and dexamethasone dose multiplied by 80 (up to a maximum starting dose of Efmody 30 mg, split as 20 mg at night and 10 mg in the morning). Efmody was taken at 23:00 hr (approximately 2/3rd of the total daily dose) and 07:00 hr (approximately 1/3rd of the total daily dose).
- The standard GC therapy that the participant was receiving prior to the study was used for participants randomised to the comparator group. The starting dose for each participant was the same as that used prior to the study.

Dose refinements/titrations could be conducted in both treatment groups as necessary after 4 weeks and 12 weeks after the participant had been re-admitted for further 24-hour 17-OHP and A4 profiles. The decision to change the dose in both treatment groups was made by 2 independent blinded physicians, who were blinded to the treatment group and made their decision based on the Adrenal Insufficiency Checklist which was completed by the local Investigator (who was blinded to the androgen results) and captured clinical signs and symptoms of under- or over-treatment, and the 17-OHP and A4 results from the 24-hour endocrine profiles. The 5 androgen samples taken between 01:00 and 09:00 from the 24-hour profile reflected the GC doses taken in the evening and the 5 samples taken between 11:00 hr and 19:00 hr reflected the morning GC doses. Dose adjustments were to be considered if 3 or more of the 5 samples showed out of range values for 17-OHP or A4. Where 17-OHP and A4 show inconsistent trends, the A4 parameter took precedence in directing dose adjustment.

Fludrocortisone dose adjustment was allowed if medically indicated and was based on BP measurements and laboratory data (goal supine PRA above the lower limit and <1.5 times upper limit of normal [ULN])

#### Non-Investigational Products

If the participant suffered an intercurrent illness or there were other reasons that additional GCs were needed, the 'sick day rules' provided by the study site were to be followed. Fludrocortisone dose adjustment was allowed if medically indicated and was to be based on BP measurements and laboratory data (goal supine PRA above the lower limit and <1.5 times ULN.

Participants were to continue to take Efmody twice daily or standard GC therapy at their usual dosing regimen when taking stress doses. Any additional doses of hydrocortisone needed were only to be taken from the safety pack and should not have been taken from the study medication pack.

# Objective

To demonstrate the superior efficacy of Efmody compared with standard GC replacement therapy in the treatment of CAH based on 17-OHP.

# **Outcomes/endpoints**

The primary efficacy endpoint was the change from baseline to 24 weeks of the mean of the 24-hour standard deviation score (SDS) profile for 17-OHP.

Secondary efficacy endpoints were: change from baseline to 24 weeks of the mean of the 24-hour SDS profile for A4 (calculated in the same way as the primary endpoint); 17-OHP and A4 by individual baseline treatment strata presented in the same manner as the primary endpoint (using 24-hour SDS profile at 24 weeks); 17-OHP and A4 levels at 09:00 hr as a responder analysis (i.e. the number of participants achieving results in the optimal range).; Changes relative to standard GC replacement therapy in body composition (DEXA) (fat mass, lean mass and total bone density) - measured at all sites except Germany.

Main exploratory endpoints were: partial area under the curve (AUC) of 17-OHP at 15:00 hr-23:00 hr, 23:00 hr-07:00 hr, and 07:00 hr-15:00h r (all refer to actual clock time of sampling); changes relative to standard GC therapy in bone markers - serum C-terminal telopeptide (CTX) and osteocalcin (after fasting) and Quality of Life (QoL) using 36-item Short Form Health Survey (SF-36), Multidimensional Assessment of Fatigue (MAF), and 5 Level Standardised Health Questionnaire (EQ-5D); use of GCs at the beginning and end of the study, presented both as individual GCs used and as calculated hydrocortisone equivalents using accepted conversion constants for the calculations.

### Sample size

A sample size of 102 subjects provides greater than 95% power and 2-sided alpha 5% to demonstrate a fall in the logarithm of the mean daily unsigned standard deviation score of 17-OHP relative to the standard glucocorticoid replacement therapy group.

### Randomisation

There was a fully stratified randomisation of participants using an Interactive Web Response System (IWRS). Stratification was based on participants' current treatment at the time of entering the study: hydrocortisone only; prednisone or prednisolone, alone or in combination with hydrocortisone; dexamethasone, alone or in combination with any other GC.

# Blinding (masking)

Since this was an open label study, no blinding was performed. However, the decision to change the dose in both treatment groups was made by independent blinded physician.

# Statistical methods

The primary efficacy variable was the natural logarithm of the mean of the 24-hour hormonal profile of the SDS for the natural logarithm of 17-OHP. The primary analysis focused on the change from baseline to Week 24 in the primary efficacy variable. The SDS was defined as the absolute (unsigned) number of SDs above or below the average of the lower and upper limit of normal using the reference
range for 17-OHP and A4 (see Table 6). The comparison between treatment groups was performed using an ANCOVA linear model, with the unadjusted mean of the primary efficacy variable being presented, along with the least-square (LS) estimated mean. The difference in LS means was presented with the associated 95% 2-sided CI and p-value. Residual plots of scaled residuals were used to check the fit of the model and assess whether there was any evidence of non-normality. Summary statistics were produced for the absolute values and change from baseline at each visit (Weeks 4, 12 and 24) for the primary efficacy variable by treatment group and pre-baseline therapy strata. The geometric mean of the 17-OHP concentration was plotted along with the 95% CIs at each timepoint over the 24-hour sampling period (15:00 hr to 15:00 hr) for each treatment group and by pre-baseline therapy strata.

The primary analysis was repeated for A4, change from baseline to Week 24 in the secondary efficacy variable. A responder analysis was also conducted to compare the response between the Efmody group and the standard GC therapy group within the efficacy evaluable analysis set using logistic regression with adjustment for pre-baseline therapy strata. A participant was considered a responder if their 09:00 hr result at Week 24 was in the optimal and reference ranges as defined in Table 6. The mean change from baseline to 24 weeks in body composition (DEXA) between the Efmody group and the standard GC therapy group was compared separately for fat mass, lean mass and total bone density using an analysis of covariance (ANCOVA) linear model. Summary statistics were produced for the absolute values and change from baseline in body composition (DEXA) at each visit (Weeks 4, 12 and 24).

Reference range	Male	female
17-OHP	1.2*-6.7 nmol/L	1.2-8.6 nmol/L
A4	1.4-5.2 nmol/L	1.0-7.0 nmol/L
Optimal range		
17-OHP	1.2-36.4 nmol/L	1.2-36.4 nmol/L

Table 3	3 reference and	l ontimal range	e used in DTUP-00	5
Table 3	s reference and	i optimai range	s used in DIUR-UU	Э

Note: the upper range for females is during the luteal phase.

\*There is no lower reference range available for 17-OHP, hence the lower limit of the optimal range was used in the derivation of the average SDS score. This enabled calculation of an 'unsigned' SDS score which was used to assess potential over-treatment as well as under-treatment. Note the Mayo Clinic laboratory reference ranges for 17-OHP were derived from a very small number of volunteers, who did not have CAH and for whom nothing else was known, e.g. time of day, co-morbidities. The appropriateness of trying to drive the CAH population into this range is questionable and therefore based on verbal feedback from clinicians who manage these patients, a broader "optimal range" has been used for 17-OHP.

Uncontrolled subjects were defined as those with at least one 17-OHP measurement in the baseline 24h profile, which exceeds the normal range.

Missing 17-OHP and A4 values (including those considered missing due to being taken outside the permitted time window) within the 24-hour hormone profile were imputed by linear interpolation of the two closest non-missing measurements to the scheduled missing timepoint (including out-of-window measurements). In the event that several values were missing from a single profile, a decision was made about the validity of the whole profile at the Data Review Meeting on a case-by-case basis.

For efficacy analyses based on the Week 12 and Week 24 visits, participants who had withdrawn from the study were assessed on the basis of the latest available 24-hour profile. When calculations had to be based upon incomplete dates, the following process was used. If the year was missing, no imputing was conducted, and the value was considered missing. If the year was populated but both month and day were missing, then the date defaulted to 1st July. If day only was missing, then the day defaulted to the 15th of the month.

There was no adjustment for multiple testing.

Following a review of the pre-defined analyses results and the apparent discrepancy between 17-OHP SDS results and absolute values, the previous EMA scientific advice was revisited and a number of post-hoc analyses advised in the 2014 were conducted on the primary endpoint as follows: 2-sided SDS score using difference from top of the range for high values and bottom of the range for low values with all values in the range scoring 0;1-sided SDS score for high values using only the lower boundary of the reference range; 1-sided SDS score for low values using only the upper boundary of the reference range. For each of the 1-sided analyses, which are anchored on the boundary of the reference range, an SDS above 4 represents a value outside the reference range.

Additional analyses were also conducted for: unsigned SDS score from the upper limit of the reference range; unsigned SDS score from the lower limit of the reference range; responders using the reference range for 17-OHP and log-transformed AUCs for 17-OHP and A4.

### Results

# Participant flow



#### Figure 9 Participant Flow

### Recruitment

Patients were recruited between September 2016 and May 2018.

# Conduct of the study

Protocol deviations are presented in Table 7.

# Table 4 Major and Minor Protocol Deviations Grouped by High Level Category in ProtocolDIUR-005 (all randomised participants)

	Number (%) of participants			
	Chronocort (N=61)	Standard GC therapy (N=61)	Total (N=122)	
Number of participants with at least one protocol deviation	54 (88.5)	54 (88.5)	108 (88.5)	
Number of participants with at least one major protocol deviation	5 (8.2)	7 (11.5)	12 (9.8)	
Inclusion criteria	0	1 (1.6)	1 (0.8)	
Local sampling	0	1 (1.6)	1 (0.8)	
Titration	3 (4.9)	5 (8.2)	8 (6.6)	
Treatment	2 (3.3)	0	2 (1.6)	
Number of participants with at least one minor protocol deviation	54 (88.5)	53 (86.9)	107 (87.7)	
Inclusion criteria	11 (18.0)	9 (14.8)	20 (16.4)	
Local sampling	1 (1.6)	0	1 (0.8)	
Study procedure	50 (82.0)	47 (77.0)	97 (79.5)	
Titration	22 (36.1)	24 (39.3)	46 (37.7)	
Treatment	10 (16.4)	12 (19.7)	22 (18.0)	

Each protocol deviation was classified as either 'minor' (unlikely to affect study outcomes) or 'major' (likely to affect study outcomes). Participants may have had more than 1 protocol deviation and were counted once per category.

High level categories: Inclusion criteria=did not meet all inclusion criteria; Exclusion criteria=met exclusion criteria; Study procedure=did not follow the procedures specified in protocol; Titration=deviated from titration process; Treatment = IMP not taken as per protocol; Local sampling=Performed endocrine sampling locally.

GC=glucocorticoid; IMP=investigational medicinal product.

Note: Efmody was previously known as Chronocort.

# Baseline data

Data from the safety analysis set (all participants who were randomised into the study and who subsequently received at least one dose of Efmody or standard GC therapy) are presented in Table 8 and Table 9.

	Number (%) of participants				
Demographic characteristic		Chronocort (N=61)	Standard GC therapy (N=61)	Total (N=122)	
Age (years)	Mean (SD)	35.2 (10.32)	37.5 (12.80)	36.3 (11.64)	
	Median (range)	35.0 (19, 61)	40.0 (19, 68)	35.5 (19, 68)	
Age group (years) n (%)	≥18 - <30	20 (32.8)	21 (34.4)	41 (33.6)	
	≥30 - <50	36 (59.0)	28 (45.9)	64 (52.5)	
	≥50 - <70 >70	5 (8.2) 0	12 (19.7) 0	17 (13.9) 0	
Sex n (%)	Male Female	19 (31.1) 42 (68.9)	25 (41.0) 36 (59.0)	44 (36.1) 78 (63.9)	
Race n (%)	White Other	60 (98.4) 1 (1.6) 1 (1.6)	60 (98.4) 1 (1.6) 0	120 (98.4) 2 (1.6) 1 (0.8)	
		0	1 (1.6)	1 (0.8)	
BMI (kg/m²)	Mean (SD) Median (range)	28.488 (6.3674) 27.780 (17.96, 43.72)	27.652 (4.3231) 27.030 (19.65, 36.84)	28.070 (5.4358) 27.060 (17.96, 43.72)	
Waist Circumference (cm)	Mean (SD) Median (range)	90.90 (16.343) 89.00 (63.0, 133.0)	90.50 (11.843) 86.00 (73.0, 119.0)	90.70 (14.214) 88.00 (63.0, 133.0)	

#### Table 5 Demographic Characteristics in DIUR-005 (Safety Analysis Set)

BMI = body mass index; GC=glucocorticoid; SD=standard deviation; n=number of evaluable participants. Data source; Section 14,table 14.1.4

Note: Efmody was previously known as Chronocort.

#### Table 6 Baseline Disease Characteristics in DIUR-005 (Safety Analysis Set)

		Number (%) of participants			
Characteristic		Chronocort (N=61)	Standard GC therapy (N=61)	Total (N=122)	
Time since CAH diagnosis	Mean (SD)	33.7 (10.23)	36.6 (12.63)	35.2 (11.54)	
(years)	Median (range)	33.5 (17, 60)	35.7 (13, 65)	34.4 (13, 65)	
Hospitalised within last 12	No	59 (96.7)	60 (98.4)	119 (97.5)	
months prior to enrolment into DIUR-005, n (%)	Yes	2 (3.3)	1 (1.6)	3 (2.5)	
Number of adrenal crises in	None	58 (95.1)	59 (96.7)	117 (95.9)	
the last year, n (%)	One	3 (4.9)	2 (3.3)	5 (4.1)	
Prior CAH medication,	Hydrocortisone	36 (59.0)	39 (63.9)	75 (61.5)	
n (%)	Prednisolone	21 (34.4)	22 (36.1)	43 (35.2)	
	Dexamethasone	5 (8.2)	5 (8.2)	10 (8.2)	
	Prednisone	3 (4.9)	2 (3.3)	5 (4.1)	

Participants who received more than one medication in the last 6 months were counted once per category CAH=congenital adrenal hyperplasia; GC=glucocorticoid; SD=standard deviation; n=number of evaluable participants.

Data source: Section 14, Table 14.1.5.

Note: Efmody is formerly known as Chronocort.

# Numbers analysed

Data are presented in Table 10.

#### Table 7 analysis sets in DIUR-005

	Number of participants		
	Chronocort	Standard GC therapy	Total
Participants randomised	61	61	122
Participants included in safety analysis set	61	61	122
Participants excluded from safety analysis set1	0	0	0
Participants included in the FAS	60	60	120
Participants excluded from the FAS1	1	1	2
Did not have at least one evaluable post- randomisation 17-OHP 24-hour profile	1	1	2
Participants included in the EES	53	52	105
Participants excluded from the EES1	8	9	17
Did not have an evaluable week 24 17-OHP 24-hour profile	4	2	6
Had at least one major protocol deviation	5	7	12

<sup>1</sup> An individual participant could be excluded for more than 1 reason.

Safety analysis set=all randomised participants who received at least 1 dose of study treatment. FAS=all randomised participants who received at least 1 dose of study treatment and had at least 1 evaluable post-randomisation 17-OHP 24-hour profile.

EES=all randomised participants who received at least 1 dose of study treatment and had an evaluable Week 24 17-OHP 24-hour profile and no major protocol deviations.

Note: Efmody was previously known as Chronocort.

# **Outcomes and estimation**

#### Treatment compliance

Overall mean participant treatment compliance across both treatment groups was 99.57% and was similar in both treatment groups.

#### Dose titrations

# Table 8 Dose Titrations Recommended by the Independent Blinded Physicians in DIUR-005(Safety Analysis Set and hydrocortisone subgroup only)

		Number (%) ( (safety analys	of participants sis set)	Number (%) of participants (hydrocortisone subgroup only)	
		Efmody (N=61)	Standard GC therapy (N=61)	Efmody (N=32)	Standard GC therapy (N=32)
Visit 2/ Week 4	Participants on treatment, n	60	60	32	31
	Participants requiring adjustment	29 (48.3)	28 (46.7)	18 ( 56.3)	16 ( 51.6)
	Dose increase	21 (35.0)	27 (45.0)	15 ( 46.9)	15 ( 48.4)
	Dose decrease	8 (13.3)	1 (1.7)	3 ( 9.4)	1 ( 3.2)

Visit 3/ Week 12	Participants on treatment, n	58	60	31	31
	Participants requiring adjustment	21 (36.2)	23 (38.3)	12 ( 38.7)	13 ( 41.9)
	Dose increase	12 (20.7)	21 (35.0)	7 ( 22.6)	12 ( 38.7)
	Dose decrease	9 (15.5)	2 (3.3)	5 (16.1)	1 ( 3.2)
Visit 3/ Week 12	Participants requiring adjustment who required adjustment at Visit 2/Week 4	11 (19.0)	17 (28.3)	6 ( 19.4)	9 ( 29.0)
	Dose increase	5 (8.6)	17 (28.3)	3 ( 9.7)	9 (29.0)
	Dose decrease	6 (10.3)	0	3 ( 9.7)	0

Percentages are calculated from the number of participants on treatment.

In the majority of cases, the Adrenal Insufficiency Checklist did not show any cause for dose adjustments, so the majority of the dose changes were based on 17-OHP results, either alone or in conjunction with the A4 results.

	Overall (safety analysis set)		Hydrocortisone only subgroup		Prednisone/prednisolone subgroup	
Variable Statistics	Efmody (N=61)	Standard GC therapy (N=61)	Efmody (N=32)	Standard GC therapy (N=32)	Efmody (N=24)	Standard GC therapy (N=24)
Body surface area (m <sup>2</sup> )	1.75	1.80	1.76	1.86	1.69	1.76
Median baseline daily dose (mg)	25.00	25.00	20.00	23.75	30.00	26.56
Median end of study daily dose (mg)	30.00	31.25	25.00	25.00	27.50	32.81
Median baseline daily dose/BSA (mg/m <sup>2</sup> /day)	13.56	14.38	11.99	12.26	16.74	15.70
Median end of study daily dose/BSA (mg/m <sup>2</sup> /day)	15.82	17.04	15.13	14.53	16.54	18.50

BSA=body surface area; GC=glucocorticoid

#### Primary endpoint

Results are presented in Figures 9, 10 and Table 10.



Y axis is presented on a logarithmic scale. The grey horizontal lines show the optimal range.

Figure 10 Geometric Mean  $\pm$ 95% CI for 17-OHP (nmol/L) Week 24 Profile by Treatment Group in DIUR-005 (EES). Note: Efmody was previously known as Chronocort.



# Figure 11 Geometric Mean $\pm 95\%$ CI for SDS Profile Showing Unsigned Deviations from the Normal Mean at Week 24 for 17-OHP by Treatment Group in DIUR-005 (EES). Note: Efmody was previously known as Chronocort.

The SDSs are calculated by counting the number of SDs which are above or below the mean of the log-transformed range. EES=efficacy evaluable analysis set; GC=glucocorticoid; SDS=standard deviation score.

# Table 10 Change from Baseline to 24 Weeks in the Primary Efficacy Variable for 17-OHP Usingan ANCOVA Model in Protocol DIUR-005 (EES) – Prespecified Analysis

Comparison b					rison between gro	between groups	
Chan	N	Unadjusted mean (SD) change from	LS mean change from	Difference in	0594 CI	2-sided	
Group	1	Daseline	basenne-	LS means	95% CI	p-value	
Chronocort	53	-0.403 (0.8499)	-0.446	-0.069	(-0.299, 0.161)	0.5521	
Standard GC therapy	52	-0.172 (0.7776)	-0.376				

The primary efficacy variable was the natural logarithm of the mean of the 24-hour SDS for the natural logarithm of 17-OHP. Lower values indicated better hormonal control. The mean of the 24-hour SDS profile for each visit was the arithmetic mean of all the SDSs with the first and last (13<sup>th</sup>) weighted one half relative to the intermediate SDSs. For each of the 13 log-transformed 17-OHP values at each visit, an SDS was calculated by counting the number of SDs that were above or below the mean of the log-transformed range. <sup>1</sup> A negative value indicates better hormonal control versus baseline.

<sup>2</sup> A difference in LS means <0 favours Chronocort.

Note: Efmody was previously known as Chronocort.

*Exploratory analysis on the primary efficacy variable: Change in 8-Hour Profiles from Baseline to 24 Weeks in the Natural Logarithm of the Mean of the SDS Profile for the Natural Logarithm of 17-OHP and A4.* 

The primary efficacy analysis was repeated using 8-hour profiles rather than the 24-hour Profiles. This analysis showed a difference between the 2 treatment groups in the 07:00 to 15:00 hour profile (difference in LS means: -0.286; 95% CI: [-0.564, -0.008]; p=0.0442) but not in the other 8-hour periods. No notable differences were seen between the treatment groups in the analysis of the 8-hour profiles based on prior GC therapy (hydrocortisone only, prednisone or prednisolone alone or in combination with hydrocortisone, and dexamethasone alone or in combination with any other GC).

# Table 11 Exploratory Analysis of 17-OHP 8-Hour Profiles: Change from Baseline to 24 Weeksin Primary Efficacy Variable ANCOVA Model in Protocol DIUR-005

				Compa	rison between gro	oups
Group	Ν	Unadjusted mean (SD) change from baseline <sup>1</sup>	LS mean change from baseline <sup>1</sup>	Difference in LS means <sup>2</sup>	95% CI	2-sided p-value
15:00 - 23:00		•	•			
Chronocort	53	-0.351 (1.1406)	-0.343	-0.025	(-0.347, 0.296)	0.8758
Standard GC therapy	52	-0.161 (1.0730)	-0.318			
23:00 - 07:00						
Chronocort	53	-0.200 (0.8735)	-0.251	0.139	(-0.114, 0.393)	0.2788
Standard GC therapy	52	-0.190 (0.9189)	-0.390			
07:00 - 15:00						
Chronocort	53	-0.690 (0.9610)	-0.770	-0.286	(-0.564, -0.008)	0.0442
Standard GC therapy	52	-0.210 (0.7925)	-0.484			

The partial profile was the natural logarithm of the mean of the 8-hour SDS between each time period for the natural logarithm of 17-OHP. The mean of the 8-hour SDS profile for each visit is the arithmetic mean of all the SDSs with first and last (5th) weighted ½ relative to the intermediate SDSs. For each of the 5 log-transformed 17-OHP values at each visit, an SDS was calculated by counting the number of SDs which were above or below the mean of the log-transformed range. An ANCOVA model was based on the change from baseline of the natural logarithm of the mean of the 8-hour SDS profile of 17-OHP as the dependent variable, treatment group and pre-baseline therapy as fixed effects and baseline of the natural logarithm of the mean of the 8-hour SDS profile of 17-OHP as the covariate. 1 A negative value indicates better hormonal control versus baseline.

2 A difference in LS means <0 favours Efmody. Note: Efmody was previously known as Chronocort. The analysis using 8-hour profiles rather than the 24-hour profiles was also repeated for A4. This analysis showed no differences between the treatment groups for any of the 8-hour profiles. No notable differences were seen between the treatment groups in the analysis of the 8-hour profiles based on prior GC therapy (hydrocortisone only, prednisone or prednisolone alone or in combination with hydrocortisone, and dexamethasone alone or in combination with any other GC).

#### Post-hoc analyses of the primary efficacy variable

Data of the 2-sided unsigned SDS using the difference from top of the range for high values and bottom of the range for low values (with all values in the range scoring 0) are presented in Table 15.

# Table 12 Post-hoc Analysis of 2-sided Unsigned SDS Outside the Normal Reference Range for17-OHP at Baseline and Week 24 in DIUR-005 (EES)

				Compa	rison between gro	oups
		Unadjusted mean	LS mean			
		(SD) change from	change from	Difference in		2-sided
Group	N	baseline <sup>1</sup>	baseline <sup>1</sup>	LS means <sup>2</sup>	95% CI	p-value
Chronocort	53	-1.353 (2.1780)	-1.171	-0.165	(-0.677, 0.348)	0.5253
Standard GC therapy	52	-0.822 (1.6702)	-1.007			

<sup>1</sup> Proportional weights have been used in the calculation of LS mean change from baseline estimates. A negative value indicates better hormonal control versus baseline.

<sup>2</sup> A difference in LS means <0 favours Chronocort.

Note: Efmody was previously known as Chronocort.

Data of the 1-sided SDS for high values using only the lower boundary of the reference range and for low values using only the upper boundary of the reference range is provided in Table 13. The SDS analysis of the 1-sided SDS above the lower limit of the reference range for 17-OHP demonstrated that the Efmody treated cohort had a less controlled baseline but that the Efmody groups values decreased more, i.e. moved into the reference range following Efmody treatment. The 1-sided SDS below the upper limit of the reference range for 17-OHP demonstrated that more Efmody values at baseline were at the upper end of the reference range, but the 17-OHP values decreased more with Efmody treatment, without the mean values suggesting over-treatment.

# Table 13 Post-hoc Analysis of 1-sided Unsigned SDS Above the Lower Limit of the ReferenceRange and Below the Upper Limit of the Reference Range for 17-OHP at Baseline and Week24 in Protocol DIUR-005 (EES)

				Compa	rison between gro	oups
Group	N	Unadjusted mean (SD) change from baseline <sup>1</sup>	LS mean change from baseline <sup>1</sup>	Difference in LS means	95% CI	2-sided p-value
1-sided Unsig	gned	SDS Above the Low	wer Limit of th	ie Reference R	ange	
Chronocort	53	-2.986 (3.4490)	-2.728	-0.976	(-1.895, -0.058)	0.0374
Standard	52	-1.488 (2.2330)	-1.751			
GC therapy						
1-sided Unsi	gned	SDS Below the Upp	per Limit of th	e Reference Ra	ange	
Chronocort	53	1.634 (2.1797)	1.559	0.816	(0.094, 1.539)	0.0272
Standard GC therapy	52	0.666 (1.6928)	0.743			

An ANCOVA model was based on the change from baseline of the unsigned SDS as the dependent variable, treatment group and pre-baseline therapy as fixed effects and the baseline of unsigned SDS as the covariate.

<sup>1</sup> Proportional weights have been used in the calculation of LS mean change from baseline estimates.

Note: Efmody was previously known as Chronocort.

One of the points raised in the 2014 protocol assistance, was that a 2-sided SDS was not particularly sensitive to amplitude, a point that was borne out in the pre-defined primary analysis. To examine the amplitude, an analysis of the change in range from baseline to Week 24 in 17-OHP values was conducted. This analysis shows a greater reduction in range in the Efmody group, consistent with less variable and more controlled 17-OHP concentrations (see Figure 13 and Figure 14).



The dashed horizontal lines represent the optimal and reference (normal) ranges. For the reference range, the widest range is displayed for males and females.

# Figure 12 Geometric Mean $\pm$ 95% CI of 17-OHP Over 24 Hours at Baseline and Week 24: Efmody Group in Protocol DIUR-005 (EES)



The dashed horizontal lines represent the optimal and reference (normal) ranges. Figure 13 Geometric Mean ±95% CI of 17-OHP Over 24 Hours at Baseline and Week 24: Standard GC Therapy Group in Protocol DIUR-005 (EES)

An additional post-hoc analysis was also conducted on the log-transformed AUCs for 17-OHP. The changes from baseline are provided in Table 14 This analysis showed a reduction in 17-OHP AUC in both treatment groups throughout the duration of the study. This reduction at Week 24 was greater in the Efmody group (difference in LS means: -13.771; 95% CI [-25.783, -1.758]; p=0.0251). See Table 18.

 Table 14 Summary of change from baseline in log-transformed 17-OHP 24-hour AUC profile by visit (EES)

Treatment group	Timer	point n	Absolu	Absolute values		Change from baseline	
			Mean	SD	Mean	SD	
Efmody (N=53)	Baseli	ne 53	65.202	38.526			
	Visit 2	/Week 4 53	41.253	37.584	-23.949	27.657	
	Visit 3	/Week 12 53	29.714	35.223	-35.488	35.318	
	Visit 4	/Week 24 53	27.531	36.845	-37.671	42.630	
Standard GC	Baseli	ne 52	54.049	39.225			
therapy(N=52)	Visit 2	/Week 4 52	47.923	41.211	-6.126	19.275	
	Visit 3	/Week 12 52	40.573	38.327	-13.476	28.515	
	Visit 4	/week 24 52	36.280	33.921	-17.769	29.032	

Table 15 Post-hoc analysi	s of log-transformed 17-OHP	9 24-hour AUC profile (EES	)
---------------------------	-----------------------------	----------------------------	---

		Unadjusted mean		Comparise	on betweer	ngroups	
		(SD)change from	LS mean change	Difference	e in LS	2-sided	p-
Group	Ν	baseline	from baseline	means [2]	95% CI	value	
Efmody	53	-37.671 (42.630)	-34.634	-13.771	(-25.783, -1.758)	0.0251	
Standard GC therapy	52	-17.769 (29.032)	-20.864				

#### Secondary endpoints

#### <u>1) Change from Baseline to 24 Weeks in the Natural Logarithm of the Mean of the 24-hour SDS Profile</u> for the Natural Logarithm for A4

#### Predefined analysis

Very little change was seen in both treatment groups compared to baseline, and there was no notable difference between the 2 treatment groups (difference in LS means: 0.047; 95% CI: [-0.234, 0.329]; p=0.7405).

# Table 16 Change from Baseline to 24 Weeks in the Primary Efficacy Variable for A4 Using anANCOVA Model in Protocol DIUR-005 (EES)

				Compa	rison between gro	oups
		Unadjusted mean (SD) change from	LS mean change from	Difference in		2-sided
Group	N	baseline <sup>1</sup>	baseline <sup>1</sup>	LS means <sup>2</sup>	95% CI	p-value
Chronocort	53	0.113 (0.9221)	0.122	0.047	(-0.234, 0.329)	0.7405
Standard GC therapy	52	-0.041 (0.7731)	0.075			

The primary efficacy variable was the natural logarithm of the mean of the 24-hour SDS for the natural logarithm of A4. Lower values indicated better hormonal control. The mean of the 24-hour SDS profile for each visit was the arithmetic mean of all the SDSs with the first and last (13<sup>th</sup>) weighted one half relative to the intermediate SDSs. For each of the 13 log-transformed A4 values at each visit, an SDS was calculated by counting the number of SDs that were above or below the mean of the log-transformed range.

<sup>1</sup> A negative value indicates better hormonal control versus baseline.

<sup>2</sup> A difference in LS means <0 favours Chronocort.

Note: Efmody was previously known as Chronocort.

When the geometric mean A4 24-hour profiles were plotted graphically, a similar pattern was seen to 17-OHP, with participants receiving Efmody having a flatter profile showing stable and consistent A4 levels throughout the 24-hour period, while participants receiving standard GC therapy had a rise in A4 levels overnight and in the morning before they took their first dose of GC (See Figure 15). However, it is of note that the geometric mean A4 values were below the lower limit of the reference range for the Efmody group at most time points.



Y axis is presented on a logarithmic scale.

The horizontal grey lines show the maximum reference range (across males and females).

A4=androstenedione; CI=confidence interval; EES=efficacy evaluable analysis set; GC=glucocorticoid

# Figure 14 Geometric Mean $\pm$ 95% CI for A4 (nmol/L) Week 24 Profile by Treatment Group in DIUR-005 (EES). Note: Efmody was previously known as Chronocort.

#### Post-hoc analysis

An additional post-hoc analysis was conducted on the log-transformed AUCs for A4. The absolute values and changes from baseline are provided below.

Table 17 Summary of absolute	values and change	from baseline in	log-transformed A4 24
hour AUC profile by visit (EES)			

Treatment group	Timepoint	n	Absolute values		olute values Change from baseline	
			Mean	SD	Mean	SD
Efmody (N=53)	Baseline	53	21.392	30.382		
	Visit 2/Week 4	53	8.931	30.154	-12.461	22.211
	Visit 3/Week 12	53	0.836	28.145	-20.556	23.837
	Visit 4/Week 24	53	-1.507	29.524	-22.899	26.921
Standard GC	Baseline	52	13.929	32.197		
therapy(N=52)	Visit 2/Week 4	52	10.783	35.550	-3.147	11.303
	Visit 3/Week 12	52	5.940	32.346	-7.990	15.133
	Visit 4/week 24	52	4.664	27.863	-9.265	20.439

This analysis showed a reduction in 17-OHP AUC in both treatment groups throughout the duration of the study. This reduction at Week 24 was greater in the Efmody group (difference in LS means:

-10.478; 95% CI: [-18.696, -2.259]; p=0.0130). See

Table 21.

		Unadjusted mean	LS mean	Comparison be	etween groups	
		(SD)change from	changefrom	Difference in L	.S means [2]	2-sided p-
Group	Ν	baseline [1]	baseline [1]	95% CI		value
Efmody	53	-22.899 (26.9213)	-21.336	-10.478	(-18.696, - 2.259)	0.0130
Standard GC therapy	52	-9.265 (20.4390)	-10.858			

#### Table 18 Post-hoc analysis of log-transformed A4 24-hour AUC profile (EES)

2) Change from Baseline to 24 Weeks in the Natural Logarithm of the Mean of the 24-hour SDS Profile for the Natural Logarithm of 17-OHP and A4 by Pre-Baseline Therapy Strata

The analysis conducted for the primary endpoint variable analysis of 17-OHP was repeated for each of the 3 subgroups of pre-baseline therapy strata: hydrocortisone only, prednisone or prednisolone (alone or in combination with hydrocortisone), and dexamethasone (alone or in combination with any other GC). All three subgroups showed better hormonal control at Week 24 compared to baseline in both treatment groups; however, there were no notable differences between the 2 treatment groups for any of the pre-baseline therapy strata subgroups.

#### 3)17-OHP and A4 Levels at 09:00 Hours as a Responder Analysis

#### Predefined analysis

A similar number of responders were seen in both treatment groups for both 17-OHP and A4. See Table 22.

				Compai	rison between gi	oups
Group	N	Number (%) of subjects with a response <sup>1</sup>	Adjusted response rate (%)	Odds ratio	95% CI	2-sided p-value
17-OHP						
Chronocort	53	30 (56.6)	63.6	0.99	(0.45, 2.19)	0.9877
Standard GC therapy	52	30 (57.7)	63.7			
A4						
Chronocort	53	25 (47.2)	45.5	0.93	(0.43, 2.02)	0.8498
Standard GC therapy	52	26 (50.0)	47.4			

# Table 19 Responders at 09:00 Hours at Week 24 for 17-OHP and A4 Using a Logistic Regression Model in DIUR-005 (EES). Note : Efmody was previously known as Chronocort.

<sup>1</sup> A participant was considered a responder if their 09:00 results at Week 24 were in the optimal range for 17-OHP or the reference range of A4.

An odds ratio >1 favours Chronocort. The p-value was calculated based on the likelihood ratio test which compared 2 models (1 model with pre-baseline standard GC therapy only and the other model with both treatment and pre-baseline standard GC therapy as factors).

#### Post-hoc analyses

A responder analysis was undertaken for the 09:00 17-OHP values, with a responder defined as a participant with their 09:00 results at Week 24 in the reference range for 17-OHP (rather than the optimal range used in the pre-defined analysis). At Week 24, there were 19 responders (35.8%) in the Efmody group and 16 responders (30.8%) in the standard GC therapy group (Odds Ratio=1.33; 95% CI: [0.58, 3.10]; p=0.5067).

A subsequent analysis restricted to non-responders at baseline did not show a difference between the two treatment groups. There were 18 responders (36.7%) in the Efmody group and 8 responders (22.2%) in the standard GC therapy group (Odds Ratio= 2.11, 95%CI: : [0.79, 6.07]; p=0.1404).

#### 4) Changes in Body Composition (DEXA)

Results of changes in body composition (DEXA) are presented in Table X. No significant differences between the 2 treatments groups were seen from the DEXA scans for total fat and lean mass or bone mineral density. See Table 23.

# Table 20 Change from baseline in body composition (DEXA). Note: Efmody was previously known as Chronocort.

				Compa	rison between gro	oups
Group	N	Unadjusted mean (SD) change from baseline	LS mean change from baseline	Difference in LS means	95% CI	2-sided p-value
Total Fat M	ass (l	kg)	•	· · ·		
Chronocort	43	-0.575 (3.2744)	-0.413	-0.960	(-2.294, 0.374)	0.1560
Standard GC therapy	39	0.445 (2.4660)	0.547			
Total Lean I	Mass	(kg)				
Chronocort	43	0.640 (2.3304)	0.660	0.425	(-0.455, 1.305)	0.3392
Standard GC therapy	39	0.234 (1.3689)	0.235			
Bone Miner	al De	ensity (g/cm <sup>2</sup> )				
Chronocort	35	-0.001 (0.0250)	-0.010	0.009	(-0.007, 0.025)	0.2614
Standard GC therapy	36	-0.008 (0.0399)	-0.019			

An ANCOVA model was based on the change from baseline of the parameter (total fat mass, total lean mass or bone mineral density) of DEXA as the dependent variable, treatment group and pre-baseline therapy as fixed effects and the baseline of the parameter (total fat mass, total lean mass or bone mineral density) of DEXA as the covariate. A difference in LS means <0 favours Chronocort. CI=confidence interval; DEXA=dual energy X-ray absorptiometry; EES=efficacy evaluable analysis set;

GC=glucocorticoid; LS=least squares; SD=standard deviation.

# Ancillary analyses

Subgroup analysis was performed per baseline treatment strata. These analyses were included as a secondary endpoint in the study protocol "17-OHP and A4 by individual baseline treatment strata presented in the same manner as the primary endpoint (using 24-hour SDS profile at 24 weeks)".

A large variety of post-hoc analyses were conducted, described above for the respective efficacy variables.

### Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

#### Table 21 Summary of efficacy for trial DIUR-005

<u>Title</u>: a phase III study of efficacy, safety and tolerability of Efmody compared to standard glucocorticoid replacement therapy in the treatment of congenital adrenal hyperplasia

Study identifier	DIUR-005 FudraCT number:	2015-000711-4	า	
	Clinicaltrials.gov:	NCT02716818	5	
Design	multicentre, open	-label, randomiz	ed, control	
			o monui	cablo
	Duration of Extens	i pliase.		
	Duration of Extent	son phase.	DIOK-00	0
Hypothesis	Superiority of Efm	ody compared to	o standard	glucocorticoid replacement therapy
Treatments groups	Efmody		Efmody t	twice daily, max daily dose 30
			6 months,	n=61
	Standard GC there	ару	Pre-base • 6 month	line treatment being either: Hydrocortisone only Prednisone/prednisolone Dexamethasone s, n=61
Endpoints and definitions	Primary endpoint	17-OHP	change f the 24-h for 17-0 transforr	rom baseline to 24 weeks of the mean of our standard deviation score (SDS) profile HP, presented as the SDS of log- ned 17-OHP concentration unsigned.
	Secondary endpoint	A4	change fr 24-hour S	om baseline to 24 weeks of the mean of the DS profile for A4.
	Secondary endpoint	Subgroup 17- OHP and A4	17-OHP a strata pre endpoint (	nd A4 by individual baseline treatment sented in the same manner as the primary (using 24-hour SDS profile at 24 weeks).
	Secondary endpoint	Responder analysis	17-OHP and A4 levels at 09:00 as a responder analysis (i.e. the number of participants achieving results in the optimal range for 17-OHP and withi reference range for A4).	
	Secondary endpoint	Dexa	Changes i in body co total bone	relative to standard GC replacement therapy omposition (DEXA) (fat mass, lean mass and e density)
	Exploratory endpoint	Daily GC dose	Daily GC o glucocorti daily dose	dose was calculated to assess a possible coid sparing effect. Represented as median e per body surface area (BSA) at week 24.
Database lock	14 September 203	18		
<u>Results and Analysis</u>				
Analysis description	Primary Ana	<b>lysis:</b> 17-0HP		
Analysis population and time point description	EES (efficacy e randomised into therapy, and w who had no ma Time point: 24	valuable set): cc o the study, who ho had an evalu jor protocol viol weeks	omprised al received a able Week ations.	ll participants who were at least one dose of Efmody or standard GC 24 17-OHP 24-hour hormone profile, and
Descriptive statistics and	Treatment gro	up Efmody		Standard GC therapy
esumate variability	N	53		52

	Unadjusted mean change from baseline		-0.403 -0.172		).172		
	SD	0.8499		0.7776			
Effect estimate per comparison	17-OHP	Comparison groups		1	Efmody vs standard GC therapy		
		Differ	ence in LS mea	ns	-0.069		
		95% (	95% CI -0.		-0.229, 0.161		
		P-valu	P-value (ANCOVA) 0.55		0.5521		
Notes	A secondary analysis per pre-baseline treatment strata was performed on the primary efficacy variable. No differences were observed for 17-OHP per pre-baseline treatment subgroup Many post-hoc analyses were performed on the primary efficacy variable, some of which showing significant differences between the treatment groups.						
Analysis description	Primary analysis: A4						
Analysis population and time point description	EES (efficacy evalu Time point: 24 wee	able set ks	:)				
Descriptive statistics	Treatment group		Efmody		Standard GC therapy		
	Ν		53		52		
	Unadjusted mean c from baseline	idjusted mean change -0.400 n baseline		-0.242			
	SD		0.8225		0.7800		
Effect estimate per comparison	A4		Comparison groups		Efmody vs standard GC therapy		
			Difference in l	S means	-0.041		
			95% CI		-0.266, 0.184		
			p-value		0.7100		
Analysis description	Primary analysis: responder analysis						
Descriptive statistics: 17- OHP	Treatment group		Efmody		Standard GC therapy		
	Ν	N 53 Proportion of patients (%) 30		52			
	Proportion of patier			30			
	SD		56.6		57.7		
Effect estimate per	17-OHP responders		Comparison gi	roups	Efmody vs standard GC		
comparison			Odds ratio		0.99		
			95% CI		0.45, 2.19		
			p-value		0.9877		
Descriptive statistics : A4	Treatment group		Efmody		Standard GC therapy		
	Ν		53		52		
	Proportion of patients (%		25		26		
	SD		47.2		50.0		
Effect estimate per	A4 responders		Comparison gi	roups	Efmody vs standard GC		
Companson			Odds ratio		0.93		
			95% CI		0.43, 2.02		

						,			
Notes	<b>N.B.:</b> there was a significant baseline difference between the groups; 7.5% responders in the Efmody group versus 30.8% responders in the standard therapy group								
Analysis description	Primary analysis: DEXA								
Analysis population and time point description	EES (efficacy Time point: 2	r evaluable s 4 weeks	set)						
Descriptive statistics	Treatment gro	oup	Efmody	Efmody			Standard GC therapy		
	N		43			39			
	Unadjusted m from baseline Total fat mas	nean change e (SD): s (kg)	e -0.575 (3	3.2744)		0.445	(2.4660)		
	Total lean mass (kg)		0.640 (2	0.640 (2.3304)			0.234 (1.3689)		
	Bone mineral (g/cm2)	density	-0.001 (0	).0250)		-0.00	8 (0.0399)		
Effect estimate per	Total fat mass		Comparis	Comparison groups			Efmody vs standard GC		
companson			Differenc	Difference in LS means			-0.960		
			95% CI	95% CI			-2.294, 0.374		
			p-value	p-value			0.1560		
	Total lean mass		Comparis	Comparison groups			Efmody vs standard GC therapy		
			Differenc	Difference in LS means			0.425		
			95% CI	95% CI			-0.455, 1.305		
			p-value	p-value			0.3392		
	Bone mineral density		Comparis	Comparison groups			Efmody vs standard GC		
			Differenc	Difference in LS means			0.009		
			95% CI	95% CI			-0.007, 0.025		
			p-value	p-value			0.2614		
Analysis description	Explorator	y analysis:	daily GC d	ose		•			
Analysis population and time point description	Safety analys Time point: 2	sis set 4 weeks							
Descriptive statistics	Pre-baseline Overall treatment group			Hydrocortisone on ly			Prednisolone/prednisone		
	Treatment group	Efmody	Standard GC therapy	Efmody	Standard therapy	GC	Efmody	Standard GC therapy	
	Ň	61	61	32	32		24	24	
	Median daily dose/BSA	15.82	17.04	15.13	14.53		16.54	18.50	

# Supportive study

Study DIUR-006, is a Phase 3, open-label extension study enrolled participants who completed Studies DIUR-003 or DIUR-005. Patients continued Efmody therapy or switched from their current GC therapy to Efmody. After screening, all participants underwent a full set of baseline assessments before starting treatment in this extension study. Participants entering immediately from Study DIUR-005 who were

previously on Efmody continued on the same dose of Efmody that they were receiving at the end of the feeder study. Participants from Study DIUR-005 on standard therapy, participants from DIUR-005 who had a gap between completing Study DIUR-005 and starting Study DIUR-006 during which they received standard GC therapy, and participants from Study DIUR-003 had their initial dose of Efmody determined using the hydrocortisone equivalent of their previous treatment (immediately prior to the baseline visit).

Participants returned to the study centre at 4, 12, and 24 weeks after starting Study DIUR-006, and 6monthly thereafter for follow-up assessments. Dose titration could be performed by the investigating physician at these visits. Dose adjustment was to be based on clinical symptoms using the Adrenal Insufficiency Checklist and the measurement of 17-OHP and A4 at 09.00 hr and 13.00 hr. Dose adjustments were considered if the samples showed out of range values for 17-OHP or A4. If 17-OHP and A4 showed inconsistent trends, the A4 parameter took precedence in directing dose adjustment. If there was a change of dose, an interim visit was needed in between the 6-monthly visits.

Interim data with a cut-off date of 30 April 2019 is submitted in the present application. A total of 83 participants were ongoing treatment at the time of the cut-off date.

The interim analysis set includes participants who had received at least one dose of Efmody and had completed the Visit 4 (Week 24) assessment by 30 April 2019, plus any participants who discontinued or were withdrawn prior to the data cut-off date. A total of 92 participants are included in this interim analysis: 41 who were already on Efmody, 40 who were on standard GC therapy and switched to Efmody, 6 who had a gap between completing Study DIUR-005 and starting Study DIUR-006 during which they received standard GC therapy, and 5 patients from Study DIUR-003 had their initial dose of Efmody determined using the hydrocortisone equivalent of their previous treatment (immediately prior to the baseline visit). Demographic characteristics were as follows: 31.9% male, 68.1% female, 33.0% aged 18 to <30 years, 48.4% aged  $\geq$ 30 to <50 years, and 18.7% aged  $\geq$ 50 to <70 years (no participants were aged  $\geq$ 70 years). The number of participants with data after Month 18 decreased so conclusions after this point are limited at the time of this interim analysis and thus results are reported until Month 18.

Duration of treatment was a maximum of 3.5 years in this extension study.

A reduction in the median total daily dose of Efmody was seen, falling from a median total daily dose of 30 mg during the baseline to Week 4 period (i.e. before the first dose titration period) in all participants to a median of 20 mg during the Month 12 to Month 18 period. This represents a reduction in the median total daily dose of Efmody of 10 mg over the course of the first 18 months treatment in this study which represents a clinically meaningful steroid-sparing in these participants. Participants entering from the standard GC therapy group in Study DIUR-005 tended to have a higher median dose during the baseline to Week 4 period (30 mg) compared to participants entering from the Efmody group in Study DIUR-005 (25 mg). By the Month 12 to Month 18 period, the median dose was 22.6 mg in the DIUR-005 standard GC therapy group and 20.2 mg in the DIUR-005 Efmody group. There are too few participants in Study DIUR-003 and those who completed Study DIUR-005 and had a gap before starting Study DIUR-006 at the time of this interim analysis to draw any meaningful conclusions in these groups.

An increase in the percentage of participants achieving disease control was seen at 09:00 hours for most visits compared to baseline for both 17-OHP and A4 (from 56.7% at baseline to a maximum of 71.3% at Week 12 for 17-OHP and from 53.3% at baseline to a maximum of 68.0% at Month 18 for A4. (. For the 13:00 hour results, the 17-OHP and A4 levels remained relatively constant to those seen at baseline.

Participants who entered this study from the standard GC therapy group in feeder Study DIUR-005 had a fall in the percentage of participants achieving disease control at 13:00 hours when they switched to Efmody (i.e. a change from 82.5% at baseline to 62.5% at Week 4 for 17-OHP and from 47.5% at baseline to 37.5% at Week 4 for A4), but by Week 12 the percentage of participants considered a disease responder was similar to the participants treated with Efmody in Study DIUR-005.

For all the 17-OHP evaluations, the geometric mean values remained within the optimal range but became more established in the middle of the optimal range during the evaluation period for this interim analysis (from a starting point near the bottom of the optimal range). See Figure 16. For A4 evaluations, the geometric mean values remained around the lower limit of the reference range during the same period. See Figure 17.



Y-axis is presented on a logarithmic scale. Dotted horizontal lines denote the optimal range. Note reduced participant numbers at Months 24 and 30.

Figure 15 Geometric Mean  $\pm 95\%$  CI Over Time for 17-OHP at 09:00 Hours in DIUR-006 (Interim Analysis Set)



Y-axis is presented on a logarithmic scale. The horizontal grey lines show the maximum reference range (across males and females). Note reduced participant numbers at Months 24 and 30.

Figure 16 Geometric Mean  $\pm 95\%$  CI Over Time for A4 at 09:00 Hours in Protocol DIUR-006 (Interim Analysis Set)

# 2.4.5. Clinical safety

The safety assessment is mainly based on the pooled data from DIUR-003, DUIR-005 and the long term extension study DIUR-006. This population is referred to as the "pooled population" for the remainder of this report.

Six clinical studies contributed safety data to support safety in the dossier. All the clinical studies were open label which is a limitation when analysing the safety data since unintentional bias in adverse effect reporting could be expected. Three of the clinical studies were conducted in adult patients with CAH (DIUR-003, DIUR-005 and DIUR-006). In addition, three single-dose administration studies were conducted in healthy adult volunteers (DIUR-002, DIUR-004, and DIUR-008).

Study DIUR-005 was the only study with a comparator. In this 6-months study Efmody was compared with standard glucocorticoid therapy (i.e. hydrocortisone only; prednisone or prednisolone alone or in combination with hydrocortisone; and dexamethasone alone or in combination with any other glucocorticoid) in 61+61 adult CAH patients. Results from DIUR-006 gives an overall safety profile for treatment with Efmody longer than 6 months.

# Patient exposure

In study DIUR 003 and -005 all patients (N=77) received Efmody for 6 months (the remaining 61 patients received standard CG treatment). Besides patients from DIUR-003 and -005 there were 43 patients included in study DIUR-006 who were earlier treated with standard GC and are included in the "pooled analysis". Of the 120 patients in the "pooled analysis" three patients received standard therapy in Study DIUR-005 and then switched to Efmody on Study DIUR-006. Therefore, the total patients in the "pooled analysis" adds up to 120 instead of the expected 123. Seventy-nine (79) of the 120

patients in the "pooled analysis" was exposed to Efmody  $\geq$  12 months including 43 subjects with an exposure duration  $\geq$  24 months.

With currently 91 patients included the mean total treatment duration in the second interim analysis of Study DIUR-006 was 580.8 days (i.e., approximately 19 months), with a range from 62 to 985 days. For patients who received already Efmody in Study DIUR 005 (N=61), the overall mean exposure to continuous Efmody treatment was 685.1 days (i.e. approximately 1 year 11 months), ranging from 85 to 1147 days. The follow-up of patients on Efmody is very limited.

# Adverse events (AE)

In the single dose healthy volunteer studies (doses varying from 5 to 50 mg hydrocortisone), all but 1 of the treatment-emergent adverse events (TEAEs) were mild (1 TEAE was moderate in severity), were single episodes and reported by 1 subject each. Three subjects had a total of 4 TEAEs considered related to administration of study medication: 1 subject (1.5%) with 2 events of upper abdominal pain and dyspnoea who received Efmody and 2 subjects (8.3%) with 1 event each of dyspepsia and mood swings who received Cortef (Immediate release hydrocortisone).

A total of 211 treatment-related TEAEs were reported in 68 patients (56.7%) who received Efmody. The most common treatment-related TEAEs by PT were unexpected therapeutic response (21.7%), fatigue (11.7%), headache (7.5%), and increased appetite (5.8%). All treatment related adverse events reported in the pooled population are summarised in Table 25.

	Efmody N=120	Standard GC Therapy N=61	
Preferred Term	Number of events/number of patients (% of patients)		
Total with related TEAEs	211/68 (56.7)	39/11 (18.0)	
Therapeutic response unexpected	44/26 (21.7)	1/1 (1.6)	
Fatigue	18/14 (11.7)	5/5 (8.2)	
Headache	10/9 (7.5)	1/1 (1.6)	
Increased appetite	8/7 (5.8)	2/2 (3.3)	
Dizziness	8/7 (5.8)	1/1 (1.6)	
Weight increased	7/7 (5.8)	1/1 (1.6)	
Insomnia	4/4 (3.3)	4/4 (6.6)	
Decreased appetite	6/6 (5.0)	0	
Nausea	7/5 (4.2)	1/1 (1.6)	
Asthenia	7/5 (4.2)	1/1 (1.6)	
Renin increased	3/3 (2.5)	2/2 (3.3)	
Abnormal weight gain	4/4 (3.3)	0	
Carpal tunnel syndrome	5/4 (3.3)	0	
Paraesthesia	4/4 (3.3)	0	
Impaired fasting glucose	3/3 (2.5)	1/1 (1.6)	
Sleep disorder	2/2 (1.7)	2/2 (3.3)	
Abdominal pain upper	5/3 (2.5)	0	
Abnormal dreams	4/3 (2.5)	0	
Acne	3/3 (2.5)	0	
Agitation	0	3/2 (3.3)	

Table 22 Number of events/patients (%) with related AEs in  $\ge$  2.5% patients in either treatment group by preferred term in patients with CAH (Pooled Population)

CAH=congenital adrenal hyperplasia; GC=glucocorticoid; All patients are only counted once with the worst relationship. 2 AEs in DIUR 003 Part B had no causality assigned.

Data source: Pooled Safety Table 4.2

In the overall assessment, there were few differences of note between the treatments in treatment related AEs reported (by preferred term [PT]). The most notable differences between the Efmody and standard glucocorticoid therapy pools, respectively, were observed for therapeutic response unexpected (21.7% vs 1.6%), headache (7.5% vs 1.6%), increased appetite (5.8% vs 3.3%), weight increase (including abnormal weight gain) (9.2% vs1.6%), decreased appetite (5.0% vs 0%) and nausea (4.2% vs 1,6%).

# Serious adverse event (SAE)/deaths/other significant events

There were no deaths in any of the clinical studies conducted with Efmody.

A total of 41 SAEs were reported in 19 patients (15.8%) who received Efmody. The most common SAEs were acute adrenocortical insufficiency (2.5%), gastroenteritis (3.3%), diverticulitis (1.7%); appendicitis, adrenal insufficiency, and abdominal pain (1.7%), and viral gastroenteritis and dyspnoea (0.8%). All other SAEs were only reported by 1 patient. Single SAEs in patients who received Efmody were: gastroenteritis norovirus, lower respiratory tract infection, pharyngitis, salpingitis, tonsillitis, abdominal discomfort, diarrhoea, fatigue, fall, red blood cell (RBC) microcytes, hypokalaemia, arthritis, intervertebral disc protrusion, breast cancer, depressed level of consciousness, loss of consciousness, and anxiety. All SAEs resolved.

# Laboratory findings

On average, there were no clinically meaningful changes over time or differences between the treatment groups in haematology or biochemistry variables or urinalysis. Further, the changes reported over time or differences between the treatments for the vital signs (weight, BMI and waist circumference) are not clinically relevant.

None of the healthy volunteers had a corrected QT interval by Bazett (QTcB)/QTcF interval that was greater than 500 msec, or a change in QTcB/QTcF interval that was greater than 60 msec. Further, there were no clinically relevant differences observed in vital signs or 12-lead ECG between Efmody and immediate-release hydrocortisone.

# Vital signs

In the comparative study DIUR-005, there were small increases from baseline to the end of study in both the Efmody and standard GC therapy groups for mean weight (+0.87 and +1.01 kg, respectively), BMI (+0.330 and +0.346 kg/m2, respectively), and waist circumference (+0.21 and +0.96 cm, respectively). These small increases were not sustained in the DIUR-006 extension study, where instead of a small decrease from baseline to Month 24 in mean weight (-0.28 kg) and BMI (-0.083 kg/m2).

# Other significant adverse events

### **Adrenal crises**

Overall, available safety data from study DIUR-003, DIUR-005 and DIUR-006 did not indicate any increased risk for adrenal crisis with Efmody compared to standard GC therapy. The risk for adrenal crisis is reflected in the proposed SmPC in section 4.4.

There were no SAEs or TEAEs considered indicative of an adrenal crisis in studies DIUR-002, DIUR-003, DIUR-004 or DIUR-008.

### Signs and symptoms of adrenal insufficiency and over treatment

The diagnosis of adrenal crisis used were published by Allolio, 2015. These criteria include the general accepted criteria (2 issues out of the following: hypotension (systolic blood pressure <100 mmHg), nausea or vomiting, severe fatigue, fever, somnolence, hyponatraemia (<132 mmol/l) or hyperkalaemia (as judged by characteristic ECG changes)or hypoglycaemia). The frequency of signs and symptoms of adrenal insufficiency or over-treatment (among others fatigue, sleeping difficulties, muscle weakness, weight gain, headache and increased appetite) was higher in the Efmody group (35 patients (57.4%)) compared to the standard GC-treatment (26 patients (42.6%)). In this section all AEs are included regardless of the assigned relation with the treatment).

#### • <u>Signs and symptoms of adrenal insufficiency</u>

In the Efmody group, the proportion of subjects reporting headache and fatigue as symptoms of under-treatment were reduced early (4 weeks) after initiation of Efmody. Headache reduced from 13.1% at baseline to 3.3% (week 4) and 0% at the visits thereafter. Fatigue reduced from 18.0% at baseline to 6.6% at week 4 and thereafter varied between 6.6-8.2%. In the standard GC therapy group a slight decrease overtime was noted for fatigue with 14.8% at baseline and week 4. Thereafter, the frequency varied between 8.2% and 11.5%.

#### • Signs and symptoms of over-treatment

In the Efmody group, changes from baseline of >5 percentage points in the frequency of participants with signs and symptoms of over-treatment were observed for sudden weight gain (1.6% at baseline, 11.5% at Week 4 and 9.8% at Week 24/End of study) and in the standard GC therapy group, a change in frequency with >5 percentage points was noted for fatigue (0% at baseline, 6.6% at Week 12), sudden weight gain (0% at baseline, 6.6% at Week 24 and 8.2% at end of study), and increased appetite (0% at baseline, 6.6% at Week 24 and end of study) for the standard GC therapy group.

In DIUR-006, signs and symptoms of adrenal insufficiency or over-treatment were reported for 45 patients (49.5%) with 22 participants (24.2%) having signs and symptoms due to over-treatment and 32 participants (35.2%) due to under-treatment. The most frequently reported symptoms of adrenal insufficiency were headache (highest incidence of 5.5% at Visit 2/Week 4) and fatigue (highest incidence of 8.8% at Visit 4/Week 24), and the most frequently reported symptoms of over-treatment were increased appetite (highest incidence of 6.6% at Visit 2/Week 4), sudden weight gain (highest incidence of 7.7% at Visit 3/Week 12), headache (highest incidence of 5.5% at Visit 2/Week 4) and sleeping difficulties (highest incidence of 4.4% at Visit 2/Week 4).

Overall, patient switching from standard GC therapy in DIUR -005 to Efmody in study DIUR-006, reported sign and symptoms related to over treatment with higher frequencies compared to the group of patients that continued treatment with Efmody without a gap between DIUR-005 and DIUR-006. Patients without a gap of Efmody treatment when entering DIUR-006 from DIUR-005, had fewer reports of overtreatment in the extension study.

#### <u>Unexpected therapeutic benefit or detriment effect</u>

In study DIUR-005 unexpected therapeutic benefit was reported for 10 patients (16.4%) in the Efmody group and one patient (1.6%) in the standard GC therapy group. These events can be summarised as improvement of mood, alertness and energy in 6 patients, improvement in reproductive hormone regulation in 5 patients (with more regular menstrual cycles being reported in 4 patients), and other improvements in 3 patients. One patient in the standard GC therapy group had an improvement in reproductive hormone regulation (more regular menstrual cycle). Due to the lack of information

considering the correctness of the pre-baseline regimen the beneficial effect – although clearly observed – cannot be attributed to the Efmody treatment as a less optimal pre-baseline treatment regimen cannot be excluded.

Besides the unexpected beneficial effect of Efmody some of the patient report adverse events (4) that can be considered a detriment effect. Adverse events considered detriment were less alert-"somnolence", menstrual deterioration-"menses irregular", increased hair loss "alopecia" and increased hirsutism "hair growth abnormal".

# Safety in special populations

#### Gender

Although the overall frequency of TEAEs appear not different between the sexes, the frequency of SAE is higher in women compared to men. On an AE level the following SAE are reported more by females than by men (nausea (9.5% males vs. 21.8% females), headache (33.3% males vs. 44.9% females) and pyrexia (16.7% males vs. 28.2% females. While dizziness (26.2% males vs. 12.8% females) and arthralgia (21.4% males vs. 10.3% females) were more frequently reported by male than by female patients. Given the limited patient population (61 patients on Efmody and 61 on standard GC treatment) and follow-up (about 6 months) these differences are considered change findings. The only notable difference between the gender groups was for infections and infestations, with females having a higher number of these events (14 events in 9 females [11.5%] compared to 2 events in 2 males [4.8%]). However, a variety of different PTs within the SOC infections and infestations were reported as SAEs, and no specific pattern could be identified.

In the safety study pool 7 SAEs were reported in 4/42 males (9.5%), and 34 SAEs were reported in 15/78 females (19.2%). The only SAE PTs reported by more than two subjects were "gastroenteritis" (4 events reported by 4 females, no such event was reported in males) and "adrenocortical insufficiency acute" reported in three subjects (5 events in 2 females and one event in one male). To note is that one patient had recurrent episodes of gastroenteritis and associated adrenal crises and reported 5 SAEs. Overall, no specific difference of clinical relevance in SAE pattern between males and females could be noted.

#### Race and age

Given the fact that all but 5 patients were Caucasian and all but 2 patients were within the 18-64 age an analysis by race and age is considered not necessary.

#### Preceding GC treatment

There were no meaningful differences between the previous treatments in the proportion of patients with TEAEs or the characteristics of the TEAEs. The number of patients previously treated with dexamethasone alone or combined with any other GC was too low for meaningful comparison with the other previous treatments.

#### Use in renal and hepatic impairment

Patients with clinical or biochemical evidence of renal and hepatic impairment respectively, were excluded from the Efmody trial programme.

# Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies have been conducted, which is considered acceptable by the CHMP.

## Discontinuation due to adverse events

Three (3) subjects across the patient and healthy subject study pools discontinued study intervention due to TEAEs. One patient treated with Efmody in Study DIUR-005 (1/61, 1.6%) discontinued Efmody due to TEAEs of mild nausea, increased body temperature, increased appetite, depressed mood, and hyperhidrosis; 1 patient treated with Efmody in Study DIUR-006 (1/91, 1.1%) discontinued treatment due to carpal tunnel syndrome; and 1 subject treated with Efmody in Study DIUR-004 (1/18, 5.6%) discontinued treatment due to upper abdominal pain and dyspnea.

# 2.4.6. Post marketing experience

No post-marketing data are available. According to the applicant, the medicinal product has not been marketed in any country.

# 2.4.7. Discussion on clinical aspects

Hydrocortisone is a well-known and well-characterised substance, with a known mechanism of action.

Based on the reference product and scientific literature (Le Roux et al., 2002; McKay and Cidlowski, 2003), the pharmacokinetic profile of hydrocortisone (distribution, metabolism and elimination) has been adequately characterised and the proposed SmPC information is considered in line with the state of scientific knowledge.

In line with the current Guideline on the pharmacokinetics and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1), the modified release formulation properties were characterised in vivo regarding (i) the rate and extent of absorption, (ii) fluctuations in drug concentrations at steady-state, (iii) inter-subject variability in pharmacokinetics, (iv) dose proportionality, (v) factors affecting the performance of the modified-release formulation, and (vi) the risk of unexpected release characteristics, e.g. dose dumping (see quality part). The applicant also used pharmacokinetic data in order to evaluate which formulation and dosage regimen that would best mimic the physiological circadian serum cortisol profile over the day.

In the bridging study (DIUR-004), after administration of Efmody, serum cortisol Tmax was observed later (0.88h vs 4.5h), Cmax was 17% lower and AUC 19% was higher compared to the 20 mg immediate release reference product, showing a delayed-release properties of Efmody, expected for a modified release formulation.

The 5, 10 and 20 mg formulations were dose-proportional. In addition, although not dose linear, linear pharmacokinetics were observed . The use of the different 5, 10 and 20 mg formulations is acceptable, as comparable relative pharmacokinetics can be expected.

The applicant developed a PBPK model to support the indication in children from the age of 12. Simulations indicated that dosing of Efmody based on either body weight (mg/kg) or body surface area (mg/m2) will result in a cortisol pharmacokinetic profile comparable to adults. However, the simulations are not considered adequate for making claims on the exposure in the adolescent population. Nonetheless, dosing in adolescents is endorsed based on the titration guided dosing regimen.

No specific dose recommendation is needed for subjects with renal or hepatic impairment, elderly, gender or race, in line with known SmPC recommendations of hydrocortisone, in which no specific dose recommendations are indicated for orally administered hydrocortisone. Additionally, known interactions of hydrocortisone have been included in the SmPC which is agreed, as it is not expected that the interaction profile of Efmody will differ from that of other oral hydrocortisone release formulations. No formal dose-finding study was performed for Efmody. The starting dose, titration regimen and dosing regimen was based on phase 1 PK studies and study DIUR-003 and consisted of a start dose of 30 mg Efmody, 10 mg in the morning and 20 mg in the evening. This regimen was shown to mimic physiological cortisol rhythm in the phase I studies and was considered adequate for control of androgen secretion. The dosing advice in the SmPC is based on the international treatment guidelines, which is considered appropriate.

In the context of CAH, 17-OHP and A4 were assessed as biomarkers for treatment response in study DIUR-003 and are used as pharmacodynamic endpoints in study DIUR-005. This is acceptable since in clinical practice, androgen levels are used to guide treatment, and in CAH, the suppression of androgens is a specific goal of the GC replacement therapy.

Study DIUR-003 was conducted to confirm the efficacy of the two daily dosing regimen in suppressing androgen secretion and to inform on dose and study design of the subsequent phase 3 study. The study design is considered adequate to provide this proof of concept. It is not considered sufficient to provide evidence to confirm the hypothesis that Efmody can provide superior androgen control compared to standard treatment since the study did not contain a control arm. The patient population and titration regimen were largely the same as that of the phase 3 study.

On standard treatment, a rise in ACTH levels was observed from 03:00 hrs, reaching a plateau from 07:00 hrs to 13:00 hrs, before declining after 17:00 hrs. On Efmody, ACTH levels did not rise at 03:00hrs and were stable and notably lower than those on standard treatment through the day. The ACTH profiles observed is suggestive of the interaction between glucocorticoid therapy, the central clock, and glucocorticoid feedback. Improved androgen control was also reflected in more stable 17-OHP and A4 levels whilst on Efmody compared to standard treatment. After 6 months of treatment, 15 of 16 patients had a 09.00 hours 17-OHP level within the optimal range. For the standard therapy group this was 5 of 16 patients.

Overall, the proposed dosing regimen of 30 mg per day divided in two doses (20 mg in the evening and 10 mg in the morning) in this study provided a physiological cortisol profile and suppression of the androgen peak in the early morning via normalization of the ACTH profile. These data suggested that a twice daily dose regimen was appropriate in the phase III studies.

#### Design and conduct of phase 3 clinical studies

#### Main study DIUR-005

The general outline of this randomized, open-label study has been endorsed as part of CHMP scientific advice(s).

The primary objective of the study was to show superiority (efficacy) of Efmody compared to standard GC replacement therapy. This is understandable since the applicant aimed to show a significant benefit over standard treatment. However, the fact that patients are titrated based on 17-OHP levels, while this is also the primary efficacy variable complicates the interpretation of the results. A comparison

with only conventional hydrocortisone would have been strongly preferred as also pointed out several times in scientific advice procedures.

Patients with classical CAH due to 21-hydroxylase deficiency were included, both simple virilising and salt-wasting. Patients were to be on a minimum treatment with GC's for 6 months to try to include patients that were optimised on current treatment. The currently proposed indication includes all patients above 12 years of age with congenital adrenal hyperplasia (CAH). This is not considered an issue since GC replacement therapy forms the mainstay of CAH management, and in clinical practice, treatment will always be initiated by an experienced physician.

Patients >18 years of age were included in the studies, while the applicant proposes an indication >12 years of age. Efficacy and safety are extrapolated from adults to adolescents based on PBPK modelling (see Pharmacokinetics). From a clinical perspective, the extrapolation to adolescents is acceptable.

Patients with salt-wasting CAH were included in the study if properly managed on mineralocorticoids. Since a large proportion of the indicated patient population is treated with mineralocorticoids, this is appropriate.

Patients were randomized to receive either Efmody or to stay on their standard GC therapy. The starting dose of Efmody was calculated as prednisone/prednisolone dose multiplied by 5 and dexamethasone dose multiplied by 80 with a maximum of 30 mg Efmody per day to prevent overtreatment.

Randomization was based on three pre-treatment strata; hydrocortisone only, prednisone/prednisolone and dexamethasone. Randomization was performed stratified by baseline treatment. This is endorsed.

This was an open-label study. Blinding was considered not feasible given the wide variety of baseline therapies. This is acknowledged. To minimize bias due to knowledge of the therapy, dose titration was carried out by an independent blinded physician, which is acceptable. The primary efficacy variable was the 24-hour hormone profile, and therefore unlikely to be impacted by the physician or the participants' behaviour or measurement error due to knowledge of the treatment received.

Patients were followed for 6 months. Dose titration was possible for all treatment arms during the study based on 24h 17-OHP, and A4 profiles were taken at week 4 and 12 and an adrenal insufficiency checklist. The decisions to increase or decrease the dose were made by an independent physician. In clinical practice, this is not feasible, and dose titration is based on consistently timed hormone measurement and even more so guided by the overall clinical picture of the patient. This limits the conclusions on the daily dose, and the data are to be interpreted with caution. These findings are further discussed in conjunction with the dose titration used in the extension study DIUR-006 and its results (see further below).

The primary efficacy endpoint was the change from baseline to 24 weeks of the mean of the 24-hour standard deviation score (SDS) profile for 17-OHP. Key secondary endpoints were the change from baseline to 24 weeks of the mean of the 24-hour SDS profile for A4, 17-OHP and A4 by individual baseline treatment strata and a responder analysis for 17-OHP and A4 levels at 09:00 (i.e. the number of participants achieving results in the optimal range).

The primary efficacy analysis was based on the EES, which comprises a per-protocol set of completers, i.e. subjects with relevant data available at Week 24. According to the SAP, a corresponding primary endpoint analysis was also performed on the FAS, however, the FAS definition here does not follow the Intent To Treat (ITT) principle. Therefore, an analysis of the primary endpoint would have been expected for all randomised subjects analysed according to the randomised treatment and using an

appropriate imputation method to handle missing data. However, since only 1 subject in each treatment group is excluded from the FAS, this analysis was not further requested.

The primary efficacy variable 17-OHP and secondary efficacy variable A4 are used as biomarkers to assess treatment outcome. Since in clinical practice, 17-OHP and A4 are often used as a target for treatment; this was considered acceptable by the CHMP. Using the SDS to depict the hormone levels is common practice and is accepted, however a mean unsigned SDS has several limitations. By taking the mean, circadian rhythms are cancelled out. The unsigned SDS does not separate effects under or above the normal mean, a difference that might be clinically relevant. The SDS is also not very sensitive to amplitude, while the treatment is aimed at decreasing the early morning peak in androgen levels.

Clinical endpoints are not extensively included in the study protocol. Fat mass, lean mass and total bone density were included as secondary efficacy endpoints. Body weight could be used as a clinically relevant marker for over- or under-treatment but is prone to bias.

The study duration of 6 months is considered adequate to assess a treatment effect on biomarkers such as 17-OHP and A4. However, the effects on clinical endpoints may take longer to occur.

A responder analysis was performed as a secondary analysis. Responders are defined as patients that have hormone levels within the optimal range for 17-OHP and within the normal range for A4. This is considered clinically relevant since treatment is guided by these reference ranges in clinical practice.

An important exploratory endpoint was the use of GCs at the beginning and end of the study, presented both as individual GCs used and as calculated hydrocortisone equivalents using accepted conversion constants for the calculations.

The amendments made to the study protocol for study DIUR-005 are not considered to have affected the outcome or the interpretation of the study.

#### Supportive study DIUR-006

The primary goal of this study was to assess the long-term safety of Efmody. Long term efficacy variables included daily GC dose, the proportion of responders and the change from baseline in 17-OHP and A4 levels. This is considered relevant given the necessity for life-long treatment in this condition. In general, the lack of a control arm limits the interpretation of the data.

Patients from study DIUR-003 and DIUR-005 could be enrolled in this study. Both Efmody naïve and experienced patients were enrolled. It has to be noted that as a result, only treatment-experienced patients contribute to the information on long term safety and efficacy at the moment.

Starting dose of Efmody was calculated in the same way as in DIUR-005, as the hydrocortisone equivalent of their pre-baseline treatment.

Dose titrations were possible in this study, albeit in a different manner than that of the study DIUR-005. Since this was an uncontrolled, open-label study, dose titrations were carried out by the investigator based on only two hormone measurements; the 09.00 hr measurement to guide the evening dose and the 13.00 hr measurement to guide the morning dose. This is considered acceptable since it better resembles clinical practice than the 24 hour profiles taken in study DIUR-005.

#### Efficacy data and additional analyses

#### DIUR-005

Of the 138 patients screened, 122 patients were randomized over the two treatment arms, 61 patients per arm. The evaluable efficacy data set comprised of 53 patients for the Efmody arm and 52 patients for the standard GC therapy arm. The main reason for exclusion was a major protocol deviation.

Review of the protocol deviations (79.5% overall) showed many patients had an endocrine measurement out of window. Since 24h hormone profiles were used, this is not of concern.

Prior CAH medication was balanced due to stratification. The largest proportion of the patients used hydrocortisone only as their standard therapy, in line with common clinical practice. The second largest group used prednisolone/prednisone, and only a minor proportion of the patients used dexamethasone, making subgroup analysis for this group difficult.

There was a difference in baseline disease control between the Efmody and standard therapy group, which cannot be explained and is considered a chance finding. Glucocorticoid daily dose, measured as a hydrocortisone equivalent dose (mg/day), increased in most subjects during the study (see Table 12), likely due to the rigorous titration regimen. In contrast, an overall GC sparing effect was reported for Efmody compared to standard therapy after 24 weeks of treatment (mg/day/BSA). This was mainly driven by the dexamethasone and prednisolone/prednisone subgroup. A similar daily dose was reported in the Efmody versus the hydrocortisone C immediate release subgroup.

In the overall study population, the total median daily GC dose per BSA was 15.82 mg/m2/day in the Efmody group and 17.04 mg/m2/day in the standard therapy group (see Table 12).

#### Hormone levels

The mean of the 24-hour SDS profile of 17-OHP was negative for both Efmody and standard GC therapy group, indicating that both groups achieved more optimal hormonal control during the study, likely due to the possibility to titrate the dose based on the 24h 17-OHP and A4 profiles. This is considered beneficial for the patient, although this way of dose titration is not feasible in clinical practice. The primary endpoint, namely clinical superiority compared to the standard glucocorticoid therap, was not met. The titration possibility on the primary endpoint variable (17-OHP) might have contributed to the failure to show the clinical superiority of Efmody compared to standard GC therapy. In addition, the circadian rhythm in part cancelled out the response as was also indicated by the applicant.

A relevant clinical difference can however be observed through "eyeball statistics" in the mean 17-OHP curves (nmol/L) between Efmody and standard therapy. The early morning 17-OHP peak seems to be reduced in the Efmody group as compared to the standard GC therapy (see Figure 11 and Figure 12). In particular, at 24 weeks the 17-OHP SDS was lower in the morning period (07:00 hrs to 15:00 hrs) but not in the evening or overnight.

The applicant has performed a range of post-hoc analyses on the data to further explore the effect of Efmody on 17-OHP curves, part of these analyses were suggested through CHMP scientific advice procedures. The main relevant findings were as follows:

- The 1-sided unsigned SDS above the lower limit of the reference range for 17-OHP at baseline and week 24 showed a difference between the treatment arms (difference in LS means: -0.976; 95% CI [-1.895,-0.058]; p=0.0374). The same was shown for the 1-sided unsigned SDS below the upper limit of the reference range (difference in LS means: 0.816; 95%CI [0.094,1.539]; p=0.0272).
- A reduction in 17-OHP AUC in both treatment groups throughout the duration of the study. This reduction at Week 24 was greater in the Efmody group (difference in LS means: -13.771; 95% CI [-25.783, -1.758]; p=0.0251)
- A difference between the 2 treatment groups was observed in the 07:00 to 15:00 hour profile (difference in LS means: -0.286; 95% CI: [-0.564, -0.008]; p=0.0442) but not in the other 8hour periods.

No correction for multiplicity has been performed, and therefore these analyses should be regarded as exploratory but overall supportive for an effect of Efmody in achieving morning control of androgens.

When pre-treatment therapy subgroups were analysed separately, no difference between the treatment arms could be shown on either 17-OHP and A4 levels.

#### Responder analysis

The responder analysis is considered relevant (See Table 22). A similar number of responders were seen in both treatment groups for both 17-OHP and A4 (17-OHP: 30 responders in each group, Odds Ratio=0.99; 95% CI: [0.45, 2.19]; p=0.9877; A4: 25 responders in the Efmody group and 26 responders in the standard GC therapy group, Odds Ratio=0.93; 95% CI: [0.43, 2.02]; p=0.8498).

Although differences in baseline responder proportions, disease control and the classification of patients ending up below the lower limit of normal (LLN) as "non-responder" makes the results difficult to interpret, the proportions of patients with 17-OHP levels (09.00h) below the upper limit of the optimal range (36 mmol/L) is considered more informative. In the Efmody group 90.6% of the patients (48/53) achieved control versus 71.2% (37/52) of the patients in the standard therapy group.

#### Clinical endpoints

No clinically relevant changes were observed in bone markers. The clinical endpoints body mass and bone mineral density were measured by DEXA scan.

No differences between the 2 treatments groups were seen from the DEXA scans for total lean mass or bone mineral density. Although a reduction in total fat mass was seen, with an estimated 0.413 kg LS mean reduction in the Efmody group compared to an estimated 0.547 kg LS mean increase in the standard GC therapy group from baseline to Week 24, the overall difference between treatment groups was not statistically significant (difference in LS means: -0.960 kg; 95% CI: [-2.294, 0.347]; p=0.1560).

#### Exploratory endpoints

#### Change in Bone Markers, fasting glucose and glycated haemoglobin (HbA1c)

The majority of the results related to changes in bone markers, fasting glucose and HbA1c were not considered clinically significant, and in those that were, only a small number of participants were seen to have clinically significant changes during the study. The only difference between the treatment groups was for fasting glucose, where a higher number of clinically significant increases were seen during the study in the Efmody group compared to the standard GC therapy group, which is in line with the established mechanism of action of Efmody which normalises cortisol levels in the early morning with a corresponding normalising effect on morning glucose levels but no impact on HbA1c.

No effect of Efmody was observed on quality of life measured by several different questionnaires (SF-36, MAF, EQ-5D). As also pointed out by the applicant, this may be due to the relatively short follow up time.

Overall, the data from study DIUR-005 show that the titration regimen was likely too aggressive, with putting too much emphasis on hormonal control at the cost of potential GC overreplacement.

#### DIUR-006

In total, 92 out of 133 patients eligible for treatment decided to enrol for the extension study (DIUR-006). Although the number of patients in study DIUR-005 declining participation in the extension study was balanced between groups, the willingness to continue (or start) Efmody treatment gives an indication on the satisfaction with either the standard treatment or Efmody. The CHMP however noted that the majority of patients declined participation in the follow-up study due to administrative reasons or due to the long gap between the studies.

In DIUR-006, the dose optimization regimen was more in line with clinical practice. During the course of the study, there was an overall decline in the median daily dose recorded for all patients, while androgen control was largely maintained.

Since there is no control arm, no firm conclusions can be drawn on the dose titration data. However, the data gives some reassurance that the dose titration regimen in DIUR-005 was too aggressive and that long-term androgen control can be achieved on adrenal replacement doses of Efmody. In particular, the initial decrease in the number of participants achieving disease control for those who were on standard GC therapy and switched to Efmody, is possibly due to participants initially being on a higher dose of Efmody based on the conversion from standard GC therapy that had been intensively titrated during study DIUR-005 and so ending up below the lower limit of the reference range, but once the dose of Efmody was reduced they returned to within the reference range. In this context, the SmPC dosing information recommends the use of the lowest possible dose and for maintenance therapy, the dose must be individualised according to the response of the individual patient.

No studies have been conducted in special populations which is considerable acceptable by the CHMP.

#### Safety data and additional analyses

With 138 unique patients included in the studies the safety database on Efmody is very limited, even taken into consideration that CAH is a rare disease (prevalence is 1 - 9/100,000 therefore ample patients should be available).

Based on the limited data derived from the clinical studies, no comprehensive assessment of the safety of Efmody can be made. However, the safety profile of hydrocortisone is considered well-known. Therefore it is considered sufficient that the applicant relies on the general safety knowledge of hydrocortisone and shows in a limited safety population that Efmody does not raise any new safety issues compared with hydrocortisone or that the frequencies of AEs is different.

In the pooled analysis of patients with CAH (pooled data from study DIUR-003, -005 (patients on Efmody only) and -006) a total of 211 treatment-related TEAEs were reported in 68 patients (56.7%). The most common treatment-related TEAEs by PT were fatigue (11.7%), headache (7.5%), and increased appetite (5.8%). As such, these are the adverse event to be expected in this population of patients treated with corticosteroids. No unexpected adverse events are observed, however, a consistent increased frequency of known adverse events was observed for Efmody.

The greatest differences between the Efmody and standard glucocorticoid therapy arms in the overall occurrence of treatment related AE's, respectively, were observed for headache (7.5% vs 1.6%), increased appetite (5.8% vs 3.3%), weight increase (including abnormal weight gain) (9.2% vs1.6%), decreased appetite (5.0% vs 0%) and nausea (4.2% vs 1.6%).Most of the TEAEs were mild or moderate. The patients switching from their standard GC treatment (either hydrocortisone, prednisone, prednisolone or dexamethasone) to Efmody reported a higher frequency of adverse events, this might be explained by the open-label design of the study were the patients in the control group continued on their respective treatment. It is, therefore, not unexpected that these patients reported lesser adverse events.

The frequency of "signs and symptoms of adrenal insufficiency or over-treatment" were higher in the Efmody treated patients (57.4%) as compared to the standard GC treatment (42.6%). These AE were mainly reported during the first 12 weeks during the titration phase of the study.

No deaths were reported in any of the clinical studies conducted with Efmody.

Due to the study design, the adrenal crisis during standard glucocorticoid therapy were reported in the first six months only with no follow-up information. Those reported during the use of Efmody appeared in the follow-up phase of the clinical programme. Although there is a theoretical risk for undertreatment and adrenal crisis short after initiation/switch to a modified release formulation (Efmody), no adrenal crisis were reported during the first 6 months of treatment.

No children were included in the studies. As the proposed indication is from 12 years onwards the data of children between 12 and 18 is lacking. Literature data clearly indicate that the clinical profile observed in adolescents is comparable with the adult population, especially considering the cardiovascular risk factors. As these adolescents are near adulthood it is considered acceptable to extrapolate the results obtained with adults to the children aged 12 to 17. As adolescents approach adult size and weight, and so near completion of growth, an adult empirical dose-based strategy is used of 15-25 mg/day of hydrocortisone. Furthermore, the improved control of overnight androgen precursors might be more in line with the normal physiology. In addition, lower doses of hydrocortisone with disease control should reduce potentially adverse effects on bone mass accretion, growth and development of cardiovascular risk factors.

No data is available in elderly population.

Appropriate warnings have been made in the SmPC in line with the reference product and the known safety profile of oral hydrocortisone. Particularly, warnings on growth retardation and accelerated sexual maturation were included in line with the important potential risks from the RMP.

# 2.4.8. Conclusions on clinical aspects

The main study failed to demonstrate clinical superiority of Efmody over standard GC therapy. However, Efmody treatment provided adequate cortisol replacement for a significant proportion of CAH patients. The curves suggested optimized disease control concerning the morning 17-OHP levels. This was supported by the proportions of CAH patients with 17-OHP level (9.00 hrs) below 36 mmol/L after 24 weeks of treatment favouring Efmody.

No unexpected adverse events have been identified with Efmody. Overall, the safety of Efmody is comparable to the well known safety profile of oral hydrocortisone.

# 2.5. Risk Management Plan

#### Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Growth retardation (in off-label paediatric use) Accelerated sexual maturation (in off-label paediatric use)
Missing information	None

# Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient to further characterise the safety concerns of the medicinal product.

### Risk minimisation measures

Safety concerns	Risk minimisation measures		
Growth retardation (in off-label paediatric use)	SmPC section 4.2; statement that dosing should be individualised and that the lowest possible dose should be used.		
	SmPC section 4.2; statement that safety and efficacy in patients aged below 12 years has not been established.		
	SmPC section 4.4; statement of risk of growth retardation in growing patients.		
	SmPC section 4.8; statement that both CAH and hydrocortisone can cause growth retardation and that regular monitoring is recommended.		
	PIL section 2; statement that long term treatment with hydrocortisone can affect growth in children and young people. Your doctor will monitor your growth.		
Accelerated sexual maturation (in off-label	SmPC section 4.2; statement that dosing should be individualised and that the lowest possible dose should be used.		
	SmPC section 4.2; statement that safety and efficacy in patients aged below 12 years has not been established.		
	SmPC section 4.4; statement of risk of accelerated sexual maturation in hydrocortisone treated CAH patients.		
	SmPC section 4.8; statement that accelerated sexual maturation has been reported in hydrocortisone treated CAH patients and that regular monitoring is recommended.		
	PIL section 2; statement that CAH patients treated with hydrocortisone can show signs of sexual development or puberty earlier than usual. Your doctor will monitor your development.		

# Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

# 2.6. Pharmacovigilance

### Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

# Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

# 2.7. Product information

# 2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

# 3. Benefit-risk balance

# 3.1. Therapeutic Context

### 3.1.1. Disease or condition

The indication claimed by the applicant is "Treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults."

Congenital adrenal hyperplasia is a group of genetic disorders leading to hyperandrogenism and adrenal insufficiency. Approximately 95% of CAH cases are caused by mutations in CYP21A2, the gene encoding adrenal steroid 21-hydroxylase.

The worldwide incidence in most studies ranged from; 1:14000 to 1:18000 births.

CAH due to 21-hydroxylase deficiency is divided into the classic (severe, early-onset) form and the non-classic (mild, late-onset) form. Classic CAH can be subdivided in salt-wasting CAH (approximately two-thirds of patients) and simple-virilising CAH (one-third of patients), reflecting the degree of aldosterone deficiency

In patients were mineralocorticoids production is affected, a life-threatening salt-wasting condition manifests in the first weeks of life. In addition, all CAH patients are at risk of adrenal crisis when experiencing physiological stress, another life-threatening situation that occurred due to the lack of adequate cortisol production.

Simple-virilising CAH in males and females appeared later in childhood and is characterised by early onset of puberty, and premature completion of growth leading to short stature. Due to excess androgen formation, female patients can present with atypical or ambiguous genitalia and menstrual irregularities.

# 3.1.2. Available therapies and unmet medical need

The recommended treatment of choice is glucocorticoid replacement therapy with oral hydrocortisone.

In adults, treatment with long-acting GC such as prednisone/prednisolone or dexamethasone is also possible. Replacement therapy with long-acting GC requires less doses per day and is therefore

preferred by some patients. Since the growth-suppressive effect of long-acting GC is more potent than hydrocortisone, these products should not be used in growing patients. In addition, all patients, but especially those still growing, should always be treated with the lowest effective dose to achieve treatment goals.

To overcome the disadvantages of the available therapies, particularly, the lack of control of the early morning peak in androgen levels, new treatment approaches and GC formulations are needed that mimic the circadian rhythm of physiological adrenocortical secretion. Better control of the peak in androgen levels could lead to the prevention of long-term consequences of GC overreplacement and facilitate the restoration of fertility in patients who desire to have children.

# 3.1.3. Main clinical studies

This is an hybrid application for a modified-release formulation of hydrocortisone according to Article 10(3).

Study DIUR-004 evaluated the relative bioavailability of Efmody versus the reference product, hydrocortisone 20 mg tablet.

Study DIUR-005 was a multicentre, open-label, randomized, controlled trial to assess the efficacy and safety of Efmody in patients 18 years and above with CAH due to 21-hydroxylase deficiency. The primary objective was to demonstrate the superior efficacy of a 24-week treatment with Efmody compared to standard glucocorticoid treatment.

Patients were randomized to either receive Efmody twice daily or stay on their respective standard therapy. Groups were randomized per baseline treatment strata; hydrocortisone only, prednisone/prednisolone or dexamethasone. Efmody start dose was the hydrocortisone equivalent of their pre-baseline treatment. Dose titrations were possible based on 24-hour 17-OHP and A4 profiles at week 4 and 12 and clinical symptoms (adrenal insufficiency checklist). Decisions to change the dose were made by a blinded independent physician.

24-hour endocrine profiles (17-OHP and A4 levels) were measured at baseline, 4, 12 and 24 weeks. The primary efficacy endpoint was the change from baseline to 24 weeks in 17-OHP, depicted as the unsigned standard deviation score (SDS). Secondary endpoints included change from baseline to 24 weeks in A4 (calculated the same way as the primary endpoint), responder analysis at 09.00 hours for 17-OHP and A4 and changes relative to standard GC replacement therapy in total body mass/ fat mass/lean mass/bone mineral density as measured by DEXA scan.

At the end of the study, participants could then either return to their standard GC therapy or enter an open-label extension study (DIUR-006) and receive Efmody on an ongoing basis. The primary objective was long term safety of Efmody. Secondary efficacy variables were daily GC dose, disease control at 09.00 and 13.00 hours and change from baseline in 17-OHP and A4 levels. In this study, participants returned to the study centre at 4, 12, and 24 weeks after starting the study, and 6-monthly thereafter for follow-up assessments. Dose titration could be performed by the investigating physician at these visits. Dose adjustment was to be based on clinical symptoms (adrenal insufficiency checklist) and the measurement of 17-OHP and A4 at 09.00 and 13.00 hours.

# 3.2. Favourable effects

### Study DIUR-004

In the bridging study, after administration of Efmody, serum cortisol Tmax was observed later (0.88h vs 4.5h), Cmax was 17% lower and AUC 19% higher compared to the 20 mg immediate release
reference product , showing the expected delayed-release properties of Efmody, a modified release formulation.

#### Study DIUR-005

In the pivotal clinical study, better disease control was achieved in both treatment arms from baseline to week 24 as measured by 17-OHP. The unadjusted mean change from baseline (SDS) in 17-OHP was -0.403 for Efmody and -0.172 for the standard GC therapy.

In the 24 hour 17-OHP curve, the early morning peak was reduced in the Efmody group compared to the standard GC group. Various post-hoc analyses were conducted on the primary efficacy variable, 17-OHP, which support the effect of Efmody:

- The 1-sided unsigned SDS above the lower limit of the reference range for 17-OHP at baseline and week 24 showed a difference between the treatment arms (difference in LS means: -0.976; 95% CI [-1.895,-0.058]; p=0.0374). The same was shown for the 1-sided unsigned SDS below the upper limit of the reference range (difference in LS means: 0.816; 95%CI [0.094,1.539]; p=0.0272).
- A reduction in 17-OHP AUC in both treatment groups throughout the duration of the study. This reduction at Week 24 was greater in the Efmody group (difference in LS means: -13.771; 95% CI [-25.783, -1.758]; p=0.0251).
- A difference between the 2 treatment groups was observed in the 07:00 to 15:00 hour profile (difference in LS means: -0.286; 95% CI: [-0.564, -0.008]; p=0.0442) but not in the other 8hour periods.

An increase in responders defined as the proportion of patients having an 09.00 hour 17-OHP measurement within the optimal range, was shown for Efmody; from 7.5% at baseline to 30% at 24 weeks. In the standard therapy group, the proportion of responders was 30.8% at baseline and 30% at week 24. More importantly, after 24 weeks of treatment, 48/53 (90.6%) of patients in the Efmody group had a 09.00h 17-OHP level below 36 mmol/L, against 37/52 (71.2%) of the patients in the standard therapy group.

In addition, a post-hoc analysis showed a reduction in A4 AUC in both treatment groups throughout the study. This reduction at Week 24 was greater in the Efmody group (difference in LS means: -10.478; 95% CI: [-18.696, -2.259]; p=0.0130).

No differences were observed for 17-OHP and A4 (change form baseline to 24 weeks) per pre-baseline treatment strata.

In the overall study population, the total median daily GC dose per body surface area (BSA) was 15.82 mg/m2/day in the Efmody group and 17.04 mg/m2/day in the standard therapy group.

#### Study DIUR-006

In the long-term extension study DUR-006, an increasing proportion of patients achieved disease control as defined by 17-OHP levels (09.00 hour) being within the optimal range while further dose decreases were possible.

#### 3.3. Uncertainties and limitations about favourable effects

No data is available on patients from 12-18 years of age.

Using the SDS to depict the hormone levels is common practice and is accepted, however it has several limitations. By taking the mean, circadian rhythms are cancelled out. The unsigned SDS does

not separate effects under or above the normal mean, a difference that might be clinically relevant. The SDS is also not very sensitive to amplitude, while the treatment is targeted at decreasing the early morning peak in androgen levels.

#### Study DIUR-005

In study DIUR-005, no significant difference on the primary endpoint was observed between the treatment groups (difference in LS means: -0.069; 95% CI: -0.229, 0.161; p-value: 0.5521). Clinical superiority of Cirkono over GC replacement therapy in CAH patients was not demonstrated.

The aggressive titration regimen used in study DIUR-005 is not feasible in clinical practice. The proposed titration suggested an emphasis on the importance of driving patients into the reference range at the cost of potential over-replacement.

A wide variety of post-hoc analyses were conducted on both the primary endpoint variable and the secondary variables. However, there were no corrections for multiplicity. Therefore, the differences in outcomes cannot be regarded as statistically different, and no claims on clinical superiority versus standard GC therapy can be made.

Reference range was based on a small sample of healthy volunteers, it is questionable whether this can be extrapolated to CAH patients. The LLN was an arbitrary limit based on the detection limit of the assay. Differences in baseline responder proportion, disease control, and the classification of patients ending up below the LLN as "non-responder" were thus difficult to interpret and no conclusions can be drawn on these data.

There were no significant differences between the groups on clinical endpoints (total body mass, fat mass, lean mass, bone mineral density, bone markers, QoL).

The extension study DIUR-006 is still ongoing.

## 3.4. Unfavourable effects

In the pooled analysis of patients with CAH (pooled data from study DIUR-003, -005 (patients on Efmody only) and -006), a total of 211 treatment-related TEAEs were reported in 68 patients (56.7%). The most common treatment-related TEAEs by PT were fatigue (11.7%), headache (7.5%), and increased appetite (5.8%).

The greatest differences between the Efmody and standard glucocorticoid therapy arms in the overall occurrence of treatment-related AEs, respectively, were observed for headache (7.5% vs 1.6%), increased appetite (5.8% vs 3.3%), weight increase (including abnormal weight gain) (9.2% vs 1.6%), decreased appetite (5.0% vs 0%) and nausea (4.2% vs 1.6%). Most of the TEAEs were mild or moderate. The (serious) adverse events, laboratory findings and vital signs reported are to be expected in a population of CAH patients treated with corticosteroids. No unexpected adverse events, laboratory findings or vital signs are observed,

The frequency of "signs and symptoms of adrenal insufficiency or over-treatment" were higher in the Efmody treated patients (57.4%) as compared to the standard GC treatment (42.6%). These AE were mainly reported during the first 12 weeks during the titration phase of the study.

The frequency and timing (events/year) of adrenal crisis in the Efmody and standard GC therapy appeared comparable with no major increase in the Efmody group.

No deaths were reported in any of the clinical studies conducted with Efmody.

## 3.5. Uncertainties and limitations about unfavourable effects

With 138 unique patients included in the studies, the safety database of Efmody is limited, even taken into consideration that CAH is a rare disease (prevalence is 1 - 9/100,00). The follow-up of patients on Efmody is also very limited. Therefore, no comprehensive safety assessment can be made for Efmody.

A strong limitation with the three clinical CAH studies is that all of these had an open-label design and were unblinded for patients. Thus, susceptibility to unintentional bias in adverse effect reporting could not be excluded. Therefore, results especially when comparing treatment with Efmody vs standard GC therapy, should be interpreted with caution.

No data is available on patients from 12-18 years of age.

The patients switching from their standard GC treatment (either hydrocortisone, prednisone, prednisolone or dexamethasone) to Efmody reported an unexplained higher frequency of adverse events (headache, increased appetite, weight increase (including abnormal weight gain), decreased appetite and nausea).

#### 3.6. Effects Table

#### Effects Table for Efmody

Effect	Short Description	Unit	Treatm ent	Contr ol	Uncertainties (Un)/ Strength of evidence (SoE)	References
Favourable Effects						
17-OHP 24h	Change from Baseline to 24 Weeks	LS mean SDS	-0.446	-0.376	Difference in LS means: -0.069, 95% CI: -0.229, 0.161, p-value: 0.5521 <b>SoE:</b> effect Efmody on 17-OHP supported by various post-hoc analyses, including an associated effect on A4. Statistically significant difference between Efmody and standard group between 07.00-15.00 hours. 09.00h 17-OHP <36 mmol/L after 24 weeks of treatment: Efmody group: 48/53 (90.6%) Standard therapy group: 37/52 (71.2%) <b>Un:</b> overall picture suggests over-treatment. There were no significant differences between the groups on clinical endpoints (total body mass, fat mass, lean mass, bone mineral density, bone markers	DIUR-005
Unfavourable Effects						
Appetite	Treatment-related increase	%	5.8	3.3	Increased incidences indicate lesser control of the signs and symptoms of adrenal insufficiency	Safety dataset
	Treatment-related decrease	%	5.0	0		Safety dataset
Weight	Treatment-related increase (including abnormal weight gain)	%	9.2	1.6		Safety dataset
Nausea	Treatment-related	%	4.2	1.6		Safety dataset
Headache	Treatment-related	%	7.5	1.6		Safety dataset
Adrenal crisis		%	0	4.9	No apparent difference <b>Un:</b> The limited number of patients, timing of the crises and lack of follow- up limits the robustness of the conclusion	Safety dataset
Adrenal Insufficiency and Over-treatment <sup>1</sup>	Signs and Symptoms of Adrenal Insufficiency and Over-treatment1	%	57.4	42.6	indicates a more troublesome titration and/or control in the Efmody group <b>Un:</b> The limited number of patients, timing of the crises and lack of follow-up limits the robustness of the conclusion	Safety dataset

## 3.7. Benefit-risk assessment and discussion

## 3.7.1. Importance of favourable and unfavourable effects

Efmody is developed as a modified release formulation of a known substance, hydrocortisone. The effect of Efmody corresponds to what would be expected of a GC replacement therapy based on overall effects on biomarkers 17-OHP and A4 levels. This is clinically relevant since 17-OHP and A4 levels are generally used as both a diagnostic marker and to guide treatment in the management of CAH. As 17-OHP is a precursor of A4, these variables are correlated. Complete androgen suppression is not the aim of treatment, the titration regimen used in study DIUR-005 was considered too aggressive, overemphasizing the effect on androgens at the cost of potential overreplacement. Since in clinical practice, a more physiological dose optimization is used, this issue is considered adequately addressed through appropriate dosing recommendations in the SmPC. In addition, despite the titration regimen, a GC sparing effect was seen in the overall population. In the long-term extension study, further dose reductions of Efmody were possible without losing androgen control, suggesting a more optimal dosing. This finding is considered of additional clinical benefit for the patients, given the adverse consequences of long term GC treatment.

No clinical superiority of Efmody was shown over the standard GC therapy in study DIUR-005. 17-OHP and A4 levels were analysed by comparing the unsigned SDS over 24 hours. Using the SDS to depict the hormone levels is common practice and is accepted, however it has several limitations that might have contributed to the failure to show clinical superiority. Nevertheless, in the 24 hour 17-OHP curve, the early morning peak was reduced in the Efmody group compared to the standard GC group, suggesting a clinical relevant difference in favour of Efmody treatment. Additional post-hoc analyses were conducted to further support the superior efficacy of Efmody over standard therapy. These analyses were considered clinically relevant and supportive of the efficacy of Efmody; however, given the number of analyses without corrections for multiplicity, no conclusions on clinical superiority can be drawn. The primary analysis was also hampered by the strict titration regimen guided by 17-OHP levels for both treatment groups.

Nevertheless, the CHMP considered that the active substance of Efmody, hydrocortisone, is well known and recommended as the oral treatment of choice for CAH patients in the current clinical guidelines. The clinical characteristics of Efmody treatment (delayed release effect mimicking the physiological circadian rhythm, twice daily dosing, GC sparing effect) are considered of added clinical values for CAH patients.

Although adolescents (12-17 years) were not included in the studies, this near mature population can be considered almost fully grown exhibiting the same disease characteristics as adults. Based on literature data, the clinical profile observed in adolescents is also comparable with the adult population. Therefore, extrapolation of the adult data to the adolescents was considered acceptable by the CHMP.

Furthermore, when optimally treated with Efmody the early morning androgen peak is expected to be lower as compared to treatment with immediate-release hydrocortisone. This is considered an additional treatment improvement, especially for reducing the effect of androgens on the sexual development.

A limited assessment of relevant clinical endpoints (e.g Total body mass, fat and lean mass, bone mineral density and quality of life outcomes) was included either as secondary or exploratory endpoints. However, the CHMP noted that since both treatment groups were optimally titrated in the studies and given the short follow up time, no significant differences were observed.

The safety profile of Efmody was overall comparable to the well-known safety profile of oral hydrocortisone. A higher AE frequency in patients switching from their standard GC treatment to Efmody was noted, however this difference could be explained by the open-label design of the study where patients in the control group remained on their standard treatment, and were considered less prone to report adverse events. Furthermore, the titration of Efmody was considered less optimal, which could also explain part of the increased frequency of adverse events.

## 3.7.2. Balance of benefits and risks

Despite the pivotal study did not demonstrate clinical superiority over standard GC replacement therapy, Efmody has shown to provide adequate cortisol replacement for a significant proportion of CAH patients in the studies, which is expected with an oral hydrocortisone treatment. In addition, the pharmacokinetic profile of Efmody mimics the physiological circadian rhythm, which cannot be achieved with immediate release or long-acting GCs. The totality of the data suggested an improved androgen control with Efmody and this effect was considered clinically relevant; however, given the methodological limitations of the additional efficacy analyses, these findings could not be regarded as statistically significant. The long-term data suggested the androgen balance can be largely maintained while further dose decreases were possible, this finding is of additional clinical benefit, given the adverse consequences of long-term GC treatment.

The reported AEs are considered in line with those known for oral hydrocortisone.

Overall, the clinical characteristics of Efmody treatment (delayed release effect mimicking physiological circadian rhythm, twice daily dosing, GC sparing effect) were considered of added clinical values for CAH patients. Thus, the CHMP concluded that Efmody can be regarded as an additional treatment option next to the standard of care.

## 4. Recommendation

## Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Efmody is not similar to Plenadren within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

## Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Efmody is favourable in the following indication:

Treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

#### Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription. (See Annex I: Summary of Product Characteristics, section 4.2).

## Other conditions and requirements of the marketing authorisation

#### **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

# *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

#### **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.